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EVIDENCE-BASED CARDIOLOGY

Second edition

Edited by Salim Yusuf
John A Cairns, A John Camm, Ernest L Fallen, Bernard J Gersh

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Evidence-based Cardiology

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Preface to the Second edition

"Where is the knowledge in all that information?
Where is the wisdom in all that knowledge?"
W H Auden

The recent proliferation of carefully controlled large scale clinical trials, their meta-analyses and selective observational studies has contributed to the remarkable strides made in the management of cardiovascular disease. One of the prophesies stated in the first edition of this textbook has come to pass – namely, that management guided by external evidence is an evolving process as newer and more effective treatment modalities come to light. While successful as a critical approach for managing patients, evidence-based medicine is nevertheless a work in progress which, if allowed to rest on its laurels, will "by nature be threatened with impending obsolescence". In addition to keeping abreast of new information, there is a need to integrate and distill the information into coherent recommendations. Authors were therefore instructed to provide their recommendations including those based on qualitative judgments. The recognition of new developments in a rapidly changing dynamic field combined with the overwhelmingly positive worldwide response to the first edition have prompted the publication of this second edition.

This edition is again dedicated to providing a comprehensive compendium of best evidence for the diagnosis and management of a wide variety of cardiovascular disorders. To avoid critical information gaps as meaningful new data emerge, the text contains several new features. Because our concepts of what constitutes evidence-based medicine is subject to change we have included a completely revised introductory chapter. Appended to the printed text is a CD Rom that permits ready access to new information and periodic updates by way of a dedicated and active website. In addition, there will be available a compact hand-held (PDA) version of the text. There are new chapters on clinical trials and meta-analysis; fetal origins of cardiovascular disease; genetics; diet and cardiovascular disease; obesity; and cardiopulmonary resuscitation. Several chapters have been completely rewritten and most have undergone substantial revision. Finally, the layout of the text has been reformatted for better handling, portability, readability and affordability.

In preparing this edition the editors and contributors have subscribed to the principle that the best external evidence found in these pages are not to be considered as hierarchical choices but rather should be used judiciously with other forms of evidence be they pathophysiologic, observational or experiential. No effort has been spared in the preparation of this edition and to this end invaluable assistance has been accorded us by Judy Lindeman at McMaster University and Mary Banks and Christina Karaviotis at BMJ Books.

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Preface to the First edition

> "… if a man declares to you that he has found facts that he has observed and confirmed with his own experience, be cautious in accepting what he says. Rather, investigate and weigh this opinion or hypothesis according to requirements of pure logic, without paying attention to this contention that he affirms empirically."
>
> MOSES MAIMONIDES. *ca.* 1195

Thus did the great physician Maimonides make a plea for an evidence-based approach to medicine by admonishing his followers to seek common ground between objectivism and empiricism. If Maimonides had lived in the year 1785, he would likely have read William Withering's *An Account of the Foxglove*; a compendium of Withering's personal observations on the clinical effect of the digitalis leaf. At first blush, Maimonides would cry foul at such flagrant empiricism, demanding to know the whole of the inception cohort. It turns out that Withering, instead of selecting specific cases which would have "… spoken strong in favour of the medicine, and perhaps been flattering to my own reputation" went on to say in his Preface "I have therefore mentioned every case in which I have prescribed the foxglove, proper or improper, successful or otherwise …" thus heralding a genuine, albeit retrospective, cohort study. It took 212 years before Withering was ultimately vindicated by the results of the first large scale randomized placebo controlled trial of digoxin (*N Engl J Med* 1997; **336**: 526). Sixty-eight hundred patients with congestive heart failure, in sinus rhythm, were randomized to receive digoxin (avg dose 0·25 mg/day) or placebo in addition to ACE inhibitors and diuretics. Over a three-year period there was no statistical difference in overall mortality but digoxin proved to be effective in reducing hospitalizations due to worsening heart failure.

The advent of large scale prospective randomized clinical trials has strengthened the external evidence upon which management decisions can be made with some confidence. We have come to rely on so-called external best evidence as critical guideposts for establishing minimal criteria for treatment of many cardiovascular disorders. In the process, some myths based on putative mechanisms have been dispelled while insights into the efficacy of new treatments have been more rapidly facilitated. On the other hand there is a danger of righteous complacency which, if unchecked, could lead to a slavish dependency on statistical bottom lines and, ultimately, to "cook book" medicine. It is the intent of this textbook to present a proper balance between "objectivism and empiricism". In this regard, the very first chapter begins by defining the practice of evidence-based cardiology as "… integrating individual clinical expertise with the best available external clinical evidence from systematic research".

The textbook has four principal components. An introductory general section addresses important topics in clinical epidemiology, as applied both to the bedside and to a population. This section includes: critical appraisal of data; clinical trials methodology; quality of life measurements; health economics; and methods of decision analysis, all in the context of current clinical practice. Next follows a section on preventive strategies based on evidence that should enable the practicing physician to advise, with confidence, on risk factor modification and quality of life issues for selected patients. There follows a section on a broad range of specific cardiovascular disorders that highlight management issues based on current best evidence. Finally, the section on clinical applications is an attempt to put a clinical face on evidence derived from population statistics through the use of "live" clinical cases. Here, an attempt is made judiciously to couple external evidence with clinical expertise and a sound knowledge of cardiovascular pathophysiology. There is understandably a wide range of the kinds of evidence available to support different practices and treatments. The editors have chosen not to constrain the authors into rigid and uniform formats for each chapter. While several of the chapters have the level of evidence/recommendations graded, or key messages highlighted, a uniform format would not have been appropriate for every chapter.

This textbook is designed for a wide audience. Since cardiovascular disease comprises more than fifty percent of adult medicine, there is something here for everyone in clinical practice and at all levels of medical undergraduate and postgraduate training. Its emphasis on practical applications of research methodology and critical appraisal of data covering a cross-section of clinical topics should invite interest among those engaged in population studies, biostatistics, clinical epidemiology and health economics as well as those involved in healthcare decision analysis, quality assurance committees and stakeholders responsible for healthcare planning.

Because this textbook relies so heavily on current best evidence, it is by nature threatened with impending obsolescence. To ensure that this does not happen, the editors, in concert with the publisher, have agreed to issue up-dates periodically in the form of special supplements or updated editions, so that the text can be continually revised in accordance with emerging relevant data. In this context, it is well to bear in mind that good science always proceeds hesitantly through a series of tenuous conclusions. And so any recommendation made on the basis of available best evidence is subject to revision as we probe deeper into the mysterious nature of disease processes. One may ask of the large scale clinical trial "Why did it require more than 10,000 patients to show incontrovertible evidence that the experimental drug is effective?" Aye, there is the scientific question!

The editors wish to acknowledge the herculean efforts of Catherine Wright and Karin Dearness who kept everyone on track and offer a special appreciation to Mary Banks for her editorial expertise, patience and support.

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Glossary

Abbreviations commonly used in this book

ABI	ankle brachial pressure index
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
APSAC	anisoylated plasminogen streptokinase activator complex
APTT	activated partial thromboplastin time
ARR	associated risk reduction
AS	aortic stenosis
ASD	atrial septal defect
ASMR	age standardized mortality rate
BBB	bundle branch block
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CBVD	cerebrovascular disease
CCB	calcium-channel blockers
CCU	coronary care unit
CEE	conjugated equine estrogen
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK-MB	creatinine kinase MB isoenzyme
CPP	coronary perfusion pressure
CPR	cardiopulmonary resuscitation
CT	computerized tomography
CYA	cyclophosphamide
DA	dopamine
DALY	disability adjusted life years
DHP	dihydropyridines
DM	diabetes mellitus
DVT	deep vein thrombosis
ECG	electrocardiogram
EEG	electroencephalogram
EGF	epidermal growth factor
EMF	endomyocardial fibrosis
EOA	effective orifice area
EPS	electrophysiologic studies
FGF	fibroblast growth factor
FS	fractional shortening
GPI	glycoprotein inhibitor
HCM	hypertrophic cardiomyopathy
HDL	high density lipoprotein (HDL_2)
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOCM	hypertrophic obstructive cardiomyopathy
HRT	hormone replacement therapy
IC	intracoronary
ICD	implantable cardioverter defibrillator
ICH	intracerebral hemorrhage
IDC	idiopathic dilated cardiomyopathy
IDL	intermediate density lipoprotein
IE	infective endocarditis
IFN-γ	interferon gamma
IGF	insulin-like growth factor
IGT	impaired glucose tolerance
IL	interleukin
IM	intramuscular
INR	international normalization ratio
IQR	interquartile range
IV	intravenous
LAE	left atrial enlargement
LBBB	left bundle branch block
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LMWH	low molecular weight heparin
Lp(a)	lipoprotein
LQTS	long QT syndrome
LV	left ventricular
LVE	left ventricular enlargement
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MCP	monocyte chemoattractant protein
MHC	major histocompatibility complex
MHS	Milan Hypertensive Strain
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MUFA	monounsaturated fatty acid
NA	not available
NHLBI	National Heart Lung Blood Institute
NINDS	National Institute of Neurologic Disease and Stroke
NNT	number needed to treat
NSAIDs	non-steroidal anti-inflammatory drugs
NSTEMI	non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OR	odds ratio
P	probability
PAI	plasminogen activator inhibitor
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PDGF	platelet derived growth factor
PE	pulmonary embolism
PET	positron emission tomography
PPCM	peripartum cardiomyopathy
PSVT	paroxysmal supraventricular tachycardia
PTA	percutaneous transluminal angioplasty
PTCA	percutaneous transluminal coronary angioplasty

PUFA	polyunsaturated fatty acid
PVC	premature ventricular complex
RCT	randomized controlled trial
RFLP	restriction fragment length polymorphisms
ROSC	return of spontaneous circulation
RRR	relative risk reduction
rtPA	recombinant tissue plasminogen activator
RV	right ventricular
RVEF	right ventricular ejection fraction
RVF	right ventricular enlargement
RVH	right ventricular hypertrophy
SAECG	signal-averaged ECG
SC	subcutaneous
SK	streptokinase
SMC	smooth muscle cells
SFA	saturated fatty acid
SFA	superficial femoral artery
STEMI	ST-segment elevation myocardial infarction
TEA	thromboendarterectomy
TEE	transesophageal echocardiography
t-FA	*trans* fatty acid
TGF	transforming growth factor
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TMP	TIMI myocardial perfusion
TNF	tumor necrosis factor
TNK	tenecteplase
tPA	tissue plasminogen activator
TTE	transthoracic echocardiography
UK	urokinase
v	versus
VF	ventricular fibrillation
VPD	ventricular premature depolarization
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VUI	venous ultrasound imaging

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

Part I

General concepts and critical appraisal

Salim Yusuf, Editor

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

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1 What is evidence-based cardiology?

PJ Devereaux, R Brian Haynes, Salim Yusuf

Introduction

In 1836 the editor of the *American Journal of Medical Sciences*, Elisha Bartlett, heralded a study as "one of the most important medical works of the present century, marking the start of a new era in science".[1] What evoked such praise and suggested a paradigm shift was Dr Pierre Louis' systematic collection and numerical presentation of data on bloodletting. Louis adopted a baconian approach of collecting vast amounts of data on a large number of patients (by the standards of the early 1800s), which allowed him to systematically evaluate the efficacy of bloodletting. Louis argued that large numbers of patients and enumeration were necessary to equalize differences between treatment groups, as "by so doing, the errors (which are inevitable), being the same in two groups of patients subjected to different treatment, mutually compensate each other, and they may be disregarded without sensibly affecting the exactness of the results".[2] Louis subsequently went on to state: "a therapeutic agent cannot be employed with any discrimination or probability of success in a given case, unless its general efficacy, in analogous cases, has been previously ascertained", and thus, "without the aid of statistics nothing like real medicine is possible".[3]

The prevailing concept of illness at the time was that the sick were contaminated, whether by some toxin or contagion, or by an excess of one humour or another. This understanding of illness contained within it the idea that these states were improved by opening a vein and letting the sickness run out. Louis' finding that bloodletting hastened the death of the ill was a bombshell. George Washington had 2·4 liters of blood drained from him in the 15 hours prior to his death: he had been suffering from a fever, sore throat and respiratory difficulties for 24 hours.[4] Some have stated that in this way Washington was murdered.[5–7]

Although this is a relatively recent example, the plea for comparative evaluation was mentioned as early as the Old Testament. Throughout history there have been repeated exhortations to quantify medical or health problems and to compare outcomes in patient groups managed differently, with the goal of setting state policy or assisting individual physicians.

In this chapter we will discuss what evidence-based medicine is, and then discuss an approach to evidence-based decision making. We will use a clinical case to highlight the components of this approach, which include clinical state and circumstances, patients' preferences and actions, research evidence, and clinical expertise. At the end of the chapter we will review the application of these components of evidence-based decision making as they apply to our patient, and provide a decision aid that can be used in such a case.

What is evidence-based medicine?

Although the foundations for evidence-based medicine were laid over several centuries, an explicit philosophy, with its attendant concepts, definitions and models, has been largely developed as a formal doctrine over the last few decades. Evidence-based medicine is about solving clinical problems. Initially, the focus of evidence-based medicine was largely to find the best objective quantifiable research evidence relevant to the particular problem, and to apply that evidence in resolving the particular issue.[8] This early focus de-emphasized "intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making" and stressed "the examination of evidence from clinical research".[9] Subsequent versions have emphasized that research evidence alone is never sufficient to make a clinical decision.[10] Research evidence by itself rarely tells us what to do in individual situations, but rather it provides useful information that allows us to make more informed decisions. Clinicians must always view evidence in the context of the individual patient, and then weigh the potential benefits versus the risks, costs and inconveniences. Ideally the patient's values and preferences take precedence[10] (Figure 1.1).

Figure 1.1 is based on the first edition of *Evidence-based medicine*[11] and was published in an editorial that appeared in *ACP Journal Club* and *Evidence-Based Medicine* in 1996, along with the definition: "Evidence-based medicine is the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients".[12] The editorial also included the caveat that the definition of evidence-based medicine would evolve as new types of information emerged, and would therefore be continuously refined. The concepts of evidence-based

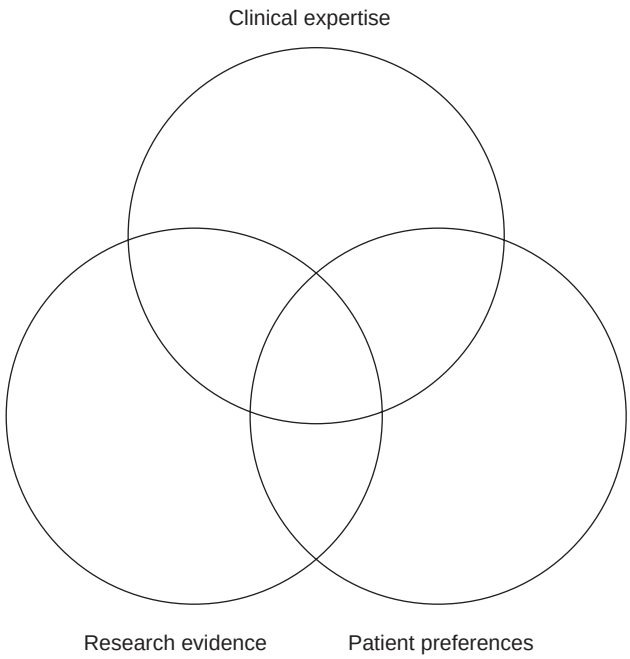

Figure 1.1 Early model of the key elements for evidence-based clinical decisions

medicine have evolved considerably and the initial model has recently been enhanced,[8] especially for what is meant by clinical expertise and the additional consideration of clinical situation and circumstances. In the next section we use this new model of "evidence-based clinical decisions" to help resolve a common clinical scenario.

Approach to evidence-based clinical decision making

New model for evidence-based clinical decisions (Figure 1.2)

Figure 1.2 depicts the evolution of the model for evidence-based clinical decisions,[8] which has more recently been redefined as "the integration of best research evidence with clinical expertise and patient values".[13] This model represents a desirable approach as to how all clinical decisions should be made. However, we acknowledge that, at present, many clinical decisions are not made in this way. For instance, at present, clinicians' individual preferences (as distinct from clinical expertise) often play a large role in their actions, leading to large "practice variations" in managing similar cases. When faced with critically ill patients with identical circumstances, different clinicians may, according to their preferences, institute aggressive life-prolonging interventions or withdraw life support.[14] Our model acknowledges that patients' preferences should be considered first and foremost, rather than clinicians' preferences, whenever it is possible to do so.

In Figure 1.2, the "clinical state and circumstances" of the patient replace "clinical expertise" as one of the key elements in clinical decisions, "patient preferences" is expanded to include patients' actions, and this element is reversed in position with "research evidence", signifying its frequent precedence. Integrating all three aspects requires judgment and clinical expertise, thus constituting a fourth overarching element. We will describe each of the components, and the role of clinical expertise in integrating them.

Clinical state and circumstances

A patient's clinical state and circumstances often play a dominant role in clinical decisions. Clinical trials provide us with results reflective of the average patient within the treatment groups of the trial, but rarely is a patient in

Clinical scenario

A family physician refers a patient requesting your input on the issue of antithrombotic therapy. The patient is an 80 year old man with a history of hypertension who 10 months ago, on routine examination, was diagnosed with atrial fibrillation. The patient suffered a major gastrointestinal bleed, requiring hospitalization, urgent endoscopy, and a transfusion the day after his atrial fibrillation was discovered (the patient had not started any antithrombotic therapy prior to his bleeding episode). He had, however, been receiving a non-steroidal anti-inflammatory drug (NSAID) for osteoarthritis. The patient has been free of any gastrointestinal symptoms since his bleed and has successfully avoided using an NSAID by using acetaminophen. Eight months earlier the patient's echocardiogram demonstrated normal valvular and left ventricular function and a left atrial measurement of 6·5 cm. Based on the duration of atrial fibrillation and the size of his left atrium, you decide that cardioversion is not an option. The patient is very worried about having a stroke, as his wife was left dependent on him for 2 years prior to her death following a major stroke. The referring physician, who recently had a patient who suffered a serious gastrointestinal bleed while on warfarin, is very concerned about the risk of bleeding, given this patient's age and recent history of gastrointestinal bleeding.

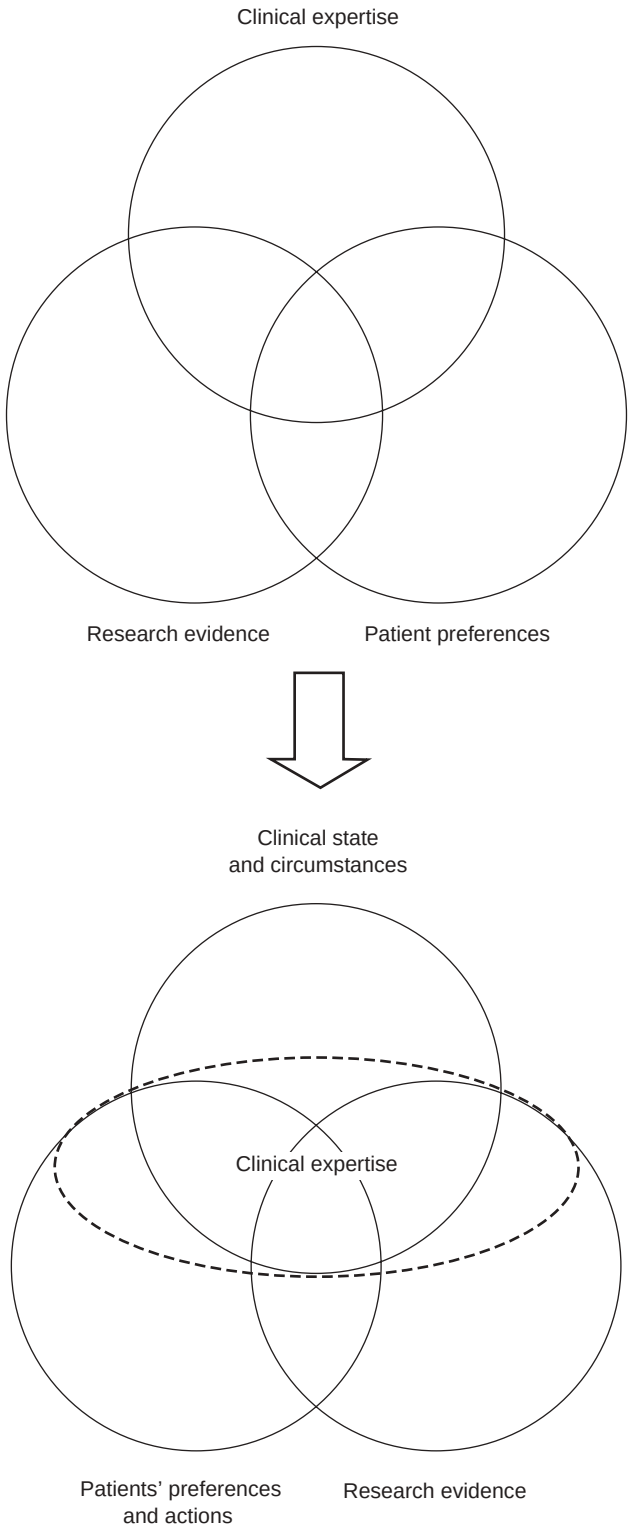

Figure 1.2 Evolving model for evidence-based clinical decisions

clinical practice the same as the average patient from a clinical trial. Individual patients have unique characteristics that typically put them at lower or higher risk of the outcome or treatment side effect than the average patient in the trial. As such, optimal clinical decisions should be individualized to the patient's clinical state. A patient who is at very high risk of a future vascular event, but at low risk of any complication from a drug (for example, a patient with a low density lipoprotein value of 8·0 mmol/l post myocardial infarction and no contraindication to statin therapy), or conversely a patient who is at low risk of the outcome and high risk of a treatment's complications (for example, a 40 year old man with atrial fibrillation without any associated stroke risk factors who has experienced a recent major gastrointestinal bleed), may find their clinical state dominating the clinical decision making process.

It is notable that the circles of clinical state and circumstances and research evidence overlap. Frequently research evidence can inform us about the influence of the clinical state and circumstances. Considering our patient, the pooled data from five randomized controlled trials (RCTs) evaluating the efficacy of warfarin in patients with non-valvular atrial fibrillation (NVAF) demonstrated an average annual stroke rate of 4·5% and a major bleeding rate of 1% in patients not receiving antithrombotic therapy.[15] The investigators who combined the five RCTs used the control patient data to develop a clinical prediction tool to estimate the annual risk of stroke. Independent risk factors that predicted stroke in control patients were increasing age, a history of hypertension, diabetes, and prior stroke or transient ischemic attack (TIA).[15] Our patient's annual risk of stroke is predicted to be about 8%, which is higher than that of the average control patient in the five RCTs, whose annual stroke rate was 4·5%.[15] Similarly, a clinical prediction tool has been developed for predicting the risk of major bleeding (defined as the loss of two units of blood within 7 days, or life-threatening bleeding) while taking warfarin therapy.[16] Independent risk factors that predict major bleeding in patients taking warfarin include age >65, history of stroke, history of gastrointestinal bleeding, recent myocardial infarction, anemia, renal failure and diabetes. (Note that many of the factors that predict a higher risk of stroke also increase the risk of bleeding.) Our patient's annual risk of major bleeding of 8% also differs from that of the average patient receiving warfarin in the five RCTs, whose annual risk of major bleeding was 1·3%. We are unaware of any clinical prediction tool for predicting major bleeding while taking aspirin, and the atrial fibrillation trials had inadequate power to estimate this. However, based on the results of the meta-analysis by the antithrombotic trialists' collaboration, we would expect aspirin to increase the risk of major bleeding from 1% to about 1·3% on average.[17]

The clinical circumstances in which you and your patient find yourselves (for example, your ability to administer and monitor a treatment) may be very different from those of an RCT. For example, the patient may not be able to obtain frequent tests of the intensity of anticoagulation. However, for a patient with the same clinical characteristics, we can frequently optimize clinical circumstances to decrease the risk

of an outcome or treatment side effect. For example, we can decrease the risk of bleeding due to warfarin therapy by more intensive monitoring. Thus, an "evidence-based" decision about anticoagulation for a patient with atrial fibrillation is not only determined by the demonstrated efficacy of anticoagulation and its potential adverse effects,[18] but will vary based on the patient's clinical state and according to individual clinical circumstances.

Patients' preferences and actions

Patients may have no views or, alternatively, unshakable views, on their treatment options, depending on their condition, personal values and experiences, degree of aversion to risk, healthcare insurance and resources, family, willingness to take medicines, accurate or misleading information at hand, and so on.[8] Accordingly, individuals with very similar clinical states and circumstances may choose very different courses of action, despite being presented with the same information about the benefits and risks of an intervention.

For our patient with NVAF, research evidence informs us about the differing preferences of patients and their physicians for antithrombotic therapy in atrial fibrillation when they weigh the competing risks of stroke and bleeding.[19] In this study,[19] participants (that is both physicians and patients) reviewed flip charts describing in detail the acute and long-term consequences of a major and minor stroke and a major bleeding event. Participants were instructed that the likelihood of a minor or major stroke was equal. The participants then underwent a probability trade-off technique which determined the minimum number of strokes that needed to be prevented before the participant felt antithrombotic therapy was justified (this value was determined for both warfarin and aspirin), given the associated increased risk of bleeding, costs and inconveniences. The same technique was also used to determine the maximum number of excess bleeds the participant would consider to be acceptable with antithrombotic therapy (determined both for warfarin and aspirin), given the benefits in terms of stroke reduction with this therapy. This study demonstrates significant variability between physicians and patients in their weighing of the potential outcomes associated with atrial fibrillation and its treatment. Patients required less stroke reduction and were more tolerant of the risk of bleeding than physicians. For example, on average, patients were willing to accept the risk of 17 extra major bleeding events in 100 patients over a 2 year period if warfarin prevented eight strokes among these 100 patients. Physicians, however, were only willing to accept 10 major bleeding events for the same level of benefit. Furthermore, physicians varied significantly in how much bleeding risk they thought was acceptable for a given stroke reduction associated with an antithrombotic agent. Hence different physicians would make very different recommendations to the same patient with identical risks of bleeding and stroke. This underscores the importance of having patient values and preferences drive clinical decision making. It is the patient who is at risk of the outcome and so, when willing and able, they should be the one to weigh the potential benefits versus the risks, costs and inconveniences.

There is debate regarding the optimal way to elicit and incorporate patient preferences into clinical decision making. One method is to discuss the potential benefits and risks with a patient and then qualitatively incorporate your impression of the patient's preferences into the clinical decision. Alternatively, at least two quantitative approaches exist: decision analytic modeling and probability trade-off technique. In a decision analytic model, a standard gamble, time trade-off or visual analog scale technique is used to determine the utility (patient value/preference) of the various outcomes. This information is then fed into a decision tree that includes the probabilities of the outcomes for all clinical decisions being considered. Using the decision tree, calculations are undertaken to determine what course of action optimally fits the patient's preferences. The probability trade-off technique presents patients with the probabilities for the various interventions being considered and then asks them to make a decision based on this information. This allows a direct and quantitative incorporation of the patient's preferences.

Proponents of decision analytic modeling question whether patients can understand probabilities to allow the appropriate incorporation of their preferences. Proponents of probability trade-off techniques wonder if a measure of utility (that is preference) in the absence of probabilities is meaningful. Only one study has directly compared decision analytic modeling with a probability trade-off technique.[20] This study focused on the primary prevention of stroke and myocardial infarction with aspirin therapy in elderly patients. Both methods (that is decision analysis and probability trade-off) were performed on all patients at separate times. This study demonstrated that treatment recommendations varied significantly, depending on which method was used. After patients were presented with their individual treatment thresholds as determined by both methods, over twice as many stated they would base their preferences on the results of the probability trade-off as opposed to the decision analysis.[20] Further research is needed to determine which of the models better represents patients' self-interests.

Regardless of what their preferences may be, patients' actions may differ from both their preferences and their clinicians' advice.[21] For example, a patient may prefer to lose weight, quit smoking and take their medications as prescribed, but their actions may fall short of achieving any of these objectives. Alternatively, they may follow the treatment as prescribed, even if they resent its imposition, adverse effects and costs. Unfortunately, clinicians' estimates of their patients' adherence to prescribed treatments

have no better than chance accuracy.[22] Thus, physicians' decisions for care will better meet the model's specifications if they are able to assess whether their patients will follow, or are following, their prescriptions.[22]

We recognize that at present patients' preferences are rarely formally incorporated in clinical practice. This may be related to lack of physician training in these approaches, a reluctance to tread unfamiliar ground, and also in many circumstances the lack of accurate quantitative information on risk and benefits, as well as clinical risk prediction tools. However, this is likely to change rapidly as clinical models can be derived from large databases and handheld computers can be utilized to quantify risks and benefits at the bedside.

Research evidence

We support a very broad definition of research evidence, namely, "any empirical observation about the apparent relation between events".[23] In keeping with this definition, research evidence includes everything from the unsystematic observation of a single physician to a systematic review of large RCTs. Not all evidence is created equal, and hence there is a hierarchy of evidence that varies depending on whether one is addressing a diagnostic, prognostic or therapeutic decision. We will focus on the hierarchy of evidence for therapeutic decisions (Box 1.1).[23]

Box 1.1 Hierarchy of evidence for treatment decisions*

Coherence of evidence from multiple sources
Systematic review of several well designed, large randomized controlled trials
Single large randomized controlled trial
Systematic review of several well designed small randomized controlled trials
Single small randomized controlled trial
Systematic review of several well designed observational studies
Single observational study
Physiologic studies
Unsystematic observation from a physician

* This hierarchy cannot be rigidly adhered to. At times a single observation may be very powerful (for example, defibrillation for ventricular fibrillation), or observational studies may provide unequivocal evidence (for example, smoking cessation and lung cancer). However, in most cases where treatment effects may be moderate, outcomes variable or the clinical course unpredictable, the proposed hierarchy is useful.

All evidence has value, and the best evidence available in the hierarchy should be given appropriate consideration, even if not at the top of the hierarchy. Therefore, the unsystematic observations of colleagues should not be dismissed when no higher level evidence exists. Indeed, unsystematic observations can lead to many important insights, and experienced clinicians usually develop a respect for the insights of their astute colleagues. However, it is equally important to recognize that unsystematic observations are commonly limited by the small number of observations, variability in outcomes, lack of objectivity, and the difficulties in integrating (for example, taking into account the natural history of a disorder, placebo effect, and a patient's desire to please) and drawing inferences from observations.[24]

All evidence has limitations. Although the majority of advances in medicine are initially uncovered through individual observations, physiologic studies, observational studies or randomized controlled trials evaluating surrogate endpoints, there have also been several extremely misleading findings that have, at times, resulted in harm. It is important to remember that contradictory results across studies on the hierarchy of evidence table are not isolated to one or two instances (Table 1.1).

Perhaps the most powerful example is the story of antiarrhythmic therapy. Despite encouraging evidence that encainide and flecainide could prevent premature ventricular beats, a large RCT demonstrated a higher mortality rate with these drugs than with placebo, such that these drugs resulted in an extra death for every 20 patients treated with encainide or Flecainide.[39] It is estimated that more Americans were killed by these drugs than died in the Vietnam War.[40]

Ideally, we would have evidence from all levels of the hierarchy and the evidence would be coherent across all levels. This would represent the most persuasive evidence. However, this rarely happens, as even RCTs may by chance frequently demonstrate contradictory findings, especially when they are small. Therefore, physicians should always aim for the highest level of evidence for clinical decision making. Clinicians can still make strong inferences, particularly when there is evidence from a systematic review of several well designed large RCTs, or simply a large single pragmatic RCT. The RCT is such a powerful tool because randomization is our only means to reduce bias in treatment comparisons by controlling for unknown prognostic factors.[41] Therefore, RCTs have the potential to provide the most valid (that is likelihood that the trial results are unbiased) estimates of treatment effect.[42] Furthermore, large RCTs with broad eligibility criteria enhance the generalizability of their findings.

An *n* of 1 randomized controlled trial is an RCT where individual patients are randomized to pairs of treatment periods, such that they receive the experimental treatment during one period and a placebo during the other.[43] Both patients and healthcare providers are blind to which period is the experimental and which the placebo. Patients continue undergoing pairs of treatment periods until they and the healthcare providers become convinced that the experimental intervention either does or does not work.[43] The advantage of an *n* of 1 RCT is that it provides evidence directly from the patient. However, this method is applicable only in a disease state that has limited fluctuation, and

Table 1.1 Some examples of contradictory results across studies at various positions in the hierarchy of evidence

Results from lower level evidence	Results from higher level evidence
Milrinone demonstrated improvement in left ventricular function during exercise[25]	A large RCT[26] and meta-analysis of several RCTs[27] demonstrated a 28% relative increase in mortality with milrinone compared to placebo
An observational study of extracranial to intracranial bypass surgery suggested a "dramatic improvement in the symptomatology of virtually all patients" undergoing the procedure[28]	A large RCT demonstrated a 14% relative increase in the risk of fatal and non-fatal stroke in patients undergoing this procedure compared to medical management[29]
A meta-analysis of 16 cohort studies and 3 cross-sectional angiographic studies (including studies of women with known coronary artery disease) demonstrated a relative risk of 0·5 (95% CI 0·44–0·57) for coronary artery disease among women taking estrogen[30]	A moderate-sized secondary prevention RCT did not demonstrate any reduction in coronary heart disease events but did demonstrate an increase in thromboembolic events in patients receiving estrogen.[31] Preliminary reports from an ongoing very large RCT (Women's Health Initiative) indicate an increased risk of MI and strokes in the first 2 years of estrogen therapy[32]
A secondary analysis of an RCT suggested that lower doses of ASA were associated with a higher risk of perioperative stroke and death in patients undergoing carotid endarterectomy[33]	A large prospective RCT showed a higher risk of perioperative stroke, myocardial infarction or death with high-dose ASA[33]
A physiologic study demonstrated that β blockers result in a decline in ejection fraction and increases in end-diastolic volume in patients with prior myocardial infarction[34]	A meta-analysis of 18 RCTs[35] and 3 large trials (CIBIS−2,[36] MERIT-HF[37] and COPERNICUS[38]) in patients with heart failure found a 32% relative risk reduction in death in patients receiving β blockers

for treatments that can be crossed over (for example, short-acting medical treatments rather than surgery) and which are targeted at symptom relief and quality of life, as opposed to serious outcomes such as myocardial infarction and death. Even then, *n* of 1 RCTs are not feasible for many patients because of lack of infrastructure to support them, such as a pharmacy that is able and willing to provide matching placebos. Also, short-term symptomatic effects of treatments may differ from their long-term effects, so that *n* of 1 trials may provide misleading answers. Similarly, if side effects occur only after prolonged treatment (for example, during to drug accumulation, as with amiodarone), then short-term crossover studies (which is what *n* of 1 trials are) may not identify the full risks associated with a treatment. As such, there has been limited implementation of *n* of 1 RCTs in cardiology, but they represent a unique opportunity (when possible and applicable) to obtain individual patient level evidence.

Considering our case of the patient with NVAF, the highest level of evidence comes from a systematic review of all the RCTs that have evaluated antithrombotic therapy in patients with atrial fibrillation.[18] This study demonstrates that warfarin reduces the relative of stroke (ischemic and hemorrhagic) by 62%, and aspirin by 22%.

Considering the risk of bleeding associated with warfarin therapy, there is an RCT that demonstrates a 50% decrease in the risk of bleeding if a patient is willing to undergo education, training and self-monitoring of prothrombin time.[44]

Clinical expertise

Evidence-based decision making requires clinical expertise to establish and balance the patient's clinical state and circumstances, preferences and actions, and the best research evidence. Before a therapeutic decision can be considered, clinical expertise is required to get the diagnosis and prognosis right. As shown above, clinical prediction tools can be extremely helpful in determining a patient's prognosis, but they are unlikely to eliminate the need for sound clinical judgment acquired through clinical experience. Sizing up the clinical circumstances has never been more challenging, as commonly there exist several potential interventions, some of which require technical expertise for their effective and safe delivery. Getting the evidence right requires the skill to identify, evaluate and apply the evidence appropriately. Communicating with patients has always been considered important. This takes on greater importance as there is a growing desire on the part of patients to be involved in decisions relating to their health. Expertise is required to provide patients with the information they need, to elicit their preferences, and to incorporate those preferences into the decision.

Currently there is no consensus on how this information should be presented to patients and how their preferences should be incorporated. However, we know that information should not be presented in relative terms (for example, warfarin will decrease your risk of stroke by 62%) because

patients assume their baseline risk is 100% even when they are instructed it is not.[45] A recent systematic review of RCTs that compared decision aids (that is interventions designed to help people make specific choices among options by providing information on those options and outcomes relevant to the patient's health) to traditional ways of involving/informing patients in decision making[46] demonstrated that decision aids, as opposed to usual care, improved the average knowledge scores of patients for the options and outcomes by 20% (95% CI 13–25), reduced decisional conflict scores (that is patients felt more certain, informed, and clear about values in their decision), and increased patient participation in decision making.[46] Where available, decision aids provide a potential means to facilitate information presentation, incorporation of preferences, and participation in the decision-making process.

The varying roles of the components of evidence-based clinical decisions

Depending on the circumstances, any of the circles in the new model could predominate. Varying the size of the circles to reflect their actual contribution to the clinical decision could portray this visually. Sometimes the clinical state or circumstance dominates the clinical decision. For example, a patient who is at very high risk of an outcome and low risk of a complication may have their clinical state dominate the decision-making process. A patient living in a remote area may not have access to anticoagulation monitoring, and this would probably dominate the decision-making process. Patient's preferences can be so strong that they act as the driving factor in the decision-making process. For example, some patients will not take blood products regardless of the clinical situation. Research evidence can be the main factor in decision making when the benefit of an intervention is moderate to large in size and the risk of treatment small, as with β blocker therapy in patients post myocardial infarction, ACE inhibitors in coronary artery disease or heart failure, or cholesterol lowering with statins. Finally, clinical expertise can predominate, especially when it is related to technical capabilities.

Application to our patient

For our patient the evidence would suggest an 8% annual risk of stroke and 1% risk of major bleeding without any antithrombotic therapy. With warfarin therapy we would expect the annual risk of stroke to decrease to 3% and the risk of major bleeding to increase to 8%. This latter could be reduced to 4% if the patient were willing to undergo self-monitoring of their prothrombin time and an education program, as discussed above.[44] With aspirin therapy we would expect the annual risk of stroke to decrease to 6% and the risk of major bleeding to increase to 1·3%.

As discussed above, there is no consensus on how to present this information to our patient or how to incorporate his preferences. We have provided a decision aid for patients that describes atrial fibrillation (Table 1.2), a major and minor stroke (Table 1.3), a severe bleed (Table 1.4), and a probability trade-off for no treatment, aspirin and warfarin therapies (Figure 1.3). The descriptions of major and minor stroke and a severe bleed are slight modifications of the descriptions developed and tested by Man-Son-Hing and colleagues.[47] We have also individualized the probability trade-off for our patient, with the knowledge that he would undergo self-monitoring of his prothrombin time if he decided to take warfarin therapy (Figure 1.4).

Once this evidence-based clinical decision is reached our job is not over. The patient will need monitoring to ensure he is able to follow through on his clinical decision. One advantage of the decision aid provided (including his individualized probability trade-off) is that the patient can take the information home and does not have to rely on his memory to recall the facts discussed during your meeting.

Table 1.2 Atrial fibrillation: the most common disorder of the heartbeat

Risk	Chances of developing atrial fibrillation increase with age and it occurs in approximately 10% of all people above the age of 75
Physical symptoms	Irregular and usually rapid beating of the heart, sensed as a fluttering in the chest. Some patients feel no symptoms and are unaware that they have atrial fibrillation
Complications	Stroke • Atrial fibrillation increases the risk of a clot developing in the heart. This clot can be swept up towards the brain, causing a stroke • The chance of developing a stroke with atrial fibrillation increases with either age greater than 65 years, high blood pressure, diabetes, heart failure, or a history of strokes or "mini-strokes" • The risk of developing a stroke with atrial fibrillation varies, depending on how many of these risk factors you have
Treatment	• There are medications that thin the blood, which help to prevent clots and therefore stroke • Because the blood is thinned there is an increased risk of bleeding

Table 1.3 ☹ Strokes ☹ can be minor or major in severity. If you have a stroke as a result of atrial fibrillation, your chance of having a minor or major stroke are equal

	Minor stroke	Major stroke
Physical symptoms	You suddenly cannot move or feel one arm and one leg	You suddenly are unable to move one arm and one leg You cannot swallow
Mental symptoms	You are unable to fully understand what is being said to you You have difficulty expressing yourself	You are unable to understand what is being said You are unable to speak
Pain	You feel no physical pain	You feel no physical pain
Recovery	You are admitted to hospital Your weakness, numbness and problem with understanding improve, but you still feel slightly weak or numb in one arm and one leg You are able to do almost all of the activities you did before the stroke You can function independently You leave the hospital after 1 week	You are admitted to hospital You cannot dress The nurses feed you You cannot walk After 1 month of physiotherapy you are able to wiggle your toes and lift your arm off the bed You remain this way for the rest of your life
Further risk	You have an increased risk of having more strokes	Another illness will probably cause your death

Table 1.4 ☹ Severe ☹ bleeding while taking warfarin or ASA: an example of a stomach bleed

Physical	You feel unwell for 2 days, then suddenly you vomit blood
Treatment	You are admitted to hospital You stop taking warfarin or ASA A doctor puts a tube down your throat to see where you are bleeding from You receive sedation to ease the discomfort of the test You do not need an operation You receive blood transfusions to replace the blood you lost
Recovery	You stay in hospital for 1 week You feel well at the end of your hospital stay You need to take pills for the next 6 months to prevent further bleeding After that you are back to normal

Bleeding from the stomach is the most common type of serious bleeding while taking warfarin or ASA; however, rarely other serious forms of bleeding can occur, such as bleeding within the head after a fall.
Warfarin or ASA can also cause minor bleeding, including bruising and nose bleeds.
Taking warfarin can mean costs and inconvenience to yourself and family. For example: need for blood tests; parking/transportation; cost of warfarin.
Taking ASA can mean costs to yourself.
For example: cost of ASA.

Limitations of evidence-based clinical decision model

This model does not consider the important roles that society, governments or healthcare organizations can play in decision making. We deliberately restricted ourselves to decisions made by patients and their healthcare providers to allow a focused exploration of the issues involved in their immediate decision making process. However, a healthcare organization may pre-empt these decisions. For example, not funding primary percutaneous transluminal coronary angioplasty in acute myocardial infarction can have an enormous impact on health outcomes, and will impose a clinical decision on all patients and physicians by eliminating this option. Physicians will have to factor in such issues when considering their patient's clinical circumstances.

Without any blood thinning medication
Chance of stroke over next 2 years
is _____ out of 100
Chance of severe bleeding over next 2 years
is _____ out of 100

ASA
Chance of stroke over next 2 years
is _____ out of 100
Chance of severe bleeding over next 2 years
is _____ out of 100

Warfarin
Chance of stroke over next 2 years
is _____ out of 100
Chance of severe bleeding over next 2 years
is _____ out of 100

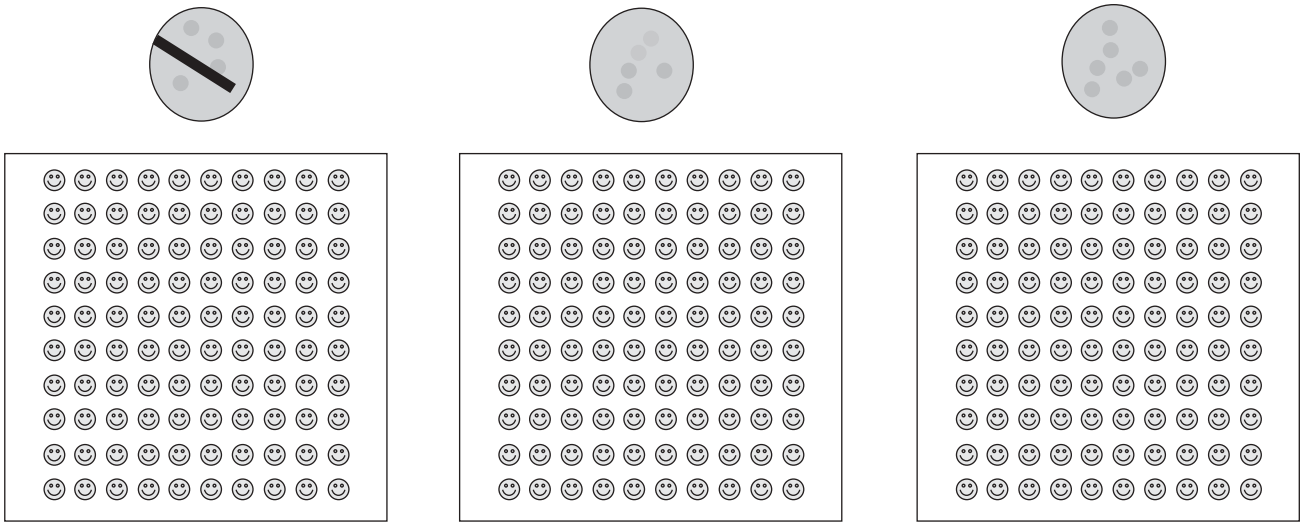

Figure 1.3

Without any blood thinning medication
Chance of stroke over next 2 years
is __8__ out of 100
Chance of severe bleeding over next 2 years
is __1__ out of 100

ASA
Chance of stroke over next 2 years
is __6__ out of 100
Chance of severe bleeding over next 2 years
is __1·3__ out of 100 (i.e.13 out of 1000)

Warfarin
Chance of stroke over next 2 years
is __3__ out of 100
Chance of severe bleeding over next 2 years
is __4__ out of 100

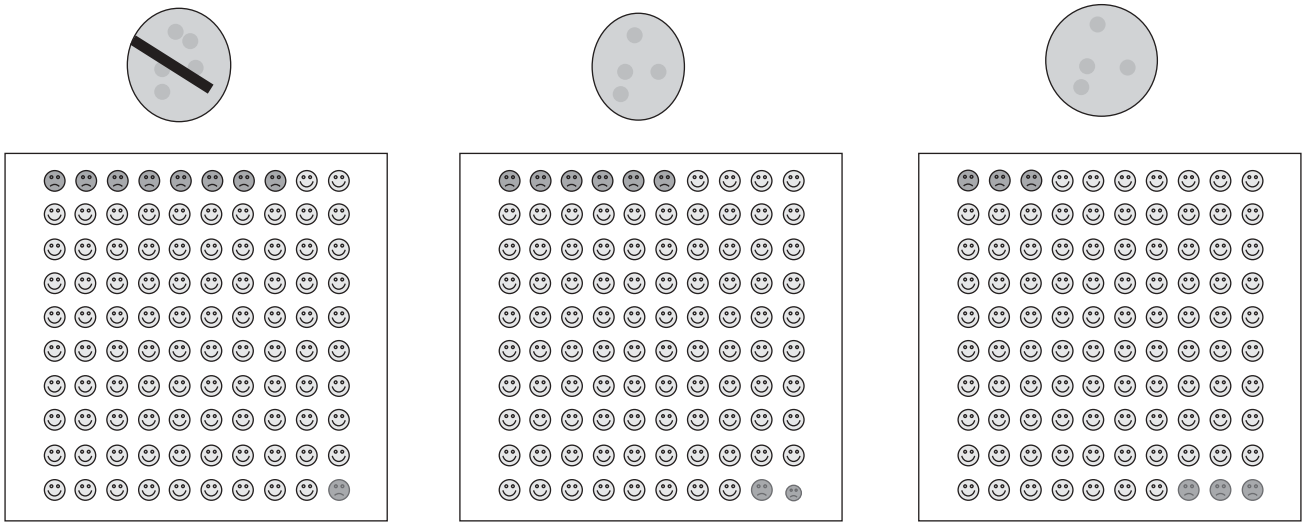

Figure 1.4

Conclusions

The foundations for evidence-based medicine have been established over the centuries but the specific philosophies, concepts, definitions and models have essentially evolved over the past few decades. Evidence-based medicine is about solving clinical problems. Evidence-based decision making depends upon utilizing clinical expertise to integrate information about a patient's clinical setting and circumstances with the best research evidence while incorporating the patient's preferences and actions.

References

1. Louis PCA. Researches on the effects of blood-letting in some inflammatory diseases, and on the influence of tartarised antimony and vesication in pneumonitis. *Am J Med Sci* 1836;**18**:102–11.
2. Louis PCA. *Researches on the Effects of Bloodletting in Some Inflammatory Diseases and on the Influence of Tartarised Antimony and Vesication in Pneumonitis*. Translated by CG Putnam. Boston: Hilliard, Gray, 1836.
3. Louis PCA. Medical statistics. *Am J Med Sci* 1837;**21**:525–8.
4. Morens DM. Death of a president. *N Engl J Med* 1999;**341**:1845–9.
5. Lloyd JU. Who killed George Washington? *Eclectic Med J* 1923;**83**:353–6, 403–8, 453–6.
6. Marx R. A medical profile of George Washington. *Am Heritage* 1955;**6**:43–7, 106–7.
7. Pirrucello F. How the doctors killed George Washington. *Chicago Tribune Magazine* 20 February 1977.
8. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP Journal Club* 2002;**136**:A11–A13.
9. Evidence-based medicine working group. Evidence-based medicine, a new approach to teaching the practice of medicine. *JAMA* 1992;**268**:2420–5.
10. Haynes RB, Sackett DL, Gray JMA, Cook DC, Guyatt GH. Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions. *ACP Journal Club* 1996;**125**:A-14. *Evidence-Based Medicine* 1996;**1**:196.
11. Sackett DL, Richardson SR, Rosenberg W, Haynes RB. *Evidence-Based Medicine: how to practice and teach EBM*. London: Churchill Livingstone, 1997.
12. Sackett DL, Rosenberg WMC, Gray JA, Haynes RB, Richardson WS. Evidence-Based Medicine: What it is and what it isn't. *BMJ* 1996;**312**:71–2.
13. Sackett DL, Straus S, Richardson SR, Rosenberg W, Haynes RB. *Evidence-Based Medicine: how to practice and teach EBM*, 2nd edn. London: Churchill Livingstone, 2000.
14. Cook DJ, Guyatt GH, Jaeschke R. Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. *JAMA* 1995;**273**:703–8.
15. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;**154**:1449–57.
16. Beyth RJ, Quinn LM, Landefeld S. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;**105**:91–9.
17. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
18. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**: 492–501.
19. Devereaux PJ, Anderson DR, Gardner MJ *et al*. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;**323**:1218–22.
20. Man-Son-Hing M, Laupacis A, O'Connor AM, Coyle D, Berquist R, McAlister F. Patient preference-based treatment thresholds and recommendations: a comparison of decision-analytic modeling with the probability-tradeoff technique. *Med Decis Making* 2000;**20**:394–403.
21. Haynes RB. Improving patient adherence: State of the art, with a special focus on medication taking for cardiovascular disorders. In: Burke LE, Okene IS, eds. *Patient Compliance in Healthcare and Research*. American Heart Association Monograph Series. Armonk, NY: Futura Publishing Co, 2001.
22. Stephenson BJ, Rowe BH, Macharia WM, Leon G, Haynes RB. Is this patient taking their medication? *JAMA* 1993; **269**:2779–81.
23. Guyatt G, Haynes B, Jaeschke R *et al*. Introduction: the philosophy of evidence-based medicine. In: Guyatt G, Rennie DR, eds. *Users' guides to the medical literature*. AMA Press, 2002.
24. Nisbett R, Ross L. *Human Inference*. Englewood Cliffs, NJ: Prentice-Hall, 1980.
25. Timmis AD, Smyth P, Jewith DE. Milrinone in heart failure: effects on exercise haemodynamics during short term treatment. *Br Heart J* 1985;**54**:42–7.
26. Packer M, Carver JR, Rodeheffer RJ *et al*. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991; **325**:1468–75.
27. Yusuf S, Teo KK. Inotropic agents increase mortality in patients with congestive heart failure. American Heart Association 63rd Scientific Sessions. Dallas (Texas), 12–15 November 1990. *Circulation* 1990;**82**(SIII):673.
28. Popp AJ, Chater N. Extracranial to intracranial vascular anastomosis for occlusive cerebrovascular disease: experience in 110 patients. *Surgery* 1977;**82**:648–54.
29. Failure of extracranial–intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. The EC/IC Bypass Study Group. *N Engl J Med* 1985;**313**:1191–200.
30. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;**20**:47–63.
31. Hulley S, Grady D, Bush T *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary artery disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**:605–13.
32. http://www.nhlbi.nih.gov/whi/hrt.htm

33. Taylor DW, Barnett HJ, Haynes RB *et al*. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 1999;**353**:2179–84.
34. Coltart J, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. *Br Heart J* 1975;**37**:357–64.
35. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;**98**:1184–91.
36. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
37. The MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–7.
38. Packer M, Coats AJ, Fowler MB *et al*. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–8.
39. Echt DS, Liebson PR, Mitchell LB. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324**:781–8.
40. Moore TJ. Excess mortality estimates. *Deadly medicine: why tens of thousands of heart patients died in America's worst drug disaster*. New York: Simon & Schuster, 1995.
41. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;**317**:1185–90.
42. Chalmers I. Unbiased, relevant, and reliable assessments in health care. *BMJ* 1998;**317**:1167–8.
43. Guyatt GH, Sackett DL, Taylor DW *et al*. Determining optimal therapy: randomized trials in individual patients. *N Engl J Med* 1986;**314**:889–92.
44. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. *Ann Intern Med* 2000; **133**:687–95.
45. Malenka DJ, Baron JA, Johansen S, Wahrenberger JW, Ross JM. The framing effect of relative and absolute risk. *J Gen Intern Med* 1993;**8**:543–8.
46. O'Connor AM, Rostom A, Fiset V *et al*. Decision aids for patients facing health treatment or screening decisions: a systematic review. *BMJ* 1999;**319**:731–4.
47. Man-Son-Hing M, Laupacis A, O'Connor A *et al*. Warfarin for atrial fibrillation: The patient's perspective. *Arch Intern Med* 1996;**156**:1841–8.

2 A critical appraisal of the cardiovascular history and physical examination

Akbar Panju, Brenda Hemmelgarn, Jim Nishikawa, Deborah Cook, Allan Kitching

There have been numerous technological advances made in the diagnosis and treatment of cardiovascular disease. In spite of this, a carefully conducted clinical examination remains the cornerstone in the initial assessment of the patient with known or suspected cardiovascular disease. Before conducting further laboratory or radiologic diagnostic tests, clinicians implicitly consider each piece of historical information and each finding from the physical examination as a diagnostic test that increases or decreases the probability of the possible diagnoses. The competency and accuracy of the clinical examination is therefore crucial, for it serves as the basis for our judgment regarding not only diagnosis, but prognosis and therapy as well.

This chapter is not intended to provide details of how to perform a cardiovascular history and physical examination, and should be read in conjunction with standard textbooks on cardiology to obtain such information. Instead, we will provide the reader with the tools to identify those features of the history and physical examination reported in the literature which are the most reliable and valid in assessing a patient with cardiovascular disease. We will focus on strategies to locate literature on the clinical examination, as well as guidelines to assess the quality of those studies. These techniques will then be applied to three common features of the cardiovascular history, namely chest pain, dyspnea and syncope, as well as common features of the physical examination, including assessment of the apical impulse, the third heart sound, central venous pressure, systolic murmurs, blood pressure and arterial pulse. We would also encourage the reader to access The Rational Clinical Examination series published in the *Journal of the American Medical Association* for further reviews on various aspects of the cardiovascular physical examination.[1–9] The following topics will be covered in this chapter:

- Strategies used to locate literature on clinical examination
- How to critically appraise this literature
- Application of the above in the cardiovascular history (chest pain, dyspnea, syncope)
- Application of the above in the cardiovascular physical examination (apical impulse, central venous pressure, systolic murmurs, blood pressure, arterial pulse).

Strategies used to locate literature on clinical examination

There are no validated strategies for locating precise and accurate information on obtaining a cardiovascular history and conducting a physical examination. A proposed strategy for searching the MEDLINE database is summarized in Box 2.1. This is the method suggested for authors of the Rational Clinical Examination series appearing in the *Journal of the American Medical Association*.[10] The first terms capture the clinical topic of interest by specifying the disease or presentation or function/dysfunction being sought. The second group of terms seeks clinical skills articles. The third group of terms is intended to find articles of high methodologic quality. An efficient strategy to locate high-quality articles would be to combine the first two groups of terms with "diagnosis (pre-exploded)" to maximize sensitivity, or with "sensitivity (textword)" to maximize specificity. This is an extension of the method suggested by the ACP Journal Club for finding high-quality articles on diagnostic tests in general.[11]

Box 2.1 Search strategy for clinical skills articles using MEDLINE

Group 1 terms

Term(s) for clinical entity of interest (for example, syncope, myocardial infarction) combined with (AND)*

Group 2 terms

- Physical examination (exploded; in title, abstract or subject heading)
- Medical history-taking (exploded)
- Professional competence (exploded)
- Diagnostic tests, routine
- Combined with (OR)*

Group 3 terms

- Sensitivity and specificity (textword; exploded)
- Reproducibility of results
- Observer variation
- Decision support techniques
- Bayes' theorem

*AND and OR represent Boolean terms (symbolic representation of relationships between sets) for combining items.

Any comprehensive search for relevant articles should include a review of reference lists from the articles found and

review articles on the topic, as well as textbooks on clinical examination, and advice from clinicians interested in clinical examination.

How to critically appraise the literature on clinical examination studies

Having located articles on the cardiovascular clinical examination, one must carefully review each study to establish its validity, or accuracy, prior to deciding whether the results obtained will aid in establishing or ruling out a particular diagnosis. We propose a strategy for evaluating the literature on clinical examination based on a framework developed for the *Users' Guides to the Medical Literature* series.[12] In assessing the validity of the study, and interpreting the results, the following points should be considered.

- Are the results of the clinical examination study valid?
    1. Was there an independent blind comparison with a reference (gold) standard of diagnosis?
    2. Was the clinical feature evaluated in an appropriate spectrum of patients (like those in whom it would be used in clinical practice)?
    3. Was the reference standard applied regardless of the result of the clinical feature?
    4. Were the methods of performing the clinical features described in sufficient detail to permit replication?
    5. Was there a description of the experience of the individuals doing the examination?
- What were the results?
    1. Are likelihood ratios for the results presented, or data necessary for their calculation provided?
    2. Has there been consideration given to reproducibility, precision, and disagreement?

The application of the initial five guides will help the reader determine whether the results of the study are likely to be valid. If the results are deemed to be valid, the reader can then go on to interpret the results presented, of which the likelihood ratio (LR) is the most important index in determining how good a particular diagnostic test is. The likelihood ratio is the probability that the results of a test would be expected in a patient with, as opposed to one without, the target disorder.

The application of these techniques for critically appraising the cardiovascular history and physical examination will now be described.

Clinical features in the cardiovascular history

Chest pain

There are many causes of chest pain, including both cardiac and non-cardiac conditions, as outlined in Figure 2.1.

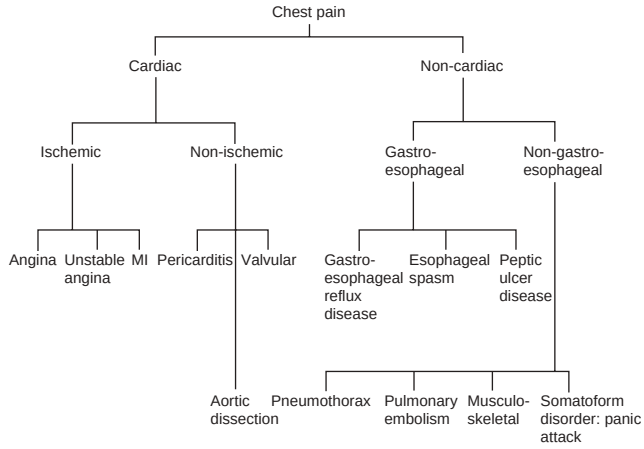

Figure 2.1 Cardiac and non-cardiac conditions presenting with chest pain

Elucidating the cause of the pain is important for both management purposes and prognosis. To ensure that the appropriate intervention is undertaken in the clinical setting, it is useful to classify patients presenting with chest pain into three categories:

1. Patients with myocardial infarction
2. Patients with myocardial ischemia but no infarction
3. Patients with non-cardiac chest pain.

The characteristics of the chest pain may help differentiate patients into the appropriate category. To identify features of the pain that might aid in classifying patients into category 1, myocardial infarction, we undertook a review of the literature using a search strategy similar to that outlined in the first section above. Relevant articles identified from this search were critically appraised using criteria outlined in the previous section. For the sake of relevance and clarity we have chosen to present only the results of those features in which a likelihood ratio of at least 2·0 or greater, or 0·5 or less, was obtained. The five studies that meet this criterion provide the best available evidence for identifying features of chest pain which aid in the diagnosis of myocardial infarction.

As outlined in Table 2.1, the features of the pain that increased the probability of a myocardial infarction included radiation, pain in the chest or left arm, and chest pain described as the most important symptom. Chest pain radiation was the clinical feature which increased the probability of a myocardial infarction the most, with a widespread distribution of pain being associated with the highest likelihood ratios. In particular, chest pain radiating to the left arm was twice as likely to occur in patients with rather than without an acute myocardial infarction, whereas radiation to the right shoulder was three times, and radiation to both the left and right arm seven times, as likely to occur in such patients. The quality of the pain, including pain described as squeezing or pressure, added little to establishing a diagnosis of myocardial infarction, with likelihood ratios of less than 2.

Table 2.1 Features of chest pain that increase the probability of a myocardial infarction

Clinical feature	References	LR (95% CI)
Chest pain radiation:		
(R) shoulder	Tierney *et al*[14]	2·9 (1·4–6·0)
(L) arm	Berger *et al*[13]	2·3 (1·7–3·1)
both (L) and (R) arm	Berger *et al*[13]	7·1 (3·6–14·2)
Pain in chest or (L) arm	Pozen *et al*[15]	2·7*
Chest pain most important symptom	Pozen *et al*[15]	2·0*

Abbreviations: CI, confidence interval; LR, likelihood ratio
*Data not available to calculate CIs.

Features of the chest pain that decrease the probability of myocardial infarction, and which therefore would be useful in ruling out a myocardial infarction, are outlined in Table 2.2. Pleuritic or positional chest pain, as well as chest pain described as sharp or stabbing, decrease the likelihood of a myocardial infarction. In addition, chest pain reproduced by palpation on physical examination was also associated with a low probability of myocardial infarction.

Table 2.2 Features of chest pain that decrease the probability of a myocardial infarction

Clinical feature	References	LR (95% CI)
Pleuritic chest pain	Tierney *et al*,[14] Lee *et al*,[16] Solomon *et al*[17]	0·2 (0·2–0·3)
Chest pain sharp or stabbing	Tierney *et al*,[14] Lee *et al*[16]	0·3 (0·2–0·5)
Positional chest pain	Lee *et al*,[16] Solomon *et al*[17]	0·3 (0·2–0·4)
Chest pain reproduced by palpation	Tierney *et al*,[14] Lee *et al*,[16] Solomon *et al*[17]	0·2–0·4*

Abbreviations: CI, confidence interval; LR, likelihood ratio
*In heterogenous studies the likelihood ratios are reported as ranges.

The precision in obtaining a chest pain history was addressed by Hickman and colleagues,[18] who assessed the interobserver agreement in chest pain histories obtained by general internists, nurse practitioners, and self-administered questionnaires for 197 inpatients and 112 outpatients with chest pain. The agreement between two internists for seven of the 10 items, including location and description of the pain, as well as aggravating and relieving factors, was substantial (κ, a measure of chance-corrected agreement, was 0·50–0·89). Agreement was slightly lower between internist and questionnaire, and between the nurse practitioners and internists, with the lowest level of agreement between nurse and questionnaire. Features of the chest pain associated with a lower probability of myocardial infarction, namely pleuritic, positional and sharp chest pain, were typically associated with a modest level of agreement for all comparisons (κ 0·26–0·62).

Although cardiac catheterization remains the definitive diagnostic procedure for allocating patients to category 2 – that is, the presence of myocardial ischemia or coronary artery disease – the character of the chest pain has also been identified as one of the most important clinical features in establishing the diagnosis of coronary artery disease.[19] The combination of typical angina and a long duration of symptoms was particularly predictive of severe disease. Although this study was undertaken in a very select group of patients (those who underwent cardiac catheterization), similar results were obtained from outpatients referred for non-invasive testing.[20] After smoking, typical angina was the variable most strongly associated with significant coronary disease (defined as >75% luminal narrowing of at least one major coronary artery). Subjects with typical angina were 13 times more likely to have significant coronary disease than those without.

There are many causes of non-cardiac chest pain, as outlined in Figure 2.1, and each condition has its own characteristic features and associated symptoms. It is beyond the scope of this chapter to identify all these conditions.

Dyspnea

Dyspnea, defined as an uncomfortable awareness of breathing, is a common complaint of both in- and outpatients. Cardiac and pulmonary causes of dyspnea are most common, with congestive heart failure, asthma and chronic obstructive pulmonary disease accounting for most complaints.[21] However, standard textbooks of internal medicine list over 30 different etiologies for dyspnea,[22] often with multiple etiologies explaining a patient's symptoms. It is often taught that the cause of dyspnea, of either the heart or the lungs, can be differentiated at the bedside by thorough history-taking. Unfortunately, such strategies to diagnose a cardiac cause for the breathless patient have been incompletely studied.

Zema and coworkers[23] looked at the value of symptoms as predictors of left ventricular systolic dysfunction in 37 patients with a clinical diagnosis of chronic obstructive pulmonary disease (COPD). Eliciting a symptom of dyspnea on exertion predicted depressed left ventricular systolic function with a sensitivity of 100% and a specificity of 20%. The symptom of orthopnea generated a sensitivity and specificity of 71% and 65%, paroxysmal nocturnal dyspnea 47% and 75%, and ankle edema 41% and 75%, respectively. All features were associated with a likelihood ratio of 2 or less. In general the study was well conducted, but the value of the results to the practicing clinician must be questioned. First, the symptoms of shortness of breath attributed to the heart

were only considered in the context of impaired left ventricular (LV) systolic function. It is now generally agreed that abnormalities in LV diastolic function also cause symptoms of dyspnea. A better gold standard would perhaps have been radionuclide ventriculographic evidence of both LV systolic and diastolic dysfunction. The generalizability of the results is also lessened by the fact that their definition of heart failure was a left ventricular ejection fraction (LVEF) <50%, when in fact the target for treatment of patients with heart failure is most often an LVEF of <40%. Finally, the study was performed in patients who first had a clinical diagnosis of COPD, when patients present with many causes of shortness of breath, not just COPD.

In summary, therefore, specific features when elicited in a patient presenting with a complaint of dyspnea are of limited usefulness in making a definitive diagnosis of impaired LV function.

Syncope

Little detailed evidence exists for either individual or clusters of clinical examination findings in the evaluation of syncope. In a prospective study of 433 syncopal patients presenting in a university setting (emergency, in- and outpatients), the history and physical examination were found to identify 55% (140) of the 254 causes ultimately found.[24] Many of the non-cardiac causes of syncope in this study were defined in clinical terms, and so provided the "diagnostic standard" for classification. The three most common non-cardiac causes were "orthostatic hypotension" (systolic drop of more than 25 mmHg, or drop of more than 10 mmHg to less than 90 mmHg with symptoms), "situational" (situations included cough, micturition and defecation, and required appropriate timing and no other identifiable cause) and "vasovagal" (requiring a precipitating event and premonitory symptoms), representing 31%, 26% and 25%, respectively, of identifiable causes of syncope overall.

Follow-up of the cohort demonstrated a 5 year mortality of 50·5% for cardiac versus 30% for non-cardiac or 24% for unknown causes. This provides some independent validation for the clinical classification criteria.

There is a need for further work in this area, particularly in developing and validating practical clinical tools to screen for psychiatric causes, to distinguish patients who will benefit from electrophysiologic testing, and to predict those who will have a positive tilt-table test.

Clinical features in the cardiovascular physical examination

Apical impulse

The apical impulse was first described by William Harvey in 1928[25] and is one of a number of palpable precordial pulsations reflecting the underlying movement of the heart and great vessels. Many criteria exist defining the normal location, size and character of the apical impulse, and many generations of medical students have been taught that an "abnormal" apical impulse may assist with the diagnosis of left ventricular enlargement and/or hypertrophy. It is only recently that evidence has been published to support these claims.

The relationship between the location and size of the apical impulse and LV size, as determined by two-dimensional echocardiography (gold standard), was evaluated by Eilen and colleagues.[26] An apical impulse lateral to the midclavicular line, defined as half the distance between the tip of the acromion process and the sternal notch, was a sensitive (100%) but not specific (18%) indicator for LV enlargement, with a likelihood ratio of only 1·2. Identification of the apical impulse <10 cm from the midsternal line was just as sensitive (100%) but only marginally more specific (33%). An apical diameter of <3 cm was a good indicator of LV enlargement, with a sensitivity of 92% and a specificity of 75%, and was almost four times as likely to occur in patients with, as opposed to those without, LV enlargement (LR=3·7).

O'Neill and coworkers[27] examined the relationship between the location of the apical impulse and the presence or absence of cardiomegaly on chest *x*-ray (defined as a cardiothoracic ratio greater than 50%). An apical impulse lateral to the midclavicular line had a sensitivity of 57%, a specificity of 76%, and a likelihood ratio of 2·4 for identifying cardiomegaly. Identification of the apical impulse >10 cm from the midsternal line was slightly more sensitive (78%) but considerably less specific (28%), and added little to establishing the diagnosis (LR=1·1). The results of this investigation must be accepted with caution, as the gold standard used in this case was chest *x*-ray, which is not a sensitive or specific marker of LV enlargement. Therefore, the validity of this gold standard must be questioned. This was, however, one of the few studies that also evaluated the variation between observers (interobserver variation) in the clinical assessment of the apical impulse, and reported good agreement on apex palpability (κ=0·72) and moderate agreement on degree of apex displacement (κ=0·56) between two physicians.

Eagle and coworkers[28] examined several clinical features in 125 inpatients with a variety of cardiac and non-cardiac diagnoses in an attempt to determine which features best predicted LVEF. In general, physician estimates of LVEF were good, with 56% being accurate within 7·5% of measured value; 27% of physicians overestimated and 17% underestimated the LVEF. Multiple regression analysis identified three clinical features most predictive of LVEF, including S_3 gallop, hypotension, and sustained LV apical impulse (defined as a palpable impulse greater than two thirds the ventricle systole).

In summary, the location, size and character of the apical impulse may be used to assess LV size, LV function and

cardiomegaly, either alone or in combination with other clinical features or simple diagnostic tests. However, a number of limitations exist, including the fact that a palpable impulse may only be found in approximately 50% of patients. In addition, the high sensitivity but low specificity associated with determining the location and size of the apical impulse make it a better test for ruling out rather than ruling in LV enlargement, which is good for screening but has limited usefulness at the bedside.

Third heart sound

Few studies have assessed the reliability and validity of detecting a third heart sound on physical examination. The studies that have been conducted suggest that the agreement between observers with respect to the presence of a third heart sound is low or moderate at best.[29–31] In one study, cardiologists, internists and residents in internal medicine examined 46 patients for the presence or absence of a third heart sound.[30] The overall interobserver agreement was poor, with a κ of only 0·18. A somewhat better agreement for the presence of a third heart sound was achieved in an earlier study by two internists and two cardiologists, with a κ of 0·40.[31] The evidence regarding the validity of the third heart sound is even more limited. Using a computerized phonocardiogram as a gold standard for the presence of a third heart sound, Lok *et al*[30] report positive and negative predictive values for identifying a third heart sound of 71% and 64%, respectively.

Although the reliability and validity of this physical examination finding may be limited, the detection of a third heart sound on physical examination may have important prognostic implications. Drazner and colleagues[32] performed a retrospective analysis of 2569 patients with symptomatic heart failure enrolled in the Studies of Left Ventricular Dysfunction treatment trial. In multivariate analyses adjusted for other markers of severity of heart failure, a third heart sound was associated with an almost 50% increased risk of hospitalization for heart failure, or death from pump failure.

Central venous pressure

The right internal jugular vein lies directly in line with the right atrium and acts as a manometer, displaying changes in blood flow and pressure caused by right atrial filling, contraction and emptying. Elevated jugular venous pressure reflects an increase in central venous pressure (CVP).

The reliability and validity of the clinical assessment of CVP have been assessed in a limited number of studies. In one study, medical students, residents and attending physicians examined the same 50 ICU patients and estimated their CVP as low (<5 cm), normal (5–10 cm) or high (>10 cm).[33] Agreement between students and residents was substantial (κ 0·65), agreement between students and attending physicians was moderate (κ 0·56), and agreement between residents and staff was modest (κ 0·30). Possible causes for disagreement include positioning of patients, poor lighting, difficulty in distinguishing carotid from venous pulsations, and variation in pressure with respiration.

As regards the relation between clinical assessments of CVP and the gold standard of simultaneous pressure measurements through a central venous catheter, one study[34] used an attending physician, a fellow, a medical resident, an intern and a student to predict whether four hemodynamic variables, including CVP, were low, normal, high or very high. The sensitivity of the clinical examination at identifying low (<0 mmHg), normal (0–7 mmHg) or high (>7 mmHg) CVP was 33%, 33% and 49%, respectively. The specificity of the clinical examination at identifying low, normal or high CVP was 73%, 62% and 76%, respectively. In another study, Eisenberg and colleagues[35] compared clinical assessments with pulmonary artery catheter readings in 97 critically ill patients. Physicians predicted CVP correctly only 55% of the time, more frequently (27%) underestimating than overestimating (17%).

Clinical assessments of a high CVP increase the likelihood that the measured CVP will be high by about fourfold; conversely, clinical assessments of a low CVP make the probability of finding a high measured CVP extremely unlikely (LR= 0·2).[33] The data demonstrate that clinical assessments of a normal CVP are truly indeterminate, with likelihood ratios approaching 1; such estimates provide no information because they neither increase nor decrease the probability of an abnormal CVP. Apart from less observer variation, CVP estimates are most accurate in patients breathing spontaneously.

The precision of the abdominojugular reflux test has not been reported, but its results will vary with the force of abdominal compression. Although this is an insensitive way to diagnose congestive heart failure, the specificity of the test is high.[36,37] Moreover, the positive likelihood ratios (6·4 when diagnosis was based on a clinical–radiographic score, and 6·0 when diagnosis was based on emergency room physician judgment) indicate that this is a useful bedside test.[1]

Systolic murmurs

Etchells and colleagues[2] have published a thorough review of the clinical examination for systolic murmurs. This included a systematic review of the literature and grading of the quality of the original articles. Quality was assessed by the sample size and recruitment (consecutive versus convenience) and whether comparison with the diagnostic standard was done independently and blindly.

Useful data for ruling aortic stenosis in or out are given in Tables 2.3 and 2.4. The reliability of the examination by cardiologists for late peaking murmur shape is good (κ 0·74), for the presence of murmurs is fair to moderate (κ 0·29–0·48),[2] but for other maneuvers may be poorer.[38]

Table 2.3 Features of the clinical examination that increase the probability of aortic stenosis

Clinical feature	LR*
Slow rate of rise of carotid pulse	2·8–130
Late peaking murmur	8–101
Soft or absent second heart sound	3·1–50

*LR, likelihood ratio: range of point estimates from original studies cited
Data from Etchells *et al*[2]

Table 2.4 Features of the clinical examination that decrease the probability of aortic stenosis

Clinical feature	LR*
Absence of a murmur	0
No radiation to right carotid artery	0·05–0·10

*LR, likelihood ratio: range of point estimates from original studies cited
Data from Etchells *et al*[2]

Studies of the clinical examination for other etiologies of systolic murmur were also reviewed but tended to be of lesser quality than those addressing aortic stenosis.

Subsequent to their original work,[2] Etchells and colleagues have gone on to develop a two-stage prediction rule for moderate–severe aortic stenosis (defined as an average valve area of less than or equal to 1·2 cm^2 or a peak gradient at or above 25 mmHg).[39] In this rule a murmur not radiating to the right clavicle was associated with a likelihood ratio of 0·1 (95% CI 0·02–0·44), significantly reducing the likelihood of aortic stenosis. If the murmur did radiate to the clavicle, the presence of 0–2 associated findings increased the likelihood ratio to 1·76 (95% CI 0·9–2·9), and 3–4 associated findings resulted in a likelihood ratio of 40 (95% CI 6·6–239), suggesting that the diagnosis of aortic stenosis is supported by a greater number of associated findings. The associated findings were reduced carotid volume, slow carotid upstroke, reduced second heart sound intensity, and murmur intensity in the second right intercostal space as loud as or louder than in the fifth left intercostal space.

Etchells and colleagues[2] point out that the majority of studies of this topic have used cardiologists as observers. The performance of non-cardiologists appears to be less accurate when studied. Further work, like their own, using a broader range of clinicians and patients, is needed to discover the value of the clinical examination in more general settings.

Blood pressure

An extensive review of the technique, reliability and validity of blood pressure (BP) measurement has been provided by Reeves.[3] As outlined in the review, two important sources of variation in BP measurement include the patient and the examiner. Random fluctuation in BP over time has been documented by the SD of readings, with a minute-to-minute variation of about 4 mmHg systolic and 2–3 mmHg diastolic, and day to day variation of 5–12 mmHg systolic and 6–8 mmHg diastolic. With respect to the examiner as the source of variability, differences of 10–8 mmHg by both physicians and nurses in routine medical practices have been noted.

Intra-arterial blood pressure measurement has been used as the gold standard to assess the accuracy of indirect BP measurement. With the indirect BP the phase I Korotkoff, or first audible sound, appears 15–4 mmHg below the direct systolic BP, whereas phase V, or disappearance of all sounds, appears 3–6 mmHg above the true diastolic BP in adults. Other factors that affect the accuracy of the indirect BP measurement, resulting in both an increase and a decrease in systolic and/or diastolic measurements, are outlined in Tables 2.5 and 2.6.

Table 2.5 Factors associated with an increase in blood pressure

Factor	Magnitude, SBP/DBP (mmHg)
Examinee	
Pseudohypertension	2–98/3–49
"White coat reaction" to physician	11–28/3–15
"White coat reaction" to non-physician	1–12/2–7
Paretic arm (due to stroke)	2/5
Pain, anxiety	May be large
Acute smoking	6/5
Acute caffeine	11/5
Acute ethanol ingestion	8/8
Distended bladder	15/10
Talking, sighing	7/8
Setting, equipment	
Leaky bulb valve	>2 DBP
Blocked manometer vents	2 to 10
Examination	
Cuff too narrow	−8–+10/2–8
Cuff not centered	4/3
Cuff over clothing	5–50
Elbow too low	6
Back unsupported	6–10
Arm unsupported	1–7/5–11
Too slow deflation	−1–+2/5–6
Too fast deflation	DBP only
Parallax error	2–4
Using phase IV (adult)	6 DBP
Too rapid remeasure	1/1
Cold season (*v* warm)	6/3–10

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure
Data from Reeves *et al*[3]

Table 2.6 Factors associated with a decrease in blood pressure

Factor	Magnitude, SBP/DBP (mmHg)
Examinee	
Recent meal	−1–1/1–4
Missed auscultatory gap	10–50 SBP
High stroke volume	Phase V can=0
Habituation	0–7/2–12
Shock (additional pseudohypotension)	33 SBP
Setting, equipment	
Faulty aneroid device	Can be >10
Leaky bulb	≥2 SBP
Examiner	
Reading to next lowest 5 or 10 mmHg or expectation bias	Probably ≤10
Impaired hearing	SBP only
Examination	
Left *v* right arm	1/1
Resting for too long (25 min)	10/0
Elbow too high	5/5
Too rapid deflation	SBP only
Excess bell pressure	≥9 DBP
Parallax error (aneroid)	2–4

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure
Data from Reeves *et al*[3]

Arterial pulse

Few studies have been undertaken to assess the reliability and validity of features of the arterial pulse in the cardiovascular examination, despite numerous descriptive accounts of its variability in different clinical conditions. Case series indicate that details regarding the presence and quality of the arterial pulse are more sensitive markers of coarctation of the aorta than aortic dissection. Absent femoral pulses or a femoral/brachial pulse discrepancy in patients was associated with a sensitivity of 88% in the diagnosis of coarctation of the aorta in patients less than 6 months of age.[40] Similar results were obtained for patients diagnosed with coarctation after 1 year of age, where weak or absent femoral pulses were associated with a sensitivity of 85%.[41]

The sensitivity of the presence and quality of the carotid, subclavian and femoral pulses in establishing a diagnosis of both proximal (primary tear in the ascending aorta with or without involvement of the arch, De Bakey classification type I and II) and distal (primary tear in the descending thoracic aorta, De Bakey classification type III) aortic dissections are outlined in Table 2.7. Proximal dissections were primarily associated with an absence or decrease in the brachiocephalic vessels, whereas distal dissections almost exclusively involved the femoral arteries.

Table 2.7 Sensitivity of the arterial pulse in the diagnosis of aortic dissection

	Aortic dissection (%)	
References	**Proximal***	**Distal†**
Lindsay and Hurst[42§]	62·5	10·5
Slater and De Sanctis[43§]	50·9	15·5
Spittell *et al*[44**]	9·0	2·4

* De Bakey classification type I and II.
† De Bakey classification type III.
§ Absence or decrease in amplitude of carotid, subclavian or femoral pulse(s).
** Absence of palpable carotid, subclavian or femoral pulse(s).

Features of the arterial pulse may also be used to determine the presence of valvular heart disease. As reported by Etchells *et al*,[2] features of the arterial pulse, including rate of rise of the carotid pulse, apical carotid delay and brachioradial delay, all increase the likelihood of establishing the diagnosis of aortic stenosis (Table 2.8).

Table 2.8 Features of the arterial pulse that increase the probability of aortic stenosis

Clinical feature	LR*
Slow rate of rise of carotid pulse	2·8–130
Apical carotid delay	∞
Brachioradial delay	6·8

* LR, likelihood ratio: range of point estimates from original studies cited.
Data from Etchells *et al*[2]

The diagnostic value of the pedal pulse examination, as an aid to establishing the diagnosis of peripheral arterial disease, has also been studied.[45] In this review the absence of both the dorsalis pedis and posterior tibial pulses was a powerful predictor for the presence of vascular disease (defined as an ankle-to-arm systolic pressure index of <0·9), with likelihood ratios ranging from 9·0 to 44·6. The presence of a femoral arterial bruit was also a strong indicator of disease, with likelihood ratios of 4·7–5·7.

Heart rate is another important component of the cardiovascular examination. The accuracy of the assessment of heart rate may be affected by both the site (apical or radial) as well as the counting interval (15, 30 or 60 seconds). With a regular rhythm, radial 15 second counts were the least accurate for both resting and rapid heart rates, whereas the 30 second counts were found to be the most accurate and efficient for rapid rates.[46] With the irregularly irregular rhythm of atrial fibrillation, however, the apical method and 60 second count have been reported to be the most accurate, with site being a more important source of error than

counting interval.[47] Using the ECG as the measure of true heart rate, the mean radial error for all counting intervals was 19·5 beats per minute, which was significantly higher than the mean apical error of 9·7 beats per minute.

Although the pulse in atrial fibrillation is typically described as "irregularly irregular", Rawles and Rowland,[48] using computerized analysis of R–R intervals and pulse volumes in patients with atrial fibrillation, disputed this assumption. In an assessment of 74 patients with atrial fibrillation they reported a non-random sequence of R–R intervals in 30%, and the presence of pulsus alternans in less than half (46%). The authors concluded that patterns of regularity of the pulse are common in patients with atrial fibrillation.

Summary

Despite the frequency with which details of the history and physical examination are used to establish or rule out a particular cardiovascular condition, there is a very limited amount of data available to support the reliability and validity of these features. The one component of the cardiovascular history which has been studied is that of chest pain in the diagnosis of myocardial infarction. Features of chest pain, particularly pain that has a wide distribution of radiation, increase the probability of myocardial infarction, whereas chest pain that is pleuritic, sharp or stabbing, positional or reproduced by palpation, decreases the probability of myocardial infarction.

The reliability and validity of various features of the cardiovascular physical examination have also received little attention in the literature. Of those that have been studied, the apical impulse has been shown to be a sensitive but nonspecific marker of LV size, which makes it useful for ruling out, rather than ruling in, LV enlargement. Clinical assessment of elevated CVP has been shown to be associated with a fourfold likelihood that the measured CVP will be high, with the abdominojugular reflex being a useful bedside test to assist in the diagnosis of congestive heart failure.

Of the cardiac murmurs, aortic stenosis has been studied the most thoroughly. Features of the clinical examination that increase the probability of diagnosing aortic stenosis include slow rate of rise of the carotid pulse, late peaking murmur, and soft or absent second heart sound. Conversely, absence of a murmur or no radiation to the right carotid artery or clavicle were features associated with a decreased probability of aortic stenosis. Recent work would suggest that the presence of an increased number of associated findings increases the likelihood of aortic stenosis.

A number of features have been shown to influence the accuracy of the indirect assessment of BP, including those related to the examinee, the examiner, the setting and equipment, and the examination itself. Assessment of the arterial pulse in diagnosing coarctation of the aorta and aortic dissection has been limited to case series, therefore estimates of sensitivity only are available. Features of the arterial pulse have been shown to be relatively sensitive markers for coarctation of the aorta and for chronic lower extremity ischemia, but less so for aortic dissection. Finally, both counting interval and site (radial versus apical) have important implications on the accuracy of heart rate assessment.

As is evident from the information presented, unfortunately, for a variety of reasons, research on clinical examination has lagged behind basic science and therapeutic research. So far, clinical examination is identified as the "art" of medicine, and by incorporating an evidence-based approach one can make clinical examination the "art and science" of medicine.

References

1. Cook DJ, Simel DL. Does this patient have abnormal central venous pressure? *JAMA* 1996;**275**:630–4.
2. Etchells E, Bell C, Robb K. Does this patient have an abnormal systolic murmur? *JAMA* 1997;**277**:564–71.
3. Reeves RA. Does this patient have hypertension? *JAMA* 1995; **273**:1211–18.
4. Choudhry NK, Etchells EE. Does this patient have aortic regurgitation? *JAMA* 1999;**281**:2231–8.
5. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. Is this patient having a myocardial infarction? *JAMA* 1998;**280**: 1256–63.
6. Turnbull JM. Is listening for abdominal bruits useful in the evaluation of hypertension? *JAMA* 1995;**274**:1299–301.
7. Badgett RG, Lucey CR, Mulrow CD *et al.* Can the clinical examination diagnose left-sided heart failure? *JAMA* 1997; **277**:1712–19.
8. Lederle FA, Simel DL. Does this patient have abdominal aortic aneurysm? *JAMA* 1999;**281**:77–82.
9. McGee S, Abernathy WB, Simel DL. Is this patient hypovolemic? *JAMA* 1999;**281**:1022–9.
10. Simel D (Section editor, Rational Clinical Examination, *JAMA*). Personal communication, December 1996.
11. McKibbon KA, Walker-Dilks CJ. Beyond ACP Journal Club: How to harness MEDLINE for diagnostic problems (Editorial). *ACP J Club* 1994;**121**:A10–A12.
12. Oxman AD, Sackett DL, Guyatt GH. Users' Guides to the Medical Literature: 1. How to get started. *JAMA* 1993;**270**: 2093–5.
13. Berger JP, Buclin R, Haller E, Van Melle G, Yersin B. Right arm involvement and pain extension can help to differentiate coronary diseases from chest pain of other origin: a prospective emergency ward study of 278 consecutive patients admitted for chest pain. *J Intern Med* 1990;**227**:165–72.
14. Tierney WM, Fitzgerald D, McHenry R *et al.* Physicians' estimates of the probability of myocardial infarction in emergency room patients with chest pain. *Med Decis Making* 1986;**6**:12–17.
15. Pozen MW, D'Agostino RB, Selker HP, Sytkowski PA, Hood WB. A predictive instrument to improve coronary-care-unit

admission practices in acute ischemic heart disease. *N Engl J Med* 1984;**310**:1273–8.
16. Lee TH, Cook EF, Weisberg M *et al.* Acute chest pain in the emergency room. *Arch Intern Med* 1985;**145**:65–9.
17. Solomon CG, Lee TH, Cook EF *et al.* Comparison of clinical presentation of acute myocardial infarction in patients older than 65 years of age to younger patients: the multicenter chest pain study experience. *Am J Cardiol* 1989;**63**:772–6.
18. Hickman DH, Sox HC, Sox CH. Systematic bias in recording the history in patients with chest pain. *J Chron Dis* 1985; **38**:91–100.
19. Pryor DB, Shaw L, Harrell FE *et al.* Estimating the likelihood of severe coronary artery disease. *Am J Med* 1991;**90**:553–62.
20. Pryor DB, Shaw L, McCants CB. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;**118**:81–90.
21. Mulrow CD, Lucey CR, Farnett LE. Discriminating causes of dyspnea through clinical examination. *J Gen Intern Med* 1993;**8**:383–92.
22. Ingram RH Jr, Braunwald E. Dyspnea and pulmonary edema. In: Wilson JD *et al.*, eds. Harrison's principles of internal medicine, 12th edn. New York: McGraw-Hill, 1991.
23. Zema MJ, Masters AP, Malgouleff D. Dyspnea: the heart or the lungs? Differentiation at bedside by use of the simple valsalva maneuver. *Chest* 1984;**85**:59–64.
24. Kapoor WN. Evaluation and outcome of patients with syncope. *Medicine* 1990;**69**:160–75.
25. Harvey W. *An anatomical disquisition on the motion of the heart and blood in animals*. London, 1928. (Translated from the Latin by Robert Willis, Barnes, Surrey, England, 1847.) In: Willius FA, Key TE. *Classics of cardiology*, vol. 1. Malabar, Florida: Robert E. Krieger, 1983.
26. Eilen SD, Crawford MH, O'Rourke RA. Accuracy of precordial palpation for detecting increased left ventricular volume. *Ann Intern Med* 1983;**99**:628–30.
27. O'Neill TW, Barry M, Smith M, Graham IM. Diagnostic value of the apex beat. *Lancet* 1989;**i**:410–11.
28. Eagle KA, Quertermous T, Singer DE *et al.* Left ventricular ejection fraction. Physician estimates compared with gated blood pool scan measurements. *Arch Intern Med* 1988;**148**:882–5
29. Westman EC, Matchar DB, Samsa GP, Mulrow CD, Waugh RA, Feussner JR. Accuracy and reliability of apical S3 gallop detection. *J Gen Intern Med* 1995;**10**:455–7.
30. Lok CE, Morgan CD, Ranganathan N. The accuracy and interobserver agreement in detecting the "gallop sounds" by cardiac auscultation. *Chest* 1998;**114**:1283–8.
31. Ishmail AA, Wing S, Ferguson J, Hutchinson TA, Magder S, Flegel KM. Interobserver agreement by auscultation in the presence of a third heart sound in patients with congestive heart failure. *Chest* 1987;**91**:870–3.
32. Drazner MH, Rame JE, Phil M, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;**345**:574–81.
33. Cook DJ. The clinical assessment of central venous pressure. *Am J Med Sci* 1990;**299**:175–8.
34. Connors AF, McCaffree DR, Gray BA. Evaluation of right heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med* 1983;**308**:263–7.
35. Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984;**12**:549–53.
36. Marantz PR, Kaplan MC, Alderman MH. Clinical diagnosis of congestive heart failure in patients with acute dyspnea. *Chest* 1990;**97**:776–81.
37. Maisel AS, Atwood JE, Goldberger AL. Hepatojugular reflux: useful in the bedside diagnosis of tricuspid regurgitation. *Ann Intern Med* 1984;**101**:781–2.
38. Spodick DH, Sugiura T, Doi Y, Paladion D, Jaffty BG. Rate of rise of the carotid pulse: an investigation of observer error in a common clinical measurement. *Am J Cardiol* 1982;**49**:159–62.
39. Etchells E, Glenns V, Shadowitz S, Bell C, Siu S. A bedside clinical prediction rule for detecting moderate or severe aortic stenosis. *J Gen Intern Med* 1998;**13**:699–704.
40. Ward KE, Pryor RW, Matson JR *et al.* Delayed detection of coarctation in infancy: implications for timing of newborn follow-up. *Pediatrics* 1990;**86**:972–6.
41. Strafford MA, Griffiths SP, Gersony WM. Coarctation of the aorta: a study in delayed detection. *Pediatrics* 1982;**69**:159–63.
42. Lindsay J, Hurst JW. Clinical features and prognosis in dissecting aneurysm of the aorta. *Circulation* 1967;**35**:880–8.
43. Slater EE, DeSanctis RW. The clinical recognition of dissecting aortic aneurysm. *Am J Med* 1976;**60**:625–33.
44. Spittell PC, Spittell JA, Joyce JW *et al.* Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990). *Mayo Clin Proc* 1993;**68**:642–51.
45. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia. *Arch Intern Med* 1998;**158**:1357–64.
46. Hollerbach AD, Sneed NV. Accuracy of radial pulse assessment by length of counting interval. *Heart Lung* 1990;**19**: 258–64.
47. Sneed NV, Hollerbach AD. Accuracy of heart rate assessment in atrial fibrillation. *Heart Lung* 1992;**21**:427–33.
48. Rawles JM, Rowland E. Is the pulse in atrial fibrillation irregularly irregular? *Br Heart J* 1986;**56**:4–11.

3 Obtaining incremental information from diagnostic tests

Raymond J Gibbons

Consider the following case history. A 75 year old male presents with a history of exertional chest pain. The patient describes substernal chest pain that he perceives as a "pressure sensation" occurring when he walks too fast, uphill, or in the cold. It is relieved by rest within a few minutes. On two recent occasions, he tried a friend's nitroglycerin tablets, and obtained even more rapid relief of his symptoms. His symptoms have never occurred at rest. The patient has a history of diabetes mellitus, hypertension, and hypercholesterolemia. He smokes one pack of cigarettes a day. Several male family members died of coronary artery disease before the age of 60. The patient underwent carotid artery surgery a year ago for treatment of transient ischemic attacks.

On the basis of his age, gender, chest pain description, and risk factors, this patient is highly likely to have significant obstructive coronary artery disease (CAD). The added, or incremental, value of any stress test for the diagnosis of the presence of disease in such a situation is very small. Out of 100 patients with this presentation, perhaps only one or two will not have obstructive CAD. The potential contribution of stress testing is therefore restricted to only these one or two patients.

This example demonstrates the importance of the concept of incremental value for diagnostic tests. In the current era of healthcare reform, it is no longer sufficient that a test simply provide "more information". The more appropriate current questions are:

- how much information does the test provide, and
- at what cost?

Increasingly, tests are also required to have a demonstrable impact on critical nodal, or decision, points with respect to patient management.

The demonstration of the incremental value of diagnostic tests requires rigorous methodology. The principles of the required methodology should be credited primarily to Dr George Diamond and his colleagues at Cedar Sinai Medical Center in Los Angeles.[1–3] First and foremost, such an analysis should reflect clinical decision making. Since clinical assessment is performed before any diagnostic tests, and usually at lower cost, parameters available from this assessment should be considered separately without any information from subsequent testing. The analysis should preferably focus on hard, demonstrable end points such as significant obstructive CAD, severe (three vessel or left main) coronary artery disease, myocardial infarction, or death. Although alternative end points, such as functional impairment, unstable angina, and the need for revascularization, are often included to increase statistical power, such end points have major limitations with respect to reversibility, subjectivity, and definite impact on patient outcome. The analysis should create appropriate models that include all available important variables. An experienced clinician always takes the patient's age, gender, and history into account in making his or her clinical decision regarding patient management, even when testing results are available. These important clinical parameters must therefore be included in any final model that reflects the clinical decision making process. The analysis must demonstrate that the additional information is statistically significant in an appropriate patient population. Analyses that demonstrate additional information in older, "sicker" inpatient populations should not be casually extrapolated to younger, "less sick" outpatients in whom testing is customarily performed. Finally, the test must provide information that is clinically significant and cost effective. In very large patient samples, differences that have little, if any, clinical significance for individual patient management may emerge as statistically significant. The potential impact on patient management in *some* patients must compare favorably with the incremental cost of the test in *all* the patients who must be tested.

This chapter will attempt to elucidate this methodology using the published data with respect to the diagnosis of significant obstructive CAD, non-invasive screening for severe CAD, and patient outcome. All of these examples are drawn from the arena of ischemic heart disease, because this entity is a predominant feature of clinical practice in cardiology, and the published literature is voluminous and extensive. However, the same principles apply to other disease entities, both cardiac and non-cardiac.

Clinical assessment

As outlined above, the initial step in any analysis designed to demonstrate incremental value is the consideration of all

the information available prior to performance of the test. This will always include the results of the history and physical examination, and may sometimes include the results of other tests already performed. This section focuses on the information available from clinical assessment.

Diagnosis of coronary disease

As demonstrated by the earlier example, clinicians often encounter patients with chest pain and suspected CAD. The ability of clinical assessment to predict the likelihood of significant obstructive CAD has been demonstrated in numerous studies. The likelihood of significant disease based on clinical assessment is appropriately labeled the "pretest probability", in statistical terms.

Age, gender, and the patient's chest pain description are the most important clinical parameters for estimating the likelihood of CAD.[4] Older patients, men, and patients with chest pain that is typical, or classic, for angina pectoris are more likely to have coronary disease. Although multiple different systems have been used to classify chest pain, the simplest and easiest was proposed by Diamond.[5] He suggested a classification based on three elements – substernal location, precipitation by exertion, and relief by rest or nitroglycerin. If all three elements are present, the chest pain is classified as "typical angina". If two elements are present, the chest pain is classified as "atypical angina". If only one or none is present, the chest pain is classified as "non-anginal chest pain".

Table 3.1 shows published estimates of pretest probability on the basis of age, gender, and chest pain description.[4] It is obvious that there is a very wide range of pretest probability, ranging from 1% for a 35 year old woman with non-anginal chest pain to 94% for a 65 year old man with typical angina. Note that a 50 year old man with atypical angina has about a 50% probability of disease.

A more comprehensive attempt to consider all clinical characteristics, including risk factors for atherosclerosis, was published from the Duke University Medical Center databank.[6] In addition to the three parameters previously discussed, this analysis found that evidence for previous infarction, smoking, hyperlipidemia, ST and T wave changes on the resting electrocardiogram (ECG), and diabetes were all highly significant predictors of the presence of coronary artery disease. Figure 3.1 shows a published nomogram for men that incorporates all of these parameters. Careful inspection of this figure demonstrates that the impact of the clinical parameters other than age, gender, and chest pain is variable. ECG and historical evidence of previous infarction have a major impact, diabetes and ECG ST-T changes have a modest impact, and lipids and smoking have a minimal impact. For example, a 50 year old male with atypical angina has a 46% pretest probability of disease in the absence of smoking, hyperlipidemia, or diabetes, a 48% pretest probability in the presence of both smoking and hyperlipidemia, and a 65% pretest probability if he has diabetes as well. In the presence of ECG Q waves and a history of MI, his pretest probability exceeds 90%.

Non-invasive screening for severe coronary artery disease

Not surprisingly, clinical parameters are also very important in estimating the likelihood of severe (three vessel or left main) CAD.[7] The same parameters that are most important for predicting the presence of disease – age, gender, and chest pain description – remain important. In addition, diabetes mellitus and history or ECG evidence of myocardial infarction are also very important. The simplest approach for estimating the likelihood of severe disease was published by Hubbard *et al.*[8] They assigned one point each for: male gender; typical angina; history and ECG evidence of myocardial infarction;

Table 3.1 Pretest probability of coronary artery disease

Age (years)	Pretest probability (%)							
	Asymptomatic		Non-anginal chest pain		Atypical angina		Typical angina	
	F	M	F	M	F	M	F	M
30–39	<1	2	1	5	4	22	26	70
40–49	1	6	3	14	13	46	55	87
50–59	4	9	8	22	32	59	79	92
60–69	8	11	19	28	54	67	91	94

From Diamond and Forrester.[4] Reprinted by permission of the *New England Journal of Medicine*, and Diamond GA. A clinically relevant classification of chest discomfort. *J Am Coll Cardiol* 1983;**1**:547–75

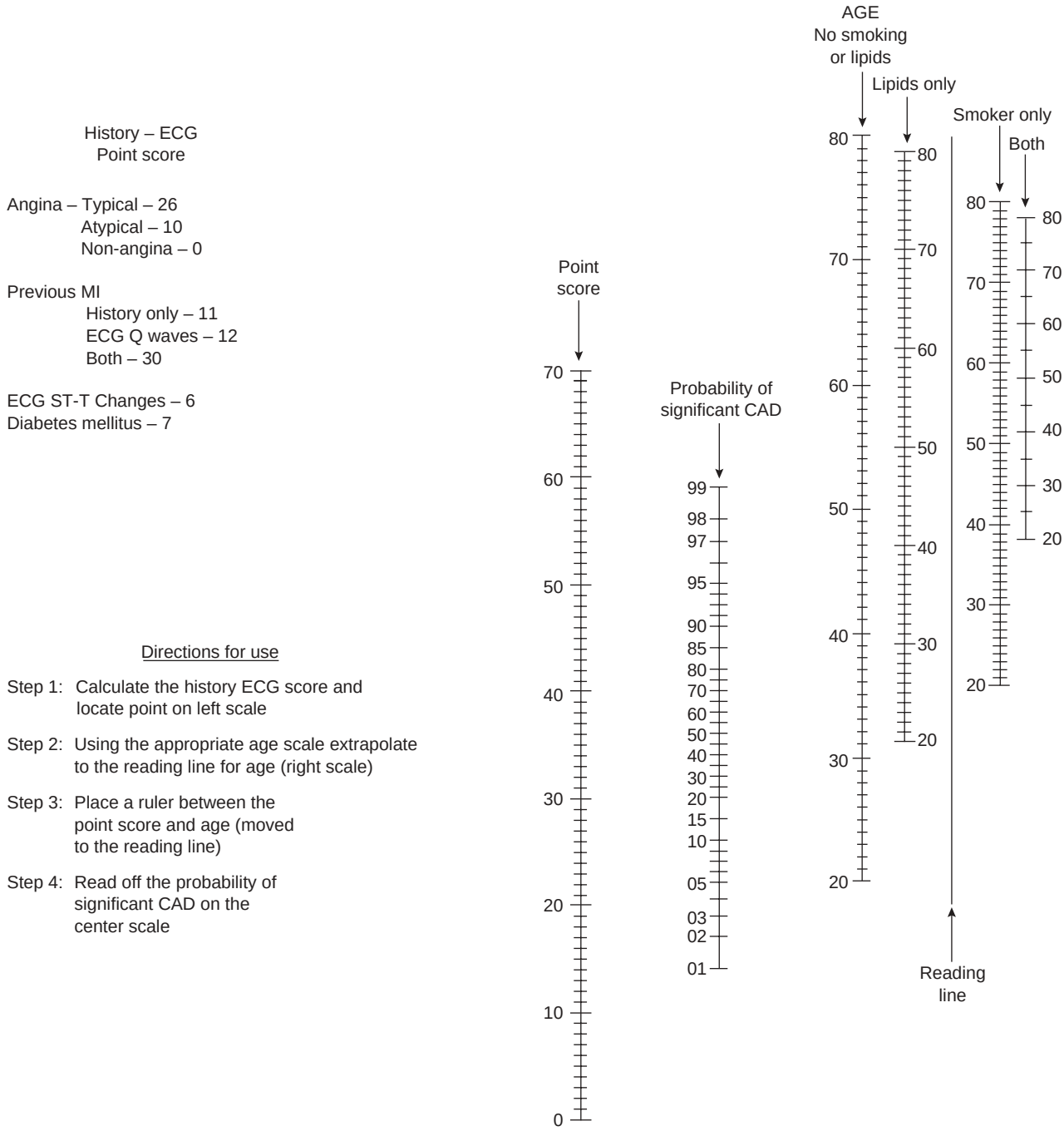

Figure 3.1 Nomogram for predicting the probability of significant coronary artery disease (CAD) in men. ECG, electrocardiogram; MI, myocardial infarction. (After Pryor *et al.*[6]) Example: A 50 year old, white male with atypical angina and diabetes mellitus, but no ECG ST changes, previous MI, smoking, or hyperlipidemia. Point score on left scale = 10 + 7 = 17. Appropriate reading line on right labeled "no smoking or lipids". Connect age 50 on this reading line to point score of 17 with a straight edge. This intersects the middle line at 60, indicating that this is the percentage probability of significant CAD.

diabetes; and insulin use. Thus, the point score had a minimum value of 0 and a maximum value of 5. Figure 3.2 shows a nomogram for the probability of severe CAD based on age and this point score. It is quickly apparent that age is an extremely important parameter for predicting severe disease.

A more comprehensive analysis on a larger number of patients was published from the Duke University Medical Center databank.[9] In addition to the five parameters already mentioned, these workers found that the duration of chest pain symptoms, other risk factors (blood pressure,

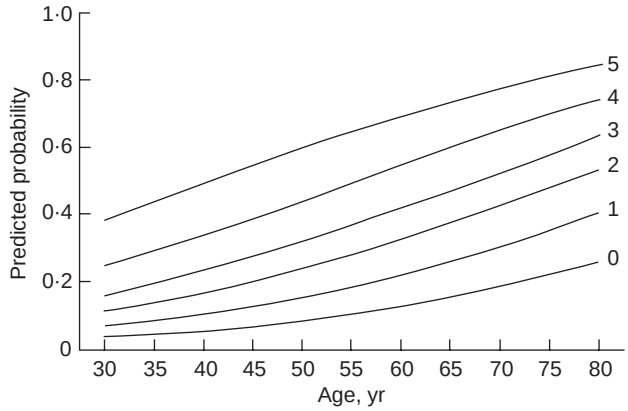

Figure 3.2 Nomogram showing the probability of severe (three vessel or left main) coronary artery disease based on a 5 point score. One point is awarded for each of the following variables – male gender, typical angina, history, and electrocardiographic evidence of MI, diabetes, and use of insulin. Each curve shows the probability of severe coronary disease as a function of age. (From Hubbard *et al*,[8] with permission.)

hyperlipidemia, and smoking), a carotid bruit, and chest pain frequency were also important determinants of the likelihood of severe CAD. However, the magnitude of their additional effect was modest.

Prediction of patient outcome

The ability of clinical assessment to predict patient outcome has been demonstrated in numerous previous studies. The largest and most important of these came from the Duke University databank[10] and the Coronary Artery Surgical Study Registry.[11] Many of the same parameters that predict the presence of disease and the presence of severe disease are also associated with adverse patient outcome. Age, gender, chest pain description, and previous myocardial infarction all have independent value in predicting patient outcome. In addition, history and physical examination evidence for congestive heart failure, history and physical examination evidence of vascular disease, unstable chest pain characteristics, and other ECG findings, such as ST-T wave changes, left bundle branch block, and intraventricular conduction delay, all have prognostic value. It is not generally appreciated how well clinical parameters perform in this regard. The Duke group reported that 37% of the patients undergoing stress testing at their institution had a predicted average annual mortality of 1% or less over the next 3 years, on the basis of clinical assessment.[11]

Several studies have shown that a normal resting ECG, and the absence of a history of prior infarction, predict a normal ejection fraction with 90% confidence,[12,13] and therefore a favorable prognosis.[14–16]

Approaches to the assessment of incremental value

Once the information available from clinical assessment (and other tests already performed) has been considered, there are a variety of conceptual and statistical approaches that can be employed to assess the incremental value of the test in question. This section will present examples of three such approaches.

Diagnosis of CAD

The application of multiple different stress tests for the diagnosis of coronary artery disease has been extensively studied. The most common approach used in this setting to demonstrate the incremental value of a new test employs Bayes' theorem.[17] This theorem indicates that the likelihood of disease following testing (post-test probability) can be calculated from the test characteristics (sensitivity and specificity) and the pretest probability. This calculated post-test probability is often plotted graphically as a function of pretest probability (Figure 3.3).

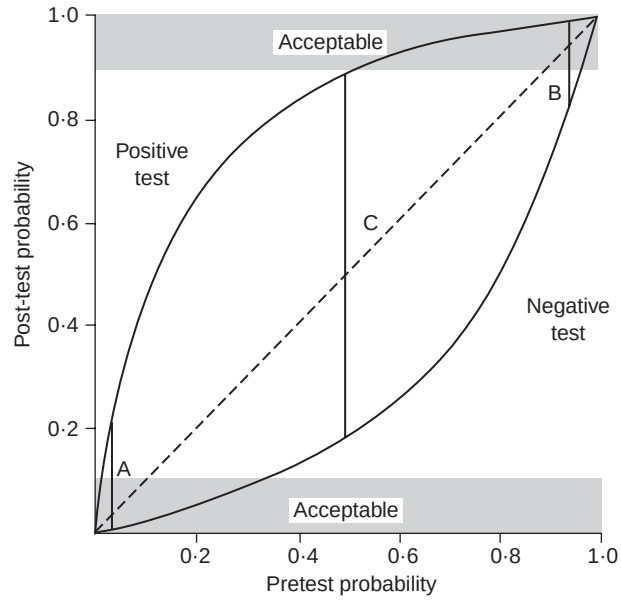

Figure 3.3 Relationship between pretest probability and post-test probability. The solid curves for positive and negative tests are plotted for a test with 80% sensitivity and a 90% specificity. Post-test probabilities that are acceptable for diagnosis (90% and 10%) are shown in the shaded zones. Line A represents a patient with a very low pretest probability; line B, a patient with a high pretest probability; line C, a patient with an intermediate probability. (Modified from Berman DS, Garcia EV, Maddahi J. Thallium-201 scintigraphy in the detection and evaluation of coronary artery disease. In: Berman DS, Mason DT, eds. *Clinical nuclear cardiology*. New York: Grune and Stratton, 1981, with permission.)

In Figure 3.3, the pretest probability is shown on the *X*-axis and the post-test probability is shown on the *Y*-axis. The dotted line represents the line of identity. The vertical distance from this line to the upper solid curve represents the increase in the probability of disease as a result of positive test. In analogous fashion, the vertical distance from this dotted line to the lower solid curve represents the decrease in probability as a result of a negative test. The solid vertical lines describe three different clinical situations.

Line A represents a patient with a very low pretest probability, such as a 40 year old woman with non-anginal pain. A negative test changes probability very little. A positive test increases probability somewhat, but the post-test probability remains well under 50%, and the test is most likely a "false positive".

Line B represents a patient with a high pretest probability of disease, such as a 65 year old man with typical angina. A positive test will increase the probability only slightly. A negative test will decrease the probability of disease somewhat, but the post-test probability remains substantially greater than 50%, so that the test is most likely a "false negative".

The final situation (line C) represents a patient with an intermediate probability of disease, such as a 50 year old male with atypical angina. A positive test in such a patient would increase the probability of disease substantially to near 90%. On the other hand a negative test would decrease the probability of disease substantially to approximately 18%.

Thus, it is evident that the incremental value of diagnostic testing is greater in patients with an intermediate probability of disease, a principle that is broadly recognized.[17]

However, it is also recognized that this kind of analysis has a number of limitations. The single curves for positive and negative tests do not take into account the degree of test abnormality. The test results are therefore better displayed for a whole range of values for a parameter that helps distinguish normal from abnormal. The best known example of this would be the magnitude of ST segment depression on treadmill exercise testing.[18] In addition, multiple other parameters are reported during a treadmill exercise test, which help to distinguish severely abnormal tests from only mildly abnormal tests.[19] Ideally, all of these parameters would be incorporated into a single "score" and a series of curves would be plotted.

Next, construction of such curves relies on the premise that the sensitivity of tests will be identical for any population of patients with disease regardless of disease prevalence. This assumption is usually invalid. As demonstrated in the previous section, those parameters which help to identify the presence of disease also help to identify the presence of severe disease. In general, the sensitivity of most tests is greater in patients with more severe disease. It is therefore quickly evident that sensitivity would be expected to vary with the prevalence of disease. This point has been demonstrated by several investigators,[20] and provides justification for the use of logistic regression analysis for diagnostic purposes.[21] Despite these limitations, bayesian analysis serves as a useful framework for understanding the potential incremental value of diagnostic tests.

Post-test referral bias, also known as work up bias or verification bias, occurs whenever the results of the test in question influence the subsequent performance of the "reference" test (sometimes referred to as the "gold standard"). This bias has been recognized for more than 20 years.[22] An early survey of the literature on exercise testing showed that only 2 of 33 studies avoided this bias.[23] The recognition of the importance of this phenomenon was emphasized in a landmark paper in 1983, which described the "declining specificity" of radionuclide angiography as a result of this bias.[24] More than 10 years ago, a monograph from the Institute of Medicine emphasized this well established concept.[25] The key question to ascertain whether postreferral bias is present is "did the results of the test being evaluated influence the decision to perform reference standard?".[26]

Although this bias potentially occurs for any diagnostic test, it is particularly important for non-invasive diagnostic tests for CAD. Patients with positive non-invasive tests are often referred to coronary angiography (the "reference" test). In contrast, patients with negative tests are often sent home without coronary angiography. The effects of this preferential referral to coronary angiography are to markedly decrease the observed specificity of the test in question and modestly increase its sensitivity.

The clearest solution to the problem of post-test referral bias is to avoid it completely by studying patients in whom the decision to proceed with the "reference" test is made before the performance of the diagnostic test in question.[25] For the diagnosis of CAD, this standard is incredibly difficult and rarely achieved. A more feasible alternative is the mathematical correction of sensitivity and specificity for post-test referral bias using one of two published formulae and information about all of the patients who were studied using the diagnostic test in question and did not proceed with coronary angiography.[27,28] There are a number of published studies demonstrating the effect of these corrections on the observed test performance for exercise electrocardiographic testing,[29] exercise echocardiography,[30] and exercise Single Photon Computed Tomography (SPECT) perfusion imaging.[31] Correction for referral bias markedly increases the specificity and modestly decreases the sensitivity of these tests. As a result, the predictive value of a positive test is improved, but the predictive value of a negative test decreases. It is generally difficult to confirm the validity of these corrections. However, a carefully designed prospective study of exercise echocardiography in women has now reported sensitivity and specificity values that are very close to those reported after correction for referral bias.[32]

Post-test referral bias has numerous important implications for the interpretation of the diagnostic literature.[32] Many of the reported sensitivity and specificity values are very likely to be erroneous.[32] Widespread misconceptions exist regarding gender differences in test performance. The post-test probability of CAD is higher for either a positive or negative test than that which would be calculated from Bayes' theorem using the reported values of sensitivity and specificity.[31]

Non-invasive screening for severe CAD

The incremental value of testing for the diagnosis of severe CAD has been studied using both bayesian analysis and logistic regression analysis. When the latter analysis is conducted properly, all of the previously discussed clinical parameters that are associated with severe coronary disease are incorporated into a model that is used to predict the probability of severe CAD. The output of such a model is a probability that ranges between 0 and 1. It is critically important that these candidate variables be "forced" into the model, even if they are statistically insignificant in the population under study. Most study populations are too small to have adequate power to detect the true significance of these variables, which has been demonstrated in very large subsets. For example, age should always be forced into such models, even if it does not appear to be significant in the particular population in question, because there is abundant evidence that it should always be considered (and indeed usually is by clinicians).

Using this approach, a second model should then be constructed which includes all of the clinical parameters, as well as pertinent new parameters from the test in question. If these parameters have statistical significance independent of the clinical parameters, the test has incremental value. This approach is demonstrated in Table 3.2, which shows the improvement in the logistic regression model for severe CAD reported by Christian *et al*,[16] when the exercise test was added to clinical parameters, and when thallium imaging parameters were added to clinical and exercise parameters. An alternative approach is to construct the receiver operating characteristic (ROC) curves, which display sensitivity and specificity as a function of the predicted probability of severe disease (the output of a logistic regression model). The area under the ROC curve can then be compared between the model that incorporates clinical parameters,

Table 3.2 Logistic regression multivariate analysis: prediction of three vessel or left main (coronary artery) disease

Model	Direction	Odds ratio (95% CI)	*P* value
Clinical			
Diabetes mellitus	Present	2·0 (1·3–3·1)	0·001
Typical angina	Present	2·3 (1·4–3·9)	0·001
Sex	Male	3·2 (1·4–4·0)	0·007
Age[a]	Older	1·4 (1·1–1·9)	0·01
$\chi^2 = 31{\cdot}3$			
Clinical and exercise			
Diabetes mellitus	Present	1·9 (1·2–3·0)	0·005
Typical angina	Present	1·9 (1·1–3·3)	0·02
Sex	Male	2·3 (0·9–5·3)	0·07
Age[a]	Older	1·2 (0·9–1·7)	0·16
Magnitude of ST depression	More	1·5 (1·3–1·8)	<0·001
Peak heart rate × peak systolic blood pressure[b]	Lower	0·9 (0·86–0·95)	<0·001
$\chi^2 = 65{\cdot}0$			
Clinical, exercise, and thallium-201			
Diabetes mellitus	Present	1·9 (1·2–3·0)	0·004
Typical angina	Present	1·8 (1·1–3·2)	0·03
Sex	Male	2·2 (0·9–5·3)	0·07
Age[a]	Older	1·2 (0·9–1·7)	0·17
Peak heart rate × peak systolic blood pressure[b]	Lower	0·9 (0·86–0·95)	<0·001
Magnitude of ST depression	More	1·4 (1·2–1·7)	0·001
Global T1-201 score (delayed – after exercise)	Higher	1·1 (1·0–1·1)	0.02
$\chi^2 = 70{\cdot}4$			

[a] Increments of 10 years (each 10-year increase in age increases the odds of severe disease 1·4-fold).
[b] Increments of 1000 units.
From Christian TF *et al*,[16] with permission

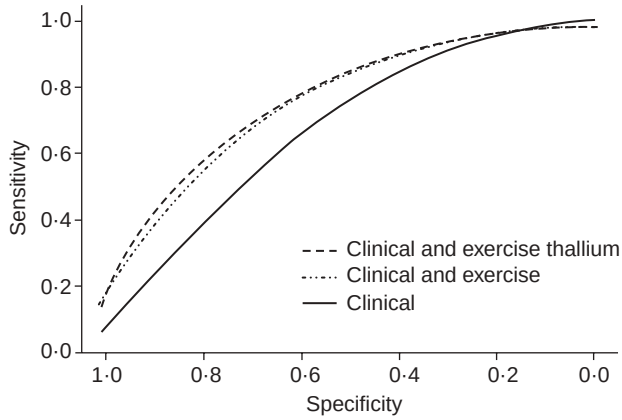

Figure 3.4 Receiver operator characteristic curves for three logistic regression multivariate models for the prediction of severe coronary disease. (From Christian *et al*,[16] with permission.)

and the model that incorporates clinical parameters and the new test parameters. Methods are available for determining the statistical significance of changes in the area under these two ROC curves.[33] An example of this approach is shown in Figure 3.4, taken from Christian *et al*[16] The clinical significance of these differences in the models (assessed by either χ^2 analysis or ROC curves) is discussed later.

Prediction of patient outcome

The demonstration of incremental prognostic value for diagnostic tests is obviously extremely important for clinical decision making. It requires strict adherence to the rigorous standards that were outlined previously. In general, very few of the published studies demonstrating prognostic value of diagnostic tests meet the strict criteria necessary to demonstrate *incremental* prognostic value for these tests. The statistical model most often used for this purpose is a linear proportional hazards, or Cox, model.[34] When strictly applied, all the previous information available to the clinician, either from clinical assessment or previous testing, should be incorporated into a linear proportional hazards model that predicts time to an event. Once again, parameters that have been clearly demonstrated in larger populations to be significant must be "forced" into such models to make sure that their contribution is not neglected. The events in question should preferably be hard end points such as death and myocardial infarction. As previously mentioned, unstable angina and the need for revascularization are alternative end points that are often included to enhance statistical power, but these have major limitations.

One of the best examples of a rigorously constructed analysis demonstrating incremental prognostic value was published by Pollock *et al* in 1992.[35] They tested the association between various combinations of variables, and time to death or myocardial infarction, in a linear proportional hazards model using the χ^2 statistic. Clinical and exercise variables were significantly better than clinical variables alone. Similarly, a model that added thallium redistribution to clinical and exercise variables was significantly better than the combination of clinical and exercise variables.

Another example of such a rigorous analysis was that reported by Christian *et al*[6] in patients with a normal resting electrocardiogram. Using a similar approach, these investigators reported that a model adding thallium variables to clinical and exercise variables did not add significantly to the model using clinical and exercise variables. Thus, in the subset of patients with a normal resting ECG, Christian *et al*[16] were unable to confirm the findings of Pollock *et al*[24]

Clinical significance and cost effectiveness

Even when statistically significant incremental value has been demonstrated for a diagnostic test using appropriate rigorous methodology, the clinical significance of the findings must be equally rigorously examined. The two fundamental issues that should be addressed are the actual impact of this incremental value on clinical decision making and, where possible, cost effectiveness. The principles of decision analysis pertinent to the first criterion will be presented in much greater detail in Chapter 7. The available published data on diagnostic testing in coronary disease that will be presented here use only rudimentary concepts with respect to decision analysis. Formal cost analysis also requires understanding of a much greater body of published knowledge, which will not be presented here. The examples presented will again be very rudimentary, but demonstrate the principle.

Diagnosis of CAD

The clinical significance of diagnostic testing can best be understood in terms of decision making thresholds. From the standpoint of diagnosis, a test will be useful primarily if it moves a significant number of patients from an "uncertain" pretest probability to an "acceptably certain" post-test probability. The exact criteria, or threshold, to be used in these classifications are clearly a matter of judgment; many investigators have chosen post-test probabilities of less than 10% and greater than 90% as criteria for definitive diagnosis.[36] Thus, non-invasive testing will be useful for diagnosis if it moves a reasonable number of patients into the shaded zone shown in Figure 3.3.

Although treadmill testing has clear incremental value for diagnosis, particularly in patients with intermediate pretest probability, as discussed earlier, its ability to move patients across such thresholds of probability appears to be very limited. Goldman *et al*[37] examined the ability of treadmill

Table 3.3 Effect of treadmill exercise test results in moving patients across various diagnostic thresholds

Threshold probability	Patients moved across (*n*)	Correctly moved	Incorrectly moved	Net increase in diagnoses (correct-incorrect)
0·10	8	6	2	4
0·90	53	33	20	13
Either 0·10 or 0·90	61	39	22	17 (5%)

From Goldman *et al*,[37] by permission of the American Heart Association, Inc.

exercise variables to classify 329 patients with CAD. Their results are summarized in Table 3.3. The pretest model was very powerful, as it classified 84% of the patients correctly. Table 3.3 shows the number of additional patients classified correctly for given thresholds of probability. For example, if 10% was considered an acceptable threshold to "rule out" CAD, eight of 324 patients were moved across this threshold, but only six were moved correctly. Similarly, for a 90% threshold to "rule in" CAD, 53 patients were moved across this threshold but only 33 were moved across correctly. As a result, the net total number of patients who were correctly moved into the diagnostic zone in Figure 3.3 was only 17, or 5% of the patient population. Thus, the clinical significance of the incremental value provided by the treadmill test appears to be very limited.

Similar rigorous analyses have been published for radionuclide angiography.[38] The results of one of these are displayed in Figure 3.5. The study group excluded men with typical angina over the age of 40 in order to eliminate most patients with a high pretest probability. Logistic regression models developed on a retrospective population were applied prospectively to a group of 76 patients. As demonstrated in Figure 3.5, eight (11%) of the 76 patients could be classified with 90% certainty on the basis of clinical variables alone. Following radionuclide angiography, 24 patients (32%) could be classified directly. Thus, the incremental value of exercise radionuclide angiography in moving patients across clinically meaningful decision thresholds appeared to be much greater than for the treadmill exercise test, as 21% of the patients were correctly classified by the radionuclide angiogram.

Similar findings have been reported for planar thallium imaging.[39,40] Unfortunately, no rigorous analyses are available for either SPECT imaging or sestamibi imaging, primarily because post-test selection bias has greatly limited the feasibility of such studies in the current era.

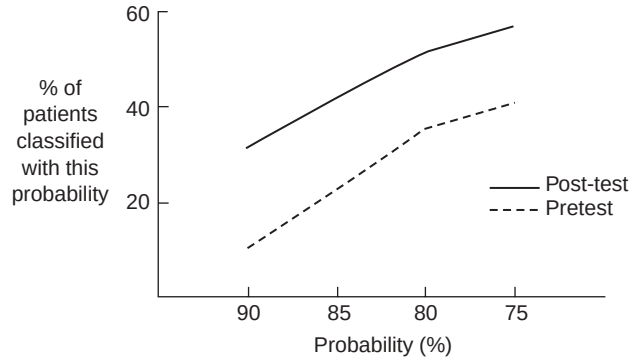

Figure 3.5 Percentage of patients classified with a given probability of coronary disease before and after exercise radionuclide angiography. The prospective study group of 76 patients excluded males of 40 years or older with typical angina. (From Gibbons *et al*,[38] with permission.)

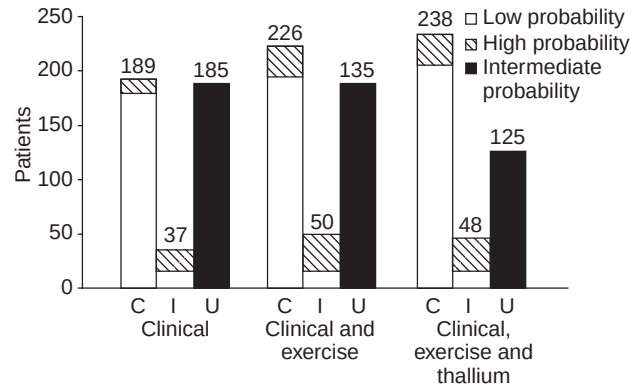

Figure 3.6 Correct (C), incorrect (I), and uncertain (U) classification of patients with three vessel or left main coronary artery disease by the use of logistic regression multivariate models. Low, intermediate, and high probability defined using: clinical variables only; clinical and exercise variables; clinical, exercise, and thallium-201 variables. (From Christian *et al*,[16] with permission.)

Non-invasive screening for severe CAD

The same threshold approach has been applied to the non-invasive identification of severe CAD. Here the ability of tests to move patients across somewhat different thresholds of probability, as assessed by logistic regression models, has been tested. Christian *et al*[16] defined a low-probability group for severe CAD as $<0{\cdot}15$, a high-risk group as $>0{\cdot}35$, and an intermediate group as 0·15–0·35. These thresholds were chosen to correspond to earlier work from Duke University reporting on the utility of the early positive treadmill test.[41] Figure 3.6 shows the results that were

obtained using this approach. Using clinical parameters alone, 189 patients (46% of the study group) were correctly classified as low or high probability. Thirty-seven patients (9%) were incorrectly classified as low or high probability. The remaining 185 patients (45% of the study group) had an intermediate probability, and were therefore in an uncertain category. The addition of exercise parameters correctly classified an additional 37 patients at the expense of 13 additional incorrect classifications, for a net of 24 additional correct classifications (6% of the study group). The addition of thallium parameters led to 12 additional correct classifications, and two fewer incorrect classifications for a net increase of 14 correct classifications (3% of the study group). These workers then used Medicare reimbursement figures to calculate the cost per additional correct classification. For exercise testing, the cost per additional correct patient classification was $1524. For thallium scintigraphy, the cost was $20 550 per additional correct classification.

Thus, this analysis demonstrated that the clinical impact was modest, and the cost was high, when thallium imaging was used in patients with a normal resting ECG to try to identify patients non-invasively with severe CAD. Although thallium scintigraphy clearly had statistically significant incremental value, it did not appear to be cost effective for this purpose.

Prediction of patient outcome

The issues of clinical significance and cost effectiveness are particularly pertinent to the application of diagnostic tests for the prediction of the patient outcome. These applications often involve relatively low-risk patient groups with few subsequent events. Tests applied to the entire population may identify a subset of patients who are at considerably increased risk.[42,43] These results will be highly statistically significant, and generate very impressive *P* values and risk ratios. However, it must be recognized that the absolute rate of events often remains too low in the high-risk patient subgroup to be clinically meaningful, and the cost of this identification is often therefore prohibitive when viewed on a per event basis.

This concept was nicely demonstrated in a study by Berman *et al*[44] on patients with a low clinical likelihood of CAD studied by SPECT sestamibi. During 20 months of follow up, only patients with an abnormal sestamibi study suffered death or myocardial infarction. This difference was statistically highly significant ($P = 0 \cdot 007$). However, this increment in prognostic value was clearly not cost effective, as noted by the authors. Although the cost analysis by the authors was quite detailed, the cost ineffectiveness of this approach is readily apparent with very simple analysis. The 107 patients in the high-risk group suffered only three events during 20 months of follow up. In order to identify the high-risk group, testing was required of 548 patients. Using a Medicare reimbursement figure of $700 per test,[16] more than $383 000 of testing would be required to identify the high-risk cohort. The cost of testing alone would therefore exceed $127 000 per possible event prevented. This simple analysis ignores the additional costs that would accrue from the subsequent cardiac catheterizations and coronary revascularizations that would be necessary in the high-risk group in order to attempt to prevent the three events. (There is obviously no certainty that the three events could actually be prevented by revascularization.)

Similar analyses have been published for screening in asymptomatic individuals. As a general principle, it should be recognized that non-invasive testing for the assessment of prognosis is far less cost effective in subsets of patients at intrinsically low risk.

Conclusion

Clinicians should recognize that an evidence-based approach to the evaluation of the incremental value of diagnostic tests is not simple or straightforward. Unfortunately, it is far easier for both clinicians and investigators to use simple, less rigorous, approaches that appear to demonstrate important incremental value for each new diagnostic test. Although convenient, such approaches lead to incorrect conclusions, and generally overestimate the added value of each new testing modality. The examples presented in this chapter should provide a framework for thinking clinicians to evaluate better new publications on new diagnostic tests. However difficult these analyses may be, and however disappointing the results, the escalating costs of healthcare demand an approach of rigorous methodology and thoughtful analysis to make certain that the *incremental* value of a diagnostic test is not only statistically significant, but clinically significant and cost effective.

References

1. Diamond G. Penny wise. *Am J Cardiol* 1988;**62**:806–8.
2. Bobbio M, Pollock BH, Cohen I, Diamond GA. Comparative accuracy of clinical tests for diagnosis and prognosis of coronary artery disease. *Am J Cardiol* 1988;**62**:896–900.
3. Ladenheim ML, Kotler TS, Pollock BH, Berman DS, Diamond GA. Incremental prognostic power of clinical history, exercise electrocardiography and myocardial perfusion scintigraphy in suspected coronary artery disease. *Am J Cardiol* 1987;**59**: 270–7.
4. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;**300**:1350–8.
5. Diamond GA. Letter: a clinical relevant classification of chest discomfort. *J Am Coll Cardiol* 1983;**1**:574–5.

6. Pryor DB, Harrell FE Jr, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. *Am J Med* 1983;**75**:771–80.
7. Weiner DA, McCabe CH, Ryan TJ. Identification of patients with left main and three vessel coronary disease with clinical and exercise test variables. *Am J Cardiol* 1980;**46**:21–7.
8. Hubbard BL, Gibbons RJ, Lapeyre AC, Zinsmeister AR, Clements IP. Identification of severe coronary artery disease using simple clinical parameters. *Arch Intern Med* 1992;**152**: 309–12.
9. Pryor DB, Shaw L, Harrell FE Jr *et al*. Estimating the likelihood of severe coronary artery disease. *Am J Med* 1991;**90**: 553–62.
10. Pryor DB, Shaw L, McCants CB *et al*. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;**118**:81–90.
11. Weiner DA, Ryan TJ, McCabe CH *et al*. The role of exercise testing in identifying patients with improved survival after coronary artery bypass surgery. *J Am Coll Cardiol* 1986;**8**: 741–8.
12. O'Keefe JH Jr, Zinsmeister AR, Gibbons RJ. Value of electrocardiographic findings in predicting rest left ventricular function in patients with chest pain and suspected coronary artery disease. *Am J Med* 1989;**86**:658–62.
13. Rihal CS, Davis KB, Kennedy JW, Gersh BJ. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol* 1995;**75**:220–3.
14. Connolly DC, Elveback LR, Oxman HA. Coronary heart disease in residents of Rochester, Minnesota. IV. Prognostic value of the resting electrocardiogram at the time of initial diagnosis of angina pectoris. *Mayo Clin Proc* 1984;**59**:247–50.
15. Gibbons RJ, Zinsmeister AR, Miller TD, Clements IP. Supine exercise electrocardiography compared with exercise radionuclide angiography in noninvasive identification of severe coronary artery disease. *Ann Intern Med* 1990;**112**:743–9.
16. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiogram. *Ann Intern Med* 1994;**121**:825–32.
17. Epstein SE. Implications of probability analysis on the strategy used for noninvasive detection of coronary artery disease. *Am J Cardiol* 1980;**46**:491–9.
18. Rifkin RD, Hood WB Jr. Bayesian analysis of electrocardiographic exercise stress testing. *N Engl J Med* 1977;**297**: 681–6.
19. Cohn K, Kamm B, Feteih N, Brand R, Goldschlager N. Use of treadmill score to quantify ischemic response and predict extent of coronary disease. *Circulation* 1979;**59**:286–96.
20. Currie PJ, Kelly MJ, Harper RW *et al*. Incremental value of clinical assessment, supine exercise electrocardiography, and biplane exercise radionuclide ventriculography in the prediction of coronary artery disease in men with chest pain. *Am J Cardiol* 1983;**52**:927–35.
21. Morise AP, Detrano R, Bobbio M, Diamond GA. Development and validation of a logistic regression-derived algorithm for estimating the incremental probability of coronary artery disease before and after exercise testing. *J Am Coll Cardiol* 1992; **20**:1187–96.
22. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978; **299**:926–30.
23. Philbrick JT, Horwitz RI, Feinstein AR. Methodologic problems of exercise testing for coronary artery disease: groups, analysis and bias. *Am J Cardiol* 1980;**46**:807–12.
24. Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJC. The declining specificity of exercise radionuclide ventriculography. *N Engl J Med* 1983; **309**:518–22.
25. Council on Health Care Technology, Institute of Medicine. *Assessment of diagnostic technology in health care*. Washington, DC: National Academy Press,1989.
26. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. *JAMA* 1994; **271**:389–91.
27. Diamond GA. An alternative factor affecting sensitivity and specificity of exercise electrocardiology (editorial). *Am J Cardiol* 1986; **57**:1175–80.
28. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics* 1983;**39**:207–15.
29. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. *Am Heart J* 1995; **130**:741–7.
30. Roger VL, Pellikka PA, Bell MR, Chow CWH, Bailey KR, Seward JB. Sex and test verification bias: Impact on the Diagnostic Value of Exercise Echocardiology. *Circulation* 1997; **95**:405–10.
31. Miller TD, Hodge DO, Christian TF, Milavetz JJ, Bailey KR, Gibbons RJ. Effects on adjustment for referral bias on the sensitivity of specificity of single photon emission computed tomography for the diagnosis of coronary artery disease. *Am J Med* 2002;**112**:290–7.
32. Gibbons RJ, Chatterjee K, Daley J, *et al*. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 1999;**33**:2092–7.
33. Wieand S, Gail M, James K, James B. A family of nonparametric statistics for comparing diagnostic tests with paired or unpaired data. *Biometrika* 1989;**76**:585–92.
34. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972;**34**:197–220.
35. Pollock SG, Abbott RD, Boucher CA, Beller GA, Kaul S. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease. Validation of models based on these tests. *Circulation* 1992;**85**:237–48.
36. Diamond GA, Forrester JS, Hirsch M *et al*. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. *J Clin Invest* 1980;**65**:1210–21.
37. Goldman L, Cook EF, Mitchell N *et al*. Incremental value of the exercise test for diagnosing the presence or absence of coronary artery disease. *Circulation* 1982;**66**:945–53.
38. Gibbons RJ, Lee KL, Pryor DB *et al*. The use of radionuclide angiography in the diagnosis of coronary artery disease: a logistic regression analysis. *Circulation* 1983;**68**:740–6.
39. Detrano R, Yiannikas J, Salcedo EE *et al*. Bayesian probability analysis: a prospective demonstration of its clinical utility in diagnosing coronary disease. *Circulation* 1984;**69**: 541–7.

40. Melin JA, Wijns W, Vanbutsele RJ *et al.* Alternative diagnostic strategies for coronary artery disease in women: demonstration of the usefulness and efficiency of probability analysis. *Circulation* 1985;**71**:535–42.
41. McNeer JF, Margolis JR, Lee KL *et al.* The role of the exercise test in the evaluation of patients for ischemic heart disease. *Circulation* 1978;**57**:64–70.
42. Rautaharju PM, Prineas RJ, Eifler WJ *et al.* Prognostic value of exercise electrocardiogram in men at high risk of future coronary heart disease: multiple risk factor intervention trial experience. *J Am Coll Cardiol* 1986;**8**:1–10.
43. Giagnoni E, Secchi MB, Wu SC *et al.* Prognostic value of exercise EKG testing in asymptomatic normotensive subjects: a prospective matched study. *N Engl J Med* 1983;**309**: 1085–9.
44. Berman DS, Hachamovitch R, Hosen K *et al.* Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99 m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1995;**26**:639–47.

4 Clinical trials and meta-analysis

Colin Baigent

Introduction

Although large effects on survival arising from certain treatments may occasionally be obvious from simple observation (as, for example, when cardioversion for ventricular fibrillation avoids otherwise certain death), the vast majority of interventions have only moderate effects on major outcomes and hence are impossible to evaluate without careful study. Enthusiasm for the biologic foundations of a particular therapeutic approach often leads to exaggerated hopes for the effects of treatment on major clinical outcomes. These hopes may be based on dramatic laboratory measures of efficacy, or on the types of surrogate outcome that are commonly studied before drugs go into Phase III or IV studies: for example, a drug may almost completely prevent experimental ischemia progressing to infarction, or practically abolish experimental thrombosis. However, these large effects on surrogate end points very rarely translate into large effects on major clinical outcomes: the overwhelming message from two decades of clinical trials in cardiology is that the net effects of most treatments are typically moderate in size.* This chapter explains why large-scale randomized evidence, either in a single "mega-trial" or in a meta-analysis of similar trials, is generally an absolute requirement if such moderate effects on major outcomes are to be characterized reliably.

It is important to appreciate that progress in cardiologic practice, and in the prevention of cardiovascular disease, has been and remains dependent on the availability of large-scale randomized trials and appropriately large-scale meta-analyses of such trials. In the management of acute myocardial infarction (MI), for example, these methods have helped to demonstrate that fibrinolytic therapy,[1–3] aspirin,[1,3,4] angiotensin-converting-enzyme (ACE) inhibitors[5–7] and β-blockers[8] all produce net benefits which, although individually moderate in size, have together produced a substantial improvement in the prognosis of acute MI. Similarly, the demonstration that ACE inhibitors produce moderate reductions in the risk of death and in the rates of hospitalization for worsening heart failure,[9] and that the addition of digoxin further reduces the need for recurrent hospitalization,[10] has improved the prognosis of congestive heart failure.

Clinical trials: minimizing biases and random errors

Any clinical study whose main objective is to assess moderate treatment effects must ensure that any biases and any random errors that are inherent in its design are both substantially smaller than the effect to be measured.[11,12] Biases in the assessment of treatment can be produced by differences in factors other than the treatment under consideration. Observational (that is non-randomized) studies in which the outcome is compared between individuals who received the treatment of interest and those who did not, can be subject to large biases.[13] Instead, the guaranteed avoidance of biases requires the proper randomized allocation of treatment and appropriate statistical analysis, with no unduly data-dependent emphasis on specific subsets of the overall evidence (Table 4.1).[12]

Avoidance of moderate biases

Proper randomization

The fundamental reason for random allocation of treatment in clinical trials is to maximize the likelihood that each type of patient will have been allocated in similar proportions to the different treatment strategies being investigated.[14] Proper randomization requires that trial procedures are organized in a way that ensures that the decision to enter a patient is made irreversibly and without knowledge of the trial treatment to which a patient will be allocated. In situations where the next treatment allocation can be deduced by those entering patients, decisions about whether to enter a

* For rare adverse effects, however, there may be large proportional differences between one treatment and another, or between treatment and control. For example, some non-steroidal anti-inflammatory drugs may substantially increase the risk of gastrointestinal bleeding. Rare adverse effects with extreme relative risks can often be recognized reliably by careful clinical observation, or by other non-randomized methods, and such relative risks are sometimes best quantified in case–control or cohort studies.

Table 4.1 Requirements for reliable assessment of MODERATE treatment effects[11,12]

1. *Negligible biases*
   (that is guaranteed avoidance of MODERATE biases)
   - Proper RANDOMIZATION (non-randomized methods cannot guarantee the avoidance of moderate biases)
   - Analysis by ALLOCATED treatments (that is an "intention to treat" analysis)
   - Chief emphasis on OVERALL results (with no unduly data-derived subgroup analysis)
   - Systematic META-ANALYSIS of all the relevant randomized trials (with no unduly data-dependent emphasis on the results from particular studies)
2. *Small random errors*
   (that is guaranteed avoidance of MODERATE random errors)
   - LARGE NUMBERS (with minimal data collection as detailed statistical analyses of masses of data on prognostic features generally add little to the effective size of a trial)
   - Systematic META-ANALYSIS of all the relevant randomized trials

particular patient may be affected, and those allocated one treatment might then differ systematically from those allocated another.[15] In the Captopril Prevention Project (CAPPP) trial,[16] for example, envelopes containing the antihypertensive treatment allocation could be opened before patients were irreversibly entered into the study. Highly significant differences in pre-entry blood pressure between the treatment groups, which were too large to have been due to chance, may well have been the result of this design weakness.[17]

Intention to treat analysis

Even when studies have been properly randomized and well conducted, moderate biases can still be introduced by inappropriate analysis or interpretation. One well recognized circumstance is when patients are excluded after randomization, particularly when the prognosis of the excluded patients in one treatment group differs from that in the other (such as might occur, for example, if non-compliers were excluded after randomization). This point is well illustrated by the Coronary Drug Project, which compared clofibrate versus placebo among around 5000 patients with a history of coronary heart disease. In this study, patients who took at least 80% of their allocated clofibrate ("good" compliers) had substantially lower 5 year mortality than "poor" compliers who did not (15·0% *v* 24·6% respectively; $P = 0{\cdot}0001$). However, there was a similar difference in outcome between "good" and "poor" compliers in the placebo group (15·1% *v* 28·3%, respectively; $P < 0{\cdot}00001$), suggesting that "good" and "poor" compliers were prognostically different even after allowing for any benefits of actually taking clofibrate.[18] If there is really no difference in outcome between two treatments, then the least biased assessment of the treatment effect is that which compares all those allocated to one treatment versus all those allocated to the other (that is an "intention to treat" analysis), irrespective of what treatment they actually received.[19]

Because some degree of non-compliance with allocated treatments is unavoidable in randomized trials, intention to treat analyses will obviously underestimate the effects produced by full compliance. However, "on treatment" analyses, which compare effects among compliant patients with those in non-compliant patients, are potentially biased, and it is more appropriate to calculate an "adjustment" based on the level of compliance and then to apply this to the estimate of the treatment effect provided by the intention to treat comparison.[20] For example, in a meta-analysis of the randomized trials of prolonged use of antiplatelet therapy among patients with occlusive vascular disease, the average compliance 1 year after treatment allocation seemed to be around 80%.[4] Application of this estimate of compliance to the proportional reduction of about 30% in non-fatal MI and stroke estimated from intention to treat analyses of these trials suggests that full compliance with antiplatelet therapy produces reductions in risk of about 35–40%.

Dangers of data-dependent emphasis on particular results

In the medical literature a particularly important source of bias is unduly data-dependent emphasis on particular trials or on particular subgroups of patients. Such emphasis is often entirely inadvertent, arising from a perfectly reasonable desire to understand the randomized trial results in terms of who to treat, which treatments to prefer, or disease mechanisms. However, whatever its origins, selective emphasis on particular parts of the evidence can often lead to seriously misleading conclusions. This is because the identification of categories of patients for whom treatment is particularly effective (or ineffective) requires surprisingly large quantities of data. Even if the real sizes of the treatment effects do vary substantially among subgroups of patients, subgroup analyses are so statistically insensitive that they may well fail to demonstrate these differences. On the other hand, if the real proportional risk reductions are about the same for everybody, subgroup analyses can vary so widely just by the play of chance that the results in selected subgroups may be exaggerated. Even when highly significant "interactions" are found, they may be a poor guide to the sizes (or even the directions) of any genuine differences, as the more extreme such results may still owe more to chance than to reality. This is particularly the case when such interactions have emerged after an overzealous examination of multiple

subgroups. For example, in the large Second International Study of Infarct Survival (ISIS-2), the 1 month survival advantage produced by aspirin was particularly clear (804 vascular deaths among 8587 patients allocated aspirin *v* 1016 among 8600 allocated placebo; proportional reduction of 23% (SD 4); $P < 0{\cdot}000001$).[1] When these overall results were subdivided by the patients' astrological birth signs, however, no fewer deaths were observed with aspirin than with placebo among patients born under Libra or Gemini (Table 4.2). Although few doctors would consider such analyses to be valid, similarly unreliable conclusions based on "exploratory" data-derived subgroup analyses are widely reported in medical journals and at scientific meetings, and may well have adverse consequences for patient care.

An example of how such subgroup analyses resulted in inappropriate management of patients is provided by the early trials of aspirin for the secondary prevention of stroke. Here, emphasis on the results in men led to a situation where, for almost 20 years, the US Food and Drug Administration approved this use of aspirin only for males; more recent evidence shows this to have been mistaken.[4] A further example is provided by the large Italian GISSI-1 trial comparing streptokinase versus control after acute MI. The overall results favoured streptokinase, but subgroup analyses suggested that streptokinase was beneficial only in patients without prior MI. Fortunately, the GISSI investigators were circumspect about this "finding",[2] and their caution turned out to have been wise, as a subsequent overview of all the large fibrinolytic trials showed that the proportional benefits were similar, irrespective of a history of MI.[21] Many thousands of patients with a previous history of MI might well have been denied fibrinolytic therapy, however, if the apparent pattern of the results in the GISSI-1 subgroups had been believed.

A similar bias may arise in a situation where several studies have addressed much the same therapeutic question but only a few of them are chosen for emphasis. This could be a source of serious bias, as chance fluctuations for or against treatment might affect this choice. It is therefore more appropriate to base inference on a meta-analysis of results from all relevant randomized trials (or, at least, on an unbiased subset of the relevant trials, such as all trials above a certain minimum sample size).[22,23] One additional advantage of such an approach is that such meta-analyses will also minimize random errors, because far more patients (and most importantly, more events) will be available for analysis. The separate trials might well be heterogeneous, but with careful interpretation of such heterogeneity it is often possible to enhance understanding of particular clinical questions.[24] Occasionally, when detailed information on individual patients is available within a really large meta-analysis that includes several thousand major outcomes, such as death[21] or cancer recurrence,[25] it may be feasible to identify particular groups of individuals in whom the benefits or hazards of treatment really are especially great. (Where it has been possible to establish cooperation between trialists before any of the trial results are known, having just a few prespecified subgroup hypotheses can provide some protection against unduly data-dependent emphasis on particular results in a large meta-analysis.[26])

Avoidance of moderate random errors

Small trials may produce false negative results

Whereas the avoidance of moderate biases requires careful attention both to the randomization process and to the analysis and interpretation of the available trial evidence, the avoidance of moderate random errors requires large numbers of events. Because major outcomes such as death may affect only a small proportion of those randomized, very large numbers of patients often need to be studied before the results can be guaranteed to be statistically (and hence medically) convincing. For example, the early trials of intravenous fibrinolytic therapy for acute myocardial infarction were individually too small to provide reliable evidence about any moderate effects of this treatment on mortality, although several did identify an increased risk of serious bleeding. As a result, fibrinolytic therapy was not used routinely until the GISSI-1[2] and ISIS-2[1] "mega-trials" provided such definite evidence of benefit that treatment patterns changed rapidly.[27] It is worth noting, however, that GISSI-1 and ISIS-2 both included more than 10 000 patients and 1000 deaths, but had they only been one tenth as large the observed reduction in mortality would not have been conventionally significant, and would therefore have had much less influence on medical practice.

Table 4.2 Unreliability of "data-dependent" subgroup analyses: ISIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction[1]

Astrological birth sign	Vascular death by 1 month		*P* value
	Aspirin	Placebo	
Libra or Gemini	150 (11·1%)	147 (10·2%)	0·5
All other signs	654 (9·0%)	869 (12·1%)	<0·0001
Any birth sign	804 (9·4%)	1016 (11·8%)	<0·0001

Small-scale meta-analyses may be unreliable

Because meta-analyses are appearing in medical journals with increasing frequency it is useful to be able to judge the reliability of such reviews – and, in particular, the extent to which confounding, biases or random errors could lead to mistaken conclusions. (In randomized trials, "confounding" exists when a comparison of some particular treatment in one group versus a control group involves the routine coadministration in one group, but not the other, of some cointervention that might affect the outcome.) To avoid any possibility of confounding, and to avoid any flexibility in the question of which trials to consider, meta-analyses should generally include only unconfounded properly randomized trials. The main problems that then remain are those of biases and random errors.

Two types of bias could affect the reliability of a meta-analysis: those that occur within individual trials, and those that relate to the selection of trials. More empirical research into the numerous biases that can occur within randomized trials would be valuable. However, it is clear from existing studies that, for example, inadequate concealment of the likely treatment allocation does quite often result in exaggerated estimates of treatment effect,[28] and that the inappropriate postrandomization exclusion of particular patients is common.[29] Such defects have unpredictable consequences for particular trials, however, and no generalizations about the likely size, or even direction, of the resultant biases are possible.

A further problem involves the process of identifying all relevant trials. Unfortunately, the subset of trials that are eventually published (and hence which are conveniently available) is often a biased sample of the trials that have been done. Trials may well be more likely to be submitted for publication if their results are strikingly positive than if they are negative or null.[30–33] Such "publication bias" can, along with other sources of bias, produce surprisingly impressive looking evidence of effectiveness for treatments that are actually useless.[34] The particular circumstances in which publication bias has contributed to producing misleading estimates of treatment are difficult to identify, and it is still more difficult to generalize about the exact size of any such bias when it does occur.

The problem of incomplete ascertainment is likely to be particularly acute within small meta-analyses that contain no more than a few hundred major outcomes and which consist mainly of small published trials. This is because results from trials with only a limited number of end points are subject to large random errors, and such trials are therefore particularly likely to generate implausibly large effect estimates. If publication bias then results in emphasis on the more promising of these small trial results, the resulting summary odds ratios are likely to be unreliable.[35] Hence, unless the particular circumstances of a small-scale meta-analysis suggest that publication bias is unlikely, it may be best to treat such results as no more than "hypothesis generating". On the other hand, a thoroughly conducted meta-analysis that in aggregate contains sufficient numbers of major outcomes to constitute "large-scale" randomized evidence[4,21,25] is unlikely to be materially affected by publication bias and, provided there are no serious uncontrolled biases (see above) within the individual component trials, is likely to be fairly trustworthy – although, even then, inappropriate subgroup analyses may generate mistaken conclusions.

Large-Scale Randomized Trials

Trials of the effects of treatments on major outcomes can only be made large if they are kept as simple as possible. In particular, as many as possible of the main barriers to rapid recruitment need to be removed. An important way in which trial design can facilitate this is to limit the amount of information that is recorded. For example, data recorded at baseline can often be restricted to important clinical details, including at most only a few major prognostic factors and only a few variables that are thought likely to influence substantially the benefits or hazards of treatment. Similarly, the information recorded at follow up need not be extensive and can be limited largely to those major outcomes that such studies have been designed to assess, and to approximate measures of compliance. (Other outcomes that are of interest but which do not need to be studied on such a large scale may best be assessed in separate smaller studies, or in subsets of these large studies when this is practicable.) Likewise, complicated eligibility criteria, inappropriately detailed consent procedures[36] and unnecessarily extensive auditing of data can all prevent the recruitment of large numbers of patients. Furthermore, if trials are complex they are likely to involve a high cost per patient, which again tends to limit their size. Either way, complexity is rarely a virtue in trials designed to assess major outcomes, whereas simplicity can sometimes lead to the rapid randomization of very large numbers of patients, and to results that change clinical practice within very short periods of time.[1,27]

The "uncertainty principle"

For ethical reasons, randomization is appropriate only if both the doctor and the patient feel substantially uncertain as to which trial treatment is best. The "uncertainty principle" maximizes the potential for recruitment within this ethical constraint (see Box on p 38).

If many hospitals are collaborating in a trial then wholehearted use of the uncertainty principle encourages clinically appropriate heterogeneity in the resulting trial population, and in large trials this may add substantially to the practical value of the results. Among the early trials of

The "uncertainty principle"

A patient can be entered if, and only if, the responsible physician is substantially uncertain as to which of the trial treatments would be most appropriate for that particular patient.

A patient should not be entered if the responsible physician or the patient is, for any medical or non-medical reason, reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison either with no treatment or with some other treatment that could be offered to the patient in or outside the trial).[37]

fibrinolytic therapy, for example, most of the studies had restrictive entry criteria that precluded the randomization of elderly patients, and so those trials contributed nothing of direct relevance to the important clinical question of whether treatment was useful in older patients. Other trials that did not impose an upper age limit, however, did include some elderly patients, and were therefore able to show that age alone is not a contraindication to fibrinolytic therapy.[21]

Thus, homogeneity of those randomized may be a serious defect in clinical trial design, whereas heterogeneity may be a scientific strength: after all, trials do need to be relevant to a very heterogeneous collection of future patients. The "uncertainty principle" not only ensures ethicality and clinically useful heterogeneity, but also is easily understood and remembered by busy collaborating clinicians, which in turn helps the randomization of large numbers of patients.

Can observational studies substitute for large-scale randomized trials?

As the resources will never be available to design large, simple trials to address all the questions of clinical interest, there have been several recent suggestions that observational studies might be able to provide reliable estimates of the effects of particular treatments. Non-randomized studies do not necessarily provide inaccurate estimates of the effects of treatments, but the point is that they cannot be **guaranteed** to produce reliable estimates because of biases that are inherent in their design. It may well be difficult or impossible to avoid such biases, or to adjust fully for their effects.[38] When non-randomized studies suggest that certain treatments have surprisingly large effects, such findings are often refuted when those treatments are assessed in large randomized trials.[39] For example, the claims of hazards with digoxin in heart failure,[40] based on non-randomized evidence, were not confirmed by the very large randomized DIG (Digitalis Investigation Group) trial.[10] Even if non-randomized comparisons happen to get the right answer then nobody will really know that they have done so. Thus non-randomized studies are of little practical value if the primary aim is to assess moderate treatment effects (whether beneficial or adverse) on major outcomes.

Summary

Many interventions in cardiological practice produce only moderate effects on major outcomes such as death or serious disability. However, even a moderate effect of treatment, if demonstrated clearly enough for that treatment to be widely adopted, can prevent disabling events or death in substantial numbers of people. Moreover, if – as in the treatment of acute myocardial infarction – more than one moderately effective treatment can eventually be identified, then the combination of two or three individually moderate improvements in outcome may collectively result in substantial health gains. In some instances sufficient information is already available from large-scale randomized trials – or, better still, from meta-analyses of those trials – to allow the balance of risk and benefit of particular treatments to be defined for particular patients. But many important questions have still not been answered reliably, and there remains a need for many more large "streamlined" megatrials, and meta-analyses of such trials, to help resolve some of the outstanding clinical uncertainties in the management of cardiovascular disease.

References

1. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **ii**:349–60.
2. GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**i**:397–402.
3. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;**336**:847–60.
4. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**:81–106.
5. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669–85.
6. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after myocardial infarction. *Lancet* 1994; **343**:1115–22.
7. Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995;**345**:686–7.

8. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986;**ii**:57–66.
9. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
10. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–33.
11. Collins R, Peto R, Gray R, Parish S. Large-scale randomized evidence: trials and overviews. In: Weatherall D, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, Vol. 1 Oxford: Oxford University Press, 1996.
12. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001;**357**:373–80.
13. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001;**357**:455–62.
14. Armitage P. The role of randomization in clinical trials. *Stat Med* 1982;**1**:345–52.
15. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;**317**:1185–90.
16. Hansson L, Lindholm LH, Niskanen L *et al.* for the Captopril Prevention Project (CAPPP) study group. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;**353**:611–16.
17. Peto R. Failure of randomisation by "sealed" envelope. *Lancet* 1999;**354**:73.
18. The Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N Engl J Med* 1980;**303**: 1038–41.
19. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I: Introduction and design. *Br J Cancer* 1976;**34**:585–612.
20. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med* 1997;**16**:1017–29.
21. Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
22. Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. *Stat Med* 1987;**6**:245–50.
23. Clarke M, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals: islands in search of continents? *JAMA* 1998;**280**:280–2.
24. Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* 1994;**309**:1351–5.
25. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992;**339**:1–15 (Part I) & 71–85 (Part II).
26. Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *Am J Cardiol* 1995;**75**:1130–4.
27. Collins R, Julian D. British Heart Foundation surveys (1987 and 1989) of United Kingdom treatment policies for acute myocardial infarction. *Br Heart J* 1991;**66**:250–5.
28. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodologic quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.
29. Schulz KF, Grimes DA, Altman DG, Hayes RJ. Blinding and exclusions after allocation in randomized controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *BMJ* 1996;**312**:742–4.
30. Dickersin K, Chan S, Chalmers TC *et al.* Publication bias and clinical trials. *Contr Clin Trials* 1987;**8**:343–53.
31. Easterbrook PJ, Berlin JA, Gopelan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;**337**:867–72.
32. Dickersin K, Min Y-I, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* 1992;**267**:374–8.
33. Dickersin K, Min Y-I. Publication bias: the problem that won't go away. *Ann NY Acad Sci* 1993;**703**:135–46.
34. Counsell CE, Clarke MJ, Slattery J, Sandercock PAG. The miracle of DICE therapy for acute stroke: fact or fictional product of subgroup analysis. *BMJ* 1994;**309**:1677–81.
35. Davey Smith G, Egger M. Misleading meta-analysis. *BMJ* 1995;**310**:742–54.
36. Doyal L. Journals should not publish research to which patients have not given fully informed consent – with three exceptions. *BMJ* 1997;**314**:1107–11.
37. Collins R, Doll R, Peto R. Ethics of clinical trials. In: Williams CJ, ed. *Introducing New Treatments for Cancer: Practical, Ethical and Legal Problems*. Chichester: John Wiley & Sons, 1992.
38. Sheldon TA. Please bypass the PORT. Observational studies of effectiveness run a poor second to randomised controlled trials. *BMJ* 1994;**309**:142–3.
39. Peto R. Clinical trial methodology. *Biomedicine* Special Issue 1978;**28**:24–36.
40. Yusuf S, Wittes J, Bailey K, Furberg C. Digitalis – a new controversy regarding an old drug: the pitfalls of inappropriate methods. *Circulation* 1986;**73**:13–18.

5 Finding current best evidence to practice evidence-based cardiology

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Staying current with new diagnostic tests, treatments, and other clinically useful new knowledge in a rapidly evolving field such as cardiology requires effort. Fortunately, this once daunting task is becoming more feasible because of new evidence-based information resources and the steady advance of information technology into clinical settings. This chapter will review ways to find current best evidence for the care of patients with cardiac problems, including both solving patient problems as they arise, and keeping up with new evidence that is ready for application in clinical practice.

The patients whom we see on a daily basis provide an excellent stimulus to staying current. They may have clinical problems that we are unfamiliar with, or that we have not recently reviewed. They may also present us with information from the media or friends to evaluate, or ask us questions that we need to research before answering. Depending on the type of center in which we work, our colleagues, teachers, and students may also ask questions or provide suggestions, making us realize that our knowledge may be "time-challenged".

To become proficient in responding to such challenges (also known as "learning opportunities"), we can make use of a growing array of specialized information resources, aided by information technology that can bring access to our fingertips, almost wherever we may be. To illustrate how patient contacts can provide us with the stimulus to keep up to date and be aware of new evidence, consider the following scenarios.

1. During your outpatient clinic, you see a 56 year old woman who recently became your patient after she moved to your community. She has been diagnosed as having an idiopathic dilated cardiomyopathy and had an echocardiogram 6 months ago that revealed a diffusely enlarged left ventricle with no segmental abnormalities. The ejection fraction was estimated to be less than 30%. You review her current condition and note that her symptoms are controlled on an angiotensin converting enzyme (ACE) inhibitor, digoxin, and a diuretic. Still, she complains of fatigue and dyspnea on moderate exertion. Before leaving, she asks if you can recommend any other medications that would help.
2. Later that day, you pass through the emergency department where an emergency physician happens to notice you. She has been working up a 65 year old man who presented with a swollen left calf. He had an ultrasound that confirmed the presence of a deep venous thrombosis. The patient is anxious to return home because his wife is ill and requires care. The emergency physician is interested in your opinion on the use of low molecular weight heparin for the treatment of deep venous thrombosis in outpatients.

These questions are consistent with the common information needs of physicians. For internists, questions arise at a rate of two questions for every three outpatients seen[1] and five questions on average for every inpatient.[2] No one knows whether cardiologists confront similar numbers of questions, but no professional discipline studied to date is immune from the need to address unanswered questions to keep up with the advance of knowledge.

How would you address each of the questions raised by the clinical scenarios? The possibilities include using an electronic bibliographic database such as MEDLINE, a specialized abstract journal like *ACP Journal Club* or *Evidence-Based Cardiovascular Medicine*, a current textbook, or the Cochrane Library. We will consider the strengths and weaknesses of these resources and apply them to the clinical problems.

MEDLINE

MEDLINE is a huge, multipurpose database of medical literature citations and abstracts produced by the US National Library of Medicine (NLM). It includes citations to almost all important clinical studies, and also a much larger volume of non-clinical studies and articles. Few other resources currently rival this scope. Accessing MEDLINE is relatively easy.[3–5] CD Rom based systems, online systems, and, most importantly, internet access are all available. Examples of CD Rom systems include OVID, Aries, SilverPlatter, and DIALOG. Online access by modem is available through vendors such as PaperChase and HealthGate.[6] Internet access is readily available (see Medical Matrix (http://www. medmatrix.org)

and Dr Felix's Free MEDLINE Page (http://www.beaker.iupui. edu/drfelix) sites for locations that offer MEDLINE access). Some of these MEDLINE systems have user fees but, at least at present, free access is available from many, led by the NLM PubMed (http://www.ncbi.nlm.nih.gov/PubMed/) internet site. This site features the earliest MEDLINE access to newly published articles and point-and-click search strategies that improve the yield of clinically useful studies on the cause, course, diagnosis, and treatment of clinical problems.

If ready access is one of MEDLINE's strengths, the skills needed to rapidly and dependably locate high quality articles that specifically address a clinical question are a weakness. A working knowledge of MEDLINE searching terminology and searching strategies is essential. Luckily, most hospital and university libraries offer training courses for MEDLINE. The NLM has also established a set of eight regional medical libraries that are charged with providing access and training for all US health personnel (+1-800-338-7657). Physicians in the UK can call the Health Care Information Service (+44-207-412-7477) for similar information, while Canadians can call the Canada Institute for Scientific and Technical Information (+1-800-668-1222).

Turning to our initial scenario, we are interested in locating information about new medical therapies for patients with idiopathic dilated cardiomyopathy. Also, it would be wise to focus initially on treatments that already have been adequately tested in well-designed clinical trials.[7] While it may be interesting to read about new medications that are being designed and tested at the laboratory level, or are undergoing early human testing, this information will not be immediately applicable in our clinical practices.

Turning to MEDLINE for assistance, we might begin searching by using a medical subject heading (MeSH) for congestive heart failure. MEDLINE indexers choose appropriate terms from a thesaurus of 14 000 specific terms and 18 000 synonyms for content and methodology. Unfortunately, these terms are not always intuitive (for example, β blockers indexed as adrenergic β antagonists). Therefore, it is often necessary to search through the MeSH vocabulary before carrying out a search. The software for all search systems includes MeSH, so it is quite easy to search for appropriate terms. For our topic, a search for CONGESTIVE HEART FAILURE leads to HEART FAILURE, CONGESTIVE.

Depending on the topic and the scope that you are interested in covering, you may also want to take advantage of two additional features of MeSH headings. Because many articles deal predominantly with two or three topics, the NLM will indicate these topics for each citation by designating them as major subjects of the article. Limiting your search to articles in which the search term has been designated as the major subject heading will be beneficial if you retrieve too many citations from using the search term without "majoring" it. Sometimes, though, you can miss important studies this way. A trial and error approach may be needed to retrieve the best studies.

"Exploding" is another useful feature of MEDLINE MeSH indexing. When articles are indexed, they are classified according to the most specific MeSH heading available. Thus, if you wish to identify all articles that deal with congestive heart failure, including those with more specific MeSH terms such as congestive cardiomyopathy, then you can do so by searching with the term EXPLODE HEART FAILURE, CONGESTIVE.

If you are searching for a topic that has not been well indexed, you may want to take advantage of textword searching. Using this approach, you are simply asking MEDLINE to search the titles and abstracts of all the citations for any occurrences of a certain sequence of letters, such as "dilated". This approach is particularly useful for new drugs or concepts that have not yet been incorporated into MeSH. MeSH is updated annually, but the lag can be considerably longer for certain terms.

If several different endings to a word may have been used, and you wish to identify them all, you can use "truncation", using the "*" symbol. For example, if you asked for RANDOM*, MEDLINE would search for RANDOM, RANDOMIZATION, RANDOMIZED, RANDOMISATION, RANDOMISED, and RANDOMLY. Be careful with truncation. The term "salmon*" retrieves not only the fish but salmonella as well! Some systems may use symbols other than "*", such as ":" or "?".

Returning to identifying new therapies for patients with significant left ventricular dysfunction, EXPLODE HEART FAILURE, CONGESTIVE is a good start, but we need to narrow in on treatments that have been tested in well-designed studies. Luckily, a number of methodological search strategies have been tested and validated for retrieving sound studies for questions relating to therapy, prognosis, etiology or cause, and diagnosis (Box 5.1).[8,9] Alternatively, you can search for a systematic review of studies. Research is currently ongoing to establish the best approach to identify systematic reviews and meta-analyses.[10] For our current search, limiting the citations to systematic reviews and meta-analyses seemed like a reasonable first step. A simple but not fully validated strategy to identify systematic reviews and meta-analyses is to identify all citations in which the publication type is designated as meta-analysis (note that in addition to indexing articles according to subject, the NLM also indexes citations according to "publication type"). Over 40 publication types are recognized, including "meta-analysis", "randomized controlled trial", and "review"), as well as citations that include the phrase "meta-anal*" as a textword, and citations that are designated as reviews in the publication type section, but also have the textword "MEDLINE" in their abstract. Putting this all together yielded the search strategy in Box 5.2 using PubMed.

Box 5.1 Optimal search strategies for identifying studies relating to treatment, diagnosis, prognosis, or etiology using MEDLINE

Treatment	
Best single term:	clinical trial.pt. ("pt" indicates publication type)
Combination of terms with best specificity:	placebo:.tw. ("tw" indicates textword) OR double.tw. AND blind:.tw.
Combination of terms with best sensitivity:	randomized controlled trial.pt. OR random:.tw. OR drug therapy (as a subheading of the subject) OR therapeutic use (as a subheading of the subject)
Diagnosis	
Best single term:	explode diagnosis
Combination of terms with best specificity:	explode "sensitivity and specificity" OR predictive.tw. AND value:.tw.
Combination of terms with best sensitivity:	explode "sensitivity and specificity" OR explode diagnosis (as a subheading of the subject) OR sensitivity.tw. OR specificity.tw. OR diagnostic use (as a subheading of the subject)
Prognosis	
Best single term:	explode cohort studies
Combination of terms with best specificity:	prognosis OR survival analysis
Combination of terms with best sensitivity:	incidence OR explode mortality OR follow up studies OR prognos:.tw. OR predict:.tw. OR course:.tw. OR mortality (as a subheading of the subject)
Etiology or cause	
Best single term:	risk.tw.
Combination of terms with best specificity:	cohort studies OR case–control studies
Combination of terms with best sensitivity:	explode cohort studies OR explode risk OR odds.tw. AND ratio:.tw. OR relative.tw. AND risk:.tw. OR case.tw. AND control:.tw.

Based on Haynes *et al*[8] and Wilczynski *et al*[9]

Box 5.2

1.	Heart failure, congestive	41 251	(PubMed automatically explodes MeSH terms)
2.	Meta-analysis[pt]	6123	(pt indicates publication type)
3.	Meta-anal*[tw]	9683	(tw indicates textword)
4.	Review[pt] AND medline[tw]	5156	
5.	#2 OR #3 OR #4	16 637	(the "OR" means that all citations in either #2 or #3 or #4 will be included)
6.	#1 AND #5	141	(the "AND" means that only citations that occur in both #1 and #5 will be identified)

Looking at the titles and abstracts of these articles, you find that one is a meta-analysis on β blockers, and the abstract suggests that these medications are almost certainly beneficial. You decide to go to the library to retrieve this paper,[11] and then to critically appraise it using the guidelines for a systematic review.[12]

Many alternative ways exist for conducting a MEDLINE search, including the one just displayed. Unfortunately, because no perfect recipe exists, what works well in one situation may not work as well in another. Combining an appropriate content term (HEART FAILURE, CONGESTIVE, in this case) with methods terms for reviews (as above) or

for sound study designs (as in Box 5.1) is a good place to start. It also has to be considered, however, that such searches are bound to take some time. This is because of the general nature of this huge biomedical research database: it is so large and comprehensive that even the extensive indexing and care that is taken in preparing it are insufficient to guarantee quick and accurate retrieval for clinical uses. Fortunately, many vendors have developed specialized subsets of MEDLINE for clinical use in cardiology. For example, Aries (http://www.kfinder.com) offers a cardiovascular disease subset (CardLine) on compact disc that you can subscribe to yourself. Instead of having 1 full year of MEDLINE on each CD Rom disc, these subsets provide journals and citations relating to a specific field for inclusion. For example, CardLine has cardiology citations from MEDLINE for the 10 most recent years on one disc.

Specialized clinical information resources

While large electronic bibliographic databases such as MEDLINE can be very helpful, they can also be very frustrating or overwhelming because of the different ways that articles can be indexed and because of the vast array of preclinical and non-clinical literature that is included. MEDLINE serves many user groups besides clinicians (basic scientists and other researchers, educators, librarians, journalists, etc.). An alternative is to use a resource that includes only methodologically sound and clinically relevant articles, such as *ACP Journal Club* (American College of Physicians (ACP-ASIM)), for internal medicine and its subspecialties, *Evidence-Based Medicine* (for all major specialties; from ACP-ASIM and from the BMJ Publishing Group), and the cardiology journal *Evidence-Based Cardiovascular Medicine* (published by Churchill Livingstone). These are available in both paper and electronic versions. In addition to including only methodologically sound articles[13] and presenting the results using a structured abstract format, these journals also include a commentary written by a clinical expert, designed to put the study findings into clinical context.

Searching *ACP Journal Club* (www.acpjc.org) using the text phrase "low molecular weight heparin" locates several relevant references, including one directly on target.[14] This report summarizes the findings of two randomized controlled trials comparing intravenous heparin administered in hospital with subcutaneous low molecular weight heparin administered at home, and both found that outpatient therapy was as safe and effective as inhospital management.

Other resources

The Cochrane Library is an increasingly valuable source of evidence summaries and trials of healthcare interventions. This new electronic database is updated quarterly and contains the collected work of the Cochrane Collaboration, an international voluntary organization that prepares, maintains, and disseminates systematic reviews of randomized trials of healthcare interventions. Available on CD Rom and via the internet (http://www.cochranelibrary.com), the Cochrane Library consists of three key sections for locating clinical evidence: the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effectiveness (DARE), and the Cochrane Controlled Trials Registry (CCTR). The CDSR consists of the full reports of Cochrane Collaboration systematic reviews as well as protocols for ongoing systematic reviews. DARE is produced by the UK National Health Services Center for Reviews and Dissemination located at the University of York. It contains citations to many non-Cochrane systematic reviews, and includes structured abstracts for many of them. The CCTR is a growing collection of over 320 000 citations to therapeutic intervention trials.

Searching the Cochrane Library is relatively easy and requires only entering a word or short phrase. The Library automatically searches all three sections for any relevant reviews or citations. Applying this to our scenarios, searching using the term "dilated cardiomyopathy" in Cochrane Library 2001, Issue 4, yields numerous citations: three citations to completed reviews in the CDSR, seven citations in the DARE, and 267 citations in the CCTR. The Cochrane reviews address the role of anticoagulation, antiplatelet agents, and digoxin in patients with a cardiomyopathy, and the structured abstracts within the DARE include a meta-analysis of β blocker studies.[15] Doing a similar search using the term "low molecular weight heparin" locates numerous references including a Cochrane review entitled "Home versus in-patient treatment for deep vein thrombosis".[16] This systematic review was updated in February 2001 and identified the two studies that were found earlier using *ACP Journal Club*.

Textbooks

At this point, you may be thinking about your textbooks. What role do these have in clinical practice and in particular with respect to staying current? Textbooks remain an important resource for clinicians in terms of anatomy and pathophysiology, the basics of practice that usually do not change very quickly, except perhaps for molecular biology. They also provide descriptions of the classic presentations of numerous disease conditions and review important aspects of the history, physical examination, and diagnostic testing. By reviewing conditions that may present with similar findings, a good textbook can also help to broaden the differential diagnosis in more complex cases. These references may also describe medication adverse effects and pharmacokinetics, and

may include historical perspectives and practical suggestions to assist in patient management.

Textbooks, however, are seldom explicit about the quality or currency of evidence used in recommendations for management. Also, there is often a passage of 3 or more years between updates of specialty textbooks, and new studies may have been published in the interval. Particularly for rapidly evolving aspects of management such as laboratory diagnosis and therapeutics, print textbooks simply cannot be trusted. Fortunately, we are now seeing the emergence of CD-ROM and Internet versions of textbooks with regular updates, such as UpToDate[17] and *Scientific American Medicine* (SAM).[18]

The internet

This brings us to the world wide web, an increasingly useful resource for locating current information, and one that our patients are accessing at an increasing rate. We have already mentioned how MEDLINE, *ACP Journal Club* and the Cochrane Library can be accessed over the web. A rapidly growing number of journals are also available online. A few examples include the *New England Journal of Medicine* (http://www.nejm.org), *Annals of Internal Medicine* (http://www.acponline.org), *JAMA* (http://jama.ama-assn.org), *BMJ* (http://www.bmj.com), and *The Lancet* (www. thelancet. com). A number of cardiology textbooks are also available over the internet, as are many clinical practice guidelines. Two websites that have extensive cardiology sections are the Medscape (http://www.medscape.com) and Medical Matrix (http://www.medmatrix.org) sites.

Journals and browsing to keep up to date

We have focused to this point on looking for evidence when it is needed. If the search is successful, the evidence can be applied immediately and this can be a powerful learning experience. But what if we don't search for evidence because we don't know that we are out of date? A complementary strategy is needed, browsing the medical literature regularly in one way or another. The difficulty is that so many journals include articles relevant to cardiology that it is impracticable to review them all. One of the best solutions is to subscribe to a journal such as *Evidence-Based Cardiovascular Medicine* that continuously scans a wide range of journals in a systematic way, according to explicit criteria, and includes structured abstracts and commentaries on methodologically sound and clinically relevant studies.

Conclusion

In summary, while the time that we devote to updating ourselves with new developments is limited, a growing number of easy-access resources are available so that we can use this time effectively. MEDLINE is more readily available now than ever, and is seeding the development of specialty-specific collections. Journals that abstract only high-quality, clinically relevant articles are appearing, and systematic reviews are becoming the norm. Internet-accessible textbooks that are regularly updated are also becoming available. Applying these resources to clinical care on an ongoing basis after appraising the quality of information and considering how it relates to our individual patient's circumstances can lead to improvements in the quality of care we provide.

Key points

- New resources are rapidly emerging that make keeping up to date with clinically significant developments in cardiology easier than ever.
- Large bibliographic databases, such as MEDLINE, are becoming more accessible to practicing physicians, and search strategies for locating high quality studies are now available.
- Specialty journals, such as *Evidence-Based Cardiovascular Medicine*, that identify and abstract methodologically sound and clinically relevant studies, also facilitate the ongoing process of staying current.

References

1. Covell DG, Uman GC, Manning PR. Information needs in office practice: are they being met? *Ann Intern Med* 1985; **103**:596–9.
2. Osherof JA, Forsythe DE, Buchanan BG *et al.* Physicians' information needs: analysis of questions posed during clinical teaching. *Ann Intern Med* 1991;**114**:576–81.
3. McKibbon KA, Walker-Dilks CJ, Beyond *ACP Journal Club*: how to harness MEDLINE to solve clinical problems (Editorial). *ACP J Club* 1994;**120**:A10–12.
4. Haynes RB, Walker CJ, McKibbon KA, Johnston M, Willan A. Performance of 27 MEDLINE systems tested by searches on clinical questions. *J Am Med Informatics Assoc* 1994;**1**: 285–95.
5. Engstrom P. MEDLINE free-for-all spurs questions about search value: who pays? *Medicine on the NET* 1996;**2**:1–5.
6. Haynes RB, McKibbon KA, Walker CJ *et al.* Online access to MEDLINE in clinical settings. A study of use and usefulness. *Ann Intern Med* 1990;**112**:78–84.
7. Sackett DL, Richardson SR, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practise and teach EBM.* London: Churchill Livingstone, 1997.
8. Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Informatics Assoc* 1994;**1**:447–58.
9. Wilczynski NL, MWalker CJ, McKibbon KA, Haynes RB. Assessment of methodological search filters in MEDLINE. *Proc Ann Symp Comp Appl Med Care* 1994;**17**:601–5.

10.Hunt DL, McKibbon KA. Locating and appraising systematic reviews. *Ann Intern Med* 1997;**126**:532–8.
11.Brophy JM, Joseph L, Rouleau JL. β-blockers in congestive heart failure. A bayesian meta-analysis. *Ann Intern Med* 2001;**134**:550–60.
12.Oxman A, Cook D, Guyatt G. Users' guides to the medical literature. VI. How to use an overview. *JAMA* 1994;**272**:1367–71.
13.Haynes RB. The origins and aspirations of *ACP Journal Club* (Editorial). *ACP J Club* 1991;**114**:A18.
14.Low-molecular-weight heparin at home was as effective as unfractionated heparin in the hospital in proximal DVT (Abstracts). *ACP J Club* 1996;**125**:2–3. [Abstracts of Koopman MM, Prandoni P, Piovella F *et al.* Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996; **334**:682–7; and Levine M, Gent M, Hirsh J *et al.* A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;**334**:677–81.]
15.Zarembsk DG, Nolan PE Jr, Slack MK, Lui CY. Meta-analysis of the use of low-dose beta-adrenergic blocking therapy in idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 1996;**77**:1247–50.
16.Schraibman IG, Milne AA, Royle EM. Home versus in-patient treatment for deep vein thrombosis (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2001. Oxford: Update Software.
17.Rose BD, ed. *UpToDate*. Wellesley, MA: UpToDate, Inc., 2001.
18.Dale DC, Federman DD, eds. *Scientific American Medicine*. New York: Scientific American Medicine, 1978–97.

6 Understanding concepts related to health economics

Mark Hlatky

Introduction

Economics is concerned with how to allocate scarce resources among alternative uses efficiently and effectively. It is a fundamental principle of economics that resources are limited relative to human wants, and that those resources have alternative uses.[1] Consequently, when people say that the cost of health care has grown too high, they mean that the quantity of resources flowing toward medical care has grown to the point where additional funds cannot be spent on other things that society values, such as education, public safety, environmental protection, public works, pensions for the retired or disabled, or assistance to the poor. The fact that most people put a very high value on health does not mean that they are willing to provide limitless resources to medical care. Indeed, even the goal of improving health and longevity may also be served by non-medical expenditures on programs such as nutritional supplements, a safe and clean water supply, police and fire protection, or safety improvements to roads, as well as by medical expenditures.

The cost of medical care has been rising steadily for the past 50 years, but it has only been in the past decade that the level of expenditures became so large as to cause alarm among policy makers, payers, and the general public (Table 6.1). The steady expansion of health care has now begun to meet substantial resistance in the large industrial countries, and new policies and payment mechanisms have been introduced to contain the rising cost of medical care. As a consequence, physicians must now consider cost as they design programs to prevent, diagnose, and treat disease. Cardiovascular diseases consume a large share of health care resources (Table 6.2), so cardiovascular specialists must be particularly knowledgeable about health economics. This chapter will attempt to outline the major principles of health economics relevant to cardiovascular medicine. First, some general concepts of health economics will be presented. Second, methods to identify and compare the costs of cardiovascular interventions will be described. Finally, the principles of cost effectiveness analysis will be discussed.

Table 6.1 US national healthcare expenditures, 2000

Category	US$ ($\times 10^9$)	Percentage
Hospital care	412·1	32
Physician services	286·4	22
Other professional services	99·0	8
Drugs, supplies	171·5	13
Nursing home care	92·2	7
Home health care	32·4	2
Other personal health care	36·7	3
Administration	80·9	6
Public health	44·2	3
Research	25·3	2
Construction	18·6	1
Total	1299·5	100

Source: *Health Affairs* 2002;**21**:207–18

Table 6.2 Resources devoted to cardiovascular care in the USA

Category	*n* ($\times 10^3$)	Percentage (of total)
Deaths[a]	934	39
Hospital admissions[b]	6344	20
Myocardial infarction	829	
Heart failure	962	
Cerebrovascular disease	961	
Operations and procedures[b]	6133	15
Cardiac catheterization	1271	
Coronary bypass surgery	355	
Coronary angioplasty	599	
Pacemaker-related	336	
Physician office visits[c]	59 996	8
Electrocardiograms	22 596	
Prescriptions[c]	176 839	16

Sources: [a] NCHS Monthly Vital Statistics Report 2001; **49**:12
[b] NCHS Advance Data 2001 (No. 319)
[c] NCHS Advance Data 2001 (No. 322)

General concepts

Various societies have adopted different systems to pay for health care, and these systems reflect societal values and the historical experience within each country. The United Kingdom has a national health service, Canada has national health insurance, France and Germany have public/private financing for health care, and the United States has a perplexing and rapidly evolving patchwork of public and private health insurance systems. These are very different systems to finance health care, and yet each is faced with the same issues of how to allocate the limited resources available to best provide health care. Each country is also facing the same steady rise of healthcare costs, despite the wide differences in the ways they finance health care.

Provision of cardiovascular services requires resources in all societies, irrespective of the method of financing or delivering health care. Coronary bypass surgery, for example, is very resource-intensive, with the operation requiring cardiac surgeons, a cardiac anesthesiologist or anesthetist, a perfusionist, several nurses, and considerable quantities of specialized supplies and equipment. Postoperative care also requires skilled nurses and physicians, with support from specialized supplies, equipment, and facilities. Each health professional involved in cardiac surgery spends the scarce resource of time to care for the patient – time that could be put to other valuable uses, such as care for other patients. The drugs used, the disposable supplies, the operating room equipment, even the hospital building, all cost money. All of these are true costs to the system, even if the coronary bypass operation is performed "for free" – that is, without charge to the patient. The scene in the operating room, the postoperative recovery areas, and the hospital wards is much the same in the United Kingdom, Canada, France, Germany, and the United States despite the different ways these societies pay for medical care. The resources used in the care of patients, and the increasing sophistication of that care, drive healthcare costs up in each of these countries, irrespective of the way such care is paid for.

Another basic concept of economics is the so-called "law of diminishing returns". This concept is illustrated in Figure 6.1, in which the quantity of resources used in health care is plotted on the horizontal axis, and the resulting health benefits on the vertical axis. In the case of the patient with an acute myocardial infarction, for example, survival would be improved as more resources are applied, such as prehospital transportation, electrocardiographic monitoring, access to defibrillation, and a competent team to deliver coronary care. Outcomes might be further improved by reperfusion therapy, but with a greater increment in survival from using a cheaper, basic approach (streptokinase, for example) relative to no therapy, than from more expensive alternatives (such as tissue plasminogen activator (tPA) or PTCA). The extra benefit from adding even more aggressive care will be smaller still, and at some point the patient may be harmed by overly aggressive care. Helping physicians define the optimal point on this curve (Figure 6.1) is one of the goals of economic analysis.

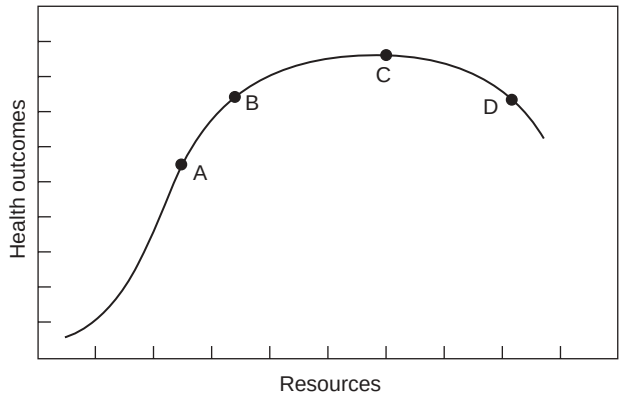

Figure 6.1 General relationship between increasing healthcare resources (horizontal axis) and health outcomes (vertical axis). At point A, outcomes are improving rapidly with increased resources and treatment is cost effective. At point B, outcomes are still improving with increased resources, but at a rate that is not cost effective. At point C, increased resources are no longer improving outcome (that is, "flat of the curve"), and at point D increased resources actually lead to worse outcomes, through iatrogenic complications and overtreatment.

Determination of costs

The cost of producing a particular healthcare service can be defined in a variety of ways. The cost of performing a coronary angiogram can be used as a specific example that will illustrate the various aspects of cost and how the cost might be measured. Performing a coronary angiogram requires a variety of resources, including radiographic equipment, trained personnel (including an angiographer and technical assistants), and specialized supplies such as catheters, radiographic contrast, and sterile drapes. The equipment needed is very expensive to purchase, and the healthcare facility where it is installed may require special renovations to assure proper radiation shielding and adequate electrical power. The capital cost for a coronary angiography laboratory will be considerable, perhaps $2–3 million, depending on the type of equipment purchased. The laboratory will have a physical lifespan of perhaps 7–10 years, although technologic innovations may lead to replacement of the equipment before the end of its physical lifespan. The cost of building an angiography suite represents a large *fixed cost* for coronary angiography, a cost that is roughly the same whether the laboratory performs 200 or 2000 angiograms per year. The cost per case is lower in the high volume laboratory, however, because the fixed equipment costs can be spread over more cases. Thus, if the equipment costs

$2·5 million and has a useful life of 10 years, the prorated share of fixed costs for each patient in the low volume laboratory performing 200 cases per year is

$$\text{Fixed costs/case} = \frac{\$2\,500\,000}{(200\ \text{cases/yr})(10\ \text{years})} = \$1250/\text{case}$$

whereas in the high volume laboratory (2000 cases per year) the prorated share of fixed costs per case would be

$$\text{Fixed costs/case} = \frac{\$2\,500\,000}{(2000\ \text{cases/yr})(10\ \text{years})} = \$125/\text{case}$$

Procedures that have high fixed costs will be performed with greater economic efficiency in centers that have sufficient volume to spread those fixed costs over a larger number of individual patients. (There may be additional advantages to larger procedure volumes as well, since the technical proficiency is higher and clinical outcomes of many procedures are usually better when performed in higher volume clinical centers.)[2–4] Procedures with lower fixed costs will have a smaller effect of volume on costs.

In contrast to the fixed equipment costs, the cost of supplies consumed in performing coronary angiography varies directly with the volume of cases performed, and the supply cost per case will be fairly constant irrespective of the volume of cases performed (apart from the small effect of discounts available to large volume purchasers). The cost of laboratory staff falls in between these two extremes, in that the hours worked in the catheterization laboratory by technical staff can be varied somewhat according to the volume of cases performed, but some staff effort is required regardless of patient volumes, such as supervisors.

Hospital overhead is also a real cost, but one that is less directly linked to any one medical service or procedure. Hospitals must pay for admitting offices, the medical records department, central administration, the laundry service, the cafeteria, housekeeping and utilities, to name just a few areas. These costs cannot be tied easily to the coronary angiography procedure in the same way as the cost of the catheters or radiographic contrast. Most facilities assign a share of these costs to patient care services according to a formula such as the step down method. Discussion of specific methods to allocate hospital overhead is beyond the scope of this chapter, but can be found in several articles and books.[5,6]

The overall effect of procedure volume on the cost per case is illustrated in Figure 6.2. In general, the cost per case declines as more cases are performed, up to the limit of the facility's capacity (for example, 2000 cases). If volume increases further, more facilities must be built, increasing the cost per case, as more fixed costs are spread over a few more patients. Figure 6.2 also illustrates the distinction between concepts of "marginal cost" and long run "average cost". The marginal cost is the added cost of doing one more case. In an already equipped and staffed coronary angiography laboratory, the marginal cost of performing one more procedure is just the cost of the disposable supplies consumed in the case: the catheters, radiographic contrast, and other sterile supplies. In the example of Figure 6.2, the marginal cost is $250 per case. The marginal cost is lower than the average cost per case ($375 per case), which also includes a prorated share of the salaries of the laboratory staff, depreciation of the laboratory equipment costs, and the facility's overhead costs.

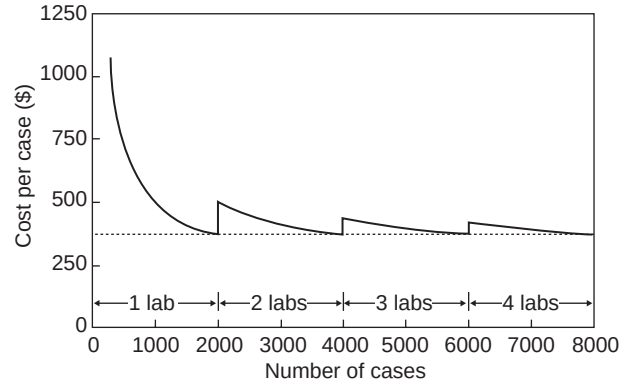

Figure 6.2 Cost per case for coronary angiography as a function of clinical volume. Assumes fixed costs per laboratory of $250 000 per year, and marginal (that is, variable) costs of $250 per case. When volume reaches 2000 cases per year in a laboratory, the model assumes an additional laboratory will be built. The dotted line indicates the "long run average" cost per case of $375.

Costs *v* charges

Costs and charges are related but distinct concepts. The cost of a medical service represents the value of the resources required to produce it. The charge for a service is a specific form of reimbursement to healthcare providers in a fee-for-service healthcare system. The cost and charge for providing a service should be quite close to one another in a competitive economic market. The reason is simple: if one provider charged an amount much higher than it actually cost to provide a service, a competitor could offer the same service at a lower price and still come out ahead. Conversely, if a provider charged less than the costs of production, the provider would lose money. These basic economic principles have not applied very well to medical care, at least until recently, because medical care has not had significant competition on prices.

In regulated or non-price competitive healthcare systems, the charge (price) for a service need not bear a close relationship to the cost of producing a service. Hospitals might choose to set high prices for some services, such as coronary bypass surgery, and use the excess revenues to subsidize other services that were less well reimbursed, such as the emergency department or, in academic centers,

medical education, and research. With greater price sensitivity on the part of healthcare payers, the subsidization of one medical service with the proceeds of another service has been sharply curtailed. While this trend has had the positive effect of bringing an element of economic reality to medicine, it has also caused dislocations and considerable harm as worthwhile endeavors have lost the funding they previously enjoyed from cross-subsidization. In the long run, medical education, clinical research, and services to uninsured or poorly insured patients should receive direct funding to replace the indirect funding by cross-subsidies, but in the transition these endeavors have been threatened due to loss of a traditional funding base.

Estimation of costs

The cost of providing a specific service, such as coronary bypass surgery, can be established in several alternative ways. In principle, one valid way to measure cost would be to identify a competitive market for medical service, and note the charge (price) for coronary bypass surgery in that market. While competitive market pricing might work well for commodities such as consumer electronic devices or farm products, it is not well suited to medical care, where there are few competitive markets. An alternative method to measure cost is to take note of the charge for a service, and apply correction factors to estimate cost more accurately. A third method to estimate costs is to examine in detail the resources used to provide a service, and apply price weights to the resources used:

$$\text{Cost}_j = \sum_i (\text{Quantity})_{ij} \times (\text{Price})_{ij}$$

The use of these different approaches to cost determination is illustrated by a study that estimated the costs savings achievable by substituting coronary angioplasty for coronary bypass surgery.[7] In that study, hospital billing records were used to construct resource consumption profiles for patients undergoing either angioplasty or bypass surgery for the treatment of stable angina. A microcosting approach was then applied to the resource consumption profiles, with the cost of a specific resource (for example, an electrocardiogram) defined either as the cost of supplies only (marginal cost or variable cost) or as the cost of supplies, personnel and equipment, but omitting overhead (average direct cost). Charges on the billing record for a service were also converted to costs by two different correction factors, also known as ratios of cost to charges. One cost–charge ratio included all direct costs of providing a service (supplies, personnel, and equipment), but omitted hospital overhead (for example, medical records, laundry, utilities, administration). The second cost–charge ratio allocated a share of hospital overhead to each service in addition to its direct costs.

As shown in Table 6.3, the cost savings attributable to substitution of angioplasty for bypass surgery varied considerably according to how costs were defined. The lowest cost savings are evident when only marginal costs are included, and fixed cost and overhead excluded. The average direct cost difference is intermediate in value, and comparable estimates of this cost savings were obtained from the use of resource consumption profiles and cost weights (method 2) or the cost-to-charge ratio method that omitted overhead (method 3). Finally, the inclusion of overhead (method 4) led to the highest absolute difference in costs.

The differences in cost as estimated using these methods is directly related to the issue of how the information is to be used or, put another way, depends on the answer to the question, "cost to whom?". A hospital manager might be most interested in the marginal cost of procedures (method 1) in looking at the effect of adding or subtracting a small number of cases to the volume performed in an institution. Under a fixed budget for cardiac services, for instance, the effect of substituting angioplasty for bypass surgery may be small, given that the personnel, equipment, and overhead are largely fixed. Performing a few extra procedures with existing facilities adds very little cost from the perspective of the

Table 6.3 Effect of different definitions of cost on the savings possible by substitution of coronary angioplasty for bypass surgery

Definition of cost	PTCA cost ($)	CABG cost ($)	Difference ($)	PTCA/CABG ratio (%)
Variable cost only	2672	4607	1935	58
Average direct cost				
By microcosting	4073	8666	4593	47
By ratio of cost-to-charges	4935	10 281	5346	48
Average cost + overhead	7530	15 367	7837	49
Charges	9556	19 644	10 088	49

Source: adapted from Hlatky *et al*[7]

head of a clinical service or a hospital manager. They may even be willing to perform a modest number of additional cases at a reimbursement level below their actual average cost, but above marginal cost, in order to increase volume and spread their fixed costs over more patients. Thus, marginal or variable costs are quite relevant to decision makers within the institution providing a service.

The perspective of a policy maker or health planner includes a longer time horizon and the possibility of adding or subtracting substantial volumes of clinical services. From this perspective, no cost is truly fixed, for personnel needs can be adjusted, and the number of facilities providing a service can be altered. This perspective is a broader one, and the costs considered are therefore more inclusive. For most policy level discussions, long run average cost is the most relevant measure.

International perspectives

With the advent of large multicenter clinical trials that enroll patients from several countries, interest has developed in cost comparisons between countries for the same service. Cost estimation as part of large randomized trials will enhance clinical decision making, for the randomized design is the strongest way to compare all outcomes of therapeutic alternatives, including cost. Extension of cost comparisons across national borders introduces a number of technical and conceptual issues that deserve discussion.

Different countries measure cost in their respective national currencies, so that readers in another country need to convert between units (for example, pounds sterling or euros to US dollars). These conversions can be done using currency exchange rates, or the closely related purchasing power parity factors. The differences between countries in units of measurement are important, but this issue is fairly simple to address.

A more thorny issue in international comparisons is differences in the relative prices of the resources used to provide a service and differences in resource profiles used to provide a service. Thus, if the cost of service *j* is defined as

$$\text{Cost}_j = \sum_i (\text{Quantity})_{ij} \times (\text{Price})_{ij}$$

then cost may differ among countries due to either differences in the quantity of resources used to provide a service, price differentials for the same resources, or both. A specific example will help illustrate these concepts (Table 6.4). Care of a patient with acute myocardial infarction given thrombolysis includes the cost of the drug, the cost of basic hospital care, and the cost of additional tests and treatments in the convalescent phase. Table 6.4 presents hypothetical costs of basic care in two countries, with monetary values expressed in dollar units for simplicity. The costs of drugs in Country 1 are higher than in Country 2, where drug prices are strictly regulated. The time spent by the hospital staff to care for the patient are quite similar in Country 1 and Country 2 (50 hours per patient for Treatment A and 54 for Treatment B, a difference due to lower complication rates with Treatment A). The average hourly compensation for hospital staff is, however, higher in Country 2, so that total personnel costs are higher as well. Thus, both cost savings and the relative costs of Treatment A and B are different in these two healthcare systems, due to different prices for the same resources used to care for a myocardial infarct patient.

There may also be differences in the level of resource use between countries, especially for discretionary procedures such as coronary angiography. Suppose that the use of Treatment A cuts the use of coronary angiography by one third, partially offsetting the higher cost of the drug. If, however, the baseline rates of angiography are different between countries, the cost implications of reducing angiography by one third in each country will be quite different (Table 6.5). A reduction by one third in the high rate of angiography in Country 1 (from 60% to 40%) provides a $200 cost offset per patient, whereas a reduction by one third in the low rate of angiography in Country 2 (from 20% to 15%) provides only a $50 cost offset per patient.

International comparisons of the cost of therapies can thus be affected by (a) differences in resource use patterns that reflect differences in practice style and the organization

Table 6.4 Effect of differences in medical prices on costs of alternative treatments

	Country 1		Country 2	
	Tx A	Tx B	Tx A	Tx B
Drug ($)	2000	200	1500	150
Nursing hours	50	54	50	54
Nursing wages ($)	30	30	35	35
Total ($)	3500	1820	3250	2040
Cost savings (A−B) ($)	1680		1210	
Cost ratio B/A	52%		63%	

Abbreviation: Tx, treatment

Table 6.5 Effect of differences in resource utilization on costs of alternative treatments

	Country 1		Country 2	
	Tx A	Tx B	Tx A	Tx B
Drug/nursing ($)	3500	1820	3250	2040
Coronary angiography	40%	60%	10%	15%
Angio cost ($)	1000	1000	1000	1000
Total ($)	3900	2420	3350	2190
Cost savings (A−B) ($)	1480		1160	
Cost ratio (B/A)	62%		65%	

Abbreviation: Tx, treatment

of medical care, and (b) by differences between countries in the prices attached to specific resources, such as healthcare wages, drugs, and supplies. Data from cost studies can be most readily applied in different practice environments if the study provides information on both resource consumption patterns and price weights attached to the specific resources used, as well as a summary cost measure. This detail is needed for readers to understand the applicability of the cost findings to their own practice settings.

Cost effectiveness analysis

The cost of providing a particular medical service can be measured, but determination of whether the service provides good value for the money spent is a more difficult judgment. Cost effectiveness analysis is a method of weighing the cost of a service in light of the health effects it confers in an attempt to facilitate the ultimate value judgment about whether the service is "worth" the cost.

Cost effectiveness analysis is one of several alternative analytic methods, each with its own strengths and limitations.[5] If two alternative therapies are either known to yield identical results or can be shown to be clinically equivalent, they can be compared on the basis of cost alone. This form of analysis, which is termed "cost-minimization analysis", is particularly appropriate to commodities such as drugs, supplies, and equipment that can be expected to yield equivalent results when applied clinically. In such situations, the relative costs of the alternatives become the predominant consideration.

Many alternative therapies are known to differ both in clinical outcomes and in cost. In this situation, both the difference in cost and the difference in effectiveness of the therapeutic alternatives must be measured and weighed against each other. When the effectiveness on intervention is measured in clinical terms (for example, lives saved, years of life added), the analysis is termed "cost effectiveness". If the clinical measures of effectiveness are translated into monetary units, the term "cost–benefit analysis" is applied. Cost–benefit analysis has been used to guide public policy in areas outside of medicine, such as in the construction of transportation systems or whether to remove or reduce environmental exposures. Cost–benefit analysis measures the effects of programs in monetary terms, so that net cost (in dollars) can be compared with net benefits (in dollars). Since there is great reluctance on the part of physicians and health policy makers to assign a dollar value to saving a life or improving a patient's function, cost effectiveness analysis rather than cost–benefit analysis has been applied predominantly to medical problems.

Cost effectiveness analysis was first applied to medical programs only 25 years ago[8,9] and has since been widely used.[10–12] The principles of cost effectiveness analysis for medical programs have recently been examined in detail by a Task Force convened by the United States Public Health Service.[13–15] A group of experts attempted to establish consensus on a number of methodologic issues, with the goal of standardizing the technical aspects of cost effectiveness analysis among studies, thereby enhancing their comparability. The principles articulated by this group are reasonable, and should guide this important field in its next 20 years.

A basic principle of cost effectiveness analysis is that the analysis should compare alternative programs, and not look at any single program in isolation. Thus, a drug to treat life-threatening arrhythmias might be compared with placebo, or an implantable cardioverter defibrillator might be compared with a drug. In essence, cost effectiveness analysis must always answer the question "cost effective compared with what?".

Another principle is that the costs included in cost effectiveness analysis should be comprehensive. The cost of a specific therapy should include the cost of the intervention itself (for example, thrombolytic therapy for acute myocardial infarction) and the costs of any complications the therapy induced (for example, bleeding), less any cost savings due to reduction of complications (such as, heart failure). The need for other concomitant therapy should also be included, which is particularly important when assessing the cost effectiveness of screening programs or diagnostic testing strategies.

The length of follow up should be sufficient to include all relevant costs and benefits – such as readmissions to the hospital due to treatment failures. Non-monetary costs directly related to the medical intervention should also be included, such as the cost of home care by the patient's family, since omission of these costs would bias assessments toward programs that rely on unpaid work by family members or volunteers. Other costs not directly related to the intervention, however, such as the patient's lost wages or pension costs, are omitted by convention from the measured costs in a cost effectiveness analysis.

Another important issue in cost effectiveness analysis is the perspective taken by the analysis. There is general agreement that the analysis should include all relevant costs, regardless of who pays them. This principle is known as "taking the societal perspective", and it assures a complete accounting of costs in the analysis. A hospital, for instance, may not care about the out of pocket costs paid directly by the patient, but these are real costs and should be considered in the analysis.

Medical costs may accrue over long periods of time, especially in preventive programs or the treatment of chronic disease. Time scales of more than a year or so bring up two related but distinct issues – inflation and discounting. The nominal value of any currency changes over time; a dollar in 1977 had more purchasing power than a dollar in 1997. Studies conducted over long time periods will need to correct for the changing value of currencies, typically by application of the Consumer Price Index (or the GDP deflator). Application of the Consumer Price Index removes the effect of inflation, but does not address the separate issue of time preference for money. Even in a country free of inflation, citizens would prefer to receive $100 today than a promise they will be paid $100 in a year. One might have to promise to pay more money in a year, say $103, to compensate for the delay. The same is true in health programs: we would prefer to be paid today instead of in the future, and we would also prefer to pay our obligations in the future rather than today. Use of a discount rate provides a way to correct for the lower value of future costs relative to current costs. The technical experts' consensus is that future costs should be discounted at a rate equivalent to the interest paid on safe investments such as government bonds in an inflation-free environment, or about 3% per year. The effect of alternative discount rates between 0% and 5–10% per year should also be checked to document the sensitivity of the analysis to future costs.

In summary, a cost effectiveness analysis should include all medical costs, including those of complications of therapy and adverse effects prevented. The study should be of sufficient duration to measure all relevant costs and benefits of the treatment. All costs and benefits should be included, regardless of who bears or receives them. In studies covering more than a year or so, corrections should be made for inflation, and 3% per year discount rate should be applied to follow up costs.

Measuring effectiveness

The effectiveness of an intervention in practice can be measured in a variety of ways, with different outcome measures most appropriate for specific applications. Physiologic end points are often used in clinical trials, with the result of therapy assessed by a laboratory measure such as millimeters of mercury for blood pressure or episodes of non-sustained ventricular tachycardia on an electrocardiographic monitor. Laboratory measures are useful in judging the physiologic effects of therapy and its mechanism of action, but these surrogate markers may not predict the ultimate effect of therapy on mortality and morbidity, as vividly illustrated by the results of the Cardiac Arrhythmia Suppression Trial (CAST).[16] Physiologic end points are also tied closely to one specific disease, making comparisons against other benchmark therapies difficult. The patient and public are most concerned with the effect of therapy on survival and on their ability to function – that is, upon the length of life and the quality of life. A common denominator measure of effectiveness is thus the life years of expected survival, or the quality adjusted life years (QALYs). This measure is relevant to patients and to the public and can be applied to virtually any therapy.

Mortality is a common end point in clinical trials, and leads directly to the measure of life years of survival. The mean life expectancy of a cohort of patients is equal to the area under a standard survival curve. The difference in life expectancy between two therapies is therefore equal to the difference in the areas under their respective survival curves. Since many clinical studies do not follow patient cohorts long enough to observe complete survival times for all patients, some assumptions and modeling of long-term survival may be needed to estimate the full survival benefit of therapy for a cost effectiveness analysis.[17]

Improvement in quality of life is often as important to patients as reducing mortality, and it is often the main goal of therapies, such as the relief of disabling angina or improvement in exercise tolerance. A quality of life measure can be translated into a scale that ranges from a low of 0·0 (the worst possible health state, usually taken as death) to 1·0 (perfect health). This quality of life measure is multiplied by the length of time a patient spends in the health state to yield a quality adjusted life year (QALY). Thus:

$$\text{QALY} = \sum_{i} Q_i \times t_i$$

where QALY = the quality adjusted life years, Q_i = the quality factor for follow up period "i" and t_i = the length of time spent in period "i". This equation shows that the effectiveness of a treatment, as measured in QALYs, can be improved

by either enhancing the patient's quality of life (Q_i) or the patient's length of life (t_i), or both.

Calculation of cost effectiveness

After the costs of therapy and the medical effectiveness of therapy have been assessed, cost effectiveness (CE) can be calculated as:

$$\text{CE ratio} = \frac{\text{Cost}_2 - \text{Cost}_1}{\text{QALY}_2 - \text{QALY}_1}$$

where Cost_1 and Cost_2 represent the costs of program 1 and program 2, respectively, and QALY_1 and QALY_2 represent the effectiveness of programs 1 and 2, respectively.

There are several implications of using this formula. First, cost effectiveness ratios that are positive (that is, >0) result if and only if one alternative has both higher cost and greater effectiveness – that is, $\text{Cost}_2 > \text{Cost}_1$ and $\text{QALY}_2 > \text{QALY}_1$ (or the reverse: $\text{Cost}_2 < \text{Cost}_1$ and $\text{QALY}_2 < \text{QALY}_1$). Cost effectiveness ratios of <0 are not generally important for decision making, since they arise only when one alternative has both lower costs and greater clinical effectiveness than the other (for example, $\text{Cost}_2 > \text{Cost}_1$, and $\text{QALY}_2 < \text{QALY}_1$). In this case, program 1 is superior in all respects: it has better outcomes and lower cost than program 2, and thus is said to "dominate" the alternative. The decision of which program to recommend is therefore simple.

Another important implication of the formula used to calculate cost effectiveness is that the ratio is undefined when the two alternatives provide equal outcomes, since when $\text{QALY}_2 = \text{QALY}_1$ the denominator in the cost effectiveness ratio is equal to zero. The implication is that when the difference in outcomes between two programs is negligible, cost effectiveness analysis is unnecessary, and the choice between two alternatives can be based on cost alone (that is, cost minimization analysis is more appropriate than cost effectiveness analysis).

Most commonly, one of two therapeutic alternatives has higher costs and greater effectiveness, and use of the formula yields a cost effectiveness ratio greater than zero. One treatment may have a cost effectiveness ratio of $5000 per year of life saved, and another might have a ratio of $75 000 per year of life saved. Since it is problematic to assign a dollar value to life, interpretation of these ratios is best made by consideration of benchmarks – other generally accepted therapies that serve as a rough gauge to an "acceptable" cost effectiveness ratio. Renal dialysis is a form of therapy that most people would consider expensive, and yet dialysis is an intervention that the USA and most other industrialized countries provide as a life saving therapy. The end stage renal disease program in the USA costs about $35 000 a year per patient, and if this therapy were withdrawn the patient would die. Thus, renal dialysis has a cost effectiveness ratio of $35 000 per year of life saved (or if one considers the reduced quality of life for a dialysis patient, perhaps $50 000 per quality adjusted year of life saved). Therapies with cost effectiveness ratios considerably more favorable than renal dialysis (that is, $<$$20 000) would be considered very cost effective, whereas therapies with cost effective ratios much higher (say $>$$75 000) would be considered too expensive.

Different societies may come to different conclusions about the level of cost effectiveness they consider good value. Wealthy countries with high per capita incomes are more willing to pay for expensive therapies than are poor countries. For instance, the percentage of gross domestic product and per capita health spending in Eastern Europe is much less than in Western Europe or North America, and these countries have not chosen to provide expensive services such as bypass surgery as readily or as frequently.

Decisions about funding programs might be more equitable and rational when guided by the relative cost effectiveness of programs. When studies use similar methods to measure cost and effectiveness, cost effectiveness ratios can be compared to rank the economic attractiveness of alternatives. Tables comparing various treatments, such as Table 6.6, have been termed "league tables" because of their similarity to the athletic league standings published in newspapers. Given the uncertainty inherent in measuring cost and effectiveness of medical interventions, and the methodologic variations among studies, only relatively large differences in cost effectiveness ratios should be considered significant. Thus, a program with a cost effectiveness ratio of $5000 per life year added is much better than one with a ratio of $30 000. Programs with ratios of $25 000 and $30 000 are so close that no firm conclusion about the relative values should be drawn.

Patient selection and cost effectiveness

Drugs and procedures in medicine are applied to different patient groups for different clinical indications. The medical effectiveness of therapies varies considerably according to patient selection. Cholesterol lowering therapy, for instance, will extend the life expectancy of a patient with multiple cardiac risk factors more than it will for a patient with the same cholesterol level and no other cardiac risk factors. Coronary bypass surgery provides greater life extension to a patient with left main coronary artery obstruction than it does to a patient with single vessel disease.[18] The cost effectiveness ratio for these therapies will therefore vary among patient subgroups due to the impact of patient characteristics on the clinical effectiveness of therapy, which forms the denominator of the cost effectiveness ratio. Similarly, the cost of a particular therapy may also vary according to patient characteristics, since the therapy itself may be more

Table 6.6 Cost effectiveness of selected cardiovascular therapies

Strategy	Patient group	Cost effectiveness[a]
Lovastatin	Post MI Men 45–54 Chol ≥ 250	Saves dollars and lives
Enalapril	CHF EF < 35%	Saves dollars and lives
Radio frequency ablation	WPW, post cardiac arrest	Saves dollars and lives
Physician counseling	Smoking	$1300
β blocker	Post-MI High-risk	$3600
CABG	Left main CAD Severe angina	$9200
β blocker	Post-MI Low-risk	$20 200
Lovastatin	Primary prevention Men 55–64 Chol > 300 Three risk factors	$20 200
tPA	Acute MI	$32 800
ICD	Sustained VT	$35 000
CABG	Two vessel CAD Angina	$42 500
Lovastatin	Primary prevention Men 55–64 Chol > 300 No other risk factors	$78 300
Exercise ECG	Asymptomatic 40 year old men	$124 400
CABG	Single vessel CAD Mild angina	$1 142 000
Lovastatin	Primary prevention 35–44 year old women Chol > 300 No other risk factors	$2 024 800

[a] $ values, dollars per year of life added.
Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; Chol, Cholesterol; ICD implantable defibrillator; MI, myocardial infarction; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome; See glossary for other abbreviations
Source: adapted from Kupersmith *et al.*[10–12]

or less expensive according to different patient subgroups, or the likelihood of costly complications may be higher or lower in different groups of patients.

The clinical effectiveness of a therapy is generally the most important factor determining cost effectiveness. The reason for this importance is (a) that clinical effectiveness of a therapy generally varies more among patients than does the cost of therapy, and (b) the value of the cost effectiveness ratio is more sensitive to changes in the denominator (effectiveness) than to changes in numerator (cost). In the last analysis, a therapy must be clinically effective before it can be cost effective. Cost effectiveness analysis relies more on the assessment of medical effectiveness than it does on determination of cost.

Diagnostic tests and cost effectiveness

Cost effectiveness analysis has been applied primarily to assess specific therapies or therapeutic strategies, for which it is natural to measure effectiveness in terms of patient outcome. The principles of cost effectiveness can be extended to analyze screening tests and diagnostic strategies as well, but some additional factors must also be considered.

Therapies are expected to improve patient outcome *directly*, by intervening in the pathophysiology of disease processes. In contrast, a diagnostic test is expected to provide the physician with information about the patient, which in turn is expected to improve management and thereby *indirectly* improve patient outcome. The value of a test is therefore linked closely with patient selection for therapy, and the value of testing may well change as new therapies are developed, or alternative tests become available.

The information provided by a test may be used in different decisions, and the test may be more or less useful in these different settings. An exercise electrocardiogram, for example, can be used as a diagnostic test for coronary disease, a prognostic test for patients with recent myocardial infarction, a monitoring test to assess the effect of antiischemic therapy, or even as a way to establish target heart rates for an exercise training program. The efficacy and cost effectiveness of applying the exercise electrocardiogram will be different for these varied uses of the information provided by the test. The value of the test will depend on the indication for which it is used, much as the value of a β blocker will vary whether it is used to treat hypertension or as secondary prevention after a myocardial infarction.

The same test (for example, the exercise ECG) applied for the same purpose (such as diagnosis of coronary disease) will provide more information in some groups of patients than in others. As discussed elsewhere in this book, a diagnostic test provides more value if used when the pretest probability of disease is intermediate than when the pretest probability is either very high or very low. The test has the most value when the result is likely to change the estimated probability of disease such that clinical management is changed. Tests that never change patient management cannot change patient outcome, which is the "bottom line" in assessing cost effectiveness.

Conclusions

Economic analysis is designed to assist decisions about the allocation of scarce resources. Physicians now must address the cost implications of clinical decisions, and be aware of the effects on scarce resources. Economic efficiency is but one of many goals, however, and issues of fairness and humaneness are also central to medical care, and must be considered as well.

References

1. Fuchs VR. *Who shall live? Health, economics and social choice*. New York: Basic Books, 1974.
2. Jollis JG, Peterson ED, DeLong ER *et al*. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 1994;**331**:1625–9.
3. Kimmel SE, Berlin JA, Laskey WK. The relationship between coronary angioplasty procedure volume and major complications. *JAMA* 1995;**274**:1137–42.
4. Hannan EL, Racz M, Ryan TJ *et al*. Coronary angioplasty volume–outcome relationships for hospitals and cardiologists. *JAMA* 1997;**279**:892–8.
5. Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1987.
6. Finkler SA. The distinction between costs and charges. *Ann Intern Med* 1982;**96**:102–10.
7. Hlatky MA, Lipscomb J, Nelson C *et al*. Resource use and cost of initial coronary revascularization. Coronary angioplasty versus coronary bypass surgery. *Circulation* 1990;**82**(Suppl. IV): IV-208–IV-213.
8. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977;**296**:716–21.
9. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;**113**:147–54.
10. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost-effectiveness analysis in heart disease, Part I: general principles. *Prog Cardiovasc Dis* 1994;**37**:161–84.
11. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost effectiveness analysis in heart disease, Part II: preventive therapies. *Prog Cardiovasc Dis* 1995;**37**:243–71.
12. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost effectiveness analysis in heart disease, Part III: ischemia, congestive heart failure, and arrhythmias. *Prog Cardiovasc Dis* 1995;**37**:307–46.
13. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA* 1996;**276**:1172–7.
14. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost effectiveness in health and medicine. *JAMA* 1996;**276**:1253–8.
15. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. *JAMA* 1996;**276**:1339–41.
16. Echt DS, Liebson PR, Mitchell LB *et al*. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–8.
17. Mark DB, Hlatky MA, Califf RM *et al*. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;**332**:1418–24.
18. Yusuf S, Zucker D, Peduzzi P *et al*. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–70.

7 Introduction to decision analysis

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The concept of evidence-based medicine challenges physicians to improve their use of the medical literature to guide their decision making in specific clinical settings. The concept is discussed extensively throughout this book. However, there are circumstances in which clinical trials do not address all of the issues of interest to a clinician. This may be because the trials do not compare the risks and benefits of all relevant treatment alternatives, or because the trials lack important data on the outcomes and costs of therapy. In these cases, researchers and clinicians are developing analytical strategies to improve their ability to synthesize the available information from the clinical literature and to help resolve these unanswered questions. One method of achieving this synthesis is the use of decision analysis, a set of mathematical strategies for aggregating information, making issues related to clinical decisions explicit, and solving for an optimal strategy under the constraints of the analysis. This decision analysis is a framework that can be used in the analysis of clinical problems as well as in economic analysis (see Chapter 6).

Decision analysis has been available to cardiologists for over 20 years.[1–3] In that time, the techniques have become more sophisticated and begun to address a broader range of questions.[4–6]

The goal of this chapter is to introduce the reader to some of the basic concepts of decision analysis and to review its use in the cardiovascular literature. For more specific information about the concepts or methods of decision analysis, the reader is referred to several excellent summary articles[2–11] or to one of the major texts in the field.[12–14]

Examples of decision analysis

In this section we present two examples of the use of decision analysis, a clinical example and an economic example. These are provided to demonstrate the steps involved in developing a decision analysis. As will be clearly demonstrated, decision analytic models must simplify reality in order to structure the problem and analysis. Although our examples are extremely simplified to illustrate the steps involved in decision analysis, many models in the clinical literature offer more complex depictions of clinical reality.[16–22,26,27,36,40,41,53–58]

Steps in decision analysis

1. Identify the strategic options.
2. Draw the tree (structure of outcomes).
3. Determine the probabilities.
4. Determine the relevant outcome measures (effects, utility, survival, costs).
5. Evaluate the tree.
6. Make a structured analysis of the problem.
7. Develop a conclusion.

A comparative clinical analysis: warfarin *v* aspirin for atrial fibrillation

For patients with non-valvular atrial fibrillation, both warfarin and aspirin have been shown to reduce the risk of stroke.[28–35] However, the effectiveness and side effects of these two treatments can vary substantially. As there has been no randomized trial of aspirin and warfarin for stroke prevention, decision analysis has been used to identify the clinical outcomes resulting from treatment with each medication.[36]

Step 1: Identify the strategic options

In terms of therapeutic benefit, patients who receive either warfarin or aspirin experience a reduction in the risk of stroke. However, patients receiving these therapies also experience risk of bleeding complications. Both stroke and hemorrhage can be either fatal or non-fatal.

Step 2: Draw the tree

Based on these facts, we can graphically depict the issue using a decision tree (Figure 7.1). The tree is displayed so that the decision of interest is on the left side of the diagram, while the strategies to be compared are in the center, and the outcomes of those strategies are on the right. There are several pieces of information included in this simple figure.

In the decision tree a choice is represented by a square, also called a "decision node". In this example, the decision node represents a choice between warfarin and aspirin. Once a decision is made, patients experience the potential

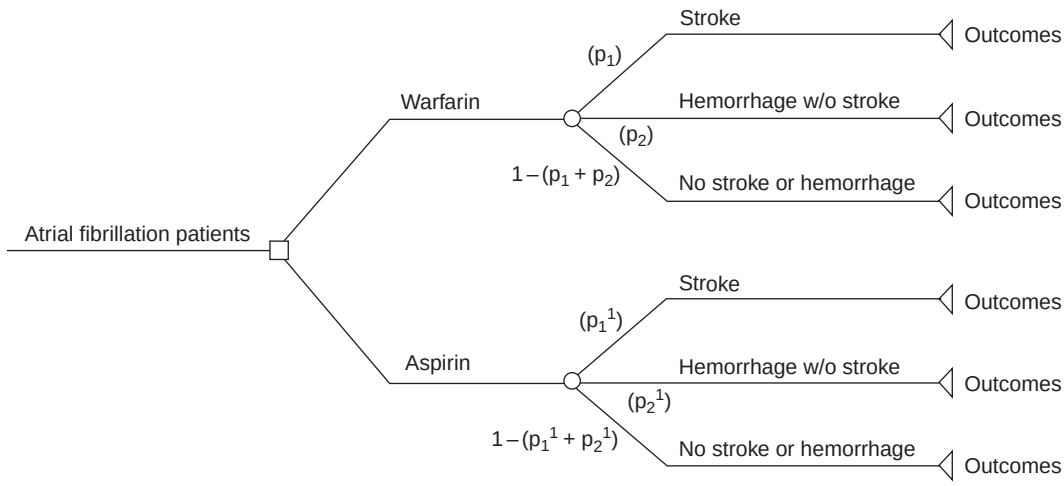

Figure 7.1 A decision tree for a comparative clinical analysis: warfarin *v* aspirin for atrial fibrillation

for different clinical events (stroke or hemorrhage). These decisions and their subsequent clinical events are represented by lines or "pathways" running through the tree diagram. Figure 7.1 contains six possible pathways: warfarin with stroke; warfarin with neither stroke nor hemorrhage; warfarin with hemorrhage but without stroke; aspirin with stroke; aspirin with neither stroke nor hemorrhage; and aspirin with hemorrhage but without stroke.

After the initial treatment decision between warfarin and aspirin has been made, subsequent outcomes occur with a defined probability such that all of the potential treatment outcomes are represented by the treatment pathways. The individual patient's achievement of a given treatment outcome (for example stroke or no stroke) is not a decision: it is, instead, a chance occurrence, where the "chance" event is represented by a circle in the decision tree.

The final treatment outcomes for each pathway are represented by triangles. These figures represent the outcomes of each treatment strategy. One, two or more outcomes can be expressed for each pathway (survival, quality adjusted survival, or costs).

Step 3: Determine the probabilities

Once a tree has been developed to depict a clinical problem, the next step is to begin to develop the data required to complete the analysis. In our example, we must identify the probability of stroke for patients in our two treatment categories and identify the potential risk of bleeding complications associated with each therapy.

Rates of stroke without therapy, outcomes of stroke, and stroke risk reduction with prophylaxis with aspirin or warfarin can be estimated from clinical trials or epidemiologic studies.[36] Rates of major hemorrhage associated with warfarin and aspirin therapy, and the outcomes of such an event, can be estimated in the same fashion.[36] However, in pooling these various data sources, investigators are left with a degree of uncertainty about these estimates. Sensitivity analysis, a method for assessing the impact of uncertainty in data analysis of clinical problems, will be discussed later, but it is an integral component of most well constructed decision analytic models.

Step 4: Determine the relevant outcome measures (effects, utility, survival, costs)

For this analysis, quality adjusted survival will be the primary outcome measure. Other possible outcome measures include event-free survival or simple survival. Analysis of quality adjusted survival uses estimates of patient preferences for a variety of possible health states for patients with stroke. Patient preferences are a measure of health-related quality of life, or utility, as defined on a 0–1 scale, in which 0·0 represents the worst imaginable health state and 1·0 denotes the best imaginable health state. Quality adjusted survival is the product of the expected survival of patients and their preferences for the different health states resulting from a stroke or hemorrhage. These data can be estimated from expert opinion, as reported in the medical literature, or derived from patient interviews.[37] Calculation of quality adjusted life years (QALYs) is described in greater detail elsewhere.[9]

Step 5: Evaluate the tree

Once data have been compiled for the specified model parameters, the next step is to analyze the tree. This requires the calculation of the expected value for each pathway of the tree. For both warfarin and aspirin therapies, the expected value of the outcome (effects, utility, survival or costs) is a weighted average of all possible treatment outcomes. This weighted average is calculated as the product of

the value of each terminal node and the probabilities of the occurrence of that node (the product of the probabilities of achieving that node). The value of each node is then summed to result in the weighted average value for the treatment (for example, the outcome for warfarin would be the weighted average of the products of the probability of stroke while taking warfarin and the outcome for stroke ($P1 \times O1$), the probability of hemorrhage without stroke while taking warfarin and the outcome for hemorrhage without stroke ($P2 \times O2$), and the probability of no stroke or hemorrhage and the outcome for no stroke or hemorrhage $\{(1 - [P1 + P2]) \times O3\}$).

A more complicated decision analysis proceeds in stepwise fashion for each set of probabilities and outcomes. This is called folding back the tree. The net result is an assessment of the outcomes for the two treatments, warfarin and aspirin. Other techniques can be used to solve more complicated problems, for which there are many branches of each tree – for example, when the risk of stroke or hemorrhage is related to the duration of treatment. (These methods are based on the probability of moving between health states over time. Analysis can also be based on "state transition models" or Markov models.)

For clinical analyses, decision trees allow an incremental analysis of the treatment benefits of one medical therapy compared to another. They are used to compare the expected utility for each branch of the tree to pick the best treatment option. The best option is the one with the highest value in terms of clinical effects (survival or utility) or the one with the smallest value in terms of cost. An incremental analysis assesses the additional benefits gained from one treatment and, thus, differs from a calculation of the absolute benefit of a treatment.

Step 6: Structured analysis of the problem

Finally, the primary analysis having been completed, investigators should examine uncertainty in their estimates using a technique called sensitivity analysis. By recognizing that a decision tree can suffer from uncertainty in the probability of each treatment strategy, investigators can ask how the results might change were the possibilities of stroke or hemorrhage to increase or decrease by 10% for each treatment arm. In a sensitivity analysis, the investigator recalculates the results of the model to address the robustness of the analysis to changes in the model specification.

Step 7: Conclusion

This decision analysis was structured to compare the outcomes of two strategies for the treatment of stroke prophylaxis – warfarin and aspirin. Such an analysis allows for an assessment of the clinical benefits of the two strategies, incorporating both the differences in risk reduction of stroke and the differences in hemorrhage resulting from the prophylactic treatment. The analysis would end with an estimate of the quality adjusted survival resulting from each treatment strategy. The results could reveal that warfarin is superior to aspirin, that aspirin is superior to warfarin, that the treatments are comparable, or that there is not enough information from which to draw a firm conclusion. The analysis would also address how sensitive the analysis was to differing model parameters. This could help define areas for further research to resolve outstanding issues in the clinical assessment.

A cost effectiveness analysis: implantable cardiac defibrillators

At present there is a great deal of debate about the most appropriate treatment of patients with arrhythmias, especially about whether implantable cardiac defibrillators (ICDs) will reduce cost and mortality for high-risk patients. Early clinical trial results address mortality issues related to the use of ICDs in high-risk populations.[38] However, there remains a great deal of concern about the findings of the study and the robustness of its results.[39] Although decision analysis cannot answer the clinical questions regarding ICD use, these techniques have been used to model the costs and effects of ICD insertion to estimate the potential cost effectiveness of this therapy, given current estimates of ICD clinical effectiveness.[40,41] To understand the decision analysis approach to this question, we will review the clinical issues and then build a decision analytic model to formalize the question.

High-risk patients experience an increased incidence of sudden cardiac death.[42] One new technology, the ICD, has been proposed as a means of reducing the incidence of sudden death in cardiac patients.[38,43–48] Patients who choose to receive this therapy must undergo a surgical procedure and maintain the device over the remainder of their lifetime.

Step 1: Identify the strategic options

In terms of treatment benefit, patients who receive an ICD have the potential for a different survival probability than patients who do not receive an ICD. From a cost perspective, patients receiving an ICD bear the additional cost of the device itself, as well as the future costs of maintaining it.

Step 2: Draw the tree

Based on this discussion, we can graphically depict the issue using a decision tree (Figure 7.2). There are four possible pathways in this figure: ICD with sudden death; ICD without sudden death; no ICD with sudden death; and no ICD without sudden death. In this simple model we consider only two health states: sudden death and no sudden death.

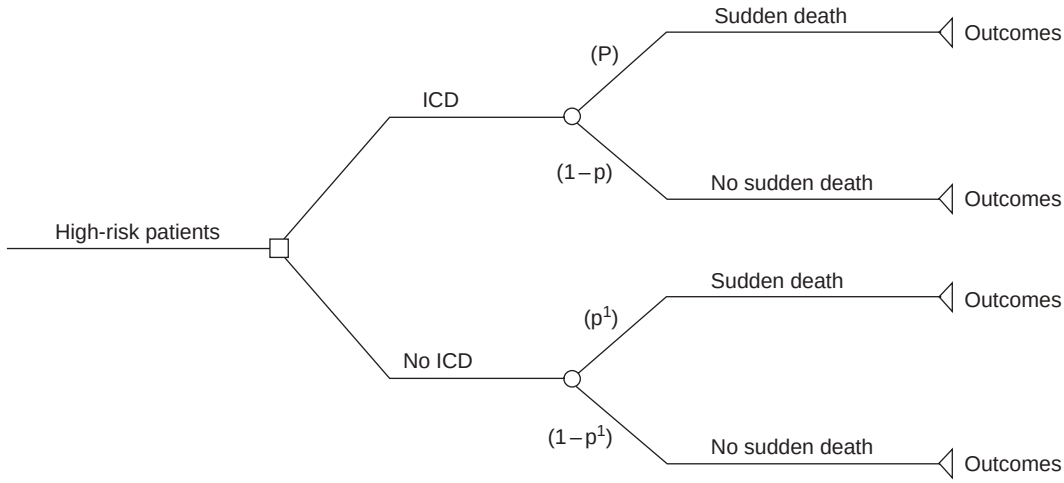

Figure 7.2 Decision tree for a cost effectiveness analysis: ICD to reduce incidence of sudden death in cardiac patients

Step 3: Determine the probabilities

Estimates of the possibility of sudden cardiac death for high-risk patients are available in the medical literature and in trials of ICDs.[43–49] Estimates of the probability of sudden death for patients receiving an ICD are available from the MADIT Study[38] or may be estimated based on clinical trial protocols for expected treatment benefits.[41] The quality of the evidence from these data sources can vary. Data from the literature on non-ICD patients, the probability of sudden death without an ICD, come from observational studies, whereas data on ICD patients come from a controversial randomized controlled trial. Thus, there is some uncertainty about these estimates.[10]

Step 4: Determine the relevant outcome measures (effects, utility, survival, costs)

Treatment benefits can be expressed in terms of survival (years of life gained) or in terms of quality adjusted survival (QALYs). Calculation of these benefits proceeds as outlined in the stroke example.

Estimates of treatment costs often must be developed from primary sources (for example, hospital accounting departments), from standard price lists for specific costs,[50] from literature reviews, or from expert opinion. Costs included in these models can include direct medical costs (the costs of medical care, such as hospital or physician costs), direct non-medical costs (the costs patients incur in receiving medical care services, such as the cost of transportation to a physician's office), indirect costs (the costs of morbidity or mortality related to disease), or intangible costs (the costs of pain and suffering related to disease).[51,52]

Step 5: Evaluate the tree

Once the data are available for all of these model parameters, the next step is to analyze the tree. For economic analyses, decision trees allow an incremental analysis of the treatment costs and benefits of one medical therapy compared to another in a cost effectiveness analysis. The incremental cost effectiveness of therapy A compared to therapy B is defined by the following formula:

$$\text{Cost effectiveness of treatment A} = \frac{(\text{Cost}_A - \text{Cost}_B)}{(\text{Effects}_A - \text{Effects}_B)}$$

where Cost_A is the cost of treatment A, Cost_B is the cost of treatment B, Effects_A are the effects of treatment A, and Effects_B are the effects of treatment B.[52] Decision trees may also allow enumeration of the costs and consequences of different treatments without comparing the costs and effects of treatment in a cost effectiveness ratio.

Step 6: Structured analysis of the problem

Sensitivity analysis would be conducted to assess the impact of uncertain values on the model. For example, because there was uncertainty in the probability of each treatment strategy, how would the results change if the possibilities of sudden death were increased or decreased by 10% for each treatment arm? Similarly, how would the results differ if ICD costs were increased or decreased by 10%? In a sensitivity analysis, the investigator recalculates the results of the model to address the robustness of the analysis to changes in the model specification.

Step 7: Conclusion

This decision analysis was structured to assess the cost effectiveness of a new therapy for the treatment of patients at high risk for sudden cardiac death. It would conclude with an estimate of the incremental effects of ICD therapy in years of life gained per patient, the incremental costs of ICD treatment per patient, and an estimate of the cost effectiveness of

ICD therapy for patients evaluated in the model. The paper would also address how sensitive the analysis was to different model parameters. This sensitivity analysis could help define areas for further research to resolve outstanding issues in the clinical assessment.

Applications of decision analysis to cardiology

The above examples offer a simplified explanation of some of the basic components of decision analysis. They also illustrate the issues that must be addressed before using the results of a decision analysis to guide clinical decision making. As when reviewing clinical trials, clinicians must assess whether the population considered in the decision analysis model is relevant to their own population. The reader must consider the strength of the evidence available to the investigator in developing the model to understand the strength of the recommendations resulting from the model. This includes not only whether the evidence was based on randomized controlled trials or on observational studies, but also whether the original studies included detailed information required by the model (for example, in the stroke analysis, whether the clinical studies reported both hemorrhage and stroke rates for the study's patients). Finally, the reader should consider the model used by the investigator to determine whether it was constructed appropriately and considered all relevant comparisons.[1,5] The models below that use lower-quality data or evidence should be considered exploratory analyses, not definitive evidence. As such, they also should be interpreted as potential rationale for future studies. Likewise, decision models that project results to new time periods, new populations and new interventions – even those that use A1a-grade evidence – should be viewed only as exploratory analyses.

Decision analysis has been used extensively in cardiology over the past several years (Table 7.1). These examples include articles from a MEDLINE search of decision analysis and cardiology from 1993 to 2001. Issues addressed have included the use of specific technologies, such as ICDs for patients at risk for sudden death, as well as specific diagnostic or pharmacologic products for defined populations of patients (for example, treatment of high blood cholesterol), and the assessment of patient management strategies for defined populations of patients (for example the selection of patients for placement on a cardiac transplant list). Each of the analyses listed in Table 7.1 will be reviewed in this section.

Table 7.1 Use of decision analysis in the cardiovascular literature

Clinical issue	Efficacy data	Cost data	Sensitivity analysis	Source	Evidence grade*
New technologies					
Inpatient ICD placement	Observational study; utility not assessed	Hospital charges; literature review for resource use data	Yes	Kupersmith *et al*[16]	B4
Outpatient ICD placement	Literature review for survival and utility estimates	Hospital and claims data; literature review for resource use data	Yes	Owens *et al*[41]	A1c
Treatment strategies for WPW syndrome	Literature review; expert opinion; authors' estimates for utility data	Cost-accounting data for 13 patients at one study center	Yes	Hogenhuis *et al*[17]	B4
Specific products					
Low *v* high-osmolality contrast media	Literature review; authors' estimates for utility data; patient survey for intangible cost estimates	Resource use from a clinical trial; literature review; costs from Canadian hospital	Yes	Barrett *et al*[18]	A1c
Simvastatin, high cholesterol	Clinical trial data; utility not assessed	Resource use from clinical trial; costs from hospitals in Sweden; employment status from clinical trial	Yes	Johannesson *et al*[19]	A1a

Table 7.1 ***Continued***

Clinical issue	Efficacy data	Cost data	Sensitivity analysis	Source	Evidence grade*
Pravastatin, high cholesterol	Clinical trial data from 2 studies; utility not assessed	Literature review and expert opinion for resource use data; costs from aggregate US hospital data	Yes	Ashraf *et al*[20]	A1c
Captopril, acute MI	Clinical trial data; utility data from 82 patients	Resource use from subset of study patients; costs from US Medicare reimbursement rates	Yes	Tsevat *et al*[21]	A1a
Estrogen replacement	Literature review; utility not assessed	Not assessed	Yes	Zubialde *et al*[22]	B2
Streptokinase *v* tPA, suspected MI	Literature review, including utility data	Resource use estimated; drug and hospital cost data from Ireland	Yes	Kellett *et al*[26]	A1a
Warfarin *v* quinidine *v* amiodarone, acute atrial fibrillation	Literature review and expert opinion, including utility data	Not assessed	Yes	Disch *et al*[27]	A1a
Warfarin *v* aspirin, stroke prophylaxis	Literature review; utility data from study of 74 patients	Resource use estimated; costs from literature review, Medicare data, and survey of pharmacies	Yes	Gage *et al*[36]	A1a
Preoperative coronary angiography and revascularization, non-cardiac vascular surgery	Literature review; utility not assessed	Literature review	Yes	Mason *et al*[55]	A1a
Treatment strategies					
CCU admission	Cohort study; utility not assessed	Hospital charges from the cohort adjusted to costs	Yes	Tosteson *et al*[56]	B4
Emergency medical services	Literature review; utility not assessed	Analysis of existing EMS program in Canada	Yes	Nichol *et al*[57]	B4
Cardiac transplantation selection	Transplant registries	Not assessed	Yes	Stevenson *et al*[58]	B4
Aortic valve replacement				Wong *et al*[59]	B4
Medical *v* surgical therapy for chronic stable angina	Expert guidelines, randomized trials, and meta-analyses; utility not assessed	Not assessed	Yes	Kwok *et al*[61]	A1a
Strategies for hypoplastic left heart syndrome	Literature review and data from 231 patients; utility not assessed	Not assessed	Yes	Jenkins *et al*[62]	B3

Table 7.1 *Continued*

Clinical issue	Efficacy data	Cost data	Sensitivity analysis	Source	Evidence grade*
Electrocardiogram algorithm to predict myocardial infarction	Retrospective cohort study; utility not assessed	Not assessed	Yes	Shlipak *et al*[63]	B2

*Evidence grades for decision analysis are complicated by the many different sources of data used in constructing the analysis. Evidence grades here are based on the data for the most important component of the analysis for the clinical portion of the decision tree. Where sources of evidence for the analysis were from a variety of sources, two grades were assigned to reflect the differing quality of data available for the analysis (see Owens *et al*.[41] for an example of grades of evidence for data incorporated into a decision analysis).
Grade A: Decision trees with the primary effect estimate from a large, high-quality study (a randomized controlled trial with more than 500 patients), or decision trees with a formal meta-analysis for the primary effect estimate.
Grade B: Decision trees with the primary effect estimate based on literature review but without a formal meta-analysis for primary effect estimate; includes evidence from case series and randomized controlled trials with fewer than 500 patients.
Grade C: Decision trees with the primary effect estimate based on expert opinion.

Decision analysis evaluating new technologies

ICD placement

Over the past several years, investigators have attempted to calculate the cost effectiveness of the ICD in patients at high risk for sudden cardiac death. Recent evidence from the Antiarrhythmics versus Implantable Defibrillators Trial indicates a decrease of 27% in 2 year mortality with ICD.[15] Kupersmith *et al*[16] assessed ICD placement on an inpatient basis for patients with and without prior electrophysiologic (EP) studies. **Grade A1c** The investigators assumed an 84% improvement in life expectancy for patients undergoing ICD therapy based on a case series of 218 non-randomized patients who received an ICD when it was assumed that the patients would have died at the time of the first event (first shock or death). In this analysis, ICD patients had a mean life expectancy of 3·78 years, whereas EP-guided drug therapy patients had a mean life expectancy of 2·06 years. Total charges for these treatments were $146 797 for ICD patients and $93 340 for the EP-guided patients. The investigators found that the cost of ICD placement, including the cost of the device and the hospitalization, would range between $27 200 and $44 000 per year of life saved.

The investigators conducted an extensive sensitivity analysis around their cost data and around the period of replacement of the ICD generator. They found that the cost effectiveness of the therapy was sensitive to the magnitude of the clinical benefit of the therapy (this included the efficacy of the therapy, as well as the estimated life expectancy for the underlying population, as represented by ejection fraction). The model was less sensitive to the cost of ICD therapy. The authors concluded that ICD use was economically attractive, especially using endocardial lead placement (based on preliminary estimates of the cost of this new procedure).*

Owens *et al*[41] assessed ICD implantation on an outpatient basis using a decision analytic model. In this analysis, the investigators modeled the potential cost effectiveness of therapy, assuming in their principal analysis that the ICD led to a 20–40% reduction in mortality. **Grade A1c** The investigators found that the cost of patients receiving ICD therapy would be $88 400, and the cost of patients receiving amiodarone therapy alone would be $51 000. For high-risk

* There are four possible outcomes of a cost effectiveness analysis: (1) the intervention will save money and be more effective than the comparison; (2) the intervention will cost money and be more effective than the comparison; (3) the intervention will save money and be less effective than the comparison; and (4) the intervention will cost money and be less effective than the comparison.[51] The first outcome is the most preferred, and the intervention will always be adopted. The last outcome is never preferred, and the intervention will never be adopted. The second and third outcomes may be preferred at times, and the interventions may be adopted, depending on the relationship between the costs and effects of the intervention (the cost effectiveness ratio). The second outcome may be adopted if the intervention yields a great enough benefit for the additional cost (in the USA, an economically attractive intervention may be one that costs less than $50 000 per year of life gained, whereas some Canadian authors have suggested that therapies that cost less than CDN$100 000 might be economically attractive).[35,53] The third outcome may be adopted if the intervention yields a small enough reduction in outcomes for the reduction in cost (for example, the same Canadian authors suggested an economically attractive intervention might be one that saves more than CDN$100 000 per year of life forgone).[35,52]

patients, the investigators reported that ICD patients would have an estimated survival of 4·18 QALYs, whereas patients treated with amiodarone alone could expect a survival of 3·68 QALYs. Investigators found that the cost effectiveness of therapy ranged from $37 300 per QALY saved for high-risk patients, assuming a 40% reduction in mortality for patients treated with the ICD compared to those treated with amiodarone alone, to $138 900 QALYs saved for intermediate-risk patients and assuming a 20% reduction in mortality for patients treated with the ICD compared to amiodarone alone. They concluded that the use of an ICD will not be economically attractive unless all-cause mortality is reduced by 30% or more compared to amiodarone.

Alternative therapies for WPW syndrome

Hogenhuis *et al*[17] determined which of five management strategies should be used for the treatment of patients with Wolff–Parkinson–White (WPW) syndrome: observation, observation until cardiac arrest-driven therapy, initial drug therapy guided by non-invasive monitoring, initial radiofrequency ablation, and initial surgical ablation. The model included the risks of cardiac arrest, arrhythmia, drug adverse effects, procedure-related complications and mortality, and assumed that radiofrequency ablation had an overall efficacy of 92% in preventing cardiac arrest and arrhythmia. **Grade B4**

For survivors of a cardiac arrest, radiofrequency ablation offered additional survival at reduced cost compared to all other treatment strategies. For patients with arrhythmia without hemodynamic compromise, radiofrequency ablation resulted in a cost of $6 600 per QALY gained in 20 year old patients and $19 000 per QALY gained in 60 year old patients without hemodynamic compromise. For asymptomatic patients, radiofrequency ablation costs from $33 000 per QALY gained in 20 year old patients to $540 000 per QALY gained for 60 year old patients. The authors conclude that their analysis supports the practice of radiofrequency ablation in patients with WPW syndrome who survive cardiac arrest. For asymptomatic patients, however, the analysis supports the current practice of mere observation, given that radiofrequency ablation was economically unattractive in this population of patients.

Decision analysis in the evaluation of specific products

Decision analysis has been used extensively in the evaluation of specific clinical products, including contrast media and pharmaceutical products.

Contrast media

Grade A1c Barrett *et al*[18] developed a decision analytic model to assess the economic impact of low- and high-osmolality contrast media for cardiac angiography. Investigators assumed that low-osmolality contrast media reduced the risk of myocardial infarction and stroke. Reduction in the risk of specific clinical events with low-osmolality contrast media was assumed to be 0% in fatal events, 25% in severe events, 80% in moderate events and 10% in minor events. The investigators found that the incremental cost per QALY gained with these media was $17 264 in high-risk patients and $47 874 in low-risk patients for a third-party payer. From a societal perspective, the corresponding costs are $649 and $35 509. The authors report that these estimates were sensitive to cost of the contrast media and the total cost of contrast media used per patient. The authors also suggest that the model is extremely sensitive to changes in assumptions regarding the efficacy of low-osmolality contrast media for the prevention of severe reactions. To allow the reader to better understand the inputs of this model, the authors include a cost–consequence analysis of the program as a separate presentation in the results. The authors concluded that, in the context of restricted budgets, limiting the use of low-osmolality contrast media to high-risk patients is justifiable. The recommendation to limit use of this medium was also justified by the lack of clinical evidence that low-osmolality contrast media prevent severe or fatal reactions.

Cholesterol reduction

Several authors have used decision analysis to investigate the cost effectiveness of therapies designed to reduce high blood cholesterol.[54] Two recent studies use clinical trial data to assess the cost effectiveness of cholesterol reduction in secondary prevention of coronary artery disease. Johanneson *et al*[19] developed an analysis based on the Scandinavian Simvastatin Survival Study, which reported that, in patients with pre-existing coronary disease, reduction in blood cholesterol resulted in a 30% reduction in overall mortality based on a median follow-up of 5·4 years. **Grade A1a** The authors modeled the effects of 5 years of cholesterol-reducing therapy on patients' outcomes, using a model based on data reported from the trial. The costs of therapy were based on the assumption that the use of cholesterol-reducing agents would not entail any additional costs for patients with pre-existing coronary disease other than the cost of medication itself, and then used data on hospitalizations to estimate the direct medical costs incurred for the treatment of cardiovascular disease.

Interestingly, this model also included the indirect costs of medical care based on the employment status of patients in the trial. The investigators found that simvastatin treatment for 5 years in 59 year old patients with a history of heart disease and a pretreatment total cholesterol level of 261 mg/dl would have a net cost of $1 524, with 0·28 years of life gained, resulting in a cost per year of life gained of $5 400 for men, and a net cost of $1 685 with 0·61 years of life gained, resulting in a cost per year of life

gained of $10 500 for women. An analysis that included direct and indirect costs showed that cholesterol reduction leads to an additional $1 065 decrease in associated morbidity cost for men and an $876 reduction in associated morbidity cost for women. The analysis was somewhat sensitive to baseline cholesterol level and patient age at the initiation of treatment, to follow-up and screening costs and to the price of simvastatin. However, treatment remained economically attractive in all of these analyses. The model was somewhat sensitive to reduction in cardiovascular risk and the risk of mortality after coronary events. The authors concluded that in patients with coronary artery disease, simvastatin therapy is economically attractive among both men and women at the ages and cholesterol levels studied.

Ashraf *et al*[20] assessed the cost effectiveness of cholesterol reduction based on 3 year data from the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) and Pravastatin, Lipids and Atherosclerosis in the Carotids (PLAC II) studies. **Grade A1c** These trials reported no statistically significant decrease in all-cause mortality, but did report a decrease in the number of coronary events in men in the group receiving drug therapy to reduce high blood cholesterol. Therapy was estimated using a Markov model based on data from the Framingham Heart Study to estimate subsequent annual morbidity and mortality rates for patients with non-fatal myocardial infarction. Costs of therapy were based on the costs of drug therapy, and hospitalization costs were derived from the cost of treatment of myocardial infarction and from expert opinion on the frequency of medical events. Investigators found that cost per year of life saved due to secondary prevention was sensitive to a number of risk factors, but ranged from $7124 per year of life saved for a male patient with three risk factors, to $12 665 per year of life saved for a male patient with one risk factor. The model was sensitive to assumptions about efficacy of therapy and cost of services. It was also sensitive to patient characteristics, such as the number of risk factors of patients receiving secondary prevention. The authors conclude that pravastatin is economically attractive compared to other widely accepted medical interventions.

A potentially serious limitation of the Ashraf *et al*[20] analysis is its strategy of deriving costs for 3 years while projecting the effects over 10 years. Specifically, the authors project years of life saved by avoiding events in the first 3 years over the next 7 years. This potentially problematic practice of generating a differential time horizon should be avoided.

Postmyocardial infarction treatment

Tsevat *et al*[21] used decision analysis to assess the cost effectiveness of captopril therapy after acute myocardial infarction (MI). **Grade A1a** In this paper, the investigators used data from the Survival and Ventricular Enlargement (SAVE) trial, which demonstrated that captopril therapy reduced mortality in patients who survived MI. The effectiveness of therapy was modeled using a decision analytic model based on all-cause mortality within the clinical trial observation period and the projected clinical benefits over a patient's lifetime. This paper also incorporated data on quality of life from a subset of patients in the SAVE trial. Cost estimates for the model were based on a subset of 123 study patients for whom hospital data were obtained for all hospitalizations in the subset. The investigators used two projection methods, a limited-benefit model and a persistent-benefit model. The limited-benefit model was more conservative in that it assumed similar annual mortality rates between captopril and control patients beyond the clinical trial period. This analysis resulted in an estimated cost effectiveness for captopril therapy ranging from $60 800 per QALY for 50 year old patients to $3 600 per QALY for 80 year old patients. The persistent-benefit model was more optimistic in that it assumed that the clinical benefits observed in the trial persisted throughout each patient's lifetime. In this analysis, the cost effectiveness ratios were similar to those in the limited-benefit model for patients aged 60–80 years, but they were substantially better for 50 year old patients. In the sensitivity analysis, the models were most sensitive to the annual cost of captopril therapy. In addition, the persistent-benefit model appeared to be more "stable" than the limited-benefit analysis. That is, when the benefits persist, there are few changes to the values of other variables that would affect the resulting cost effectiveness ratios (owing to the magnitude of the benefit), whereas if the benefits do not persist, variations in other variables do have an effect. The investigators concluded that angiotensin converting enzyme inhibitor therapy with captopril was not only effective in improving survival after MI, but also moderately economically attractive.

Hormone replacement therapy

Zubialde *et al*[22] used a decision analytic model to assess gains in life expectancy resulting from the use of estrogen replacement therapy for postmenopausal women. Efficacy data for this analysis were obtained from a review of the literature which suggested that risk reduction with estrogen therapy for coronary artery disease was between 40% and 50%. **Grade B2** The model did not assume an increased incidence in breast cancer in the principal analysis, but it did include an increased incidence of endometrial cancer. Results of the analysis suggested that the benefit of estrogen and progesterone therapy in average-risk women aged 50 years at the time of therapy initiation was 0·86 years, with a range of 0·41–1·19 years, whereas therapy in average-risk women aged 65 years at the time of therapy initiation was 0·47 years, with a range of 0·21–0·66 years. The authors reported that the benefits of estrogen and progesterone therapy were similar to the gains from cholesterol reduction to

200 mg/dl and smoking cessation. The authors concluded that significant potential benefits in life expectancy in coronary artery disease reduction, combined with the osteoporosis prevention in symptom relief, would point to greater emphasis on postmenopausal estrogen use in appropriate patients. Since the report by Zubialde *et al*[22] hormone replacement therapy has undergone additional study. A growing body of literature suggests that its predicted effects have not been fully realized,[23,24] and the results of a recent polymorphism study have further complicated matters.[25] It bears repeating here that the reliability of a decision analysis is related directly to the quality of the data on which the analysis is based. The Zubialde analysis was based on the best data of its time, but superior data from clinical trials have since called the findings into question.

Thrombolytic therapy

Kellett *et al*[26] presented a paper on the use of thrombolytic therapy for patients with suspected MI. This assessed the use of two types of thrombolytic therapy, streptokinase and accelerated tissue plasminogen activator (tPA), on patients with suspected MI. **Grade A1a** The efficacy of the two therapies was based on reports from the medical literature. The authors assessed the clinical benefits of thrombolytic therapies for patients presenting with different likelihoods of MI, given their clinical and ECG findings, different age groups, and different probabilities of death given MI. Data on clinical efficacy for the two strategies were based on the GISSI-2, ISIS-3 and GUSTO trials. The authors suggested that, for patients with a 26% probability of MI (a group with chest pain and a history of coronary artery disease but a normal ECG), thrombolytic therapy would only be beneficial if the probability of death given an MI was 20% or greater. In contrast, for patients presenting with a probability of MI of 78% (chest pain plus ST or T wave changes), thrombolytic therapy would be beneficial for all patients except those over 80 years of age who had a probability of death given an MI of 2·5% or less. The authors conclude that, for a typical 60 year old man presenting 4 hours after the onset of symptoms with definite acute MI, treatment with streptokinase in addition to aspirin would gain 150 quality adjusted life days, whereas treatment with aspirin and accelerated tPA would result in 255 quality adjusted life days, compared to no thrombolytic therapy. Thrombolytic therapy is preferred over no thrombolytic therapy as long as the probability of stroke is less than 5% for streptokinase and 8% for accelerated tPA. The cost per QALY was estimated based on the probability of acute MI, the extra days of quality adjusted life, and the probability of death given an MI. The analysis was sensitive to estimates of efficacy for both streptokinase and accelerated tPA, as well as the probability of death given thrombolytic therapy. The authors conclude that decision analysis can be a useful bedside tool to guide thrombolytic therapy. It is important to bear in mind, however, that this decision model has not been tested on actual patients.

Management of atrial fibrillation

Dirsch *et al*[27] developed a decision analytic model to assess the outcomes of four treatment strategies for patients with acute atrial fibrillation undergoing cardioversion: warfarin therapy, quinidine therapy and low-dose amiodarone therapy. **Grade A1a** Efficacy was based on a review of the literature, including randomized controlled trials, observational studies, and expert clinical opinion when necessary. Investigators found that all four treatment strategies differed by 0·2 QALYs over patients' lifetimes, with 4·55 expected QALYs for patients who undergo no treatment after cardioversion and 4·75 expected QALYs for patients who undergo cardioversion with amiodarone. Use of warfarin and quinidine therapies yielded expected quality adjusted life benefits between amiodarone and no treatment. The model was sensitive to the annual rate of bleeding on warfarin, the annual rate of stroke for patients on warfarin, the annual rate of stroke for patients with atrial fibrillation, the decrement in quality of life associated with taking warfarin, and the excess mortality of quinidine and amiodarone. The authors conclude that cardioversion followed by low-dose amiodarone to maintain normal sinus rhythm appears to be a relatively safe and effective treatment for a hypothetical cohort of patients with atrial fibrillation.

Prophylaxis of stroke

Gage *et al*[36] developed a decision analytic model to assess the cost effectiveness of warfarin and aspirin treatment for prophylaxis of stroke in patients with non-valvular atrial fibrillation. The clinical efficacy of the treatment strategies was obtained from the published literature. **Grade A1a** The quality-of-life estimates for this study were obtained by interviewing patients with atrial fibrillation. Costs were also estimated from a literature review and from a survey of national pharmacies and laboratories. The authors found that, for patients with non-valvular atrial fibrillation and no additional risk factors for stroke, warfarin would minimally affect quality adjusted survival but increase costs significantly. For patients with non-valvular atrial fibrillation and one additional risk factor, warfarin therapy resulted in a cost of $8 000 per QALY saved compared to aspirin. The model was most sensitive to the rate of stroke if no therapy was prescribed, the effectiveness of aspirin, the rates of major hemorrhage, and the disutility of taking warfarin. The authors conclude that treatment with warfarin is economically attractive (has a low cost effectiveness ratio) in patients with non-valvular atrial fibrillation and one or more additional risk factors for stroke. However, in patients with non-valvular atrial fibrillation without other risk factors for stroke, the use

of warfarin instead of aspirin would add significantly to costs with minimal additional clinical benefit.

Preoperative cardiac revascularization

Mason *et al*[55] developed an analysis to determine whether preoperative coronary angiography and revascularization improved short-term outcomes in patients undergoing non-cardiac vascular surgery with three strategies. **Grade A1a** The first was to proceed directly to vascular surgery; the second was to perform coronary angiography followed by selective coronary revascularization prior to surgery and to cancel vascular surgery in patients with severe inoperable coronary disease; and the third was to perform coronary angiography followed by selective coronary revascularization, and to perform vascular surgery in patients with inoperable coronary artery disease. The literature was scrutinized for data on the efficacy of all three strategies. The authors found that proceeding directly to vascular surgery led to a lower morbidity and cost in the base-case analysis. The coronary angiography strategy led to a higher mortality of vascular surgery in patients with inoperable coronary disease, but to a lower mortality in operable patients who did not proceed to vascular surgery. The model was sensitive to the surgical mortality rates for both catheterization and the vascular surgical procedure. The authors concluded that decision analysis indicates that vascular surgery without preoperative angiography generally leads to better outcomes, and that preoperative coronary angiography should be reserved for patients whose estimated mortality for vascular surgery is substantially higher than average.

Use of decision analysis in treatment strategies

CCU admission

Tosteson *et al*[56] used a decision analytic model to identify cost effective guidelines for admission to a coronary care unit (CCU) for uncomplicated patients without other indications for intensive care. The probabilities of death, and minor, major and life-threatening complications were based on 12 139 emergency department patients who were enrolled in a multicenter chest pain study. Cost data were available from a subset of patients in the study admitted to one study center. Under the assumption that there is a 15% relative increase in mortality when patients with acute MI are admitted to the intermediate care unit instead of an intensive CCU, the authors found that costs per year of life saved for triage to the CCU varied markedly depending on the age of the patient and the probability of MI. For 55–64 year old patients with an emergency department probability of infarction of 1%, the cost per year of life saved was $1·4 million; but when the probability of infarction was 99%, the cost per year of life saved was $15 000. Admission to the intensive care unit was generally more costly for younger patients, and use of the CCU had a cost effectiveness ratio of less than $50 000 per year of life saved when the initial probability of acute MI was greater than 57% among patients 30–44 years of age, and greater than 21% among patients 65–74 years of age. The model was sensitive to the reduction of mortality associated with the use of the intensive care unit and to the costs of the intensive care unit. The authors conclude that the CCU should generally be reserved for patients with a moderate or high probability of acute MI, unless they need intensive care for other reasons.

Emergency medical services

Nichol *et al*[57] used a decision analytic model to assess the cost effectiveness of potential improvements to emergency medical services (EMS) for patients with out-of-hospital cardiac arrest. **Grade B4** The authors developed their analysis based on a review of the effectiveness of various emergency systems from an extensive meta-analysis, costing of each component of the EMS, and community characteristics and response times for EMS. The authors also modeled a one-tier system versus a two-tier system. In the one-tier system the response team is trained in advanced life support, and in the two-tier system the first response team is trained in basic life support and the second in advanced life support. The authors found that the fixed cost of the first tier of a two-tier EMS system was $651 129 for Hamilton, Ontario, with estimates of survival of 5·2% in the one-tier system and 10·5% in the two-tier system. They found that a 1 minute reduction in response time improved survival by 0·4% in a one-tier system and by 0·7% in a two-tier system. The authors found that a change from a one-tier system to a two-tier system would result in 0·19 QALYs saved and an incremental cost of $7 700 per patient, or a cost per QALY of $40 000. Improvement in a one-tier EMS system by the addition of more basic life support providers in the first tier would result in an incremental survival benefit of 0·40 QALYs, with an incremental cost of $2 400 or cost per QALY of $53 000. An improvement in response time in a one-tier system by the addition of more providers and ambulances would achieve an incremental survival benefit of 0·2 QALYs for a cost per QALY of $368 000. The authors performed an extensive sensitivity analysis based on a combination of the model's parameters. They concluded that the most attractive options in terms of incremental cost effectiveness ratios for an EMS program would be improved response time in a two-tier EMS system, or a change from a one-tier EMS system to a two-tier system. However, the authors were concerned about the poor quality of the data available for their analysis.

Heart transplantation

Stevenson *et al*[58] used a decision analytic model to determine optimal strategies for selecting patients for cardiac

transplantation. **Grade B4** The authors developed a model based on data from cardiac transplantation databases. The decision analytic model was developed to determine the size and outcomes of the waiting list population, depending upon different strategies for listing heart transplant candidates. They found that if current practices continued all hearts would be transplanted to hospitalized candidates and newly listed urgent candidates, and 3700 outpatient transplant candidates would be listed with virtually no transplantation unless they deteriorated to an urgent status. A decrease in the upper age limit for transplantation to 55 years would reduce the number listed each month by 30%. If this strategy were to be adopted, the waiting list would reduce to one third its current size, with 50% of all hearts being available for outpatient candidates. The authors conclude that immediate provisions should be made to limit candidate listing and revise expectations to reflect the diminishing likelihood of transplantation for outpatient candidates.

Surgery for aortic stenosis

Wong *et al*[59] used decision analysis to assess whether to recommend cardiac surgery for elderly women with aortic stenosis. **Grade B4** This analysis was based on a specific case of assessing the treatment choice for an 87 year old patient with severe aortic stenosis, three vessel coronary disease, depressed left ventricular function and moderately severe heart failure. Data for the analysis were based on the medical literature. Specific data elements included in the analysis were life expectancy with and without surgery for an octogenarian, morbidity and mortality associated with surgery, and quality of life with congestive heart failure. Sensitivity analysis assessed the sensitivity of the model to assumptions used in developing the analysis and assessed the impact of patients' risk preferences regarding treatment choice. The authors also modeled valvuloplasty compared to surgery. They found that life expectancy with surgery (5·0 QALYs) was greater than that for medical therapy (1·1 QALYs). (These gains in life expectancy are substantial. Most interventions reported in the medical literature yield incremental gains in life expectancy from 0·167 to 1·2 years of life.[60]) In sensitivity analysis, surgery still had the highest life expectancy until mortality from the procedure was greater than 70%. Valvuloplasty was the best strategy if the patient was not the best candidate for surgery or, perhaps, in cases in which the perioperative mortality rate was greater than 50%. They concluded that even in the later decades of life, aortic valve surgery is substantially preferable to medical therapy.

Treatment strategies for chronic stable angina

Kwok *et al*[61] used a decision analytic model to simulate a randomized controlled trial of coronary artery bypass graft surgery versus medical therapy for chronic stable angina. **Grade A1a** The authors developed a Markov model that incorporated current American College of Cardiology/American Heart Association guidelines, baseline data from a meta-analysis of randomized trials of the two therapies, and risk reduction data from randomized trials and meta-analyses. The outcome measures of interest were 5 and 10 year mortality, as well as incidence of non-fatal myocardial infarction. The authors conducted a base-case analysis of the two therapies, which they supplemented with annual fixed transition probabilities to account for a steady linear increase in mortality observed in the meta-analysis. They also conducted two subgroup analyses, one to examine 5 year mortality and infarction rates for patients with triple vessel disease, the other to examine the same outcomes for patients with impaired left ventricular function. In the base-case and subgroup analyses, the authors found that both therapies increased overall and infarction-free survival. The relative advantage of surgery over medical therapy found in this study mirrored the findings of previous trials. One-way and multiway sensitivity analyses yielded absolute differences of less than 2% for overall and infarction-free survival rates, except that use of the upper limit of aspirin therapy's relative reduction of myocardial infarction yielded a 3% increase in infarction-free survival among patients receiving medical therapy. The authors concluded that therapeutic advances have improved outcomes for both medical and surgical patients, as well as preserving the advantages of surgery, thereby confirming that the conclusions of previous bypass trials remain valid.

Treatment strategies for hypoplastic left heart syndrome

Jenkins *et al*[62] used a decision analytic model to determine the optimal treatment strategy for maximizing 1 year survival among patients with hypoplastic left heart syndrome. **Grade B3** Using data from the literature and from a data set of 231 patients treated at four US surgical centers, the authors obtained probabilities for the following treatment strategies: complete staged surgery; stage 1 surgery as an interim to transplantation; patient listing, then stage 1 surgery if no donor is found within 1, 2 or 3 months; and patient listing without surgery until transplantation. The authors conducted one- and two-way sensitivity analyses on all probabilities in the decision tree to determine the values at which the optimal treatment strategy would change. In the base-case analysis, transplantation within 1 month emerged as the preferred strategy, followed by staged surgery if no donor is available after listing the patient for 1 month. These results were sensitive to several probability thresholds, including stage 1 and stage 2 mortality rates, the surgical center's 3 month organ donation rate, and the transplantation mortality rate. Centers with high organ donation rates are best served by a strategy of listing without surgery

until transplantation. Those with low donation rates, however, should perform staged surgery. In two-way sensitivity analyses, the authors found that the highest 1 year survival rates were achieved with staged surgery; patient listing, then stage 1 surgery at 1 month; and listing without surgery until transplantation. The authors concluded that each surgical center can determine its optimal treatment strategy with an algorithm that uses the center's organ donation rates and stage 1 survival outcomes, as well as individual patients' risk factors for mortality and organ availability.

Use of electrocardiogram to predict myocardial infarction

Shlipak *et al*[63] used a decision analytic model to assess the clinical utility of a previously reported electrocardiogram (ECG)-based algorithm to predict myocardial infarction in patients with left bundle branch block (LBBB). **Grade B2** The authors developed probability data for their analysis by first conducting a retrospective cohort study of patients presenting with LBBB on their initial ECG. The subsequent decision analysis was performed to determine which of the following strategies would constitute optimal therapy: thrombolysis for all patients with LBBB; no treatment for these patients; or use of the ECG-based algorithm to screen patients for the appropriateness of thrombolysis. The authors found that the ECG algorithm had low sensitivity and would predict less than 10% of myocardial infarctions in patients presenting with LBBB and acute symptoms. As a screening test, the algorithm resulted in a survival rate less than that yielded by thrombolysis and similar to that yielded by no therapy. In one-way sensitivity analysis, thrombolysis was always the optimal strategy. In two-way sensitivity analyses thrombolysis was always preferred, unless the ECG-based algorithm had a sensitivity greater than 85%. If the ECG algorithm were used as a screening test for thrombolytic therapy, almost no patients with LBBB and myocardial infarction would receive the treatment. The authors conclude that the ECG algorithm is a poor predictor of myocardial infarction and that thrombolysis should be used for all patients with LBBB and symptoms of myocardial infarction.

Summary

Decision analysis offers powerful techniques to better understand uncertain clinical decisions in cardiology. Increasing use of these techniques has already shown them to be very valuable in clinical and policy decision making in a variety of settings. Decision analysis may be most useful when clinical trial data do not clearly answer the clinical issue; when the clinical trial concludes that there are differences in risks and benefits across two treatment groups; when the relevant outcomes were not collected as part of the clinical trial; or when the decision maker is concerned with both clinical benefits and costs. Readers of a decision analysis paper should consider the strength of the evidence underlying the analysis, whether the model was constructed appropriately from a clinical perspective, and whether all relevant comparisons were included in the model.[5,6]

Key points

- Decision analysis may be most useful when clinical trial data do not clearly answer the clinical issue; when the clinical trial concludes that there are differences in risks and benefits across two treatment groups; when the relevant outcomes were not collected as part of the clinical trial; or when the decision maker is concerned with both clinical benefits and costs.
- Sensitivity analysis is used to assess the impact of uncertainty on decision analytic models.
- In reviewing a decision analysis paper, the reader must assess whether the population considered in the model is relevant to the clinician's population, the strength of the evidence available to the investigator in developing the model, and whether the model used by the investigator is constructed appropriately by including all relevant comparisons.
- Decision analysis has been used to assess a wide variety of clinical issues in cardiology.

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References

1. Paulker SA. Coronary artery surgery: the use of decision analysis. *Ann Intern Med* 1976;**85**:8–18.
2. Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Part 1 – getting started. *Med Decis Making* 1997;**17**:123–5.
3. Stason WB, Weinstein MC. Allocation of resources to manage hypertension. *N Engl J Med* 1977;**296**:732–9.
4. Kassirer JP, Moskowitz AJ, Lau J, Pauker SG. Decision analysis: a progress report. *Ann Intern Med* 1987;**106**:275–91.
5. Richardson WS, Detsky AS. User's guide to the medical literature: VII. How to use a clinical decision analysis: A. Are the results of the study valid? *JAMA* 1995;**273**:1292–5.
6. Richardson WS, Detsky AS. User's guide to the medical literature: VII. How to use a clinical decision analysis: B. What are the results and will they help me in caring for my patients? *JAMA* 1995;**273**:1610–13.
7. Greenberg ML, Malenka DJ, Disch DL. Therapeutic strategies for atrial fibrillation: the value of decision analysis. *Cardiol Clin* 1996;**14**:623–40.

8. Detsky AS, Naglie G, Krahn MD, Redelmeier DA, Naimark D. Primer on medical decision analysis: Part 2 – building a tree. *Med Decis Making* 1997;**17**:126–35.
9. Naglie G, Krahn MD, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 3 – estimating probabilities and utilities. *Med Decis Making* 1997;**17**: 136–41.
10. Krahn MD, Naglie G, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 4 – analyzing the model and interpreting the results. *Med Decis Making* 1997;**17**:142–51.
11. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5 – working with Markov processes. *Med Decis Making* 1997;**17**:152–9.
12. Weinstein MC, Fineberg HV *et al. Clinical decision analysis*. Philadelphia: WB Saunders, 1980.
13. Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical decision making*. Boston: Butterworth–Heinemann, 1988.
14. Petitti DB, Sidney S, Quesenberry CP Jr, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke* 1997;**28**:280–3.
15. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**: 1576–83.
16. Kupersmith J, Hogan A, Guerrero P *et al.* Evaluating and improving the cost-effectiveness of the implantable cardioverter-defibrillator. *Am Heart J* 1995;**130**:507–15.
17. Hogenhuis W, Stevens SK, Wang P *et al.* Cost-effectiveness of radiofrequency ablation compared with other strategies in Wolff–Parkinson–White syndrome. *Circulation* 1993;**88**: 437–46.
18. Barrett BJ, Parfrey PS, Foley RN, Detsky AS. An economic analysis of strategies for the use of contrast media for diagnostic cardiac catheterization. *Med Decis Making* 1994;**14**: 325–35.
19. Johannesson M, Jönsson B, Kjekshus J *et al.* Cost-effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *N Engl J Med* 1997;**336**:332–6.
20. Ashraf T, Hay JW, Pitt B *et al.* Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease. *Am J Cardiol* 1996;**78**:409–14.
21. Tsevat J, Duke D, Goldman L *et al.* Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol* 1995;**26**:914–19.
22. Zubialde JP, Lawler F, Clemenson N. Estimated gains in life expectancy with use of postmenopausal estrogen therapy: a decision analysis. *J Fam Pract* 1993;**36**:271–80.
23. Hulley S, Grady D, Bush T *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.
24. Herrington DM, Reboussin DM, Brosnihan KB *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;**343**:522–9.
25. Herrington DM, Howard TD, Hawkins GA *et al.* Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med* 2002;**346**:967–74.
26. Kellett J, Clarke J. Comparison of accelerated tissue plasminogen activator with streptokinase for treatment of suspected myocardial infarction. *Med Decis Making* 1995;**15**:297–310.
27. Dirsch DL, Greenberg ML, Holzberger PT, Malenka DJ, Birkmeyer J. Managing chronic atrial fibrillation: a Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. *Ann Intern Med* 1994;**120**:449–57.
28. The European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischæmic attack or minor stroke. *Lancet* 1993;**342**:1255–62.
29. Connolly SJ. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;**18**:349–55.
30. Ezekowitz MD, Bridgers SL, James KE *et al.* Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;**327**:1406–12.
31. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation (SPAF) Study: final results. *Circulation* 1991;**84**:527–39.
32. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stoke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;**343**:687–91.
33. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen aFASAK Study. *Lancet* 1989; **i**:175–9.
34. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–11.
35. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;**146**:473–81.
36. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995;**274**: 1839–45.
37. Solomon NA, Glick HA, Russo CJ, Schulman KA. Patient preferences for stroke outcomes. *Stroke* 1994;**25**:1721–5.
38. Moss AJ, Jackson Hall W, Cannom DS for the Multicenter Automatic Defibrillator Implantation Trial (MADIT) Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.
39. Friedman PL, Stevenson WG. Unsustained ventricular tachycardia – to treat or not to treat? *N Engl J Med* 1996; **335**:1984–5.
40. Boyko W, Schulman KA, Tracy CM, Glick H, Solomon AJ. The economic impact of prophylactic defibrillators. *J Am Coll Cardiol* 1997;**29**(2 Suppl A):256A.
41. Owens DK, Sanders GD, Harris RA *et al.* Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Ann Intern Med* 1997;**126**:1–12.
42. Schatzkin A, Cupples LA, Heeren T *et al.* The epidemiology of sudden unexpected death: risk factors for men and women in the Framingham Heart Study. *Am Heart J* 1984;**107**:1300–6.

43.Pinski SL, Trohman RG. Implantable cardioverter-defibrillators: implications for the nonelectrophysiologist. *Ann Intern Med* 1995;**122**:770–7.
44.The Coronary Artery Bypass Graft (CABG) Patch Trial Investigators and Coordinators. The CABG Patch Trial. *Prog Cardiovasc Dis* 1993;**36**:97–114.
45.Cardiomyopathy Trial Investigators. The cardiomyopathy trial. *Pacing Clin Electrophysiol* 1993;**16**:576–81.
46.The DEFIBRILAT Study Group. Actuarial risk of sudden death while awaiting cardiac transplantation in patients with atherosclerotic heart disease. *Am J Cardiol* 1991;**68**:545–6.
47.AVID Trial Investigators. Antiarrhythmics Versus Implantable Defibrillators (AVID) – rationale, design, and methods. *Am J Cardiol* 1995;**75**:470–5.
48.Connolly SJ, Gent M, Roberts RS *et al.* Canadian Implantable Defibrillator Study (CIDS): study design and organization. *Am J Cardiol* 1993;**72**:103F–8F.
49.Hine LK, Laird NM, Hewitt P, Chalmers TC. Meta-analysis of empirical long-term antiarrhythmic therapy after myocardial infarction. *JAMA* 1989;**262**:3037–40.
50.Health Care Financing Administration. Revisions to payment policies and adjustments to the relative value units under the physician fee schedule for calendar year 1995; Final rule. *Fed Reg* 2 December 1995.
51.Eisenberg JM, Schulman KA, Glick H, Koffer H. Pharmacoeconomics: economic evaluation of pharmaceuticals. In: Strom BL, ed. *Pharmacoepidemiology*, 2nd edn. New York: John Wiley & Sons, 1994.
52.Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;**113**:147–54.
53.Naimark DM, Detsky AS. The meaning of life expectancy: what is a clinically significant gain? *J Gen Intern Med* 1994;**9**:702–7.
54.Glick H, Heyse JF, Thompson D *et al.* A model for evaluating the cost-effectiveness of cholesterol-lowering treatment. *Int J Technol Assessment Hlth Care* 1992;**8**:719–34.
55.Mason JJ, Owens DK, Harris RA, Cooke JP, Hlatky MA. The role of coronary angiography and coronary revascularization before noncardiac vascular surgery. *JAMA* 1995;**273**:1919–25.
56.Tosteson ANA, Goldman L, Udvarhelyi S, Lee TH. Cost-effectiveness of a coronary care unit versus an intermediate care unit for emergency department patients with chest pain. *Circulation* 1996;**94**:143–50.
57.Nichol G, Laupacis A, Stiell IG *et al.* Cost-effectiveness analysis of potential improvements to emergency medical services for victims of out-of-hospital cardiac arrest. *Ann Emerg Med* 1996;**27**:711–20.
58.Stevenson LW, Warner SL, Steimle AE *et al.* The impending crisis awaiting cardiac transplantation: modeling a solution based on selection. *Circulation* 1994;**89**:450–7.
59.Wong JB, Salem DN, Paulke SG. You're never too old. *N Engl J Med* 1993;**328**:971–5.
60.Naimark DM, Detsky AS. The meaning of life expectancy: what is a clinically significant gain? *Med Decis Making* 1992;**12**:344.
61.Kwok YS, Kim C, Heidenreich PA. Medical therapy or coronary artery bypass graft surgery for chronic stable angina: an update using decision analysis. *Am J Med* 2001;**111**:89–95.
62.Jenkins PC, Flanagan MF, Sargent JD *et al.* A comparison of treatment strategies for hypoplastic left heart syndrome using decision analysis. *J Am Coll Cardiol* 2001;**38**:1181–7.
63.Shlipak MG, Lyons WL, Go AS *et al.* Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction. *JAMA* 1999;**281**:714–9.

8 Assessing and changing cardiovascular clinical practices

C David Naylor, David A Alter

Research into cardiovascular clinical practice has grown early enormously in volume and sophistication since the early twentieth century, driven by the worldwide prominence of atherosclerotic vascular diseases. The sheer volume of research literature has made it virtually impossible for even a subspecialist to stay abreast of her/his field. There is insufficient time for any evidence-oriented practitioner to critically appraise the full array of individual studies relevant to practice, and a real risk that, as the years go by, his/her filtering of the literature will prove misleading.

One solution is for practitioners to rely increasingly on integrative reports. As documented throughout this volume, evidence on a particular clinical topic is often usefully compiled in published meta-analyses, decision analyses, or practice guidelines. These integrative reports synthesize the best evidence available from multiple research studies to help define what a practitioner ought to do when confronted with a particular clinical situation.

While information uptake from integrative reports is necessary to ensure that clinical care evolves in evidence-driven directions, it may not be sufficient. For decades, researchers have shown that the rates of provision of various cardiovascular services vary inexplicably across regions and among nations. Some of this variation is random; some represents reasonable disagreement in the absence of definitive evidence about best practices. However, when practices are examined more closely using explicit criteria for appropriateness of care, it has become clear that actual practice sometimes differs sharply from what the evidence suggests ought to be done, raising concerns about quality of care. Quality concerns are further galvanized by evidence that technical skill and patient outcomes vary among procedural specialists. Not surprisingly, then, concerns with costs and quality of care have led a growing cadre of researchers, clinical leaders, facility managers, third party payers, and public policy makers to examine what clinicians do, and to seek ways to change clinical practice.

Assessing and changing clinical practice is central to the discipline commonly known as health services research. This chapter accordingly provides an introduction to some of the key methods of health services research as applied to cardiovascular medicine and surgery.

By definition this chapter demands a different treatment than later chapters where it is possible to provide integrative summaries of evidence to inform contemporary practice or steer future research. Since our focus is on how evidence is translated into clinical action, it stands to reason that there will seldom be one "right answer". Practice will instead be shaped not just by evidence, but by values and circumstances or context. Thus, it is important for the reader to suspend judgment as to whether there is necessarily one right health system, or one right profile of services for all populations with a given cardiovascular condition. A corollary of this point is that hundreds of descriptive and analytical studies have been published in cardiovascular health services research, many of which are context-specific. Our hope is to use a small number of these studies to heighten the reader's understanding of analytical principles and general lessons. For consistency, the examples will relate to clinical management of coronary artery disease, not to primary and secondary prevention. However, the conceptual frameworks are applicable to all areas of cardiovascular care. It is hoped that the evidence-oriented reader will be able to generalize the methodological insights from this chapter to his/her particular clinical and research context.

The specific objectives of this chapter are three:

- to outline the challenges and opportunities in gathering evidence about how health care is delivered;
- to describe and provide illustrations of the various types of studies done to evaluate processes and outcomes of care; and
- to examine some of the interventions that can be undertaken to improve the quality of cardiovascular care.

Gathering evidence about health care: challenges and opportunities

Study designs

Randomized controlled clinical trials are the most rigorous tool for confirming causal relationships between a given outcome and intervention or factor. Most randomized clinical

trials are designed to test the efficacy of an intervention within a controlled and stable environment. In contrast, health services research focuses on assessing and improving the provision of care in usual practice settings. Observational studies of health services may be cross-sectional or cohort designs. Cross-sectional studies or survey designs offer convenient one-off snapshots of patient populations, providers, or practice settings. Disease- and procedure-specific inception cohorts have the advantage of delineating relationships of particular variables to outcomes over time.

Cross-sectional and cohort methodologies can also be combined in a single study. For example, Payne and Saul[1] undertook a mail survey of a random sample of 16 750 residents of the Sheffield (UK) region, and found that 4·0% of subjects had symptoms suggestive of angina pectoris. The prevalence of angina was significantly higher in neighborhoods with lower socioeconomic status, but these same areas had significantly lower rates of mechanical revascularization. In other words, variations in service profiles were inversely related to ecological markers of both population need and population deprivation – obvious grounds for concern about access or equity of services use. The authors went further, however, and used data linkage methods to determine procedures that were actually provided to individuals identified as having angina. In so doing, they effectively shifted from a cross-sectional study reliant on ecological inferences to a full-fledged cohort design. They found that among subjects reporting angina who lived in affluent neighborhoods, 11·2% had undergone procedures, as compared to 4·2% in less affluent areas ($P=0·03$). Similar socioeconomic-related disparities in cardiovascular processes of care have been well described in both private and publicly-funded healthcare systems.[2,3]

Intervention studies in health services research focus on effectiveness and efficiency rather than efficacy. Quasi-experimental designs and formal randomized clinical trials are brought into play to test interventions designed to improve care. However, for obvious reasons, it is often providers, clinics, hospitals, or regions that are randomized rather than patients.[4]

Whatever the internal validity of the design chosen, health services researchers face a recurrent challenge to prove the external validity of their work. Some of the published literature in health services research consists of local or regional quality assurance projects with uncertain generalizability, and evidence-oriented practitioners may not find these studies applicable in their own context.

Data sources and collection

Health services researchers use both primary and secondary data sources. *Primary data* are collected by design to answer specific research questions, whereas *secondary data* are used for multiple purposes and their use for research purposes may be unplanned. Administrative databases designed for purposes of health service funding and administration are among the most common secondary data sources used in assessing clinical practice. Databases specifically constructed for ongoing epidemiologic surveillance of medical care, such as clinical registries, sit on the cusp between primary and secondary data, in that they are valuable for management and quality assurance, but are usually designed to meet specific research objectives as well.

Prospective primary data collection is costly but crucial for complex variables that are poorly covered in most secondary data sources – for example, patients' quality of life and psychosocial status. Retrospective primary data collection through chart reviews is also possible, but can be costly and time-consuming. It is best focused on routinely-recorded variables. For example, in charts of patients hospitalized with acute myocardial infarction (AMI), data on variables such as presenting symptoms, heart rate, blood pressure, ECGs, and cardiac enzymes are almost uniformly recorded. Absent primary data collection, there is always a risk that researchers will frame their questions around convenient access to data rather than addressing pressing issues.

Researchers often combine primary and secondary data collection, or incorporate multiple data sources to address specific research questions. For instance, a study may assess patients' short-term outcomes using self-administered health status questionnaires, and then track their subsequent use of health services and outcomes through administrative data. As an inexpensive solution to the limitations of single secondary databases, many researchers now link data across multiple administrative databases to provide better patient characterization and longitudinal follow up.[5] Finally, linkage of samples from randomized clinical trials to administrative databases is becoming more common both to provide accurate and cost efficient follow up of clinical trial populations and to enable comparison of the characteristics and outcomes of trial participants to the broader populations from which they are drawn.[6]

Data quality

Inaccurate measurement or recording is a particular concern when information comes from secondary data sources that are not designed for research or epidemiologic surveillance of medical care. For instance, Jollis *et al*[7] compared information about cardiac risk factors in an administrative database in patients undergoing angiography with information collected prospectively for a clinical database. A chance-corrected measure of agreement (kappa statistic) showed moderate to poor agreement as follows: hypertension (56%), heart failure (39%), and unstable angina (9%). Hannan *et al*[8] found similar discrepancies in comparing a cardiac surgery registry to an administrative database in New York State. While the accuracy of coding in

administrative databases appears to be improving over time,[9,10] significant undercoding of comorbidities still exists, especially among the elderly.[10,11]

As noted above, limited or inaccurate data in insurance databases or computerized hospital discharge abstracts may be supplemented or corrected by chart audits. A more efficient approach is to establish registries geared to measuring key patient characteristics, process-of-care elements, and relevant outcomes. Registries are proliferating in cardiovascular medicine and surgery, especially for acute ischemic syndromes and coronary surgery. This has led, however, to a new challenge – that is, agreement on a set of core data elements and definitions so that reliable comparisons can be drawn across registries from different jurisdictions.

Key measures

Processes of care

Process of care is an umbrella term, encompassing all inputs into the clinical encounter that are relevant to the effectiveness and efficiency of the service provided. Process measures of particular interest for this chapter are the clinical decision-making patterns of physicians and other health professionals, as these reflect the uptake and use of evidence from the literature of medicine. Other inputs may also be relevant, such as hospital staffing ratios and qualifications of providers. Not infrequently, researchers use characteristics of the admitting hospital as ecologic proxies for processes of care that may affect individual patients.[12–14] In this respect, hospital volumes for specific diagnoses or procedures are often taken as proxies for the expertise or experience of the relevant providers. Some measures are intermediate. Waiting times for services and lengths of stay, for example, are at once indicators of the process of care, and outcomes of interest to patients, professionals, and administrators alike.

Outcomes

The most important outcomes studies in cardiovascular care are conventional randomized trials used to test the efficacy of novel interventions, as described elsewhere in this volume. However, non-randomized outcomes studies have a role in assessing practice patterns. These studies allow for the evaluation of therapies and the natural history of disease in real-world settings.[15,16] In some cases where randomization is simply not feasible (for example, socioeconomic status as a factor in prognosis), they also allow us to isolate patient characteristics from process-of-care factors to help elucidate pathophysiologic mechanisms of disease.[17,18] Perhaps most importantly, a cardiovascular service may be provided to the right patient at the right time, and for the right reasons, but be delivered in a technically substandard fashion that leads to needlessly poor outcomes. Non-randomized outcomes studies are therefore useful indicators of quality of care for technically demanding services.[19]

Outcomes of interest, after Kerr White, can be conveniently remembered as the six "Ds": death, disease, dysfunction, disability, distress, and dissatisfaction.[20] The easiest outcomes for health services researchers to measure are those that are defined objectively and usually captured in large insurance databases or computerized hospital administrative data. These include death, routinely-coded complications following surgery, or hospital re-admissions. Linkage to vital status registries is also performed to track out-of-hospital deaths. Unfortunately, health services researchers have often failed to assess other outcomes, such as functional status, symptom relief, or overall quality of life, that are very important to patients and their physicians.[21]

Assessing processes and outcomes of care

Assessing processes of care

Descriptive studies

Health services research gained considerable momentum in the 1970s and 1980s from studies pioneered by Wennberg and Gittelsohn,[22,23] which documented unexplained geographic variations in rates of services. These early studies were a population-wide extension of research done in single hospitals or in public and private prepayment plans starting in the 1930s and showed variations in how different physicians managed apparently similar patients. However, Wennberg and coworkers coupled computerized systems of hospital discharge abstracts to census data and showed that citizens living in one area were significantly more or less likely to undergo certain procedures than those living in other areas. They also showed that greater variations were generally demonstrable when procedures were more discretionary or elective, or where there was uncertainty about the indications for the procedure or service of interest.[24,25] In these latter instances, values and circumstances apparently interact strongly with evidence in driving decisions about service provision.[26]

Such descriptive studies continue to appear in the health services literature. They involve simple rates or proportions, with various numerators and denominators. Possible numerators include primary care visits or encounters, specialized diagnostic and therapeutic services, composite measures of use, such as overall numbers of hospital bed-days used per 10 000 residents, or even mean expenditures per capita on health care for all types of services. Denominators may tally patients according to the clinics or hospitals that they use, or by their residency in a given geographic area. These two denominators may be melded into hospital market shares – for example, the total population living in an area where a specified percentage of all patients receive their cardiac care at the hospital of interest.

Several statistical summary measures are used in variations analyses.[27,28] Computational details and statistical properties of these measures are beyond the scope of this chapter. What matters is that the degree of variation should be both statistically significant and suggestive of meaningful differences from the standpoint of quality, accessibility, or efficiency of care provision. Thus, examination of the patterns of service and potential outcome implications is arguably more illuminating than the focusing on specific summary measures.

The interpretive challenges of such descriptive studies are illustrated by evidence assembled with clinical and/or administrative data showing sex differences in treatments for patients hospitalized with acute myocardial infarction (AMI).[29–31] Sex differences in care have been found in several nations, but the relationship between gender and service intensity is not consistent.[32–34] The debate about the gender gap in service intensity is likely to continue until there is clearer evidence from randomized trials to delineate whether and how men and women with otherwise similar cardiovascular disease should be managed differently.

Variations in processes of care have been well documented to extend beyond patient factors. As one example of this genre, Chen *et al*[35] documented significant interhospital variations in length of stay after AMI in Ontario. These variations persisted after adjustment for various factors such as coronary angiography on the index admission, patients' age and sex, and comorbidity as inferred from secondary diagnoses on discharge abstracts. In almost any jurisdiction and for almost any cardiovascular service where interpractitioner, interinstitutional, or interregional variations in patterns of service provision have been sought, they are demonstrable.

In sum, descriptive studies showing process-of-care variations are tantamount to screening tests in medical practice. They raise the possibility that there may be a problem with quality, efficiency, or accessibility. However, the finding of statistically significant variations is predicated on a null hypothesis that processes of care should vary no more than would be expected on the basis of the play of chance. Most such studies apply direct or indirect standardization to control for differences in the age–sex profile of the populations being compared, but may not consider myriad other sources of variation (Box 8.1). In response to that limitation, researchers may either develop evidence-oriented criteria to examine decision making at the level of the individual case, or try to link processes and outcomes of care in the same study as a means of inferring a causal connection. We examine both types of studies below.

Box 8.1 Sources of regional/institutional variation in service profiles

- Age and sex composition
- Age/sex specific disease incidence
- Random variation with time and place
- Availability and practice organization, such as
  - primary care
  - specialist services
  - hospital services/bed provision
  - overall funding levels
  - methods of payment
  - alternative services
- Referral patterns
- Practice styles of service providers
- Variations in patient expectations, demands, health education/behaviors
- Rates of previous service (for example, organ removal where relevant)

Criteria-based utilization analyses

Given the limitations of descriptive studies that delineate variations in processes of care, health services researchers have developed other methods to determine whether the right service is provided to the right type of patient for the right reasons at the right time and place. One approach is implicit reviews of case records, drawing on the individualized judgments of expert clinicians. Unfortunately, lack of standardization renders implicit reviews unreliable.[36,37] Explicit criteria, which form the basis for most process-of-care analyses in the literature, have the advantages of standardization and consistency, as well as transparency. Where necessary, trained staff can apply them retrospectively to medical records without a major time commitment from clinicians. These studies are described in America as "utilization reviews" and in the UK as "clinical audits".[38]

Process-of-care audits have the advantage of efficiency in comparison to outcomes studies as quality management tools. Bad outcomes caused by negligence and incompetence are (happily) rare. Technical competence does not necessarily equate with good judgment and appropriateness of service provision. Moreover, bad outcomes from *under*-treatment are hard to detect because the impact of modern cardiovascular care is often to make life only a little better on average for patients or to reduce their risk of otherwise rare events. For example, from overviews of randomized placebo-controlled trials we know that β blockers confer about a 25% *relative* reduction in mortality in the first year after a myocardial infarction. For a cohort of medium-risk patients, this equates to an *absolute* reduction in cumulative postdischarge mortality from 4% to 3%. To show such a mortality difference on a comparative outcomes audit of two practices (80% power, 2-sided alpha of 0·05), we require over 5000 patients per practice; but a 1% mortality difference presumes absolutely no use of β blockers in the practice with poorer outcomes. A more realistic assumption would be that about 70% of eligible patients receive β blockers in the practice with worse outcomes versus over 95%

in the exemplary practice. Based on the randomized trials, this equates to perhaps a 0·2% increase in mortality. To detect such a small difference in mortality would require over 100 000 patients per practice! In contrast, one could simply examine charts to see whether patients were getting β blocker prescriptions, versus 70% in the other practice, one would only need to examine about 75 charts in each practice for a reliable assessment.

This latter audit is simple in another respect. We can basically use randomized trial inclusion and exclusion criteria to decide who should be getting the drug, make sure there are no obvious contraindications or medication intolerances documented on the medical record, and tally whether patients are getting the treatment that they ought to be getting. In general, however, audits require close attention to the validity, application, and applicability of the criteria chosen (Box 8.2).[38]

Box 8.2 User's guide to appraising and applying the results of a process-of-care audit

- *Are the criteria valid?*
  - Was an explicit and sensible process used to identify, select, and combine evidence for the criteria?
  - What is the quality of the evidence used in framing the criteria?
  - If necessary, was an explicit, systematic, and reliable process used to tap expert opinion?
  - Was an explicit and sensible process used to consider the relative values of different outcomes?
  - If the quality of the evidence used in originally framing the criteria was weak, have the criteria themselves been correlated with patient outcomes?
- *Were the criteria applied appropriately?*
  - Was the process of applying the criteria reliable, unbiased, and likely to yield robust conclusions?
  - What is the impact of uncertainty associated with evidence and values on the criteria-based ratings of process of care?
- *Can you use the criteria in your own practice setting?*
  - Are the criteria relevant to your practice setting?
  - Have the criteria been field-tested for feasibility of use in diverse settings, including settings similar to yours?

Adapted from Naylor and Guyatt[38]

Validity of audit criteria

To be valid, the criteria must have a direct link either to improving health (as is obvious with β blockers for secondary prevention after AMI) or to lowering resource use without compromising health outcomes. There should be an explicit and sensible process to identify, select, and combine the relevant outcomes-based evidence.

The hierarchy of evidence outlined above by Kitching, Sackett and Yusuf applies here. Evidence from randomized trials is strongly preferred, but evidence from observational sources cannot be ignored. For example, from observational studies within trials, it is plain that the largest survival benefits with thrombolytic therapy are obtained when treatment is administered early.[39] It would be unethical to randomize patients to receive thrombolysis on a delayed or urgent basis to determine how large these effects are. Thus, guidelines now recommend that thrombolytic therapy be administered, wherever possible, within 30 minutes of a pateint's arrival to hospital.[40] Studies from America,[41] Canada,[42] the UK,[43] Italy,[44] and New Zealand[45] have all documented remediable problems with treatment delays in administering thrombolytic agents to eligible patients. All are classic examples of criteria-based audits.

If only some of the indications for a particular service under audit will be covered by high quality evidence, then weaker sources of evidence, inference, and expert opinion must often be brought into play, usually through formal panel processes. Such panels should include an explicit process for selecting panelists, and a sensible, systematic method for collating their judgments. In this respect, the RAND group has pioneered multispecialty panel methods that are widely emulated.[46–48] Scenarios are compiled that describe a potential indication for the procedure or clinical service in question. Each expert panelist independently rates hundreds of different case scenarios on a risk–benefit scale. Scenarios are re-rated at a panel meeting after patterns of interpanelist agreement and disagreement are shown anonymously and discussed. The final set of panelists' ratings then determines whether a given indication is deemed potentially appropriate, uncertain, or inappropriate.

With this method, it is not clear whether the appropriateness ratings for any given indication rest primarily on research evidence or inference, extrapolation, and opinion. The relative values placed on different outcomes are also unclear. For example, in randomized trials of CABG versus percutaneous transluminal coronary angioplasty (PTCA),[49–52] PTCA has a slightly lower early mortality, along with lower initial costs and more rapid recovery from the procedure. Longer term mortality data are similar, but CABG patients appear to achieve better symptom relief, have decreased use of medication, and require fewer subsequent procedures.[53] When an expert panel addresses the respective appropriateness of PTCA and CABG, the findings reflect these trade offs, but we cannot be sure that patients themselves would make the same choices. The conflation of facts and values in panel-based criteria is highlighted by studies showing that the nationality of a panel markedly affects the criteria and results of applying them to cardiovascular procedures (Table 8.1).[26,54] Indeed, available evidence would also suggest that hospital practice settings and resource availability influence panel-based criteria.[55] Nonetheless, the RAND methods compare very favorably with those used to create several utilization review tools now in widespread use.[38]

Table 8.1 Categorization of appropriateness of indications for cardiovascular procedures based on actual audits in the field: cross-national differences in expert panel assessments

Procedure	Location/sample	Year	*n*	Panel nationality	Appropriate	Uncertain	Inappropriate
Coronary artery bypass graft	USA, 4 hospitals in Washington State	1979–80	386	American	62	25	13
		1979–82		British	41	24	35
	UK, 3 hospitals in Trent region	1987–88	319	American	67	26	7
				British	57	27	16
	Canada, 13 hospitals in Ontario and British Columbia	1989–90	556	American	88	9	3
				Canadian	85	11	4
	USA, 15 hospitals in New York State	1990	1336	American	91	7	2
				Canadian	85	10	6
Coronary angiography	USA, 4 hospitals in Washington State	1979–80	376	American	50	23	27
		1979–82		British	11	29	60
	USA, Medicare beneficiaries in 3 states	1981	1677	American	74	9	17
				British	39	19	42
	UK, 3 hospitals in Trent region	1987–88	320	American	71	12	17
				British	49	30	21
	Canada, 20 hospitals in Ontario and British Columbia	1989–90	533	American	77	18	5
				Canadian	58	33	9
	USA, 15 hospitals in New York State	1990	1333	American	76	20	4
				Canadian	51	39	10

Adapted from Naylor[26]
The data show the appropriateness ratings for sets of identical patient charts as described. Each set of charts was assessed according to criteria derived by expert panels based in the listed countries.

Application and applicability of the audit criteria

Application of explicit process-of-care criteria often rests on data derived from retrospective chart reviews by professional auditors. The audit process must therefore be reliable. Biases can be introduced through skewed sampling of practitioners, hospitals, and patients. Even a meticulous audit, however, may miss mitigating factors. Thus, in many instances, if the explicit review shows potential problems with the appropriateness of a service, the case is assessed by experienced clinicians to preclude "false positives".

It is also crucial that enough cases be reviewed to draw robust conclusions. For example, in one study, RAND researchers used explicit criteria to assess the appropriateness of PTCA in 1990 for 1306 randomly selected patients in 15 randomly selected New York State hospitals.[54] The inappropriate utilization rate varied by hospital from 1% to

9% ($P = 0{\cdot}12$). Differences of this magnitude, if real, could be important to patients, payers, and policy makers. Thus, this sample size may have been insufficient for the investigators to confirm important differences in quality among hospitals.

Although the task is subjective, end users must consider intangibles such as local medical culture and practice circumstances before accepting audit criteria that may not be relevant. The stronger the evidence on which the criteria are based, the less one needs to consider local factors; for example, few medical cultures would reject aspirin for AMI – a cheap and simple drug treatment that has been definitively proven to yield reductions in mortality. With weaker evidence and higher costs, however, the judgments are less straightforward.

Last, even if criteria are sufficiently valid and relevant, training times and other costs must be considered. Special logistical problems arise when criteria are used for concurrent case management rather than retrospective utilization review. Any errors associated with concurrent care management will have immediate consequences for individual patients and physicians. Nonetheless, many American hospitals already do a range of concurrent reviews.

The use of chart audits to infer appropriateness

Table 8.1 shows the proportion of appropriate, inappropriate, and "uncertain" indications for cardiac procedures as randomly audited in the USA, UK, and Canada.[26,56–58] Since all the procedures shown are used many times more often in the USA than in the UK, it seems almost paradoxical that the proportions of inappropriate cases are not much higher in the USA. The literature has suggested that relationships between appropriateness of care and cardiovascular service intensity are similarly weak within nations.[25,58–60]

However, two studies shed a slightly different light on this issue. The rates of all major coronary procedures in New York State, USA are about twice as high as in Ontario, Canada.[61] Figure 8.1 shows the relative rate of isolated coronary artery bypass surgery (CABG) for the two jurisdictions by age and anatomy. Overall, only 6% of CABG patients in Ontario versus 30% of patients in New York had limited coronary artery disease – one or two vessel disease without proximal left anterior descending (PLAD) involvement. However, more patients in New York had left mainstem disease (23% *v* 16%, $P < 0{\cdot}001$). In relative terms, the differences are most dramatic among elderly persons. For example, New York brings 17 times as many persons over the age of 75 to surgery with anatomic patterns of coronary disease that are not associated with life expectancy gains after CABG. Nonetheless, much of this extra use could pass an appropriateness audit, since 90% of the persons with limited coronary anatomic disease in New York had moderate to severe angina before surgery.[61]

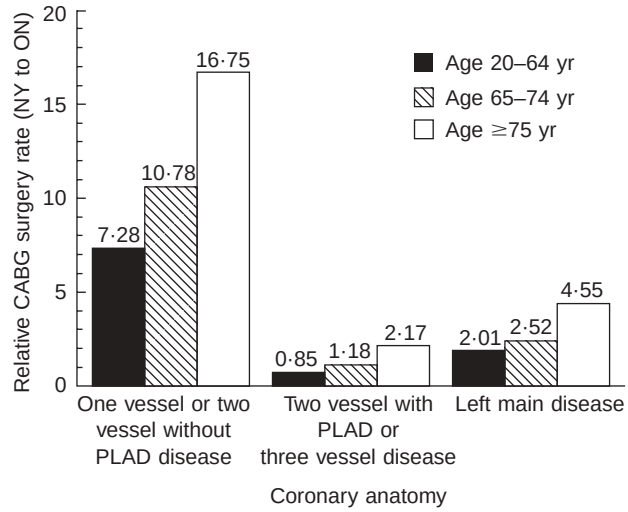

Figure 8.1 Relative rate of isolated CABG for New York State (NY) and Ontario (ON) according to age and disease anatomy. Adapted from Tu *et al*.[61] PLAD, proximal left anterior descending.

A reasonable inference is that major increases in capacity, and expansion of population-based services rates, are associated with *diminishing marginal returns*. The Canadian approach – fixed budgets in a universal health system, and "managed delay" with organized waiting lists[62] – seems to promote more efficient use of resources, with patients receiving surgery primarily if they are likely to have life expectancy gain. However, restricted use of coronary angiography leads to some implicit rationing that affects primarily the elderly, and a certain proportion of patients at all ages with left mainstem disease are not detected and/or do not undergo surgery.

A second study[63] of CABG develops this argument more strongly. Rather than using appropriateness criteria from an expert panel, Hux *et al* based their case-specific process assessments on a meta-analysis of randomized trials by Yusuf *et al*[64] Whereas the broad category of "appropriate" care as defined by expert panels includes a range of risk–benefit ratios, a trials-based assessment allowed estimation of the degree of potential 10 year survival benefit conferred by CABG surgery among patients for whom, by and large, it was appropriate. Hux *et al* found that only 6% of 5058 Ontario patients undergoing isolated CABG in 1992–93 fell in the low benefit category – that is, patients for whom there is no survival advantage from early CABG. However, the degree of anticipated benefit differed according to the center where surgery was provided. For instance, the proportion of patients in a high-benefit category ranged from 65·2 to 79·9% ($P < 0{\cdot}001$). Significantly more patients were in a high-benefit category in hospitals serving areas with lower population-based rates of CABG. Analyzing the data by site of residence, there was an inverse relationship between marginal degree of life expectancy gains and the surgical rates for each county.[63]

In sum, if one accepts that overtly inappropriate services are unlikely to be commonplace in any health system, the relationship between appropriateness of care and population-based services rates can be redefined. Rather than seeking to relate the prevalence of bad judgment to high service intensity, or decrying health systems with low service intensity for rationing care, researchers might better assess whether the marginal returns of other forms of cardiovascular care are indeed smaller in areas where those services are used more frequently. The policy decision then becomes one of trade offs: given competing demands on scarce healthcare resources, at what point do the marginal returns of particular cardiac services become low enough that further investment in those services cannot be justified?

Evidence-oriented clinicians must be positioned to contribute to these debates by marshaling comparative utilization data that help decision makers make explicit determination of the likely yields from funding different sets of cardiovascular and non-cardiovascular services. Arguably, they must also use these evaluative tools to safeguard their patients against inappropriate *underuse* of necessary services.

Again, explicit process-of-care criteria can be helpful. For example, analytical variations studies using American data have repeatedly shown that black and uninsured patients have lower coronary angiography rates than those who are insured.[65–67] Laouri *et al*[68] drew on audit data from four teaching hospitals in Los Angeles and assembled a cohort of 352 patients who met explicitly defined criteria for the necessity of coronary angiography as established by an expert panel. The patients were tracked forward for 3 months and, after adjustment for confounding factors, those managed in the public hospital system had a 35% rate of angiography versus 57% for private hospital patients ($P < 0{\cdot}005$).

Two recent studies incorporate appropriateness criteria to provide further evidence for underuse of coronary interventions. The first by Guadagnoli *et al*[69] examined variations in coronary angiography after AMI in approximately 50 000 elderly Medicare beneficiaries in the USA. Among those patients with ACC–AHA class 1 indications, coronary angiography was used less often among Medicare beneficiaries enrolled in managed-care plans than among those with fee-for-service coverage. Moreover, utilization rates among elderly patients with class I indications for angiography were low in both groups (37% *v* 46%), suggesting room for improving the care of such patients with acute myocardial infarction. In contrast, the rate of angiography use among those with ACC–AHA class III indications (where angiography was deemed not useful) was similarly low (13%) in both groups. The second prospective study applied appropriateness ratings for coronary revascularization procedures to 2552 patients identified at the time of coronary angiography for various indications. Among 908 patients with indications appropriate for PTCA, 34% were treated medically. Among 1353 patients with indications appropriate for CABG, 26% were treated medically. Relating processes to outcomes, the research team also found that medically-treated patients deemed appropriate for revascularization were more likely to experience adverse events downstream.[70]

The lesson, simply put, is that evidence must be sought for both inappropriate *overuse* and *underuse* of cardiovascular services in any and all healthcare systems.

Outcomes studies and process–outcome relationships

Types of outcome studies

Researchers, clinicians, and administrators alike are also drawing on outcomes with increasing frequency as a means of assessing quality of care. To repeat a point made earlier, various biases threaten the validity of inferences drawn from these non-randomized studies; but they have a useful role both in monitoring quality of care and as a source of evidence when randomization is not feasible or appropriate.

Just as studies in the 1960s and 1970s showed geographic and institutional variations in broad markers of processes of care, so also did the 1980s and 1990s see the publication of research demonstrating significant mortality differences across physicians,[71] hospitals,[72] regions,[73] and health systems.[74] The magnitude of mortality variations has been meaningful, even amongst relatively homogeneous groups of patients. For example, Tu *et al* demonstrated marked interhospital and interregional variations in 1 year risk-adjusted mortality rates for patients hospitalized between 1994 and 1997 in one Canadian province. Mortality ranged from 20·8% to 27·4% across regions, and from 17·6% to 32·3% across hospitals admitting 100 or more AMI cases per year.[75] Regional variations persist even in highly selected subpopulations of patients. Pilote *et al* demonstrated that 1 year AMI mortality rate across eight US census regions ranged from 8·6% to 10·3% among the population enrolled in GUSTO-1.[73]

As with descriptive studies of variations in process of care, these high-level outcomes studies function largely as screening tests: they often raise more questions than answers. Researchers use multivariate analyses to adjust for prognostic differences in the patient populations being compared. However, since patients are not randomized to different sites or regions, there is uncertainty about the extent to which unmeasured variation in patient characteristics accounts for the residual outcomes variation. Furthermore, the higher the level of comparison and the longer the follow up, the more uncertain the causal inferences become. Regional differences in long-term AMI outcomes, for example, may reflect genetic differences in populations, environmental factors, regional variation in health behaviors and socioeconomic status, as well as more conventional factors such as variations in processes of care

on the index hospitalization and follow up interventions (for example, revascularization or rehabilitation).

For convenience, we suggest that outcomes analyses in health services research can be classified variously as *quality-of-care screening studies* or *process/outcome hypothesis studies*.

Quality-of-care screening studies focus on outcomes to detect variations in quality of care. They are most powerful when applied to short-term outcomes that are closely tied to a particular episode of illness or procedure, and a provider or institution. In these circumstances, causal inferences are more straightforward. Their applicability is clearest for technically demanding procedures, such as PTCA or CABG, where variations in outcomes are taken as proxies for operator skill. However, even in such instances, other factors in pre- and perioperative care may be important. For relatively homogeneous diagnoses, outcomes studies may also sometimes be a useful screen to determine if detailed process-of-care analyses are required. For example, if inhospital mortality were found to be similarly low across a whole set of institutions, there would be little rationale for undertaking a major audit of processes of care.

Ultimately, the goal of such studies is to isolate one or more process-of-care factors that can be modified to lead to consistently better outcomes. Outcomes analyses may also be used to validate process-of-care criteria or their application, for example, the study of underuse of revascularization by Hemingway *et al* cited above.[70] In this sense there is overlap between the two categories of non-randomized outcomes studies. But an important distinction should also be drawn. Quality-of-care studies are concerned with the applicability of existing evidence in a particular context. Other outcomes studies may be initiated with a view to deriving or supporting generalizable hypotheses about the process–outcome relationship. They are poor cousins to randomized trials from the standpoint of strength of evidence. For true efficacy assessments, randomized trials are usually possible and always preferable, given the unavoidable biases of observational studies.[76] A poorly conducted non-randomized outcomes comparison for quality management purposes may at worst mislead patients and tarnish the reputation of a number of capable cardiologists or cardiac surgeons. A poorly conducted non-randomized outcome comparison of two treatments may, if taken seriously, misguide clinical practice worldwide.

That caveat aside, these process/outcome hypothesis studies can be useful to illustrate unanticipated harm from interventions, test the external validity of randomized trial results, generate hypotheses about interventions that may be worth testing with formal experimental designs, and, in special circumstances, provide an acceptable level of evidence for adopting a particular intervention.

There are many methods available for examining the relationship between processes of care and outcomes. The simplest method is to draw broad causal inferences using ecological comparisons, for example, correlating differences in processes and outcomes across two or more institutions or jurisdictions. However, the greater the difference between service settings being compared, the more difficult it is to be sure that patients were similar, or to isolate which aspects, if any, of the process of care relate to the outcomes observed. This is especially true when comparisons are made on a broad geographic footing between regions or countries in which populations and processes of care differ in many ways. In these latter comparisons, we are obviously veering away from the use of non-randomized outcomes data to benchmark technical quality of care for homogeneous procedures, and entering the more complex realm of process/outcome hypothesis studies.

This genre is typified by several studies[77–80] showing that Canadian patients have more symptoms, worse functional status, or higher death/re-admission rates after AMI than do American patients. The reasons for these differences, however, are unclear. For example, Mark *et al*[78] in a GUSTO-1 substudy found that, while rates of revascularization were much higher in the USA, Canadians drew their post-MI care more often from family physicians and general internists, while Americans relied more on cardiologists and received more cardiac rehabilitation services.[78] In other words, revascularization was only one factor among many that might explain differences in outcomes across two health systems.

In an effort to limit the effects of competing process factors, analysts have borrowed the concept of instrumental variables from econometrics.[81] This approach compares patients' outcomes according to some characteristic that sharply distinguishes the care of two or more groups of patients. Thus, one might attempt to elucidate the impact of differences in the rate of revascularization across hospitals with and without on-site interventional capacity. Alter *et al*[72] recently used such a design to show that hospitals with on-site revascularization facilities had a lower rate of non-fatal composite outcomes (recurrent cardiac hospitalization and emergency department visits), and were also 3·5 times more likely to refer patients to myocardial revascularization procedures. Yet, despite the markedly higher rates of invasive procedures, the non-fatal outcome advantages of invasive-procedure hospitals were actually explained by their teaching status!

In sum, given the relatively weak inferences possible from most observational studies of outcomes, alternative strategies for ensuring the quality of medical care should always be considered. It will often be feasible and more efficient to use randomized trials or meta-analyses of trials to establish optimal management strategies, and then ensure that quality of care is maintained by monitoring the process of care in that well-proven practices are consistently applied to eligible patients. On the other hand, for high volume and technically demanding procedures where reasonable risk

adjustment methods can be brought into play, outcomes measurement has merit for quality control so long as the results are interpreted carefully. Finally, studies aimed at delineating process–outcome relationships will continue to be valuable, but researchers and evidence-oriented practitioners alike will often find that the interpretation of the findings plunges them into a thicket of causes, effects, and epiphenomena.

Special challenges in non-randomized outcomes studies

In this section, we delve more deeply into some of the analytical challenges of non-randomized outcomes studies. Many types of biases have been described in the literature,[82,83] but selection bias is a recurrent concern whether one is comparing the outcomes of two cardiac surgeons, or using non-randomized data to develop hypotheses about the effectiveness of pharmacologic or non-pharmacologic therapies in real-world settings. Indeed, the ubiquity of selection bias in health services research arises from the fact that ordinary good judgment in practice inevitably means that there are systematic differences in the characteristics of patients who are selected for particular interventions as compared to those who are not.

Patients selected post-MI to undergo coronary angiography, for example, are often younger and healthier than other MI victims.[72,82] The survival benefits observed for those undergoing angiography may therefore be due to prognostic characteristics rather than to revascularization consequent upon angiography. This latter phenomenon is known as confounding and is a common result of selection biases. Confounding occurs when particular factors are associated with both a study (process) variable and the outcome of interest.

Researchers therefore routinely employ some form of multivariate analysis to adjust for imbalances in prognostic factors between groups under study. A complementary strategy is to confirm the consistency of the findings after restricting the analysis to a relatively *low*-risk subgroup of the patients being examined.[76] Eliminating patients in higher risk categories associated with more widely varying physiologic states increases the likelihood of a "level playing field" for comparisons.

For many common procedures and diagnoses, researchers can draw on validated prognostic indices and risk-adjustment algorithms as signposts in carrying out study-specific multivariate analyses. For frequently studied procedures such as CABG, major studies have tended to show relative consistency in the types of prognostic clinical factors that must be taken into account for risk adjustment purposes.[84] Not surprisingly, risk-adjustment models appear to perform somewhat better with clinical as compared to administrative data.[85] However, the key to predictive performance appears to be better data, not more variables. Studies have suggested that the accuracy of risk-adjustment models reaches a plateau after use of only a few key variables. Tu *et al*,[86] for example, examined risk-adjusted hospital mortality rates for CABG with multisite registry data. They determined that six core variables in a risk-adjustment model (age, gender, emergency surgery, previous CABG, LV dysfunction, left main disease) permitted modest discrimination between patients who did and did not die postoperatively (area under the receiver operating characteristic [ROC] curve = 0·77). Statistical performance improved only trivially with the inclusion of six additional characteristics, and the relative rankings in the risk-adjusted mortality rates between hospitals did not change. Notwithstanding these studies, the ultimate number as well as the type of clinical variables required in a risk-adjustment model will obviously depend upon the disease being assessed, the processes and outcomes of interest, and the unit of analysis (for example, risk-adjusted mortality rates per physician *v* per hospital).

Propensity scores can also be used to contain the impact of confounding.[87] This method reduces the entire collection of background characteristics into a single composite characteristic (that is, the propensity to receive treatment *v* no treatment), which is then used to subclassify patients further into categories of relative equal propensities. Accordingly, the case-mix composition of patients with similar propensities is balanced, and outcome differences can be directly compared between those receiving and not receiving treatment.

While not a solution for confounding *per se*, hierarchical statistical modeling has recently found favor as a useful analytical tool in outcome studies.[88,89] Data in health research frequently exist in an ordered hierarchical structure: that is, patients are managed by physicians who practice within hospitals. In contrast, traditional multivariate techniques ignore the natural hierarchy of data and treat each observation as if it were independent (Figure 8.2).

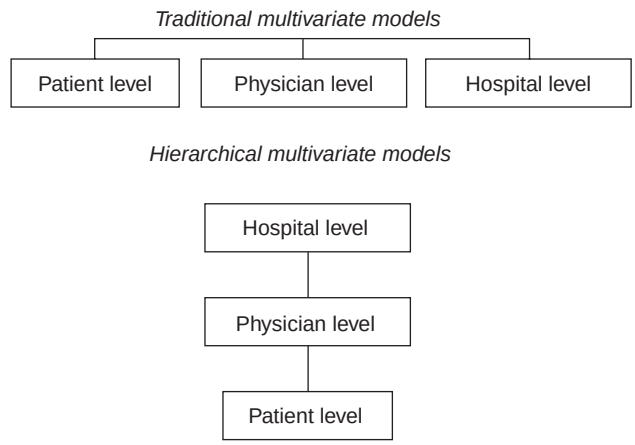

Figure 8.2 Schematic view of hierarchical *v* traditional models

The use of hierarchical modeling makes intuitive sense since patients may share higher-level characteristics, leading to observations that are not necessarily independent of one another. The existence of standardized inhospital processes of care (for example, treatment protocols and care maps) may result in greater homogeneity in treatments across patients admitted to a particular institution. Accordingly, the use of traditional multivariate analyses may lead to an artificially inflated number of independent observations and an underestimate in the magnitude of standard error and potential alpha error.[90]

While the embedding of multivariate analyses in a hierarchical structure has obvious advantages, neither this technique nor fastidious risk-adjustment methods can match the effectiveness of randomization when balancing the case-mix distribution between two groups, especially because researchers and quality-of-care evaluators are unlikely to know all the prognostic factors that interact with processes of care and may alter outcomes. Moreover, even if key prognostic confounders are known, they may not all have been measured or recorded accurately. Box 8.3 sets out some general principles that may be useful when researchers appraise non-randomized outcome studies.[38]

Box 8.3 User's guide to appraising an observational outcomes study

- Are the outcome measures accurate and comprehensive?
- Were there clearly identified, sensible comparison groups?
- Were all important determinants of outcome measured accurately and reliably?
- Were the comparison groups similar with respect to important determinants, other than the one of interest?
- Was multivariate analysis used to adjust for imbalances in patient prognostic factors and other outcome determinants?
- Did additional analyses (particularly in low-risk subgroups) demonstrate the same results as the primary analysis?
- Did any multivariate analysis take into account natural heirarchies in the data, such as clustering of patients within providers' practices and/or within institutions?

Adapted from Naylor and Guyatt[38]

Changing practice patterns

General considerations

Practices clearly change over time in response to published evidence. At times, these changes can be rapid and dramatic, particularly when an innovation is associated with overwhelmingly positive risk–benefit ratios and is feasible for large numbers of practitioners to adopt. This model of knowledge-based practice change is termed *passive diffusion*. Its impact is heightened by the extent to which the mass media pick up major medical advances, and by the marketing initiatives of drug and device manufacturers. However, as implied by studies showing unexplained and undesirable variations in practice patterns, the model of passive diffusion leads to inconsistent uptake of evidence into practice.

How, then, can evidence be incorporated into practice more consistently, and what happens when data are in hand showing either that practice departs sharply from what available evidence suggests should be the norm, or that technical competence is below standard? How can the gap between "is" and "ought" in medical care be closed? These questions relate to changing physician (and system) performance, and follow logically from work done to measure or assess practice processes and outcomes.

Although there is limited randomized evidence on this topic for specific aspects of cardiovascular care, a wealth of experience – some unhappy – has shown that direct incentives and disincentives, financial and otherwise, can have a major impact on practice. Bonuses are paid in American managed care organizations if practitioners meet certain financial and clinical performance targets. Within the UK National Health Service, meeting targets for prespecified preventive services leads to extra payments for general practitioners; and the new rating system for hospital trusts offers administrative autonomy and preferential access to capital funding as a reward for strong performance on measures of quality, accessibility, and efficiency. Simply shifting the mode of physician payment may be an effective way of modifying behavior. For example, exponents of fee-for-service remuneration of cardiovascular medicine and surgery argue that salary and capitation schemes impose a risk of underservicing. Critics of fee-for-service argue that it undervalues quality and cognitive services, and creates a conflict of interest that promotes the use of procedures. As to non-financial incentives and disincentives, the range of options includes merit awards, disciplinary proceedings, and litigation.

Arguably more relevant to the evidence-oriented practitioner is the available information on non-administrative mechanisms to improve physician performance that rely on voluntary knowledge- or information-based change. Such initiatives have the advantage of calling forward the better instincts of health professionals who, with few exceptions, seek first to serve patients as competently as possible.

Exponents of clinical guidelines initially believed that dissemination of guidelines might prove a key component in catalyzing knowledge-based improvements in physician performance.[91] Guidelines would usefully compile the totality of relevant evidence on several related aspects of a clinical condition, treatment, or procedure. The evidence-oriented practitioner would no longer have to comb through the clinical literature, critically appraise it, and keep the relevant materials at hand or in her/his memory. The guideline would instead provide a convenient source of definitive

evidence. Furthermore, because inference, expert judgment, values, and circumstances could be used in developing guidelines, clinicians would be able to rely on regionally-developed guidelines to navigate the many "grey zones" of clinical practice[26] where evidence alone was insufficient. Finally, guidelines could be developed, endorsed and disseminated by authorities with clinical credibility, lending weight to evidence that might otherwise appear rather impersonally in clinical journals.

Lomas[92] termed this latter approach the model of *active dissemination*, and criticized its prospects for success on the grounds that it ignored other factors in the practice environment, and presupposed that information acquisition alone leads to behavior change. The available evidence does suggest that there is some impact from more active approaches to informing and educating physicians about relevant clinical advances or guideline content.[93] However, the more passive the educational process, and the more removed it is from physicians' own practice context, the less likely it appears to succeed.

Researchers and administrators have accordingly developed an array of non-coercive interventions designed to improve physician performance (Box 8.4). In 1995 Davis *et al*[94] and Oxman *et al*[95] conducted systematic reviews of all the available controlled studies of the effects of these strategies on physicians' and other health professionals' performance. They included any strategy designed to persuade physicians "to modify their practice performance by communicating clinical information". Purely administrative interventions or financial and similar applied incentives and disincentives were excluded.

There were 99 studies involving physicians and a further three on other health professionals' behavior. Most of the studies on physician performance focus on internists or family physicians, and specific cardiovascular studies are limited in number to date. Single-intervention studies had positive effects on process or outcome parameters in 49/81 (60%) of trials where they were applied. Short educational seminars or conferences and dissemination of educational materials (printed or in audiovisual format) were least effective of all the single-intervention modalities explored. This finding supports proponents of implementation as opposed to dissemination.

Simple audit-and-feedback studies had limited impact. However, it is important to distinguish the types of studies that fall into this category. For example, in randomized studies from the early 1980s, investigators showed that a computer-based monitoring system with reminders and feedback led to significantly better follow up and blood pressure control for patients with hypertension.[96,97] Two controlled studies by Pozen *et al*[98,99] showed that a point-of-service strategy to facilitate implementation of a predictive algorithm for chest pain diagnosis reduced inappropriate use of coronary care units. These studies can best be regarded as "reminder" studies because there is continuous feedback at point of service. Audit-and-feedback studies that appear to be ineffective are those where data are collected and cumulated about processes or outcomes, and fed back only intermittently to practitioners without mechanisms to ensure local buy-in, to address local barriers to change, or to rectify specific gaps in clinical knowledge that may be associated with aberrant practice patterns.

The latter distinction also highlights the fact that feedback can occur concurrently with service provision or retrospectively (that is, after the service has been provided). Concurrent audit and feedback arguably is taken to its

Box 8.4 Some methods used to alter physician performance/behavior

- **Education materials:** Distribution of published or printed recommendations, including practice guidelines and audiovisual materials or electronic publications.
- **Conferences:** Participation of healthcare providers in conferences, lectures, workshops, or traineeships outside their practice settings.
- **Outreach visits:** Use of a trained person who meets with providers in their practice settings to provide information. The information given may include feedback on the provider's performance.
- **Local opinion leaders:** Use of providers explicitly nominated by their colleagues to be "educationally influential".
- **Patient-mediated interventions:** Any intervention aimed at changing the performance of healthcare providers for which information was sought from or given directly to patients by others (for example, direct mailings to patients, patient counseling delivered by others, or clinical information collected directly from patients and given to the provider).
- **Audit and feedback:** Any summary of clinical performance of healthcare over a specified period, with or without recommendations for clinical action. The information may have been obtained from medical records, computerized databases or patients or by observation.
- **Reminders:** Any intervention (manual or computerized) that prompts the healthcare provider to perform a clinical action. Examples include concurrent or intervisit reminders to professionals about desired actions such as screening or other preventive services, enhanced laboratory reports or administrative support (for example, follow up appointment systems or stickers on charts).
- **Marketing:** Use of personal interviewing, group discussion (focus groups) or a survey of targeted providers to identify barriers to change and the subsequent design of an intervention.
- **Local consensus processes:** Inclusion of participating providers in discussion to ensure agreement that the chosen clinical problem is important and the approach to managing it appropriate.

Modified from Oxman *et al*[95]

administrative conclusion in utilization management programs that refuse to authorize payment for a cardiovascular procedure unless the patient meets certain criteria, or in mandatory second opinion programs. These types of programs were not included in the reviews by Davis *et al*[94] and Oxman *et al.*[95]

The methods that had the most consistent effects were: outreach visits including formal academic detailing and opinion-leader studies, where an educationally influential physician was nominated by local peers to be the vector for the information; physician reminder systems at point of service; and patient-mediated methods, including reminders or educational materials. If two or more modalities were combined, then the effects were greater – that is, combining two effective methods (for example, academic detailing with support from a local opinion leader) had more impact than combining two less effective methods (for example, audit-and-feedback combined with a one-day seminar). Multifaceted interventions showed the strongest effects, with 31 of 39 (79%) positively affecting processes or outcomes of care.

Davis *et al*[94] noted that most interventions appear to have a greater impact on process-of-care measures and other indices of physician performance, than on patient outcomes. They postulated that this may be because the clinical interventions themselves have limited impact (a rationale for the power argument given earlier), and because patients do not always accept physician recommendations. They also suggest that a recurring weakness in interventions designed to improve processes and outcomes of care is a failure to conduct a needs analysis that addresses barriers to change.

These systematic reviews of practice-change interventions do not provide definitive evidence about which behavior change interventions are most effective and efficient in particular contexts or clinical conditions. This is because the studies cover a wide range of clinical condition and provider groups, rendering inferences across studies difficult. As in any meta-analysis, cross-study inferences involve nonrandomized comparison with all their potential pitfalls. Furthermore, factorial designs in behavior changes studies have been more the exception than the rule, and it is therefore usually unclear as to which element(s) in a multifactorial strategy was (were) truly effective. Nonetheless, the evidence from controlled trials does suggest that practice changes are best achieved by combining credible evidence or information with active local strategies of implementation using multifactorial methods. Such multifactorial initiatives are further supported in a recent qualitative study examining factors leading to increasing β blocker use after AMI.[100] Hospitals with greater improvements in β blocker use over time, when compared to those having less or no improvement, were more likely to have shared goals, substantial administrative support, strong physician leadership advocating β blocker use, and incorporation of credible data feedback programs.

The case of outcomes report cards

The interest in outcomes measurement to assure technical competence has led to statewide initiatives whereby all cardiac surgery centers in New York and Pennsylvania, USA, are mandated to provide clinical data to permit compilation of publicly released mortality "report cards" on their CABG patients. (More recently, cardiovascular report cards have included interregional and hospital-specific AMI mortality rates, process indicators, (for example, evidence-based therapies and cardiac intervention rates post-AMI),[75,101] and patient satisfaction with hospital care.[102])

The CABG report cards provide a final case study that bridges some of the material presented above on outcomes assessment and behavior change. In New York between 1989 and 1992, inhospital postoperative mortality of CABG showed an unadjusted relative decline of 21%.[103,104] Patients were apparently becoming sicker in the same period, so that the risk-adjusted mortality decline was computed as 41%. Exponents of outcomes reporting claim that this improvement was catalyzed by a reporting system that provided relevant data to patients, administrators, and referring physicians.[103,104] There can be no doubt that the New York and Pennsylvania report cards have pinpointed problems with a few operators who had very poor technical outcomes. The key question is how much of the overall improvement in mortality can be attributed to public outcomes reportage.

Some critics contend that the trend is confounded by two factors. More assiduous coding of risk factors would artefactually increase the overall expected mortality, and surgeons could generate better mortality profiles by selectively turning down high-risk patients, even though such patients may have most to gain from CABG. There has indeed been a striking increase in the prevalence of various reported risk factors in the New York database since its inception. For example, prevalence of congestive heart failure rose from 1·7% in 1989 to 7·6% in 1991; renal failure rose from 0·4% to 2·8%, chronic obstructive pulmonary disease (COPD) from 6·9% to 17·4% and unstable angina from 14·9% to 21·8% in the same period.[105] As well, a survey[106] of randomly selected cardiologists and cardiac surgeons in Pennsylvania found that about 60% of cardiologists reported greater difficulty in finding surgeons who would operate on high-risk patients; a similar number of surgeons reported that they were less willing to operate on such patients. However, this type of survey is weak evidence for harm done by untoward case selection, and internal New York data do not support such a trend in the state.[107]

A more telling criticism is the fact that ecological correlations between falling mortality and initiation of reportage are tantamount to a case series in medicine. They provide weak and uncontrolled evidence for causation. In fact, the above-noted survey[106] of randomly selected cardiologists in Pennsylvania showed that most referring physicians did not

view the Pennsylvania guide as an important source of information because of concerns about inadequate risk adjustment, unreliable data, and the absence of indicators of quality other than mortality. Schneider and Epstein[108] later surveyed patients undergoing cardiac surgery in Pennsylvania to determine the impact of the statewide consumer guide to the performance of hospitals and individual surgeons. Only 12% of the patients were aware of the guide before undergoing a CABG, and less than 1% knew the correct rating of their hospital or surgeon or reported that such information had any meaningful influence on their selection of a provider for open-heart surgery.

It is perhaps not surprising that, more generally, a recent overview by Marshall *et al*[109] found little evidence for consumer-driven market shifts arising from public report cards about specific diseases or procedures. It appears more plausible that the publication of outcomes "report cards" facilitates change by sensitizing politicians, public servants, and the governing bodies of hospitals to the existence of outcome variations. For example, after the publication of the CABG "report card", New York State insisted on attainment of center-specific minimum case volumes before certifying any cardiac surgery program.

On the other hand, in the absence of any report cards, the drop in post-CABG mortality in neighboring Massachusetts[110] has rivaled that seen in New York and Pennsylvania. Technical improvements in surgery, together with closer quality monitoring at the institutional level, appear to be the primary reason for these improved outcomes.

Given what has been learned about physician behavior change, the controversy about the New York State and Pennsylvania programs is hardly surprising. These externally mandated experiments in outcomes assessment contrast with initiatives that involve influential professionals and promote local buy-in from the outset. O'Connor discusses elsewhere in this volume the successful regional collaboration for continuous quality improvement that was developed in northern New England by involving cardiac surgeons in a systematic examination and improvement of processes and outcomes of care.[111–113] In Canada, a similar cooperative venture exists through the Cardiac Care Network of Ontario, which draws together representatives of all major cardiovascular referral centers in the province.[114] Historically, confidential report cards on mortality and length of stay were generated for the chief of cardiac surgery and CEO (cheif executive officer) at each center, using risk adjustment algorithms coauthored by leaders of the Cardiac Care Network itself.[84] CABG outcomes in Ontario are comparable to those in New York and Pennsylvania. Moreover, as in Massachusetts, the trend to improved outcomes antedates the report card system.[115,116] Most recently, hospital-specific CABG outcomes in Ontario have been made available to the public.

In summary, the unresolved issues with public outcomes report cards include validity and reliability of the data and the risk adjustment algorithms, as well as inadvertent adverse effects (for example, avoidance of high-risk patients, and consumers' or referring physicians' focus on point estimates rather than statistically reliable ranges). Potential harm to the public from substandard technical competence must be weighed against needless patient anxieties and confusion, along with harm to skilled health workers and fine institutions caused by poorly founded and widely publicized inferences about inferior outcomes. Debate continues, but it is untenable to assume that all hospitals or providers are equally technically competent, and the public has an unequivocal right to receive reliable and current data on physician and hospital performance. Thus, the trend must inexorably be toward greater public reporting of both process and outcome indicators of quality of care. The challenges for evidence-oriented practitioners are to ensure that the right indicators are chosen, that reliable data are analyzed appropriately, and that responsible reporting mechanisms are developed.

Conclusions

Assessing cardiovascular practices involves observational methods that can focus on either processes or outcomes of care. Methodologies for process-of-care assessments range from simple descriptive studies revealing variations in practice, to highly sophisticated case-specific audits using explicit criteria. Process-of-care assessments are more efficient than outcomes assessments in many respects, and lend themselves to measuring both over- and underuse of necessary cardiovascular services, thereby shedding light on quality and accessibility of care.

Observational outcomes measurement is nonetheless useful in assessing provider or institutional quality of care for high volume and relatively homogeneous procedures where technical skill is a factor. These comparisons must be made with caution, given the inevitable influence of unrecognized confounding through selection biases inherent in routine practice. The use of well-validated risk adjustment algorithms is imperative to improve the chances that differences in outcomes arise from the technical quality of care provided, rather than from differences in prognostic characteristics of patients themselves. Observational outcomes studies can also be undertaken cautiously to illustrate unanticipated harm from interventions, test the external validity of randomized trial results, generate hypotheses about interventions that may be worth testing with formal experimental designs, and, very rarely, provide an acceptable level of evidence for adopting a particular intervention.

To reduce general inconsistencies in the uptake of evidence into practice, and to redress instances where process or outcomes of clinical care are measured and found wanting, several proven strategies are available. First, while new

evidence published in journals or distilled into educational materials and practice guidelines does change practice through passive diffusion, evidence is most likely to have an impact if actively disseminated and made relevant and salient locally to practitioners. Strategies to achieve this end include:

- reminder systems
- concurrent audit and feedback
- local outreach through academic detailing
- patient-mediated interventions
- local involvement of an educationally influential practitioner, and
- a local needs assessment with a consensus among providers on the issues as well as the barriers and facilitators to positive change.

In conclusion, the practitioner of evidence-based cardiovascular medicine and surgery is increasingly challenged to stay abreast of his or her field and to maintain technical competence in performing ever more exacting procedures. Information systems in practice can and will be re-engineered to be more conducive to evidence-based clinical decision making. However, it will also remain important to assess practice patterns on a systematic basis, to share that information with patients and providers, and wherever necessary, take steps to improve physician performance with a view to optimizing the quality, accessibility, and efficiency of cardiovascular care.

References

1. Payne N, Saul C. Variations in use of cardiology services in a health authority: comparison of coronary artery revascularisation rates with prevalence of angina and coronary mortality. *BMJ* 1997;**314**:257–61.
2. Alter DA, Naylor CD, Austin P, Tu JV. Effects of socioeconomic status on access to invasive cardiac procedures and on mortality after acute myocardial infarction. *N Engl J Med* 1999;**341**:1359–67.
3. Anderson GM, Grumbach K, Luft HS, Roos LL, Mustard C, Brook R. Use of coronary artery bypass surgery in the United States and Canada. Influence of age and income. *JAMA* 1993;**269**:1661–66.
4. Krieger J, Collier C, Song L, Martin D. Linking community-based blood pressure measurement to clinical care: a randomized controlled trial of outreach and tracking by community health workers. *Am J Public Health* 1999;**89**:856–61.
5. Tu JV, Naylor CD, Austin P. Temporal changes in the outcomes of acute myocardial infarction in Ontario, 1992–1996. *Can Med Ass J* 1999;**161**:1257–61.
6. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. *J Am Coll Cardiol* 1996;**27**:1335–42.
7. Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbaier LH, Mark DB. Discordance of databases designed for claims payment versus clinical information systems. Implications for outcomes research. *Ann Intern Med* 1993;**119**:844–50.
8. Hannan EL, Kilburn H, Jr, Lindsey ML, Lewis R. Clinical versus administrative data bases for CABG surgery. Does it matter? *Med Care* 1992;**30**:892–907.
9. Fisher ES, Whaley FS, Krushat WM *et al.* The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. *Am J Public Health* 1992;**82**:243–8.
10. Dixon J, Sanderson C, Elliott P, Walls P, Jones J, Petticrew M. Assessment of the reproducibility of clinical coding in routinely collected hospital activity data: a study in two hospitals. *J Public Health Med* 1998;**20**:63–9.
11. Green J, Wintfeld N. How accurate are hospital discharge data for evaluating effectiveness of care? *Med Care* 1993;**31**:719–31.
12. Krumholz HM, Chen J, Murillo JE, Cohen DJ, Radford MJ. Admission to hospitals with on-site cardiac catheterization facilities :impact on long-term costs and outcomes. *Circulation* 1998;**98**:2010–16.
13. Every NR, Larson EB, Litwin PE *et al.* The association between on-site cardiac catheterization facilities and the use of coronary angiography after acute myocardial infarction. Myocardial Infarction Triage and Intervention Project Investigators. *N Engl J Med* 1993;**329**:546–51.
14. Di Salvo TT, Paul SD, Lloyd-Jones D *et al.* Care of acute myocardial infarction by noninvasive and invasive cardiologists: procedure use, cost and outcome. *J Am Coll Cardiol* 1996;**27**:262–9.
15. Rochon PA, Anderson GM, Tu JV *et al.* Age- and gender-related use of low-dose drug therapy: the need to manufacture low-dose therapy and evaluate the minimum effective dose. *J Am Geriatr Soc* 1999;**47**:954–9.
16. Krumholz HM, Radford MJ, Wang Y, Chen J, Marciniak TA. Early beta-blocker therapy for acute myocardial infarction in elderly patients. *Ann Intern Med* 1999;**131**:648–54.
17. Evans RG. Introduction. In: Evans RG, Barer ML, Marmor TR, eds. *Why are some people healthy and others not? The determinants of health of populations*. New York: Aldine de Gruyter, 1994.
18. Fiebach NH, Viscoli CM, Horwitz RI. Differences between women and men in survival after myocardial infarction. Biology or methodology? *JAMA* 1990;**263**:1092–96.
19. Meehan TP, Radford MJ, Vaccarino LV *et al.* A collaborative project in Connecticut to improve the care of patients with acute myocardial infarction. *Conn Med* 1997;**61**:147–55.
20. White KL. Improved medical care statistics and the health services system. *Public Health Rep* 1967;**82**:847–54.
21. Outcomes and the management of health care. Health Services Research Group. *Can Med Ass J* 1992;**147**:1775–80.
22. Wennberg J, Gittelsohn. Small area variations in health care delivery. *Science* 1973;**182**:1102–8.
23. Wennberg J, Gittelsohn A. Variations in medical care among small areas. *Sci Am* 1982;**246**:120–34.
24. Wennberg JE, Barnes BA, Zubkoff M. Professional uncertainty and the problem of supplier-induced demand. *Soc Sci Med* 1982;**16**:811–24.
25. Wennberg J. Which rate is right? *N Engl J Med* 1986;**314**:310–11.

26.Naylor CD. Grey zones of clinical practice: some limits to evidence-based medicine. *Lancet* 1995;**345**:840–2.
27.Diehr P, Cain KC, Kreuter W, Rosenkranz S. Can small-area analysis detect variation in surgery rates? The power of small-area variation analysis. *Med Care* 1992;**30**:484–502.
28.Diehr P, Cain K, Connell F, Volinn E. What is too much variation? The null hypothesis in small-area analysis. *Health Serv Res* 1990;**24**:741–71.
29.Petticrew M, McKee M, Jones J. Coronary artery surgery: are women discriminated against? *BMJ* 1993;**306**:1164–6.
30.Jaglal SB, Goel V, Naylor CD. Sex differences in the use of invasive coronary procedures in Ontario. *Can J Cardiol* 1994;**10**:239–44.
31.Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *N Engl J Med* 1991;**325**:221–5.
32.Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? *Ann Intern Med* 1992;**116**:785–90.
33.Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med* 2000 **343**:8–15.
34.Weintraub WS, Kosinski AS, Wenger NK. Is there a bias against performing coronary revascularization in women? *Am J Cardiol* 1996;**78**:1154–60.
35.Chen E, Naylor CD. Variation in hospital length of stay for acute myocardial infarction in Ontario, Canada. *Med Care* 1994;**32**:420–35.
36.Quality of care: 1. What is quality and how can it be measured? Health Services Research Group. *Can Med Ass J* 1992;**146**:2153–8.
37.Quality of care: 2. Quality of care studies and their consequences. Health Services Research Group. *Can Med Ass J* 1992;**147**:163–7.
38.Naylor CD, Guyatt GH. Users' guides to the medical literature. XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. *JAMA* 1996;**275**:1435–9.
39.Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
40.The Heart and Stroke Foundation of Canada, the Canadian Cardiovascular Society and the Canadian Association of Emergency Physicians for the Emergency Cardiac Care Coalition. Recommendations for ensuring early thrombolytic therapy for acute myocardial infarction. *Can Med Ass J* 1996;**154**:483–7.
41.Rogers WJ, Bowlby LJ, Chandra NC *et al.* Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. *Circulation* 1994;**90**:2103–14.
42.Cox JL, Lee E, Langer A, Armstrong PW, Naylor CD. Time to treatment with thrombolytic therapy: determinants and effect on short-term nonfatal outcomes of acute myocardial infarction. Canadian GUSTO Investigators. Global Utilization of Streptokinase and + PA for Occluded Coronary Arteries. *Can Med Ass J* 1997;**156**:497–505.
43.Birkhead JS. Time delays in provision of thrombolytic treatment in six district hospitals. Joint Audit Committee of the British Cardiac Society and a Cardiology Committee of Royal College of Physicians of London. *BMJ* 1992;**305**:445–8.
44.GISSI–Avoidable Delay Study Group. Epidemiology of avoidable delay in the care of patients with acute myocardial infarction in Italy. A GISSI-generated study. *Arch Intern Med* 1995;**155**:1481–8.
45.Porter G, Doughty R, Gamble G, Sharpe N. Thrombolysis in acute myocardial infarction: reducing in hospital treatment delay. *N Z Med J* 1995;**108**:253–4.
46.Park RE, Fink A, Brook RH *et al.* Physician ratings of appropriate indications for six medical and surgical procedures. *Am J Public Health* 1986;**76**:766–72.
47.Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care* 1986;**2**:53–63.
48.Park RE, Fink A, Brook RH *et al.* Physician ratings of appropriate indications for three procedures: theoretical indications vs indications used in practice. *Am J Public Health* 1989;**79**: 445–7.
49.Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med* 1994;**331**:1037–43.
50.King SB III, Lembo NJ, Weintraub WS *et al.* A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med* 1994;**331**:1044–50.
51.Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;**341**:573–80.
52.Rodriguez A, Boullon F, Perez-Balino N, Paviotti C, Liprandi MI, Palacios IF. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. *J Am Coll Cardiol* 1993;**22**:1060–7.
53.Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996;**335**:217–25.
54.Hilborne LH, Leape LL, Bernstein SJ *et al.* The appropriateness of use of percutaneous transluminal coronary angioplasty in New York State. *JAMA* 1993;**269**:761–5.
55.Ayanian JZ, Landrum MB, Normand SL, Guadagnoli E, McNeil BJ. Rating the appropriateness of coronary angiography – do practicing physicians agree with an expert panel and with each other? *N Engl J Med* 1998;**338**:1896–1904.
56.Brook RH, Kosecoff JB, Park RE, Chassin MR, Winslow CM, Hampton JR. Diagnosis and treatment of coronary disease: comparison of doctors' attitudes in the USA and the UK. *Lancet* 1988;**1**:750–3.
57.McGlynn EA, Naylor CD, Anderson GM *et al.* Comparison of the appropriateness of coronary angiography and coronary

artery bypass graft surgery between Canada and New York State. *JAMA* 1994;**272**:934–40.
58. Chassin MR, Kosecoff J, Park RE *et al.* Does inappropriate use explain geographic variations in the use of health care services? A study of three procedures. *JAMA* 1987;**258**:2533–7.
59. Leape LL, Park RE, Solomon DH, Chassin MR, Kosecoff J, Brook RH. Does inappropriate use explain small-area variations in the use of health care services? *JAMA* 1990;**263**: 669–72.
60. Wennberg JE. The paradox of appropriate care. *JAMA* 1987;**258**:2568–9.
61. Tu JV, Naylor CD, Kumar D, DeBuono BA, McNeil BJ, Hannan EL. Coronary artery bypass graft surgery in Ontario and New York State: which rate is right? Steering Committee of the Cardiac Care Network of Ontario. *Ann Intern Med* 1997;**126**:13–19.
62. Naylor CD, Sykora K, Jaglal SB, Jefferson S. Waiting for coronary artery bypass surgery: population-based study of 8517 consecutive patients in Ontario, Canada. The Steering Committee of the Adult Cardiac Care Network of Ontario. *Lancet* 1995;**346**:1605–9.
63. Hux JE, Naylor CD. Are the marginal returns of coronary artery surgery smaller in high-rate areas? The Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. *Lancet* 1996;**348**:1202–7.
64. Yusuf S, Zucker D, Peduzzi P *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–70.
65. Goldberg KC, Hartz AJ, Jacobsen SJ, Krakauer H, Rimm AA. Racial and community factors influencing coronary artery bypass graft surgery rates for all 1986 Medicare patients. *JAMA* 1992;**267**:1473–7.
66. Hadley J, Steinberg EP, Feder J. Comparison of uninsured and privately insured hospital patients. Condition on admission, resource use, and outcome. *JAMA* 1991;**265**:374–9.
67. Hannan EL, Kilburn H, Jr, O'Donnell JF, Lukacik G, Shields EP. Interracial access to selected cardiac procedures for patients hospitalized with coronary artery disease in New York State. *Med Care* 1991;**29**:430–41.
68. Laouri M, Kravitz RL, French WJ *et al.* Underuse of coronary revascularization procedures: application of a clinical method. *J Am Coll Cardiol* 1997;**29**:891–7.
69. Guadagnoli E, Landrum MB, Peterson EA, Gahart MT, Ryan TJ, McNeil BJ. Appropriateness of coronary angiography after myocardial infarction among Medicare beneficiaries. Managed care versus fee for service. *N Engl J Med* 2000;**343**:1460–6.
70. Hemingway H, Crook AM, Feder G *et al.* Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001;**344**:645–54.
71. Tu JV, Austin PC, Chan BT. Relationship between annual volume of patients treated by admitting physician and mortality after acute myocardial infarction. *JAMA* 2001;**285**:3116–22.
72. Alter DA, Naylor CD, Austin PC, Tu JV. Long-term MI outcomes at hospitals with or without on-site revascularization. *JAMA* 2001;**285**:2101–8.
73. Pilote L, Califf RM, Sapp S *et al.* Regional variation across the United States in the management of acute myocardial infarction. GUSTO-1 Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *N Engl J Med* 1995;**333**:565–72.
74. Yusuf S, Flather M, Pogue J *et al.* Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. *Lancet* 1998;**352**:507–14.
75. Tu JV, Austin P, Naylor CD, Iron K, Zhang H. Acute myocardial infarction outcomes in Ontario. In Naylor CD, Slaughter PM, eds. *Cardiovascular health and services in Ontario. An ICES Atlas.* Toronto: Institute for Clinical Evaluative Sciences, 1999.
76. Wen SW, Hernandez R, Naylor CD. Pitfalls in nonrandomized outcomes studies. The case of incidental appendectomy with open cholecystectomy. *JAMA* 1995;**274**:1687–91.
77. Rouleau JL, Moye LA, Pfeffer MA *et al.* A comparison of management patterns after acute myocardial infarction in Canada and the United States. The SAVE investigators. *N Engl J Med* 1993;**328**:779–84.
78. Mark DB, Naylor CD, Hlatky MA *et al.* Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States. *N Engl J Med* 1994;**331**: 1130–5.
79. Pilote L, Racine N, Hlatky MA. Differences in the treatment of myocardial infarction in the United States and Canada. A comparison of two university hospitals. *Arch Intern Med* 1994;**154**:1090–6.
80. Fu Y, Chang WC, Mark D *et al.* Canadian-American differences in the management of acute coronary syndromes in the GUSTO IIb trial: one-year follow-up of patients without ST-segment elevation. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) II Investigators. *Circulation* 2000;**102**:1375–81.
81. McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994; **272**:859–66.
82. DeLong ER, Nelson CL, Wong JB *et al.* Using observational data to estimate prognosis: an example using a coronary artery disease registry. *Stat Med* 2001;**20**:2505–32.
83. Sackett DL. Bias in analytic research. *J Chronic Dis* 1979;**32**: 51–63.
84. Tu JV, Jaglal SB, Naylor CD. Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. *Circulation* 1995;**91**:677–84.
85. Krumholz HM, Chen J, Wang Y, Radford MJ, Chen YT, Marciniak TA. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation* 1999;**99**:2986–92.
86. Tu JV, Sykora K, Naylor CD. Assessing the outcomes of coronary artery bypass graft surgery: how many risk factors are enough? Steering Committee of the Cardiac Care Network of Ontario. *J Am Coll Cardiol* 1997;**30**:1317–23.
87. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;**127**:757–63.
88. Rice N, Leyland A. Multilevel models: applications to health data. *J Health Serv Res Policy* 1996;**1**:154–64.

89. Diez-Roux AV, Link BG, Northridge ME. A multilevel analysis of income inequality and cardiovascular disease risk factors. *Soc Sci Med* 2000;**50**:673–87.
90. Duncan C, Jones K, Moon G. Context, composition and heterogeneity: using multilevel models in health research. *Soc Sci Med* 1998;**46**:97–117.
91. Standards, guidelines and clinical policies. Health Services Research Group. *Can Med Ass J* 1992;**146**:833–7.
92. Lomas J. Retailing research: increasing the role of evidence in clinical services for childbirth. *Milbank Q* 1993;**71**:439–75.
93. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;**342**:1317–22.
94. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA* 1995;**274**: 700–5.
95. Oxman AD, Thomson MA, Davis DA, Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *Can Med Ass J* 1995;**153**: 1423–31.
96. Barnett GO, Winickoff RN, Morgan MM, Zielstorff RD. A computer-based monitoring system for follow-up of elevated blood pressure. *Med Care* 1983;**21**:400–9.
97. Dickinson JC, Warshaw GA, Gehlbach SH, Bobula JA, Muhlbaier LH, Parkerson GR, Jr. Improving hypertension control: impact of computer feedback and physician education. *Med Care* 1981;**19**:843–54.
98. Pozen MW, D'Agostino RB, Selker HP, Sytkowski PA, Hood WB, Jr. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease. A prospective multicenter clinical trial. *N Engl J Med* 1984; **310**:1273–8.
99. Pozen MW, D'Agostino RB, Mitchell JB *et al.* The usefulness of a predictive instrument to reduce inappropriate admissions to the coronary care unit. *Ann Intern Med* 1980;**92**:238–42.
100. Bradley EH, Holmboe ES, Mattera JA, Roumanis SA, Radford MJ, Krumholz HM. A qualitative study of increasing beta-blocker use after myocardial infarction: Why do some hospitals succeed? *JAMA* 2001;**285**:2604–11.
101. Tu JV, Austin P, Rochon PA, Zhang H. Secondary prevention after acute myocardial infarction, congestive heart failure and coronary artery bypass graft surgery in Ontario. In: Naylor CD, Slaughter PM, eds. *Cardiovascular health and services in Ontario: an ICES Atlas.* Toronto: Institute for Clinical Evaluative Sciences, 1999.
102. Decker B, MacInnes R. Assessing the importance of report cards rating patient satisfaction. *Health Syst Lead* 1997; **4**:16–18.
103. Hannan EL, Kilburn HJ, Racz M, Shields E, Chassin MR. Improving the outcomes of coronary artery bypass surgery in New York State. *JAMA* 1994;**271**:761–6.
104. Hannan EL, Siu AL, Kumar D, Kilburn H, Jr, Chassin MR. The decline in coronary artery bypass graft surgery mortality in New York State. The role of surgeon volume. *JAMA* 1995; **273**:209–13.
105. Green J, Wintfeld N. Report cards on cardiac surgeons. Assessing New York State's approach. *N Engl J Med* 1995; **332**:1229–32.
106. Schneider EC, Epstein AM. Influence of cardiac-surgery performance reports on referral practices and access to care. A survey of cardiovascular specialists. *N Engl J Med* 1996;**335**: 251–6.
107. Hannan EL, Siu AL, Kumar D, Racz M, Pryor DB, Chassin MR. Assessment of coronary artery bypass graft surgery performance in New York. Is there a bias against taking high-risk patients? *Med Care* 1997;**35**:49–56.
108. Schneider EC, Epstein AM. Use of public performance reports: a survey of patients undergoing cardiac surgery. *JAMA* 1998; **279**:1638–42.
109. Marshall MN, Shekelle PG, Leatherman S, Brook RH. The public release of performance data: what do we expect to gain? A review of the evidence. *JAMA* 2000;**283**:1866–74.
110. Ghali WA, Ash AS, Hall RE, Moskowitz MA. Statewide quality improvement initiatives and mortality after cardiac surgery. *JAMA* 1997;**277**:379–82.
111. O'Connor GT, Plume SK, Olmstead EM *et al.* A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *JAMA* 1996; **275**:841–6.
112. O'Connor GT, Plume SK, Olmstead EM *et al.* A regional prospective study of in-hospital mortality associated with coronary artery bypass grafting. The Northern New England Cardiovascular Disease Study Group. *JAMA* 1991;**266**: 803–9.
113. Malenka DJ, O'Connor GT. A regional collaborative effort for CQI in cardiovascular disease. Northern New England Cardiovascular Study Group. *Jt Comm J Qual Improv* 1995; **21**:627–33.
114. Tu JV, Naylor CD. Coronary artery bypass mortality rates in Ontario. A Canadian approach to quality assurance in cardiac surgery. Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. *Circulation* 1996;**94**:2429–33.
115. Ivanov J, Weisel RD, David TE, Naylor CD. Fifteen-year trends in risk severity and operative mortality in elderly patients undergoing coronary artery bypass graft surgery. *Circulation* 1998;**97**:673–80.
116. Tu JV, Naylor CD. Coronary artery bypass mortality rates in Ontario. A Canadian approach to quality assurance in cardiac surgery. Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. *Circulation* 1996;**94**:2429–33.

Part II

Prevention of cardiovascular diseases

Salim Yusuf, Editor

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

9 Global perspective on cardiovascular disease

K Srinath Reddy

Introduction

In the second half of the 20th century, cardiovascular diseases (CVD) became the dominant cause of global mortality and a major contributor to disease related disability. In the first half of the 21st century this pattern will become even more pervasive as the CVD epidemic accelerates in many developing regions of the world, even as it retains its primacy as the leading public health problem in the developed regions.[1–7]

In 2000, CVD accounted for 16·7 million deaths globally.[1] Coronary heart disease (CHD) and stroke were then leading contributors, with a death toll of 6·9 million and 5·1 million, respectively. According to estimates provided by the World Health Organization, in 1998 30·9% of all global deaths were due to CVD. Both men and women experienced these burdens, with CVD contributing to 28% of the deaths in the former and 34% of the deaths in the latter.[2] The low and middle income countries contributed 78% of all CVD deaths, and 86·3% of disability adjusted life year (DALY) loss attributed to CVD that year. Although these large absolute burdens reflect the large population sizes of the developing countries, proportional mortality rates of deaths attributable to CVD have also been rising in these countries, from 24·5% in 1990 to 28·5% in 1998. The relative importance of CHD and stroke vary across regions and from country to country. For example, more than twice as many deaths from stroke occurred in the developing countries as in the developed countries.[3] CHD was the dominant form of CVD in the developed countries, Latin America and India, whereas stroke was the leading cause of cardiovascular death in sub-Saharan Africa, China and other parts of Asia. Developing countries such as Argentina, Colombia and China now have CVD mortality rates higher than those of most other countries. Argentina currently exceeds many European and North American countries in its CVD mortality rate.[7]

The rise and recent decline of the CVD epidemic in the developed countries have been well documented.[8–11] The identification of major risk factors through population based studies, and effective control strategies combining community education and targeted management of high-risk individuals, have together contributed to the fall in CVD mortality rates (inclusive of coronary and stroke deaths) that has been observed in almost all industrialized countries. It has been estimated that, during the period 1965–90, CVD related mortality fell by 50% or so in Australia, Canada, France and the United States, and by 60% in Japan.[8] Other parts of western Europe reported more modest declines (20–25%).[8] The decline in stroke mortality has been more marked than the decline in coronary mortality. In the USA the decline in stroke mortality commenced nearly two decades earlier than that in coronary mortality and maintained a sharper rate of decline.[10] During the period 1979–89, the age-adjusted mortality from stroke in that country declined by about one third, and the corresponding decline in coronary mortality was 22%.[10] In Canada, Japan, Switzerland and the United States, stroke mortality has declined by more than 50% in men and women aged 65–74 years since the 1970s.[11] In Japan, where stroke mortality outweighs coronary mortality, the impressive overall decline in CVD mortality is contributed principally by the former.

However, recent trends in some of the developed countries have been of some concern. A flattening of age adjusted mortality rates for major cardiovascular diseases in the USA has been reported since 1990, with an especially well documented absence of a decline in stroke mortality since that year (Figure 9.1). This has been accompanied by

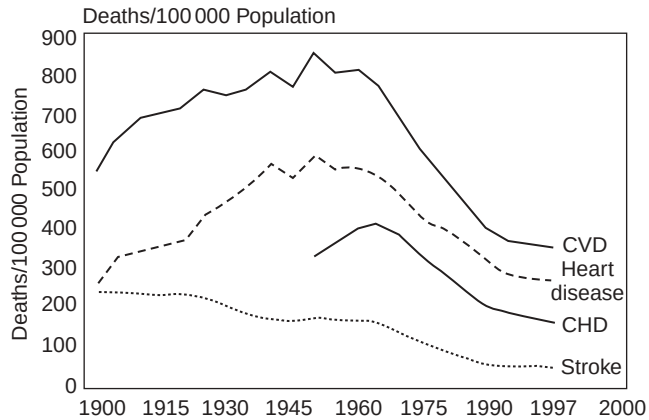

Figure 9.1 Age adjusted (to 2000 standard) mortality rates for major cardiovascular diseases in the United States from 1900 to 1997[12]

an increase in mortality from congestive heart failure. Lack of decline in incidence of CHD and stroke, fall in the rate of decrease in cardiovascular risk factor levels and rising levels of obesity since 1990 have all been incriminated as factors responsible for such a plateau effect on CVD mortality rates in the USA over the past decade.[12]

The discordant trend of rising CVD mortality rates in eastern and central Europe, however, is in sharp contrast to the decline in western Europe.[4] In countries such as Bulgaria and Hungary, CHD mortality rates are now the highest in the world in both men and women, and are still rising.[8] The average life expectancy in Russian males has fallen rapidly in recent years to below 60 years, a phenomenon to which rising CVD rates have contributed substantially.[13–15] Considerable variations in CVD mortality trends have been described across central and eastern Europe.[16] Whereas Poland has demonstrated a recent decline in CVD mortality, many other countries are still manifesting a rise. The 25% decline in CHD mortality observed in Poland during 1991–93 has been attributed to an increase in the consumption of fresh fruit and vegetables.[17]

Rheumatic heart disease (RHD) is also a major burden in the developing countries: it is the most common CVD in children and young adults. Although it is rare in the developed countries, at least 12 million persons are currently estimated to be affected by RHD globally.[2] More than 2 million require repeated hospital admission and 1 million will need heart surgery over the next 20 years.[2] Annually, 500 000 deaths occur as a result of RHD, and many poor persons, who are preferentially affected, are disabled because of lack of access to the expensive medical and surgical care demanded by the disease. The prevalence of RHD in the developing countries ranges from 1 to 10 per 1000 and the incidence of rheumatic fever ranges from 10 to 100 per 100 000, with a high rate of recurrence.

Early age of CVD deaths in developing countries

Although the present high burden of CVD deaths is in itself an adequate reason for attention, a greater cause for concern is the early age of CVD deaths in the developing countries compared to the developed countries. For example, in 1990 the proportion of CVD deaths occurring below the age of 70 years was 26·5% in the developed countries, compared to 46·7% in the developing countries.[4] The contrast between the truly developed "established market economies" (22·8% of CVD deaths <70 years) and a large developing country such as India (52·2%) was even sharper.[3] Therefore, the contribution of the developing countries to the global burden of CVD, in terms of disability adjusted years of life lost, was 2·8 times higher than that of the developed countries.

Epidemiologic transition and the evolution of the CVD epidemic

What is the "transition"?

The health status and dominant disease profile of human societies have been historically linked to the level of their economic development and social organization at any given stage. The shift from nutritional deficiencies and infectious diseases as the major causes of death and disability, to degenerative disorders (chronic diseases such as CVD, cancer, diabetes) has marked the economic ascent of nations as they industrialized. This has been called the epidemiologic transition.

The economic and social changes that propel this transition are related to a rise in per capita income; greater investments in public sanitation, housing and healthcare; assured availability of adequate nutrition; and technological advances in medical care. Life expectancy rises as causes of childhood and early adult mortality decline. This, in turn, leads to a decline in fertility. The age profile of the population changes from a pyramidal distribution dominated by the young to a columnar structure where adults and the elderly progressively expand their numbers. This has been described as the demographic transition. Because the disease profile is also linked to the age profile of the population, the health transition encompasses the effects of the epidemiologic and demographic transitions.

CVD profile at different stages of the epidemiologic transition

The model of epidemiologic transition originally described by Omran,[18] with three phases (the age of pestilence and famine; the age of receding pandemics; the age of degenerative and manmade diseases), was later modified to include a fourth phase, the age of delayed degenerative diseases.[19] Life expectancy increases progressively from around 30 years in the first phase to over 70 years in the fourth phase. The shift to a dominant chronic disease profile occurs in the third phase. As the average life expectancy exceeds 50–55 years, the proportionate mortality due to CVD begins to exceed that of infectious diseases.[20]

The transition occurs not only between the broad disease categories but also within them. The disease profile within CVD alters at each phase of the epidemiologic transition. In the first phase (the age of pestilence and famine), CVD accounts for 5–10% of deaths.[20] The major causes of CVD are, however, related to infectious and nutritional deficiencies. Thus, RHD and cardiomyopathies (for example, Chagas' disease) are the main CVD in this phase. Even as countries emerge from this phase, the residual burden of chronic valvular heart disease and congestive heart failure often remains for some time. These effects are still evident in sub-Saharan Africa and parts of South America and south Asia.[20]

In the second phase (the age of receding pandemics), the decline in infectious disease that accompanies socioeconomic development ushers in changes in diet. As the subsistence nutrition changes to more complete diets, the salt content of the food increases. Hypertension and its sequelae (hypertensive heart disease and hemorrhagic stroke) now affect the population, whose average age also has risen with increased life expectancy.[20] Some residual burden of RHD and cardiomyopathies is also evident. These non-atherosclerotic diseases contribute to 10–35% of deaths. This pattern currently prevails in parts of Africa, north Asia and South America.[20]

In the third phase (the age of degenerative and manmade disease), accelerated economic development and increased per capita incomes promote lifestyle changes in diet, physical activity, stress and addictions. A diet rich in calories, saturated fat and salt is accompanied by reduced physical activity through the increased use of mechanized transport and sedentary leisuretime pursuits. The metabolic mismatch leads to obesity, increased blood lipids, diabetes and elevated blood pressure. Tobacco consumption, especially cigarette smoking, starts as a pleasurable pastime and turns into a severe addiction. These factors result in the onset of clinically manifest atherosclerotic vascular disease (CHD, atherosclerotic stroke and peripheral vascular disease) at around 55 years of age. Such patterns first occur in the upper socioeconomic classes, who have disposable income to expend on rich diets, tobacco and transport vehicles. Several countries in South America and Asia currently manifest this pattern. As the epidemic advances further and involves all social strata, with homogenization of risk behaviors and risk factors across the population, the death toll of CVD rises to range between 35% and 65% of all deaths. This scenario is currently observed in eastern Europe.

In the fourth phase (the phase of delayed degenerative disease) a number of changes occur in the society to modify risk behaviors and reduce risk factor levels in the population. Health research augments the knowledge of CVD risk factors. The desire to reduce the adverse impact of CVD on individuals, as well as on the society, steer the community as well as the policymakers to apply this knowledge to disease prevention and health promotion. Community awareness through education, as well as its ability to exercise healthy choices through supportive regulatory measures, empowers its members to adopt healthier lifestyles. Saturated fat and salt consumption declines and leisuretime physical activity and exercise programs are avidly pursued. With concerns about the effects of active and passive smoking, tobacco consumption falls. Simultaneously, medical research makes available new technologies which are very effective in saving lives, modifying the course of disease and reducing the levels of risk factors. All of these changes, in unison, delay the onset of disease, lower the age standardized mortality rates and reduce the disability. The contribution of CVD to total mortality falls to 50% or below. These patterns are now established in most of North America, western Europe and New Zealand.[20]

Recent developments in some countries of eastern Europe, with sharp declines in life expectancy and other health indices, led to a fifth phase of health transition being postulated.[6] In this stage of "social upheaval and health regression" the CVD spectrum too may witness a reversal, with CHD and stroke occurring at younger ages, resulting in a fall in life expectancy as in Russia.

Variations in the transition

There are, however, variations on this theme. Even within Europe, for example, northern Europe and the Mediterranean countries have differences in CVD mortality rates which are better explained by cultural differences in diet than by the level of economic development.[21] Japan has so far avoided the CHD epidemic.[6] Whether recent changes in diet, with a rise in mean plasma cholesterol levels in the population, combined with high smoking rates, will lead to a major CHD epidemic in the future remains to be seen.

The question of "arrested epidemiologic transition" is also raised with respect to some of the developing countries. If poverty continues to be a major problem for them, will they experience the CVD epidemic in its full fury or will the pre-transitional diseases of nutrition and infection continue to occupy the center stage? Even now, there is evidence that the social gradient has begun to reverse for risk factor levels and even for morbidity measures in some populations in the developing world.[4] Unless economic development is greatly stunted in some countries, it is likely that the model of epidemiologic transition will be applicable to most of the developing countries.

The transition to the atherothrombotic phase of the epidemic may be preceded by a sharp fall in the burden of hemorrhagic stroke. The recent decline in CVD mortality reported from South Korea reflects such a fall in the contribution from hemorrhagic stroke, whereas thrombotic stroke and coronary heart disease have just begun to rise.[22] Whether adherence to traditional diets will result in a continued decline of CVD in South Korea, or CHD rates will rise further to push up the CVD mortality rates, remains to be studied. Cuba and Chile have also been cited as examples of developing countries with declining CVD mortality rates, despite high life expectancy. The model of "health transition", although very useful, is not immutable and is likely to vary according to both level of development and the nature of public health responses to social transition.

The model of health transition should also not lead to complacency regarding the high absolute burdens and early deaths in the developing countries. For example, even in a country in "early transition", such as Tanzania, the stroke mortality rate in the age group 15–59 years in rural and

urban areas is two to four times higher than that in the UK in a similar age group.[23]

Early and late adopters

The pace of epidemiologic transition will vary both between and within countries. Usually lifestyle changes towards risk-prone behaviors occur first in the higher socioeconomic groups and urban communities, for whom the innovations of modernity are more easily accessible and affordable. As these innovations diffuse and become routinely available at prices amenable to mass consumption, the poorer sections and rural communities also join the CVD bandwagon. Soon the awareness of CVD risks, as well as the economic independence to make healthy lifestyle choices in relation to diet and leisuretime exercise (along with the greater ability to access healthcare), moves the "early adopters" in the affluent and urban strata into a reduced risk zone. The burden of CVD is then largely concentrated in the lower socioeconomic groups and rural populations, who continue to practice high-risk behaviors and display elevated risk factor levels.[20] These "late adopter" groups also will slowly alter their behaviors, lower their levels of risk and reduce their burden of CVD as healthcare responses to the CVD epidemic become universally effective.

This is the evolutionary profile of the CVD epidemic, as evident from the analysis of mature epidemics in industrial nations and the advancing epidemics in the developing countries. Differences within and between countries, suggested by cross-sectional views at any point in this evolution, should not obscure the longitudinal perspective of an evolving epidemic in which most countries will traverse similar paths, albeit at different times determined by their pace of development. Global shifts in CVD risk factors and their reflection in global CVD trends indicate that all countries and communities have far more in common in terms of disease causation than the differences that demarcate them. The challenge of epidemiologic transition is not whether it will happen in the developing countries, but whether we can apply the available knowledge to telescope the transition and abbreviate phase three of the model in these countries.

Projections

The Global Burden of Diseases study[15] estimates that annual mortality from non-communicable diseases will rise from an estimated 28·1 million deaths in 1990 to 49·7 million in 2020. CVD, which accounts for a large proportion of these, will rise as a result of the accelerating epidemic in the developing countries. CHD will continue to be the leading cause of death in the world and, in terms of disability adjusted life years (DALY) lost, will rise from its fifth position in 1990 to top the DALY table in 2020.[15] Men as well as women in the developing countries will experience the largest rise in CHD and stroke mortality rates across the world (Table 9.1).

Table 9.1 Global % change in CHD and stroke mortality 1990–2020 (adapted from Murray and Lopez[3])

	CHD		Stroke	
	Men	Women	Men	Women
Developed countries	+48	+29	+56	+28
Developing countries	+137	+127	+124	+107
World	+100	+80	+106	+78

The profile of DALY loss attributable to CVD in 1990 in various regions of the world and the projected estimates for 2020 (Table 9.2) also indicate a large rise.[3] Among the developed countries, the sharp decline in the industrial nations is partly offset by the rise in the former socialist countries.

Table 9.2 Contribution of cardiovascular disease to DALY loss (percentage of total) (adapted from Murray and Lopez[3])

Region	1990 (%)	2020 (%)
World	10·85	14·7
Developed countries	25·7	22·0
Developing countries	8·9	13·8

Deaths attributable to tobacco, a risk factor for CVD and other chronic diseases, are projected to rise from 3·0 million in 1990 to 8·4 million in 2020. The largest increases will be in India, China and other developing countries in Asia, where tobacco-attributable deaths will rise from 1·1 million to 4·2 million in 2020.[24]

Mechanisms that propel a CVD epidemic in developing countries

Demographic changes due to the epidemiologic transition

A major public health challenge, identified by recent analyses of global health trends, is the projected rise in both proportional and absolute CVD mortality rates in the developing countries over the next quarter century. The reasons for this are many.[4] In the second half of the 20th century, most developing countries experienced a major surge in life expectancy. This was principally as a result of a decline in deaths occurring in infancy, childhood and adolescence, and was related to more effective public health responses to perinatal, infectious and nutritional deficiency disorders and to improved economic indicators, such as per capita income,

and social indicators such as female literacy in some areas. These demographic shifts have augmented the ranks of middle-aged and older adults. The increasing longevity provides longer periods of exposure to the risk factors for CVD, resulting in a greater probability of clinically manifest CVD events. The concomitant decline in infectious and nutritional disorders (competing causes of death) further enhances the proportional burden due to CVD and other chronic lifestyle related diseases.

The ratio between deaths due to pretransitional diseases (related to infections and malnutrition) and those caused by post-transitional diseases (such as CVD and cancer) varies among regions and between countries, depending on factors such as the level of economic development and literacy, as well as availability of and access to healthcare. The direction of change towards a rising relative contribution of post-transitional diseases is, however, common to and consistent among the developing countries.[25] The experience of urban China, where the proportion of CVD deaths rose from 12·1% in 1957 to 35·8% in 1990, illustrates this phenomenon.[26]

Population expansion and aging

Despite relative declines in fertility, the continuing growth of populations in the developing countries will also increase the absolute numbers at risk of CVD. The world population is expected to rise from 5·71 billion in 1995 to 8·29 billion in 2025. Combined with changes in the demographic profile, this will result in a large number of adults who are potentially vulnerable to CVD.

At present there are an estimated 380 million people aged 65 or more, including around 220 million in the developing countries. By 2020, the figures are projected to reach more than 690 million and 460 million, respectively.[2] In India, for example, the population is expected to rise from 683·2 million in 1981 to somewhere between 1253·8 and 1480·5 million in 2021. Simultaneously, the proportion of adults aged 35 years or above will rise from 28·4% of the population to 42·4%.[27]

Increased standard of living leading to deleterious health behaviors

A third reason to arouse concern is that, if population levels of CVD risk factors rise as a consequence of adverse lifestyle changes accompanying industrialization and urbanization, the rates of CVD mortality and morbidity could rise even higher than the rates predicted solely by demographic changes. Both the degree and the duration of exposure to CVD risk factors would increase as a result of higher risk factor levels, coupled with a longer life expectancy. The increase in body weight (adjusted for height), blood pressure and cholesterol levels in Chinese population samples aged 35–64 years between the two phases of the Sino-MONICA study (1984–86, 1988–89), and the substantially higher levels of most CVD risk factors in urban population groups compared to rural population groups in India, provide evidence of such trends.[26] The increasing use of tobacco in a number of developing countries will also translate into higher mortality rates from CVD, lung cancer and other tobacco related diseases, and undesirable alterations in diet and physical activity are also having adverse effects on cardiovascular health.

The global availability of cheap vegetable oils and fats has resulted in greatly increased fat consumption in low-income countries in recent years.[28] The transition now occurs at lower levels of the gross national product than previously, and is further accelerated by rapid urbanization. In China, for example, the proportion of upper income persons who were consuming a relatively high-fat diet (>30% of daily energy intake) rose from 22·8% to 66·6% between 1989 and 1993. The lower and middle income groups too showed a rise (from 19% to 36·4% in the former, and from 19·1% to 51·0% in the latter).[28] The Asian countries, traditionally high in carbohydrates and low in fat, have shown an overall decline in the proportion of energy from complex carbohydrates along with an increase in the proportion of fat.[28] The globalization of food production and marketing is also contributing to the increasing consumption of energy-dense foods that are poor in dietary fiber and several micronutrients.[29]

The rising tobacco consumption patterns in most developing countries contrast sharply with the overall decline in the industrial nations.[30] Recent projections from the World Health Organization suggest that by the year 2020 tobacco will become the largest single cause of death, accounting for 12·3% of deaths worldwide.[24] India, China and countries in the Middle Eastern crescent will by then have tobacco contributing to more than 12% of all deaths. In India alone, the toll attributable to tobacco will rise from 1·4% in 1990 to 13·3% in 2020.[24] A large component of this will be in the form of cardiovascular deaths.

Thrifty gene

A "programming" effect of factors promoting selective survival may also determine individual responses to environmental challenges and, thereby, the population differences in CVD. The "thrifty gene" has been postulated to be a factor in promoting the selective survival, over generations, of persons who encountered an adverse environment of limited nutritional resources.[31] Although this may have proved advantageous in surviving the rigors of a spartan environment over thousands of years, the relatively recent and rapid changes in environment may have resulted in a metabolic mismatch. Thus a salt-sensitive person whose forefathers thrived despite a limited supply of salt now reacts to a salt-enriched diet with high blood pressure. It has also

been hypothesized that populations subjected to food scarcity have undergone selection of a gene which increases the efficiency of fat storage through an oversecretion of insulin in response to a meal. Although this favors survival in a situation of low caloric availability, a current excess of caloric intake may lead to obesity, hyperinsulinemia, diabetes and atherosclerosis. Similarly, an insulin-resistant individual whose ancestors may have survived because a lack of insulin sensitivity in the skeletal muscle ensured adequate blood glucose levels for the brain in daunting conditions of limited calorie intake and demanding physical challenges, may now respond to a high-calorie diet and a sedentary lifestyle with varying degrees of glucose intolerance and hyperinsulinemia. Although such mechanisms seem plausible, their contribution to the acceleration of the CVD epidemic in the developing countries remains speculative.

Maternal–fetal exposures as a cause of midlife CVD

A recently reported association which, if adequately validated by the tests of causation, may have special relevance to the developing countries is the inverse relationship between birth size and CVD in later life.[32–38] The "fetal origins hypothesis" states that adverse intrauterine influences, such as poor maternal nutrition, lead to impaired fetal growth, resulting in low birthweight, short birth length and a small head circumference. These adverse influences are postulated to also "program" the fetus to develop adaptive metabolic and physiologic responses which facilitate survival. These responses, however, may lead to disordered responses to environmental challenges as the child grows, with an increased risk of glucose intolerance, hypertension and dyslipidemia in later life, with adult CVD as a consequence. Although some supportive evidence for the hypothesis has been provided by observational studies, it awaits further evaluation for a causal role. If it does emerge as an important risk factor for CVD, the populations of developing countries will be at an especially enhanced risk because of the vast numbers of poorly nourished infants born in the past several decades. The steady improvement in child survival will lead to a higher proportion of such infants surviving to adult life, when their hypothesized susceptibility to vascular disease may manifest itself.

Ethnic diversity

Although ethnic diversity in CVD rates, risk factor levels and risk factor interactions are evident from population studies, the extent to which genetic factors contribute is unclear. It is only after demographic profiles, environmental factors and possible programming factors are ascertained and adjusted for that differences in gene frequency or expression can be invoked as a probable explanation for interpopulation differences in CVD.[39] The extent to which chronic diseases, including CVD, occur within and among different populations is determined by genetic–environmental interaction, which occurs in a wide and variable array, ranging from the essentially genetic to the predominantly environmental. This is perhaps best illustrated by the knowledge gained from studies in migrant groups, where environmental changes due to altered lifestyles are superimposed on genetic influences. These "natural experiments" have been of great value in enhancing the understanding of why CVD rates differ among ethnic groups. The classic Ni-Hon-San study of Japanese migrants revealed how blood cholesterol levels and CHD rates rose from Japan to Honolulu and further still to San Francisco, as Japanese communities in the three areas were compared.[40] The experience gleaned from the study of south Asians, Chinese and Pima Indians further elucidates the complexities of ethnic variations in CHD.[41–43] The comparison of Afro-Caribbeans, south Asians and Europeans in the UK brought out the sharp differences in central obesity, glucose intolerance, hyperinsulinemia and related dyslipidemia between the three groups, despite similar profiles of blood pressure, body mass index and total plasma cholesterol.[44] However, urban–rural comparisons within India,[27] as well as migrant Indian comparisons with their non-migrant siblings,[45] reveal large differences in these conventional risk factors. Thus, where the environment is common but gene pools differ, the non-conventional risk factors appear to be explanatory of risk variance, whereas when the same gene pool is confronted with different environments, the conventional risk factors stand out as being of major importance.

To what extent ethnic diversity in response to CVD risk factors influences the course of the CVD epidemic in different developing countries remains to be studied. However, the experience of some of the migrant groups (for example, south Asians) portends severe epidemics in the home countries as they advance in their transition.

Strategies to deal with the coronary epidemic

CVD prevention

Evolving concepts of risk factors

Risk factor – Decades of research, embracing evidence from observational epidemiology and clinical trials, have demonstrated that CHD is multifactorial in causation. The term "risk factor" was first used in the context of CHD.[46] Several such risk factors have been identified, ranging from the established "major" factors such as smoking, elevated blood cholesterol and hypertension, to the recently investigated factors such as homocysteine and lipoprotein a. A risk factor must fulfill the criteria of causality: strength of association (high relative risk or odds ratio), consistency of

association (over many studies), temporal relationship (cause preceding the effect), dose–response relationship (greater the exposure, higher the risk), biologic plausibility, experimental evidence and, very importantly, evidence from human studies.

"Clinical" v "prevention" norms – The need to make "clinical" decisions related to the management of these risk factors led to a definition of threshold levels of risk and practice guidelines. These "clinical norms" erroneously came to be identified, by the health professionals as well as the community, as also representing the prevention norms. The former are defined by evidence of benefit exceeding risk when an intervention reduces a risk factor below a particular level (the net benefit being demonstrated in clinical trials specifically designed for that purpose). The latter, however, are usually identified from observational studies (long-term longitudinal prospective studies of large cohorts) and denote the optimal values of the risk factor at which the risk of developing disease is minimal.

The targeting of individuals is promoted by the "clinical" approach of healthcare providers, who seek to identify persons at "high risk" of disease or its outcomes for intensive investigation and intervention. Thus thresholds are defined to categorize persons with "high cholesterol" or "high blood pressure" and to implement individualized control strategies. Attention and action above this threshold often contrast with indifference and inertia below it.

As trial evidence is gathered, the clinical norms may progress towards the prevention norms, as in the case of cholesterol or hypertension, where the thresholds for intervention have been lowered dramatically in the last decade. They may, however, remain higher than the prevention norms, as clinical trials may be conducted at a stage in the natural history where the risks of prior exposure may not be completely reversible, and also because the intervention may itself be associated with some adverse effects. Thus the benefits of lowering a risk factor may appear less than those that may occur by preventing its rise in the first place.

The continuum of risk – It is clear that even though lifestyle disorders afflict some individuals, they arise from causes that are widespread in the population as a whole. Risk factors such as cholesterol and blood pressure operate in a continuum of progressively increasing risk, rather than through an all-or-none relationship suggested by cut-off values. For example, a systolic blood pressure (SBP) in the range 130–139 mmHg carries a higher risk for both heart attacks and strokes than values in the range 120–129 mmHg. Whereas an SBP of 180 mmHg carries a much higher risk for an individual than 140 mmHg, the number of persons in any population who have SBP values in the range 130–139 mmHg is higher than those with values of 180 mmHg or higher. The Multiple Risk Factor Intervention Trial's cohort study in the United States (MRFIT) revealed that of all heart attacks which are attributable to SBP, 7·2% arise from the 0·9% of the population that represents the 180+ mmHg range, whereas 20·7% of all such heart attacks occur in the 22·8% which has pressures in the range 130–139 mmHg[47] (Figure 9.2). Similarly, 57% of all excess deaths attributable to diastolic blood pressure occur in the range 80–95 mmHg, compared to only 15% which occur in the high range of 105–130 mmHg.

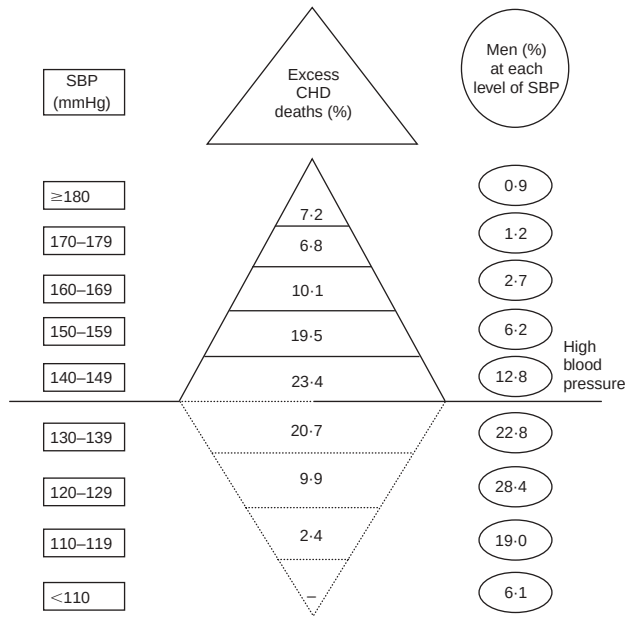

Figure 9.2 The risk pyramid for blood pressure and coronary heart disease (CHD): baseline SBP and CHD death rates for men screened in MRFIT[37] (adapted with permission from Stamler *et al*[36])

This dichotomy is also clearly seen in the Framingham Study on coronary risk factors.[49] People with a blood cholesterol level of 300 mg/dl run three to five times the risk of CHD as people at a cholesterol level of 200 mg/dl. At cholesterol levels over 300 mg/dl, 90 out of 100 persons developed the disease in the next 16–30 years of follow up in Framingham. At cholesterol levels under 200 mg/dl the rate was 20 out of 100 during the same period. However, more than twice as many people developed CHD with cholesterol levels under 200 mg% all their lives as did those with cholesterol levels over 300 mg%. This is because a 20% fraction of a 45% segment of the population is a much larger number than a 90% fraction of a 3–5% segment of the population.[49]

Thus, for most causal factors there is a "risk pyramid". Those at the top of the pyramid are at the highest individual risk of disease, but those at the lower levels account for the largest number of cases in the community because they

constitute the largest segment of the population. Any approach that targets only those at the highest risk produces limited gains for the community, despite conferring definite benefits to the individuals in that category.

The concept that "sick individuals arise from sick populations" was propounded and proved by Geoffrey Rose.[50,51] He demonstrated that risk factor "distributions" throughout the population are predictive of disease burden in that community. The mean (average) levels of a risk factor across different populations correlate with the proportions of high-risk individuals in those populations, whatever the cut-off value. Thus, as the average population blood pressure value among populations rises, the proportion of hypertensive individuals also rises. In each population there are groups who represent the extremes of the risk profile (very low risk *v* very high risk). However the proportion at "high risk" would be determined by the average value of that risk factor in the population. This in turn is dependent on the dominant behaviors that characterize the society at each stage of its development.

Multiplicative risk – The process of identifying and estimating the independent risk associated with any single risk factor led to clinical and preventive strategies to target it in isolation. However, observational studies like Framingham and MRFIT have clearly revealed that the coexistence of multiple risk factors confers a magnified risk which is multiplicative rather than merely additive. A smoker with modest elevations of cholesterol and diastolic or systolic blood pressure is at a greater risk of coronary death than a non-smoker with severe hypertension or marked hypercholesterolemia. In the MRFIT study, a non-smoker with SBP less than 118 mmHg and a total serum cholesterol level less than 182 mg% had a 20-fold lower risk of coronary death than a smoker with a SBP exceeding 142 mmHg and a serum cholesterol exceeding 245 mg% (age adjusted CHD mortality of 3·09 *v* 62·11, per 10 000 person years). A smoker who has a SBP of 132–141 mmHg and a serum cholesterol of 203–220 mg% has a CHD mortality risk of 28·87 per 10 000 person years, compared to a risk of 12·36 in a non-smoker with an SBP below 118 mmHg but with a serum cholesterol exceeding 245 mg%.[52]

The demonstration of such multiplicative risk has led to the concept of "comprehensive cardiovascular risk" or "total risk", quantifying an individual's overall risk of CVD resulting from the confluence of risk factors.[48] Both clinical and preventive strategies are veering away from unifactorial risk reduction to multifactorial risk modification, to reduce this overall risk in individuals as well as in populations.

High-risk approach for prevention

Having recognized that environmental risk factors do not affect only a few individuals in isolation but are spread across populations, with a continuous rather than a threshold relationship to disease, how should that influence disease control strategies? The health policy debate, until recently, was on whether to focus the control strategies on individuals at the highest risk of disease (in view of their markedly elevated risk factor levels) or on the population as a whole (aiming to achieve modest reductions in the risk of most members of that community). The high-risk approach aims to identify persons with markedly elevated risk factors and therefore at the highest risk of disease.[50] These individuals are then targeted by interventions which aim to reduce the risk factor levels. If successful, the benefits to individuals are large, because the individuals risks are large. However, as the number of persons in this high-risk category is proportionately much smaller than that in the moderate-risk group, the overall benefits to society are limited in terms of deaths or disability avoided. The strategy also does not minimize the risk for the individuals concerned. Although a fall of blood cholesterol from 300 mg% to 240 mg% does indeed reduce the risk, even this attained value poses greater risk than 200 mg%. Thus there is still a substantial residual risk, despite the impressive risk reduction owing to the change from the initial cholesterol levels. Further, this strategy is behaviorally inappropriate.[50] An individual with high blood cholesterol levels may be advised to eat low-fat food, but can he strictly adhere to it if his family and friends consume a very different diet? The main advantage of the high-risk approach, however, is that physicians as well as patients are highly motivated to act, because the projected risks compel attention and the benefits of reduction appear attractive.[50]

Population approach for prevention

In contrast, the population approach aims at reducing the risk factor levels in the population as a whole, through community action.[50] Because there is a continuum of risk associated with most risk factors, this mass change will result in mass benefit across a wide range of risks. Although individual benefits are relatively small, the cumulative societal benefits are large ("the prevention paradox"). The strategy is also behaviorally more appropriate.[50] If the eating habits in the community alter towards preferred consumption of foods with lower saturated fat and salt content and a greater daily intake of fresh fruit and vegetables, even the high-risk individual on a prescribed diet will find a supportive ambience which does not mark him out as a deviant from social norms. If a new generation grows up in an environment where healthy behavior is considered common practice, its average blood cholesterol level may remain below 200 mg% rather than around 240 mg%, and thus be at a lower risk than even the beneficiary of the high-risk strategy. However, the risks and benefits of such a strategy are less obvious to those in the moderate-risk range. The motivation for change is therefore not as strong as for those in the high-risk

group. The gratification of achieving readily identifiable success in high-risk individuals, through drugs or other powerful interventions, is also denied to the physicians in the population strategy, where the potential beneficiaries, though many, are faceless and nameless. Because such "anonymity of prevention" denies the pleasure of individual rescue acts, physician motivation for community counseling is neither strong nor sustained.[50] Policymakers, however, can ill afford to ignore the imperatives of investing in a population approach which will pay large long-term dividends in the control of lifestyle diseases. Health professionals too must recognize the benefits of this strategy to play a strong advocacy role for health-promoting behaviors in the community.

The success of the population strategy has been demonstrated both in developed countries (for example, Finland)[53] and in some developing countries (for example, Mauritius).[54] The North Karelia Project demonstrated large reductions in CVD mortality (50·1% in males and 63·5% in females), CHD mortality (53·4% and 59·8%) and all-cause mortality (39·5% and 40·4%) during the 20-year intervention period. These accompanied changes in CVD risk factors following community-based intervention programmes. Impressive reductions in cigarette smoking, prevalence of hypertension and mean population cholesterol levels, as well as increases in leisuretime physical activity, were noted during the period 1987–92 consequent upon lifestyle intervention programs in Mauritius.

The impact of the population strategy is likely to be large, as suggested by an estimate that if every American had a diastolic blood pressure value a mere 2 mmHg lower than his or her current value, the number of heart attacks that could be prevented would exceed those that could be avoided by effectively treating every person with a diastolic pressure of 95 mmHg or higher. The corresponding benefit for preventing paralytic strokes would be 93% of those avoided by drug therapy.[55] Such blood pressure changes can be effectively achieved and sustained through modest reductions in weight and salt intake or through exercise.

Combining the strategies

These strategies are not mutually exclusive but are synergistic, complementary and necessary. The risks and benefits demonstrated in high-risk individuals serve to educate the community about risk factors, whereas the population approach makes it easier to achieve the desired level of lifestyle change in high-risk individuals. The population-based lifestyle-linked risk reduction approach is particularly relevant in the context of the developing countries, where it is necessary to ensure that communities currently at low risk are protected from the acquisition or augmentation of risk factors ("primordial prevention"). This is true for adults in the rural regions of most developing countries, as well as for children in all populations. It is also eminently applicable to moderate-risk groups in urban areas, where lifestyle-based risk modification will help avoid drug therapy, with its attendant economic and biologic costs. There will still be some who need such pharmacologic or technologic interventions because of their high-risk status. However, their numbers too will decrease as the risk profile of the whole community gradually shifts.

Case management

Despite these preventive strategies, several individuals will manifest clinical disease because risks are not totally eliminated in the community or because genetic susceptibility is strongly expressed. The success of preventive efforts will reduce their number as well as delay the age of onset of clinical events. Those who develop disease will require optimal clinical care, which can avert early death, reduce disability and ensure an adequate quality of life. This mandates early detection of disease.

The cost effectiveness and safety of these diagnostic and therapeutic techniques would have to be established through appropriately designed clinical research. This scientific evidence has to be translated into practice guidelines, which then need to be widely disseminated. The rapid diffusion of these guidelines across various levels of healthcare and their sustained impact on clinical practice will ensure that the burden of cardiovascular disease in the community is mitigated through appropriate application of available knowledge. Postmyocardial infarction risk reduction through thrombolytic agents, aspirin, β blockers, ACE inhibitors and statins is clearly illustrative of the benefits of such evidence-based clinical care.[56–61]

The decline in CVD mortality rates in industrial countries is the collective result of population-based prevention strategies improving the risk factor profile of communities, a high-risk approach of targeted interventions to protect individuals with markedly elevated risk factor levels, and case management strategies to salvage, support and sustain those presenting with clinical problems. These strategies are not diverse and divisive but are continuous and complementary in the effort to control the incidence and impact of CVD.

The enormous need for evidence-based medicine in developed and developing countries

CVD related expenditure in developed countries

The management of CVD is often technology intensive and expensive. Procedures for diagnosis or therapy, drugs, hospitalization and frequent consultations with healthcare providers all contribute to high costs, both to those affected and to society. In developed countries they already account for

about 10% of direct healthcare costs, equal to between 0·5% and 1% of a country's gross national product.[2] As life expectancy increases and the duration of the therapy becomes prolonged, the costs may further escalate until preventive strategies succeed in greatly reducing the incidence of CVD.

CVD related expenditure in developing countries

The costs of CVD related healthcare have not been clearly estimated in the developing countries.[62] However, high expenditure on tertiary care in most of these countries probably has a large contribution from CVD. As the epidemic advances many more will be affected, escalating the costs of CVD related healthcare. This may divert scarce resources intersectorally from developmental activities, and intrasectorally from the "unfinished agenda" of infectious and nutritional disorders. As the epidemic matures, the social gradient will reverse and many of the poor who are then afflicted will be unable to afford or access the expensive healthcare that CVD demands.

Need for evidence-based medicine

The need for cost effective prevention and case management is, therefore, urgent. These practices need to be based on the best available evidence which is generalized to the context of each developing country. Where such evidence is unavailable or insufficient to guide policy and practice, health research must quickly address those information needs. International cooperation can greatly further these efforts to acquire, appraise, analyze and apply such knowledge. *Evidence* from health research must do *justice* to the needs of public health! Evidence-based cardiovascular medicine must pursue this advocacy to secure acquittal from CVD for countries under the trial of epidemiologic transition. However, the recommendations also need to be context specific and resource sensitive, in accordance with the specific needs of different regions. The challenge for cardiovascular research is to provide for such relevant knowledge generation, and the challenge for public health and clinical practice is to provide for effective knowledge translation. The course and consequences of the global cardiovascular epidemic should not merely be predicted, but ought to be favorably altered by responding to these challenges.

References

1. *The World Health Report 2001*. Geneva: World Health Organization, 2001.
2. *The World Health Report 1997*. Geneva: World Health Organization, 1997.
3. Murray CJL, Lopez AD. *The Global burden of disease: A comprehensive assessment of mortality and disability from disease, injuries and risk factors in 1990 and projected to 2020*. Boston: Harvard University Press, 1996.
4. Reddy KS, Yusuf S. The emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998;**97**: 596–601.
5. Howson CP, Reddy KS, Ryan TJ, Bale JR (eds) *Control of cardiovascular disease in developing countries. Research, development and institutional strengthening*. Washington, DC: National Academy Press, 1998.
6. Yusuf S, Reddy S, Ounpuu S, Anand S. Global Burden of Cardiovascular Diseases. Part I: General Considerations, the Epidemiological Transition, Risk Factors, and Impact of Urbanisation. *Circulation* 2001;**104**:2746; Part II: Variations in Cardiovascular Disease by Specific Ethnic Groups and Geographic Regions and Prevention Strategies. *Circulation* 2001;**104**:2855.
7. American Heart Association. *2000 Heart and Stroke Statistical Update*. Dallas, TX: American Heart Association, 1999.
8. Lopez AD. Assessing the burden of mortality from cardiovascular disease. *Wld Hlth Stat Q* 1993;**46**:91–6.
9. Feinleib M, Ingster L, Rosenberg H, Maurer J, Singh G, Kochanek K. Time trends, cohort effects and geographic patterns in stroke mortality. United States. *Ann Epidemiol* 1993;**3**:458–65.
10. Whelton PK, Brancati FL, Appel LJ, Klag MJ. The challenge of hypertension and atherosclerotic cardiovascular disease in economically developing countries. *High Blood Press* 1995;**4**:36–45.
11. Marmot M. Coronary heart disease: rise and fall of a modern epidemic. In: Marmot M, Elliott P, eds. *Coronary heart disease epidemiology. From aetiology to public health*. Oxford: Oxford University Press, 1992.
12. Cooper, Cutler J, Desvigne-Nickens P *et al.* Trends and disparities in coronary heart disease in the United States. Findings of the National Conference on Cardiovascular Disease Prevention. *Circulation* 2000;**102**:3137–47.
13. AR. The epidemiologic transition: a key of the epidemiology of population change. *Millbank Mem Fund Q* 1971;**49**: 509–38.
14. Bobadilla JL, Costello CA, Mitchell F (eds) *Premature death in the new independent States*. Washington, DC: National Academy Press, 1997.
15. Notzon FC, Komarow YM, Ermakov SP *et al.* Causes of declining life expectancy in Russia. *JAMA* 1998;**279**: 793–800.
16. Chenet L, Mckee M, Fulop N *et al.* Changing life expectancy in central Europe: Is there a single reason? *J Public Health Med* 1996;**18**:329–36.
17. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality for ischaemic heart disease in Poland since 1991. *BMJ* 1998;**317**:678.
18. Omran AR. The epidemiologic transition: a key of the epidemiology of population change. *Millbank Mem Fund Q* 1971;**49**:509–38.
19. Olshansky SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Millbank Mem Fund Q* 1986;**64**:355–91.
20. Pearson TA, Jamison DT, Trejo-Gutierrez H. Cardiovascular disease. In: Jamison DT, ed. *Disease control priorities in developing countries*. New York: Oxford University Press, 1993.

21. Verschuren WMM, Jacobs DR, Bloemberg BPM *et al.* Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five year follow-up of the Seven Country Study. *JAMA* 1995;**274**:131–6.
22. Suh I. Cardiovascular mortality in Korea: a country experiencing epidemiologic transition. *Acta Cardiol* 2001;**56**:75–81.
23. Unwin N, Setel P, Rashid S *et al.* Noncommunicable diseases in sub-Saharan Africa: where do they feature in the health research agenda? *Bull WHO* 2001;**79**: 947–53.
24. *Tobacco or health: First global status report*. Geneva: World Health Organization, 1996.
25. Bulatao RA, Stephens PW. *Global estimates and projections of mortality by cause 1970–2015. Pre-working paper 1007*. Washington, DC: Population Health and Nutrition Department, World Bank, 1992.
26. Yao C, Wu Z, Wu J. The changing pattern of cardiovascular diseases in China. *Wld Hlth Stat Q* 1993;**46**:113–18.
27. Reddy KS. Cardiovascular disease in India. *Wld Hlth Stat Q* 1993;**46**:101–7.
28. Drewnowski A, Popkin BM. The nutrition transition: new trends in the global diet. *Nutr Rev* 1997;**55**:31–43.
29. Lang T. The public health impact of globalisation of food trade. In: Shetty PS, McPherson K, eds. *Diet, nutrition and chronic disease. Lessons from contrasting worlds*. Chichester: Wiley, 1997.
30. Peto R. Tobacco – the growing epidemic in China. *JAMA* 1996;**275**:1683–4.
31. Thrifty genotype rendered detrimental by progress [editorial]. *Lancet* 1989;**ii**:839–40.
32. Barker DJP, Martyn CN, Osmond C, Haleb CN, Fall CHD. Growth *in utero* and serum cholesterol concentrations in adult life. *BMJ* 1993;**307**:1524–7.
33. Martyn CN, Barker DJP, Jespersen S, Greenwald S, Osmond C, Berry C. Growth *in utero*, adult blood pressure and arterial compliance. *Br Heart J* 1995;**73**:116–21.
34. Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens* 1996;**14**:935–41.
35. Joseph KS, Kramer MS. Review of evidence on fetal and early childhood antecedents of adult chronic disease. *Epidemiol Rev* 1996;**18**:158–74.
36. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Early growth, adult income, and risk of stroke. *Stroke* 2000; **31**:869–74.
37. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker D. Fatal and childhood growth and hypertension in adult life. *Hypertension* 2000;**36**:790.
38. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Early growth coronary heart disease in later life: longitudinal study. *BMJ* 2001;**322**:949–53.
39. Reddy KS. Coronary heart disease in different racial groups. In: Yusuf S, Wilhelmsen L, eds. *Advanced issues in prevention and treatment of atherosclerosis*. Surrey: Euromed Communications, 1996.
40. Robertson TL, Kato H, Rhoads GG *et al.* Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol* 1977;**39**:239–49.
41. Enas EA, Mehta JL. Malignant coronary artery disease in young Asian Indians: thoughts on pathogenesis, prevention and treatment. *Clin Cardiol* 1995;**18**:131–5.
42. Li N, Tuomilehto J, Dowse G *et al.* Prevalence of coronary heart disease indicated by electrocardiogram abnormalities and risk factors in developing countries. *J Clin Epidemiol* 1994;**47**:599–611.
43. Sievers ML, Nelson RG, Bennet PH. Adverse mortality experience of a southwestern American Indian community: overall death rates and underlying causes of death in Pima Indians. *J Clin Epidemiol* 1990;**43**:1231–42.
44. Chaturvedi N, McKeigue PM, Marmot MG. Relationship of glucose intolerance to coronary risk in Afro-Caribbeans compared with Europeans. *Diabetologia* 1994;**37**:765–72.
45. Bhatnagar D, Anand IS, Durrington PN *et al.* Coronary risk factors in people from the Indian Subcontinent living in West London and their siblings in India. *Lancet* 1995;**345**:404–9.
46. Kannel WB, Dawber TR, Kagan A, Revotskie N, Strokes J III. Factors of risk in the development of coronary heart disease – six-year follow-up experience. *Ann Intern Med* 1961; **55**:33–50.
47. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med* 1993;**153**:598–615.
48. WHO Expert Committee. *Hypertension Control in Populations*. World Health Organization Technical Report No 862. Geneva: World Health Organization, 1996.
49. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 1992;**2**:23–8.
50. Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985;**14**:32–8.
51. Rose G, Day S. The population mean predicts the number of deviant individuals. *BMJ* 1990;**301**:1031–4.
52. Neaton JD, Kuller LH, Wentworth D, Borhani NO, for the Multiple Risk Factor Intervention Trial Research Group. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed for five years. *Am Heart J* 1984;**108**:759–69.
53. Puska P, Tuomilehto J, Aulikki N, Enkki V. *The North Karelia Project. 20 years results and experiences*. Helsinki: National Public Health Institute, 1995.
54. Dowsen GK, Gareeboo H, George K *et al.* Changes in population cholesterol concentrations and other cardiovascular risk factor levels after five years of non-communicable disease intervention programme in Mauritius. *BMJ* 1995; **311**:1255–9.
55. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med* 1995;**155**:701–9.
56. Matching the Intensity of Risk Factors Management with the Hazard for Coronary Disease Events (27th Bethesda Conference). *J Am Coll Cardiol* 1996;**27**:957–1047.
57. Antiplatelet Trialists Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I. Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:235–46.
58. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;**260**:2088–93.

59. Walsh JT, Gray D, Keating NA *et al.* ACE for whom? Implications for clinical practice of post-infarct trials. *Br Heart J* 1995;**73**:470–4.
60. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
61. Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**: 1001–9.
62. Chockalingam A, Balaguer-Vinto I (eds) *Impending Global Pandemic of Cardiovascular Diseases. Challenges and opportunities for the prevention and control of cardiovascular diseases in developing countries and economies in transition (World Heart Federation)*. Barcelona: Prous Science, 1999.

10 Tobacco: global burden and community solutions

Terry F Pechacek, Samira Asma, Nicole Blair, Michael P Eriksen

Introduction

While smoking is universally known to be deadly, few are aware of precisely how deadly. In the United States, smoking is the leading preventable cause of death, killing over 440 000 people each year, wasting 5 million years of potential life and costing over $75 billion in health expenditures. Since the first Surgeon General's Report on smoking in 1964, over 10 million Americans have died from smoking. If current trends continue, an additional 25 million Americans alive today, including 6·4 million children, will die a painful and premature death caused by smoking. While the United States statistics are appalling, the global projections are even more dire. Globally, if current trends continue, the number of people killed by tobacco will more than triple to 10 million a year by the year 2025. The only ray of hope is that the precursors for the projected global tobacco epidemic are not yet all in place. While high smoking rates among men are nearly universal, the same cannot be said for women and teens. Thus, despite the unprecedented toll of tobacco and the gloomy projections, there is the potential for prevention.

This chapter will explore that potential, particularly for coronary heart disease, by:

1. examining the current global burden of tobacco and future projections
2. reviewing the mixed evidence for community-based tobacco control interventions
3. proposing a new and dynamic model for community-based tobacco control, based on state innovations, proven to be effective in the United States, that may be able to be applied throughout the world.

Current global burden of tobacco and future projections

Worldwide, the only two major causes of death whose effects are now increasing rapidly are HIV and tobacco. If current smoking patterns persist, there will be about one billion deaths from tobacco during the twenty-first century, compared to "only" about 0·1 billion (100 million) during the whole of the twentieth century. About half of these deaths will be in middle age (35 to 69) rather than old age, and those killed by tobacco in middle age lose, on average, more than 20 years of non-smoker life expectancy.[1] Tobacco use is estimated to have caused about 4 million deaths a year, more or less evenly split between developed and developing countries. These numbers reflect smoking patterns several decades ago, and worldwide cigarette consumption has increased substantially over the past half century.[2] Currently, about 30% of young adults become persistent smokers, and relatively few quit. The main diseases by which smoking kills people are substantially different in America, where vascular disease and lung cancer predominate;[1] in China, where chronic obstructive pulmonary disease causes even more tobacco deaths than lung cancer;[3,4] and in India, where almost half the world's tuberculosis deaths take place and the ability of smoking to increase the risk of death from TB may well be of particular importance.[5,6]

There are already a billion smokers, and by 2030 about another billion young adults will have started to smoke. If current smoking patterns persist, worldwide mortality from tobacco is likely to rise from about four million deaths a year currently to about 10 million a year around 2030 and will rise somewhat further in later decades. This means that tobacco use will cause about 150 million deaths in the first quarter of the century and 300 million in the second quarter. Predictions beyond that are inevitably speculative, but if over the next few decades a quarter to a third of the young adults become persistent smokers and about half are eventually killed by their habit, about 15% of adult mortality in the second half of the century will be due to tobacco, implying some 600 million to 900 million tobacco deaths between 2050–2099.[7]

First, globally in 1995, 29% of the world's population aged 15 years and over smoked daily (Table 10.1). Low-income and middle-income countries whose populations account for four fifths of the global adult population, accounted for 82% of the world's smokers. East Asia and the Pacific, which includes China, accounted for 36% (43 million) of all smokers, but only 32% of the population aged 15 years and over. Overall, smoking prevalence was highest in Europe and Central Asia at 40% and lowest in Sub-Saharan Africa at 18%.

For both males and females, there was wide variation in smoking prevalence between regions. The prevalence of smoking amongst males was highest in East Asia and the Pacific, and in Europe and Central Asia, at about 60% in each case, and lowest in Sub-Saharan Africa at 29%. Among females, the prevalence of smoking was highest in Europe and Central Asia at 26% and lowest in South Asia at 5% (for cigarettes and bidis combined) and Middle East and North Africa at 6%.

Second, the prevalence of smoking amongst males was higher overall for men (47%) than for women (11%). WHO data at country level suggest that the proportion of men who smoke is well above 50% in many low-income and middle-income countries:

- 82% in Indonesia,
- 78% in the Philippines,
- 75% in Cuba,
- 72% in China.[2]

Globally, males account for four in five of all smokers.

The majority of epidemiologic studies suggest that individuals who avoid starting to smoke in adolescence or young adulthood are unlikely ever to become smokers. Nowadays, the overwhelming majority of smokers start before age 25, often in childhood or adolescence (Figure 10.1); in high-income countries, eight out of 10 begin in their teens. In middle- and low-income countries for which data are available, it appears that most smokers start in their early twenties, but the trend is towards younger ages. For example, in China between 1984 and 1996, there was a significant increase in the number of young men aged between 15 and 19 years who took up smoking. A similar decline in the age of starting has been observed in high-income countries.

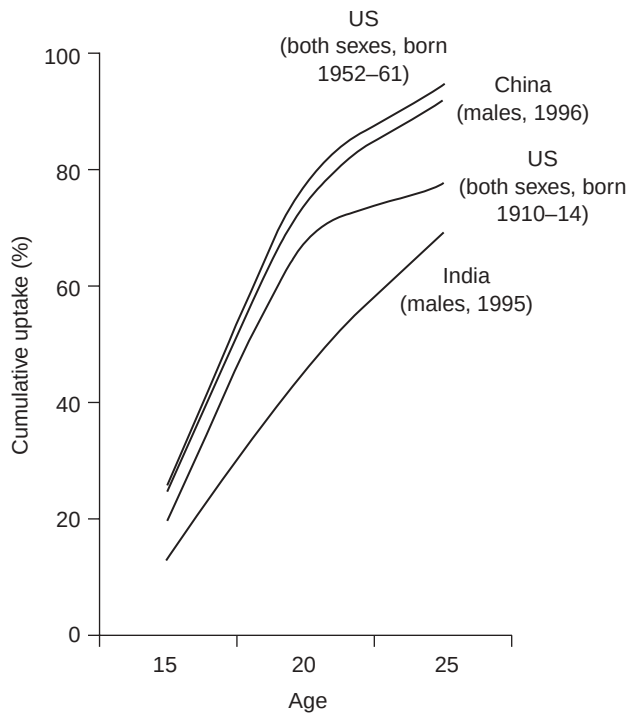

Figure 10.1 Smoking initiation age in China, India and the United States. Source: Gupta 1996; USDHHS 1989 and 1994; Chinese Academy of Preventive Medicine 1997

Tobacco: a risk factor for coronary heart disease

It is well established that prolonged smoking is an important cause of chronic disease. Prolonged smoking causes many diseases in addition to lung cancer, notably other cancers and chronic respiratory and cardiovascular diseases. However, the toll of death and disability from smoking outside the high income countries has yet to be felt. This is because the diseases caused by smoking can take several decades to develop. Even when smoking is common in a population, the damage to health may not yet be visible. The alarming size of the hazards now observable in populations that have been smoking for many decades.

Thus in the first 20 years of follow up of the British doctors, cohort (1951–71), smokers had, on average, about a 1·5 to twofold higher death rate at each age, similar to the excess reported in other studies around that time (see Table 10.1). With longer duration of smoking, death rates of smokers have increased substantially so that during the second period of follow up (1971–91), smokers in middle age had a threefold higher death rate than non-smokers. A similar excess mortality ratio was found in the CPS-II cohort based on follow up in the latter half of the 1980s. These relative risks suggest that, on average, a smoker who begins smoking in young adult life and continues to do so has at least a 50% chance of eventually being killed by tobacco, either in middle age or in old age.

The evidence from these two studies on the disease-specific risks associated with smoking are similar.[8] Current smokers have about a 20-fold higher death rate from lung cancer than never smokers, among whom lung cancer death rates have remained low and constant. There is epidemiologic evidence to suggest that this is also the case in other populations. For example, based on the two American Cancer Society studies with follow up to 1959–65 and 1982–86 respectively, lung cancer death rates among lifelong non-smokers were remarkably constant at 15·4 and 14·7 per 100 000 (age-standardized) for men, and 9·6 and 12·0 for women; the rates for current smokers were 187·1 and 341·3 for men, and 26·1 and 154·6 for women.[9] Smokers also incur a 10–20-fold excess mortality from chronic obstructive lung disease (primarily chronic bronchitis and emphysema), and a risk of death from major vascular diseases that is about twice that of non-smokers.

The excess mortality of smokers from vascular disease is particularly noteworthy. Vascular disease death rates are typically much higher than those for cancer or other causes

Table 10.1 Prevalence of smoking among adults aged 15 and over, by World Bank region, 1995

World Bank Region	Smoking prevalence (%)			Total smokers	
	Males	Females	Overall	(millions)	(% of all smokers)
East Asia and Pacific	61	4	33	413	36
Europe and Central Asia	57	26	40	145	13
Latin America and Caribbean	40	21	30	95	8
Middle East and North Africa	44	5	25	40	3
South Asia (cigarettes)	21	1	11	88	8
South Asia (*bidis*)	21	4	13	99	9
Sub-Saharan Africa	29	9	18	59	5
Low-income & Middle-income	49	9	29	939	82
High-income	38	21	29	205	18
World	47	11	29	1143	100

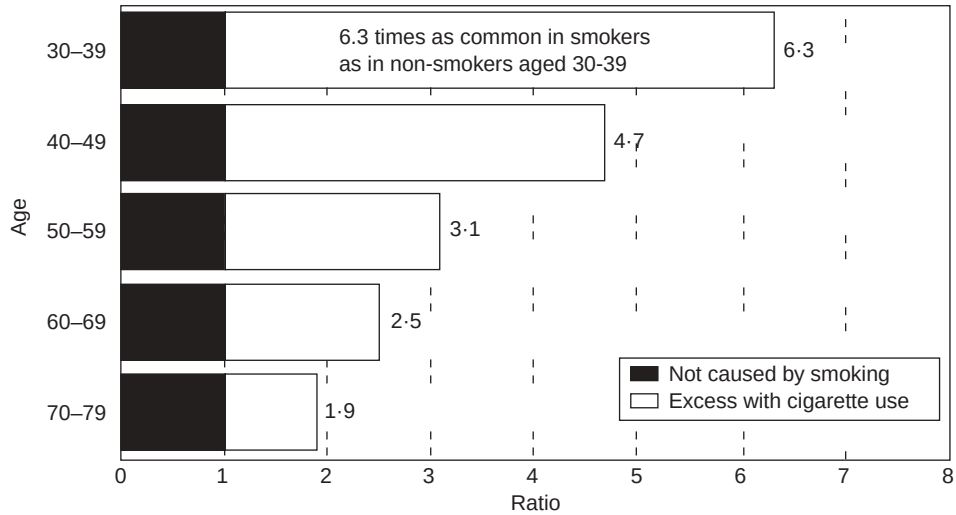

Figure 10.2 *Source*: Based on the ISIS study of over 10 000 UK heart attacks, Parish *et al*. Cigarettes smoking, Lar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. *BMJ* 1994;**311**:471–7[10]

associated with smoking. Cardiovascular diseases (especially ischemic heart disease and stroke), therefore, contribute more to smoking-attributable deaths at a population level than do other causes, including lung cancer for which the relative risk is much higher, although this pattern will change as cardiovascular disease mortality declines. Finally, it is worth noting that the all-age excess mortality ratio of about 2 from cardiovascular diseases masks a very significant age gradient in relative risks. This is clearly shown in Figure 10.2 based on a large (46 000 persons) case–control study carried out in the United Kingdom.

At younger ages (<50 years), smokers have a five to six times higher death rate than non-smokers, with the relative excess declining with age. What these data suggest is that if a smoker dies from vascular disease before about the age of 50 years, there is a 70–80% chance that smoking caused it, and that this is the prinicipal mechanism through which smoking causes a threefold excess mortality rate in middle age.

Cigarette smoking is only one of several causative factors that produce disease. This is especially true for ischemic heart disease where smoking interacts synergistically with other factors such as hypercholesterolemia and hypertension to greatly increase risk of heart disease. Evidence suggests that the independent risk attributable to smoking is comparable to that of other major risk factors.[10] This interaction with dietary parameters probably explains the currently lower proportions of ischemic heart disease attributable to smoking in populations such as China where low-fat diets have predominated.[3]

The extent to which smoking is responsible for deaths from diseases other than lung cancer varies substantially from one population to another. For example, smoking is particularly cardiotoxic for people who already have other risk factors such as high blood cholesterol. The range of other diseases that are caused by smoking is so extensive that the influence of other specific risk factors may effectively average

out even in different populations. For example, although in many developing countries, cholesterol levels are low (limiting the cardiotoxic effects of tobacco), a high prevalence of respiratory diseases may greatly increase the pulmonary vulnerability to tobacco.[11]

Smokers have twice the risk of heart attack compared with non-smokers. Smoking is also a major risk factor for sudden death from heart attack, with smokers having two to four times the risk of non-smokers. The risk increases with the number of cigarettes smoked. Overall, cigarette smokers have coronary heart disease (CHD) rates 70% higher than those of non-smokers, with heavy smokers dying from CHD at a rate two to three times that of non-smokers.[1] In addition, recent epidemiologic evidence shows that never-smokers exposed to environmental tobacco smoke (ETS) have an increased risk not only for lung cancer but also for cardiovascular disease. Two recent prospective trials[12–14] and meta-analyses[15] estimate the relative risk for cardiovascular diseases at 1·2 to 1·3 individuals exposed to ETS.[12–15] Of the deaths caused by ETS, the number of deaths from heart disease is about three times the number of non-cardiac deaths[16].

Cardiovascular deaths account for a significant portion of adult deaths in all countries. Worldwide, slightly more than 50 million people are estimated to have died in 1990, 53% of whom were males. Ischemic heart disease (IHD) was the leading cause of death worldwide, accounting for just under 6·3 million deaths – 2·7 million in established market economies (EME) and formerly socialist economies of Europe (FSE); 3·6 million in the developing regions. Stroke was the next most common cause of death (4·38 million deaths – almost 3 million in developing countries), closely followed by acute respiratory infections.[17] Of the various coronary heart disease pathologies, IHD and stroke predominate in the developed regions, accounting for 75–80% of all cardiovascular deaths. Stroke is proportionately more important as a cause of cardiovascular disease death in FSE (31%) than in EME (25%). Rheumatic heart disease is estimated to cause between 1% and 6% of all CHD deaths in the developing regions (and about 2·4% globally). The category labeled as inflammatory heart disease (pericarditis, endocarditis, myocarditis, and cardiomyopathies) accounts for similar proportions of CHD deaths, being highest in Sub-Saharan Africa (SSA) (7·8%). It is also worth noting the substantial contribution of IHD in all developing regions, ranging from 52% of cardiovascular deaths in India to 26% in SSA. Stroke, on the other hand, is by far the leading cause of cardiovascular deaths in China and SSA, causing roughly half of all coronary heart disease deaths in 1990.[18]

Future projections

Policy makers must be concerned not so much by the current mortality from past smoking patterns, but by the much larger death rates that are projected in coming decades as a result of current smoking, especially for low- and middle-income countries.

Smoking-attributable deaths are projected to increase for two reasons: first, increases in the susceptible population size; and second, increase in age-specific disease rates. For example in China, male per capita consumption of cigarettes rose 10-fold between 1952 and 1992. The incidence of lung cancer in China has increased more than sixfold during the period 1970 to 1980,[19] and is likely to increase 7·5-fold in the near future. During the same period, the population that will contract lung cancer will increase fourfold. The net result is that 30 000 lung cancer deaths per year in 1975 will increase to 90 000 per year by 2025.

Tobacco will cause 0·5 billion deaths among smokers alive today. At some point in the second decade of the twenty-first century, annual deaths from tobacco will average 10 million a year. This total may appear earlier or later. Depending on smoking patterns, there will be about 450 million tobacco deaths between 2000 and 2050.[8] Projections beyond 2050 are more uncertain. If the proportion of people taking up smoking continues, as at present, to be between one quarter and one third of young adults then, given population growth, an additional 500 billion tobacco deaths are expected in the second half of the twenty-first century. Thus, in the twenty-first century overall, tobacco would be expected, on current patterns, to kill about one billion people, or ten times as many people in the twentieth century.[7]

Direct estimates for China based on retrospective and prospective studies[3,4] suggest that, on current patterns, smoking may account for one in three of all adult male deaths in China, or about 100 million of the 300 million Chinese males now aged 0–29. Annual tobacco deaths will rise to 1 million before 2010 and 2 million before 2025, when young adults of today reach old age. Similar preliminary estimates for India based on large retrospective and prospective studies suggest that about 30% of all male deaths in middle age are attributable to smoking and about 80 million Indian males currently aged 0–34 will eventually be killed by tobacco.

Projections of tobacco mortality based on econometric models by Murray and Lopez suggest that there will be 8·3 million tobacco-attributable deaths per year in 2020. These researchers have predicted elsewhere that global deaths attributed to tobacco would rise from 6% of all deaths in 1990 to about 12% in 2020.[18]

Worldwide, a very large increase in deaths from non-communicable diseases (group 2) is expected, with a rise in annual mortality from an estimated 28·1 million deaths in 1990 to 49·7 million in 2020. Conversely, annual mortality from communicable maternal, perinatal, and nutritional disorders (group 1) is predicted to decline from 17·2 million in 1990 to 10·3 million in 2020 (Figure 10.3).

It is of interest to examine how DALYs (disability adjusted life years is a measure of life lost due to disability or premature

death) from various leading causes are expected to change over the next three decades (Figure 10.4). Figure 10.5 shows the change in cause of mortality. IHD is projected to be the leading cause of disability and death by 2020. It has been plausibly predicted that the current global total of about 3 million deaths per year from tobacco (2 million developed, 1 million developing) would reach approximately 10 million deaths per year (3 million developed, 7 million developing) during the second quarter of next century (Figure 10.6). This would mean that over 200 million of today's children and teenagers will be killed by tobacco, as well as a comparable number of today's adults, predicting that a total of about half a billion of the world's population today will be killed by tobacco. About 250 million will die in middle age (35–69), with each person losing about 20 years of life.[20]

In terms of DALYs, the contribution of tobacco is projected to increase to account for nearly 9% of worldwide burden (18·2% of burden in developed countries and 7·7% in developing countries) in 2020 (Figure 10.7). Tobacco is also projected to cause about 12% of deaths worldwide (17·7% of deaths) in developed countries and 10·9% in developing countries) by 2020 (Figure 10.8). DALYs from cancers are expected to rise from 5·1% to 9·9% of the worldwide total in 2020. The proportionate share of the global burden of disease due to cardiovascular diseases is projected

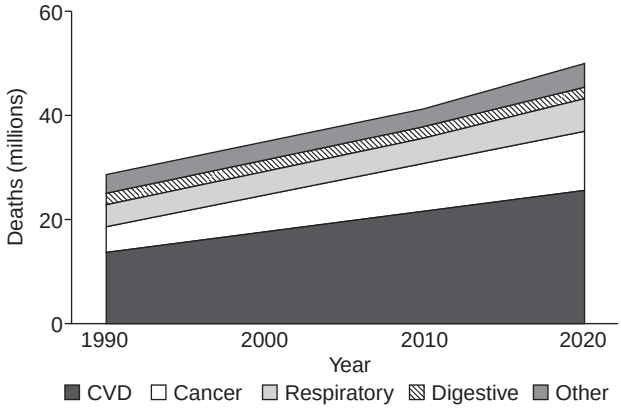

Figure 10.3 Baseline projections of deaths from group 2 causes, world, 1990–2020 (from Murray and Lopez, 1996, with permission)

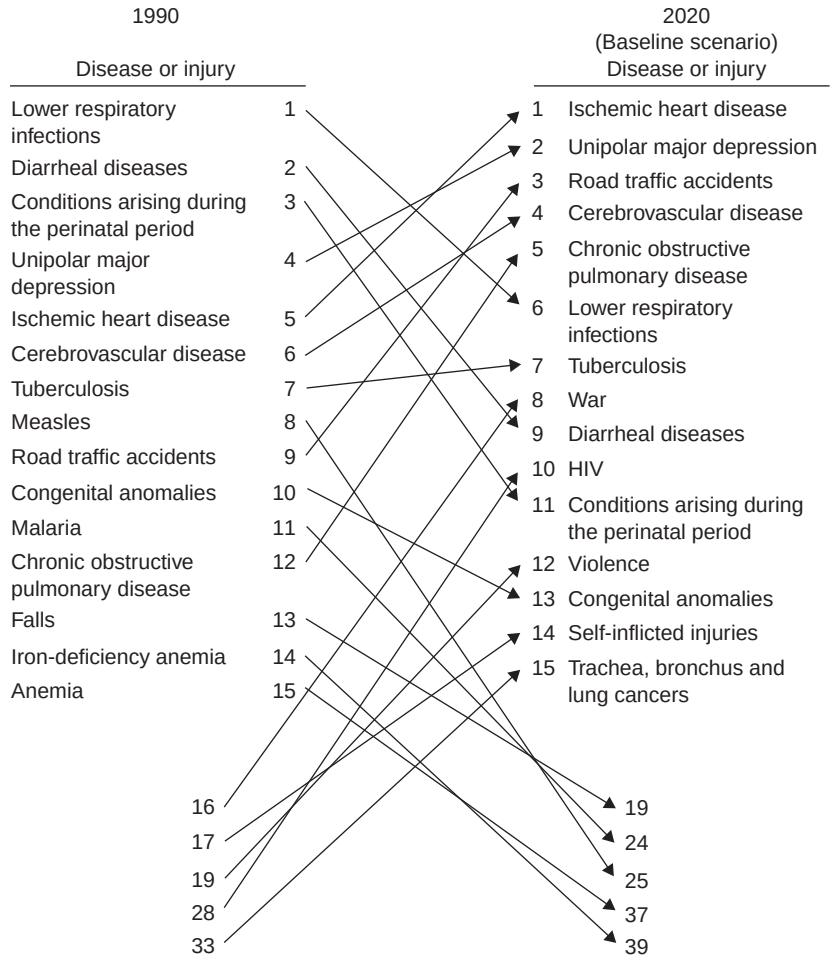

Figure 10.4 Change in rank order of DALYs for the 15 leading causes, world, 1990–2020 (from Murray and Lopez, 1996, with permission)

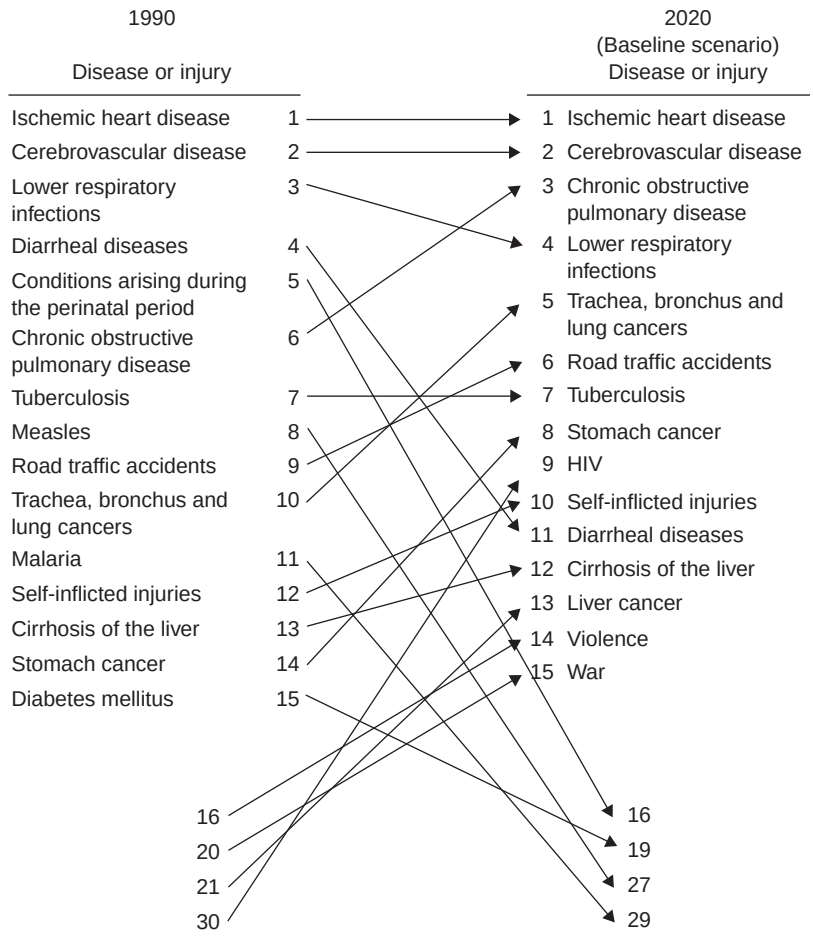

Figure 10.5 Change in rank order of deaths for the leading 15 causes, world, 1990–2020 (from Murray and Lopez, 1996, with permission)

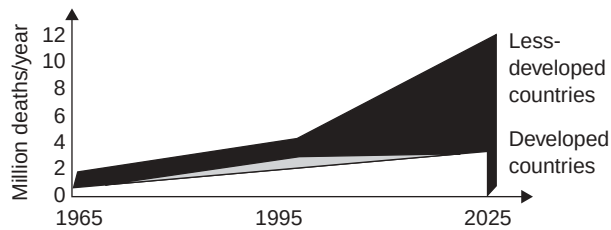

Figure 10.6 Annual deaths attributed to tobacco (WHO Program on Substance Abuse; WHO, 1995 A48/9)

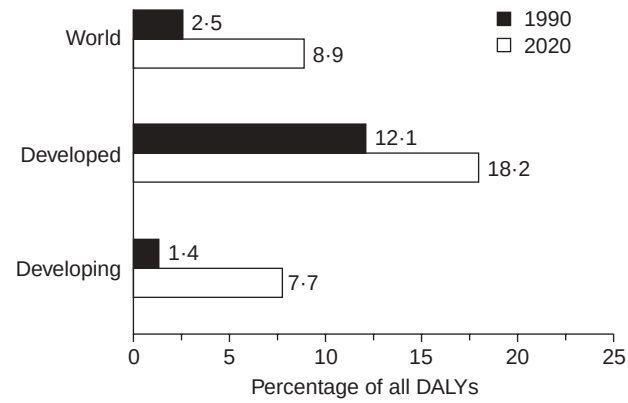

Figure 10.7 Tobacco as a cause of DALYs, 1990 and 2020 (WHO Program on Substance Abuse)

to rise from 11·1% to 14·75%.[17] In conclusion, tobacco is projected to be the leading cause of death and disability globally.

Community solutions

The relationship between smoking and cardiovascular morbidity and mortality was extensively documented throughout the last half of the twentieth century. Therefore, the reduction of tobacco use within populations has been a recommended strategy in the primary and secondary prevention of cardiovascular diseases for many years.[21] However, the development and testing of specific strategies to implement

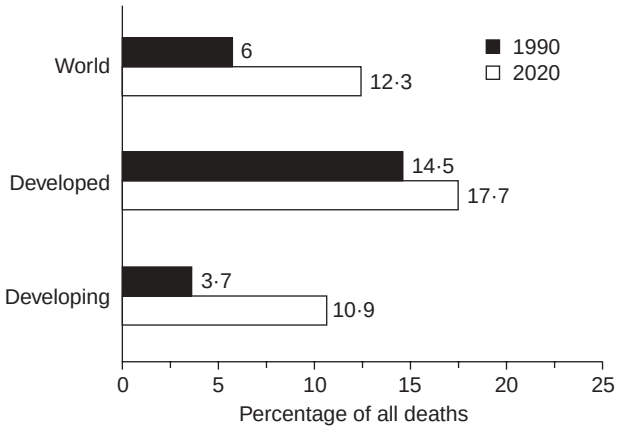

Figure 10.8 Tobacco as a cause of death, 1990 and 2020 (WHO Program on Substance Abuse)

this recommendation has proceeded more slowly. During this interval, there has been a paradigm shift from an individual or clinical approach to smoking prevention and cessation to a more public health or population-based approach.[22–24] Community-based cardiovascular prevention trials started in the early 1980s were conducted during this shift in paradigm.[25] Results from all of these trials showed significant declines in the prevalence of smoking overall; however, the declines in the intervention communities did not exceed the declines in the comparison communities by a statistically significant amount in several of the trials[26–28] nor in a joint analysis of the three US community trials.[29]

The community-based cardiovascular prevention trials initiated in the 1980s recognized that the critical behaviors related to cardiovascular risk (for example, diet, exercise, smoking) all involved individual choices but also involved societal or cultural barriers and enticements, monetary and opportunity costs, local and regional policies, and other communitywide factors.[25] The intervention methods which were developed in these trials shared many common elements, but largely were restricted from applying an ecological and policy oriented health promotion approach that combines educational, political, regulatory, and organizational supports for changes in the target health behaviors.[30] Green and Richard posit that the early community-based cardiovascular prevention trials could rely on an expansion of the traditional health education models which would initiate change in early adopters in societies.[30] However, as the rate of diffusion of the adoption of heart-healthy lifestyle changes (including smoking cessation) accelerated, these more traditional approaches lost efficacy.

The smoking cessation results from the community-based cardiovascular prevention trials initiated in the 1980s must be viewed as modest at best. While the Stanford Five-City Project observed a significantly greater decline (+13%) in smoking rates in the intervention communities among the cohort samples,[28,31] no effect on smoking rates was observed in the cross-sectional surveys by end of treatment[28,31] or at the follow up during which the comparison communities were declining somewhat, but not significantly, more rapidly than the intervention communities.[32] In the Minnesota Heart Health Project, the long-term smoking cessation results were mixed, with evidence of an intervention effect only for women in cross-sectional survey data.[26,33] Unexpectedly strong secular declines in smoking prevalence, especially among men, were observed in comparison communities. In the Pawtucket Heart Health Program, the prevalence of cigarette smoking declined slightly, but not significantly, more in the comparison community.[27]

More recently, the German Cardiovascular Prevention Study has reported more encouraging treatment effects for smoking, observing a 6·7% decline in smoking, with the strongest effect in men.[34] Among men, the prevalence of smoking among 25–69 year olds declined from 41·8% in 1985 to 39·2% in 1991 in the national reference sample, in comparison with the significantly greater decline from 44·5% to 37·4% in the intervention regions. This result is consistent with the diffusion model posited by Green[30] that the largely individually oriented health educational approaches applied in the community-based cardiovascular prevention trials initiated in the 1980s have their largest impact among populations who are at the earlier stages of adoption of the recommended preventive lifestyle.

In addition to the community-based cardiovascular prevention trials initiated in the 1980s, the Community Intervention Trial for Smoking Cessation (COMMIT) was started in the late 1980s. COMMIT focused solely on smoking cessation and built upon the initial experience in the ongoing cardiovascular prevention trials. Additionally, COMMIT was planned as a randomized community trial with 11 pairs of communities and had adequate power to detect relatively small intervention effects.[35] The modest effects observed in this trial were very sobering for the public health community. No cessation effect was observed for the "heavy" smokers (defined as smoking 25 or more cigarettes per day at baseline) for whom the trial was specifically designed. Among the evaluation cohorts of light-to-moderate smokers, a significantly greater quit rate (30·6% *v* 27·5%) was observed over the 4 year intervention period, with the effect strongest among the less educated residents of the communities.[36,37] Overall, the prevalence of smoking declined slightly, but non-significantly, more in the intervention communities (3·5 percentage points) than in the comparison communities (3·2 percentage points). While the COMMIT intervention protocol sought to apply the best smoking cessation strategies available, investigators were limited in their ability to be involved in many of the ecological and policy oriented health promotion strategies which Green and others[25,30] recommend due to the federal sources

of funds for the study. While an intervention "receipt index" of the strategies applied significantly correlated with quit rate differences across the 11 community pairs among the light-to-moderate smokers, process data showed that implemented protocol did *not* change many important intermediate variables (for example, MD/DDS counseling rates, worksite smoking bans, public attitudes toward smoking).

Several reviewers have provided some perspectives on the modest smoking cessation effects which have been observed in these community trials.[38–40] Common themes are: (1) the difficulty in observing intervention effects relative to the large secular declines in cardiovascular risk factors, including smoking, occurring during the period when the trials were implemented, and (2) the need for a more comprehensive health promotion approach to be applied. Concurrent with the implementation of these intervention trials, a broader national movement to reduce tobacco use emerged with a focus on the principles of health promotion. This concept, which included an organized approach to changing social, economic, and regulatory environments, emerged as a more effective mechanism for population behavior change than traditional health education, and included mobilization at the national, state, and local level.[41]

In 1991, the National Cancer Institute launched the American Stop Smoking Intervention Study for Cancer Prevention (ASSIST) program as a 7 year demonstration project. ASSIST included 17 states, and was the largest tobacco control project in the United States ASSIST was predicated on a coalition model, and was designed to demonstrate that a comprehensive, coordinated intervention effort could significantly reduce smoking and tobacco use. In 1993, CDC began the Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT) program, which provided funding for 32 states to build capacity in state health departments to conduct effective tobacco control. Based on the lessons learned from ASSIST, IMPACT, and large state programs such as those of California and Massachusetts, the National Tobacco Control Program (NTCP) was developed to support all 50 states, seven territories, and the District of Columbia plan, establish, and evaluate comprehensive tobacco prevention and control programs.[41]

Through evidence-based analyses of California and Massachusetts, in-depth involvement with settlement States, and published evidence of effective tobacco control strategies, the federal government has set forth "best practices" recommendations for state-based programs which contain the following elements[42]:

- community programs to reduce tobacco use
- chronic disease programs to reduce the burden of tobacco-related diseases
- school programs
- enforcement
- statewide programs
- counter-marketing
- cessation programs
- surveillance and evaluation
- administration and management.

Because tobacco use is ultimately an individual behavior, educational and clinical public health approaches have historically been individually focused. In the area of tobacco use prevention among youth, this has been particularly true. In the past two decades, however, excellent social-psychological approaches have been applied to school-based prevention programs.[41] Evidence shows that school-based smoking prevention programs that identify social influences to smoke and teach skills to resist those influences have demonstrated consistent and significant reductions in adolescent smoking prevalence, and that larger-scale implementation of intensive interventions can achieve long-term reductions in cigarette smoking among young people.[41] The durability of this effect is enhanced by community wide programs that involve parents, mass media, community organizations, and other elements of an adolescent's social environment.[42] Educational strategies, conducted in conjunction with community and media-based activities, can postpone or prevent smoking onset in 20–40% of adolescents.[41] Unfortunately, the full range of recommended community wide efforts to modify the social environments of adolescents,[42] including removal of pervasive imagery-based pro-tobacco advertising, significant tobacco tax increases, enhanced enforcement of minors' access laws, and well financed and sustained youth oriented counter-advertising campaigns, need to be applied in conjunction with experimentally tested school-based tobacco use prevention curricula and tobacco-free school policies.

The efficacy of a comprehensive approach to youth tobacco use prevention was originally demonstrated in Massachusetts and California, who funded their programs with dedicated excise tax dollars. During the period of the 1990s when smoking rates among the youth in the United States were consistently increasing, rates in Massachusetts and California appear to have risen more slowly[43] and even declined among 7–8 graders in Massachusetts.[44] With the influx of revenues resulting from state settlements with the tobacco industry and increases to state tobacco excise taxes, additional states, such as Minnesota, Florida, Arizona, and Oregon have also been able to implement comprehensive tobacco control programs.[41]

In many ways, efforts to assist adult smokers to quit smoking have made the slowest progress in the paradigm shift from the clinical to the public health model. However, advancements in treating tobacco use and nicotine addiction were summarized in a recent guideline: *Treating tobacco use and dependence: a clinical practice guideline*, published by the

US Public Health Service. The guideline provides a blueprint to healthcare professionals and health insurance providers for implementing appropriate medical services that will help treat nicotine addiction. Less intensive interventions, as simple as physicians advising their patients to quit smoking, can produce cessation rates of 5–10% per year. More intensive interventions, combining behavioral counseling and pharmacologic treatment, can produce 20% to 25% quit rates in one year.[45] The most significant and sustained declines in population levels of cigarette consumption have been observed in states where changes in the social environments rather than enhanced clinical services have been the focus of the programs.[46] For example, studies have found that moderate or extensive laws for clean indoor air are associated with a lower smoking prevalence and higher quit rates.[41] There is clear and compelling scientific evidence which demonstrates that increasing the price of cigarettes is an effective way to prevent smoking initiation among youth, promote smoking cessation among adults, and reduce cigarette consumption among continuing smokers.[41] Therefore, because increased excise taxes increase the price of cigarettes, they provide a cost effective short-term strategy to reduce tobacco use. Research indicates that for every 10% increase in price, overall smoking rates would decrease by 3–5%, and as high as 7% among youth.[41] Studies of smokeless tobacco products suggest that increasing their prices would reduce the prevalence of smokeless tobacco use as well.[41] Even greater decreases can be achieved when an adequately funded comprehensive tobacco prevention and control programs are combined with a price increase.

This has been demonstrated in California, where a tobacco control program has been funded by excise tax revenues since 1989, and tobacco rates have declined at rates two or three times faster than the rest of the country. California also has the distinction of being the first state to demonstrate a reduction in tobacco-related deaths. The incidence of lung cancer in California has declined significantly faster than in other parts of the United States and this state has also seen dramatic declines in cardiovascular disease death rates.[47]

Tobacco products have been largely unregulated in comparison to other consumer products. While the importance of nicotine addiction is now well recognized as a factor maintaining tobacco use behaviors,[48] regulatory efforts to decrease the addictiveness of the product are only now emerging.[49] Smokers receive very little information regarding chemical constituents when they purchase a tobacco product. Without information about toxic constituents in tobacco smoke, the use of terms such as “light” and “ultra light” on packaging and in advertising may be misleading to smokers. Also, because cigarettes with low tar and nicotine contents are not substantially less hazardous than higher-yield brands, consumers may be misled by the implied promise of reduced toxicity underlying the marketing of such brands.[41]

Currently all 50 states and the District of Columbia have tobacco control programs in place that have the potential to achieve positive results in reducing tobacco use. CDC has synthesized an evidence-based comprehensive framework for statewide programs to reduce tobacco use. The framework integrates four program goals with four program components; optimally, each of the goals would be fully addressed in the implementation of each of the components, within each of the *Best practices* guidelines. The program goals for reducing tobacco use statewide include:

- Prevent initiation among young people.
- Promote quitting among adults and youth people.
- Eliminate exposure to environmental tobacco smoke.
- Identify and eliminate disparities among population groups.

The program components for reducing tobacco use statewide include:

- community interventions
- counter-marketing
- program policy and regulation
- surveillance and evaluation.

Aggressive and comprehensive tobacco control programs in a number of states have produced substantial declines in cigarette use. The findings from multiple states were reviewed by the US Surgeon General in the report, *Reducing tobacco use*.[41] For example:

- In California, home to one of the longest-running tobacco control programs, the overall prevalence of tobacco use has declined at nearly twice the rate of that in the United States. The declines in the rates of lung cancer and heart disease have also been significantly faster than in other parts of the country. California is also the first state to experience a decrease in tobacco-related deaths.
- In 1992, Massachusetts initiated a comprehensive statewide tobacco control program. From 1992–2000, per capita consumption declined by 36%, when the rate of decline in the remaining 48 states was only 16%. A decline in smoking prevalence among adults was also greater than in the rest of the country (excluding California). From 1995–1999, smoking declined by 70% among 6th graders, and by 38% among 7th and 8th grade students.
- Florida’s tobacco control program, which combined a counter-marketing media campaign, community-based activities, education and training, and an enforcement program, in concert with a state excise tax increase, has effectively reduced teen tobacco use. Among middle school students, tobacco use declined by 47%, from 18·5% in 1998 to 9·8% in 2001. Among high school students, current cigarette use declined by 30%, from 27·4% in 1998 to 9·0% in 2001.

- With the support of a dedicated excise tax, Arizona was able to begin funding a comprehensive tobacco control program in 1996 that includes all nine *Best practices* components. From 1996 to 1999, the proportion of healthcare providers encouraging patients to quit smoking increased significantly. Also during this time, smoking prevalence has declined significantly in women and men, whites and Hispanics, and people with low income and low education.
- With the support of a dedicated excise tax, Oregon launched a comprehensive statewide tobacco control program in 1997. From 1997–1999, Oregon experienced a 2·3% decline in consumption from 1996 to 2001, and in prevalence of smoking among adults, pregnant women, and youth. By following the lessons learned by more experienced states, Oregon was able to operate more efficiently, and has seen reductions in prevalence in spite of spending less than the *Best practices* minimum guidelines. This "Oregon Model" is now being quickly diffused out to other states to guide the development of newly funded programs.

  The Oregon program included an implementation of CDC's *Guidelines for school health programs to prevent tobacco use and addiction* in 30% of their schools. This demonstration found that a comprehensive school-based tobacco prevention program that includes tobacco-free school policies and community involvement as one component of a statewide tobacco program may contribute to reductions in current smoking among 8th graders. Also, the significantly greater declines in smoking prevalence in the schools that rated high and medium on implementation criteria emphasize the importance of monitoring activity in funded programs and the need for on-going assistance to facilitate implementation of evidence-based recommendations.

As results are obtained from these most recent states as well as continuing data from California and Massachusetts, our understanding of the potential effectiveness of the full multicomponent population-based approach to tobacco prevention and control will be expanded. However, the data already sufficient for the US Surgeon General to conclude that if the recommended intervention strategies were fully implemented, rates of tobacco use in the US could be cut in half by the year 2010.[41]

References

1. Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr. *Mortality from smoking in developed countries 1950–2000*. Indirect estimates from National Vital Statistics. Oxford: Oxford University Press, 1994.
2. World Health Organization. *Tobacco or health: global status report*. Geneva: WHO, 1997.
3. Liu B-Q, Peto R, Chen Z-M. Emerging tobacco hazards in China: 1 Retrospective proportional mortality study of one million deaths. *BMJ* 1998;**317**:1411–22.
4. Niu SR, Yang G-H, Chen Z-M. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. *BMJ* 1998;**317**:1423–4.
5. Gajalakshmi CK, Peto R. Tobacco epidemiology in the state of Tamil Nadu, India. The Proceedings of the XV Asia Pacific Cancer Conference in Chennai, 1999.
6. Gupta PC, Mehta HC. Cohort of all cause mortality among tobacco users in Mumbai, India. *Bull World Health Organ* 2000;**78**(Suppl.7):877–83.
7. Peto R, Lopez AD. The future worldwide health effects of current smoking patterns. In Koop EC, Pearson CE and Schwarz RM eds. *Global health in the 21st century*. New York: Jossy-Bass, 2000.
8. Peto R, Chen ZM, Boreham J. Tobacco: the growing epidemic. *Nat Med* 1999;**5**:15–17.
9. Thun MJ, Day-Lally C, Myers DG *et al.* Trends in tobacco smoking and mortality from cigarette use in cancer prevention, Studies I (1959 through 1965) and II (1982 though 1988). In: National Cancer Institute. *Changes in cigarette-related disease risks and their implication for prevention and control. Smoking and tobacco control, Monograph 8*. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NIH Pub No 97–4213), 1997.
10. US Department of Health and Human Services. *Reducing the health and consequences of smoking: 25 years of progress* (A report of the Surgeon General). Atlanta, GA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention of Health Promotion, Office on Smoking and Health, 1989. DHHS Publication (CDC) 89–8411.
11. US Department of Health and Human Services. *The health consequences of smoking: cardiovascular disease*. (A report of the Surgeon General.) DHHS publication PHS 84-50204. Rockville, MD: Public Health Service Office on Smoking and Health, 1984.
12. Steenland K, Thun M, Lally C, Heath C. Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. *Circulation* 1996;**94**:622–8.
13. Kawachi I, Colditz GA, Speizer FE *et al.* A prospective study of passive smoking and coronary heart disease. *Circulation* 1997;**95**:2374–9.
14. Howard G, Wagenknecht LE, Burke GL *et al.* for the ARIC investigators. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) study. *JAMA* 1998;**279**:119–24.
15. Glantz SA, Parmley WW. Passive smoking and heart disease: epidemiology, physiology, and biochemistry. *Circulation* 1991; **83**:1–2.
16. Glantz, SA, Parmley WW. Passive and active smoking: a problem for adults. *Circulation* 1996;**4**:596–8.
17. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997;**349**:1502.
18. Murray CJL, Lopez AD, eds. *The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge, MA: Harvard University Press, 1996.

19.Sidel R, Sidel VW. *The health of China*. Boston: Beacon Press 1982.
20.Peto R, Lopez AD, Boreham J, Thun M. Health C Jr, Doll R. Mortality from smoking worldwide. *Br Med Bull* 1996;**52**: 12–21.
21.World Health Organization. *Report of the WHO expert committee on smoking control. Controlling the smoking epidemic*. WHO Technical Report Series No. 636; Geneva: WHO, 1979.
22.Jeffery TW. Risk behaviors and health. *Am J Psychol* 1989; **44**:1194–202.
23.Lichtenstein E, Glasgow RE. Smoking cessation: what have we learned over the past decade? *J Consult Clin Psychol* 1992;**60**:518–27.
24.National Cancer Institute. *Strategies to control tobacco use in the United States: a blueprint for public health action in the 1990s*. Smoking and Tobacco Control Monographs No. 1. Rockville, MD: US Department of Health and Human Services, National Cancer Institute, 1991.
25.Luepker RV. Community trials. *Prev Med* 1994;**23**:602–5.
26.Luepker RV, Murray DM, Jacobs DR *et al.* Community education for cardiovascular disease prevention: risk factor changes in the Minnesota Heart Health Program. *Am J Public Health* 1994;**84**:1383–93.
27.Carleton RA, Lasater TM, Assaf AR *et al.* The Pawtucket Heart Health program: community changes in cardiovascular risk factors and projected disease risk. *Am J Public Health* 1995;**85**: 777–85.
28.Farquhar JW, Fortmann SP, Flora JA *et al.* Effects of community wide education on cardiovascular disease risk factors. *JAMA* 1990;**264**:359–65.
29.Winkleby MA, Feldman HA, Murray DM. Joint analysis of three US community intervention trials for reduction of cardiovascular disease risk. *J Clin Epidemiol* 1997;**50**:645–58.
30.Green LW, Richard L. The need to combine health education and health promotion: the case of cardiovascular disease prevention. *Promotion Educ* 1993;**Dec**:11–17.
31.Fortmann SP, Taylor CB, Flora JA, Jatulis DE. Changes in adult cigarette smoking prevalence after five years of community health education: the Stanford Five-City Project. *Am J Epidemiol* 1993;**137**:82–96.
32.Winkelby MA, Taylor CB, Jatulis D, Fortmann SP. The long-term effects of a cardiovascular disease prevention trial: the Stanford Five-City Project. Am J Public Health 1996;**86**: 1773–9.
33.Lando HA, Pechacek TF, Pirie PL *et al.* Changes in adult cigarette smoking in the Minnesota Heart Health Program. *Am J Public Health* 1995;**85**:201–8
34.Hoffmeister H, Mensink GBM, Stolzenberg H *et al.* Reduction of coronary heart disease risk factors in the German Cardiovascular Prevention Study. *Prev Med* 1996;**25**:135–45.
35.Gail MH, Byar DP, Pechacek TF, Corle DK, for the COMMIT Study Group. Aspects of statistical design for the community intervention trial for smoking cessation (COMMIT). *Control Clin Trials* 1992;**13**:6–21 and erratum, *Control Clin Trials* 1993;**14**:253–4.
36.The COMMIT Research Group. Community intervention trial for smoking cessation: I. Cohort results from a 4-year community intervention. *Am J Public Health* 1995;**85**:183–92.
37.The COMMIT Research Group. Community intervention trial for smoking cessation: II. Changes in adult cigarette smoking prevalence. *Am J Public Health* 1995;**85**:193–200.
38.Winkleby MA. The future of community-based cardiovascular disease intervention studies (Editorial). *Am J Public Health* 1994;**84**:1369–72.
39.Fisher EB: The results of the COMMIT Trial. *Am J Public Health* 1995;**85**:159–60.
40.Susser M. Editorial: The tribulation of trials – intervention in communities. *Am J Public Health* 1995;**85**:156–8.
41.US Department of Health and Human Service. *Reducing Tobacco Use* (A Report of the Surgeon General). DHHS Publication (CDC), August 2000.
42.Centers for Disease Control and Prevention. *Best practices for comprehensive tobacco control programs – August 1999*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1999.
43.Centers for Disease Control and Prevention. Cigarette smoking before and after an excise tax increase and an antismoking campaign. *MMWR* 1996;**45**:966–70.
44.Briton NJ, Clark TW, Baker AK, Posner J, Soldz S, Krakow M. Adolescent tobacco use in Massachusetts. Trends among public school students 1984–1996. Boston: Health and Addictions Research, 1997.
45.US Department of Health and Human Services, Public Health Service. *Treating tobacco use and dependence. Clinical practice guideline*. Rockville, MD: US Department of Health and Human Services, Public Health Service, 2000.
46.Green LW, Johnson JL. Dissemination and utilization of health promotion and disease prevention knowledge: theory, research, and experience. *Can J Public Health* 1996;**87**:S11–17.
47.Centers for Disease Control and Prevention. Declines in lung cancer rates – California, 1988–1997. *MMWR* 2000;**47**: 1066–9.
48.Fiore MC, Novotny TE, Pierce JP *et al.* Methods used to quit smoking in the US: do cessation programs help? *JAMA* 1990;**263**:2760–5.
49.Consensus Statement. The Agency for Health Care Policy and Research Smoking Cessation Clinical Practice Guideline. *JAMA* 1996;**275**;1270–80.

11 Tobacco and cardiovascular disease: achieving smoking cessation

Godfrey H Fowler

Worldwide, there are about one billion current smokers and about three million die annually from their smoking, half before the age of 70; this includes about 150 000 annually in the UK and half a million in the USA.[1] Even in countries where the health hazards of smoking are widely acknowledged, it remains a common behavior: in the USA and Canada, for example, about a quarter of all adults smoke, and, in the UK, the situation is worse with about one third of adults smoking.

Cardiovascular disease, in particular ischemic heart disease, is the commonest smoking-related cause of death in developed countries.[2] This is because, although the relative risk of death from cardiovascular disease in smokers, compared with non-smokers, is much lower than the relative risk from cancer (in particular lung cancer) and chronic obstructive lung disease, ischemic heart disease is much the commonest cause of death in these countries. Overall, the relative risk of death from cardiovascular disease in smokers compared with non-smokers is roughly doubled, though this varies with the different cardiovascular diseases and is greater at a younger age. Passive smoking also increases the risk of cardiovascular disease but the extent of this increase remains uncertain.[3,4]

Strategies for tobacco control

Strategies for reducing the health consequences of smoking should aim to:

- reduce the uptake of smoking by young people;
- increase the numbers of smokers stopping smoking;
- encourage a shift to less harmful tobacco use;
- decrease exposure to environmental tobacco smoke.

Reducing the uptake of smoking by young people is a priority in many countries. Laws to ban tobacco sales to those below a certain age and to prohibit tobacco advertising and promotion are common in developed countries but are frequently contravened. Other measures include restrictions on smoking in public places, fiscal policies to increase the cost of smoking, and a variety of educational programs. In spite of these, smoking prevalence in teenagers has remained remarkably resistant to change over the last decade, and in the UK about a quarter of young people are regular smokers by the age of 16 years.

Modification of cigarettes, particularly with regard to tar yield, over the last two or three decades has undoubtedly contributed to less harmful tobacco use, but it should be emphasized that this is no substitute for tobacco avoidance. However, although such changes have certainly contributed to a decline in lung cancer, possible benefits from these changes relating to cardiovascular disease have not yet been established with certainty.[5]

Decreased exposure to environmental tobacco smoke is a desirable objective in itself but, again, the contribution this might make to reducing cardiovascular disease risk is very difficult to estimate.

For established smokers, smoking cessation is the most important step for safeguarding future health, and this chapter will consider evidence-based methods of achieving this objective.

Evidence of benefits from smoking cessation

Many observational epidemiologic studies have investigated the effect of stopping smoking on smoking-related diseases, and there is a wealth of evidence that, not only is tobacco smoking a major risk factor for cardiovascular disease, but also stopping smoking reduces this risk. **Grade B** However, there is less agreement about the rate at which the risk attenuates after smoking cessation. In the 20 year follow up of the British Doctors Study, for example, excess risk was halved within 2 or 3 years of smoking cessation, and by 10 years the risk had returned to that of a non-smoker (Figure 11.1).[6]

However, follow up of the cohort men in the British Regional Heart Study indicates that attenuation of risk is much slower, and even men who had given up smoking for more than 10 years still had an increased risk, compared with non-smokers (Figure 11.2).[7]

Following myocardial infarction (MI), smoking cessation confers substantial benefits and is particularly important. In one observational study, stopping smoking halved both the number of non-fatal recurrences and the number of cardiovascular deaths (Figure 11.3).[8]

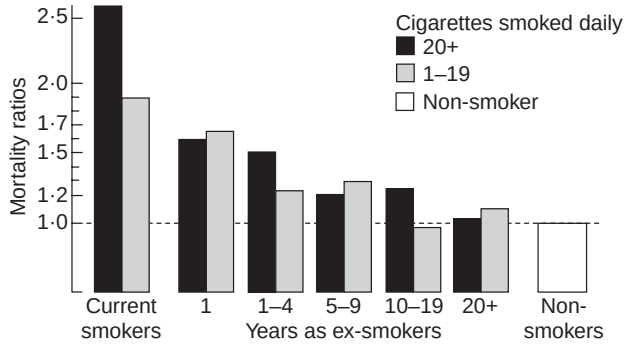

Figure 11.1 Diminished risk of death from coronary heart disease in former light and heavy smokers. Both light and heavy smokers show a steady decline in risk after stopping until, after 10–20 years, it is little different from the risk of non-smokers. (Source: Royal College of Physicians. *Smoking or health?* London: Pitman Medical, 1977.)

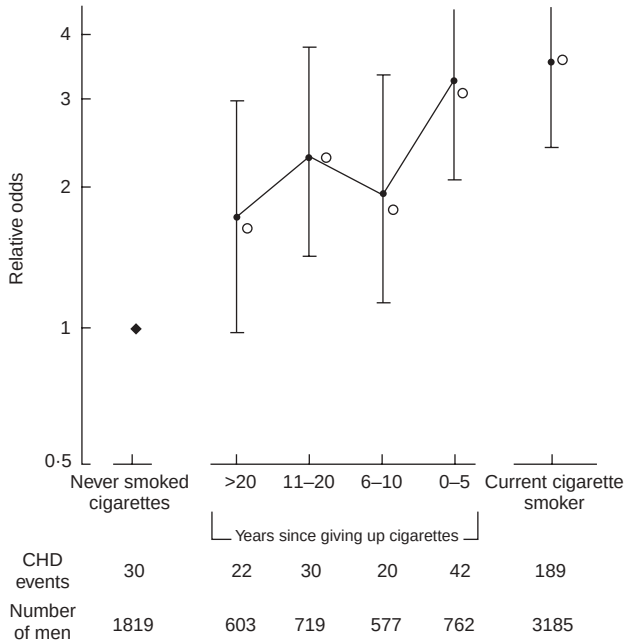

Figure 11.2 Relative odds of a major CHD event in relation to years since stopping smoking cigarettes. (Source: Cook *et al.*[7])

In another study, follow up over 13 years of post-MI patients showed a 37% mortality in those who had stopped smoking, compared with 82% mortality in those who continued smoking.[9] Furthermore, a UK trial of smoking cessation advice in smokers with evidence of ischemic heart disease showed a (non-significant) 13% difference in cumulative CHD deaths over 20 years in those given smoking cessation advice, compared with those who were not.[10]

The mechanisms through which tobacco smoking mediates its adverse cardiovascular effects are largely unknown and certainly multiple. There is evidence that smoking contributes to both the atherosclerotic and the thrombotic processes; free radical damage to vascular endothelium has been demonstrated, as have effects on platelet survival, platelet aggregation, and fibrinogen levels.[11–13]

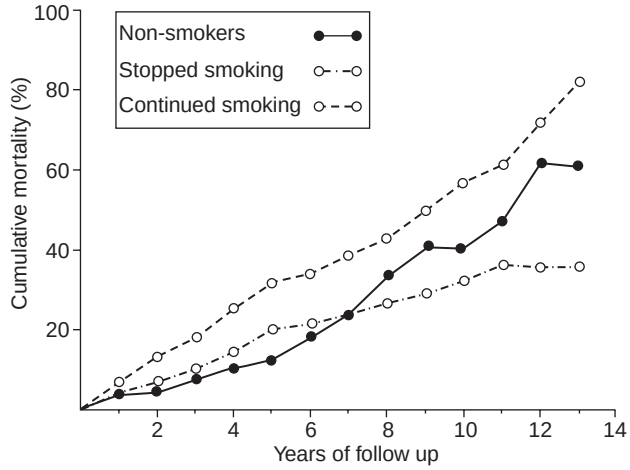

Figure 11.3 Cumulative mortality for 498 survivors of a coronary attack by smoking habit. Life-table curves start 2 years after attack. Average annual mortality was 6.5% in non-smokers, 3.7% in those who stopped smoking, and 10.2% in those who continued smoking. (Source: Daly *et al.*[8])

The nature of tobacco smoking

Before individual smoking interventions and cessation methods are considered, it is helpful to review briefly the nature of tobacco smoking and the consequent implications for interventions.

Tobacco smoking is a complex behavior to which psychologic, social, and pharmacologic factors contribute.[14] Its acquisition is almost invariably in adolescence, as the result of desire for experimental rebellious behavior, which is perceived as adult and encouraged by peer group pressure. However, pharmacologic addiction usually then becomes a factor determining persistence of the behavior, making it difficult to stop because of the addictive effects of nicotine and the discomforts associated with withdrawal. Although the balance between psychologic factors and pharmacologic addiction varies from smoker to smoker, there is now increasing awareness of the importance of nicotine addiction in maintaining smoking behavior, and the powerful nature of this addiction has been compared with addiction to heroin or cocaine.[15]

The evidence basis for smoking cessation

Emphasis on smoking cessation in individual established smokers is a vital component of any tobacco control strategy and should complement efforts to prevent the uptake of smoking by young people. Individual approaches to both cessation and avoidance can only be supplementary

to "whole population" approaches, including legislation (banning sales to "minors" and controlling advertising promotion), restrictions on smoking, public information and campaigns, tax measures, and so on. **Grade A**

For many established smokers, stopping smoking is very difficult, for both behavioral and psychopharmacologic reasons, and only a minority of established smokers ever succeed in stopping for good. Most of those who succeed in stopping find the process of stopping is a dynamic one rather than a single discrete event (Figure 11.4).

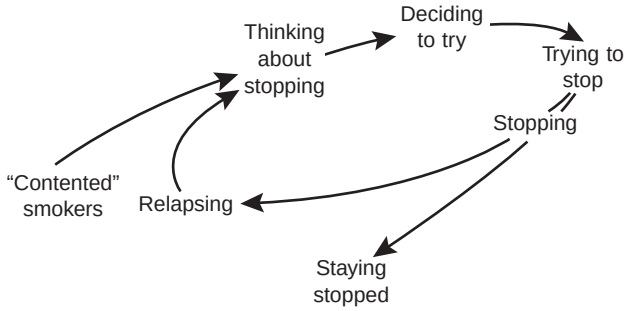

Figure 11.4 Stopping smoking is a process

Relapses are common and eventual success is usually the outcome of many attempts. Motivation to stop and confidence in the ability to succeed are important predictors of success. Relapse in the first few weeks is a common pattern, but the tendency to relapse declines as time progresses and most of those who manage to avoid relapse for a year are then able to achieve sustained abstinence.

The great majority of those smokers who do achieve long-term smoking cessation do so on their own without any special aids or assistance, but research has shown that smoking cessation advice and support from a health professional and the use of smoking cessation aids can enhance the chances of success.[17]

As already indicated, motivation to stop smoking is critical to success and this motivation may be determined by a variety of concerns – personal health, family health, financial anxieties, social pressures, and so on. The so-called Stages of Change model acknowledges different levels of motivation and activity, from precontemplation through contemplation, preparation and action, to maintenance or relapse.[18] Identification of the stage at which an individual smoker is can enable motivational or interventional methods to be targeted more appropriately (though the evidence basis for the effectiveness of such targeting is currently lacking).

A favorable factor is that the majority of smokers in many countries report that they want to quit smoking and have tried to do so, often many times. They also cite advice from a health professional as being important to them in influencing their motivation to quit. Surprisingly perhaps, only a minority of smokers say they have ever been asked by a doctor about smoking and advised to stop.[14]

Community interventions

Community- or population-based smoking cessation interventions have been implemented in a number of settings. Typically, they involve use of mass media to promote public awareness and education, to encourage health professionals to raise smoking as an issue in consultations with patients, and to offer self-help materials. Evaluation of the effectiveness of such programs is difficult and they are discussed in Chapter 10.

Individual advice

Nicotine addiction is now acknowledged as a treatable condition[16] and there is substantial scientific evidence of the effectiveness of behavioral and pharmacologic interventions. Individual smoking interventions by health professionals have been extensively studied.[17] An early and influential trial in the UK was conducted by Russell and colleagues in general practices in London in the 1970s. In this study, over 2000 smokers attending their general practitioners for routine consultations were randomly allocated to a non-intervention control group and three intervention groups:

- **Grade B** completion of a brief smoking questionnaire;
- brief (1–2 minutes) smoking cessation advice; and
- brief advice supplemented with a simple self-help smoking cessation leaflet.

Smoking cessation rates achieved at 1 month and sustained for 1 year were 1·6%, 3·3%, and 5·1% respectively in the three intervention groups compared with 0·3% in the control group (Figure 11·5).[19]

Many similar randomized controlled trials of simple, brief smoking cessation advice in medical settings have subsequently been conducted and this finding of a small percentage of biochemically validated long-term smoking cessation, resulting from such interventions, has been replicated.[20]

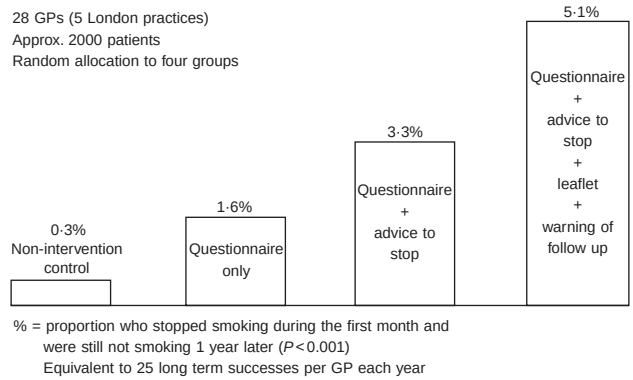

Figure 11.5 Effect of GP's advice against smoking. (Based on Russell *et al.*[19])

Nicotine replacement therapy (NRT)

The advent of nicotine chewing gum in the 1970s provided the first specific pharmacologic "treatment" for smoking cessation. **Grade B** Subsequent development of transdermal nicotine patches, nicotine nasal sprays, and nicotine oral inhalers has increased the range of products available. The objective in using these "nicotine replacement" products is to provide a temporary alternative source of nicotine to allay withdrawal symptoms and so enhance the potential for smoking cessation. Large placebo-controlled trials have clearly demonstrated that the use of such products as an adjunct to advice from a health professional can approximately double smoking cessation rates, compared with placebo.[21,22] Several systematic reviews of the many trials that have now been conducted with them have confirmed the benefits and shown that all preparations are effective, but the evidence is particularly substantial for nicotine gum and nicotine patches.[23,24] Both appear to have similar effectiveness but, because of greater social acceptability, ease of use, and simpler compliance, transdermal patches have been found by many to be preferable, though gum appears more effective for the most dependent smokers. A summary of the effectiveness of NRT and estimates of the number needed to treat (NNT) to achieve one success are provided in Table 11.1.

Table 11.1 Nicotine replacement therapy preparations and abstinence

NRT preparation (*n* of trials)	% Quitting		OR (95% CI)	NNT
	Active	Control		
Gum (39)	18·2	10·6	1·6 (1·5–1·8)	13
Patches (9)	20·5	10·8	2·1 (1·6–2·6)	10
Nasal spray (1)	25·9	9·9	2·9 (1·5–5·7)	6
Inhaler (1)	15·2	5·0	3·0 (1·4–6·6)	10

Abbreviations: NRT, nicotine replacement therapy; OR, odds ratio

Concern has been expressed about the use of NRT in patients with cardiovascular disease because of the potential adverse effects of nicotine on the cardiovascular system. In considering this issue, it is important to be aware that use of NRT is advocated only as a temporary substitute source of nicotine in those already self-administering this drug through tobacco smoking. It is also important to bear in mind that blood levels of nicotine achieved with NRT are substantially lower than those achieved by moderate or heavy smoking. Furthermore, there is no evidence that nicotine itself contributes to the atherogenic or thrombotic processes, unlike tobacco smoking.

In a placebo-controlled randomized trial specifically investigating the safety of transdermal nicotine patches in patients with cardiac disease, no increase was found in rates of arrhythmia, MI, or death in high-risk patients (with a history of MI or coronary revascularization procedure, or of angina, heart failure, arrhythmia, peripheral vascular disease, or cerebral vascular disease) in those using nicotine patches compared with those using placebo patches.[25] A review of the potential adverse effects of NRT in patients with cardiovascular disease concluded that there is no evidence to justify the withholding of these products in such patients who smoke and are motivated to stop.[27]

Bupropion (Zyban)

Originally developed as an antidepressant, bupropion (which is an inhibitor of neuronal uptake of norepinephrine, dopamine and serotonin) was found to apparently aid smoking cessation. Subsequent evidence from placebo-controlled trials[26] has confirmed this and indicate that it is at least as effective as NRT. Although side effects are rare, there is a risk of seizures in about 1 in 1000 users. It should not therefore be used by patients who have a past history of seizures and who are on drugs known to lower the threshold for seizures; this includes antipsychotics, antidepressants, antimalarials, theophylline, quinalones, and sedating antihistamines.

There is no evidence of other adverse effects in patients with cardiovascular disease and it may therefore be used by such patients. Whereas NRT should be started only when stopping smoking is actually attempted, bupropion treatment needs to be initiated 2 weeks before the attempt is made. The limited evidence currently available suggests that the combination of NRT and bupropion may be more effective than either alone, but more research is needed to elucidate this.

Review of cessation studies

Grade A In a comprehensive systematic review of 188 randomized controlled trials of the efficacy of a wide range of interventions aimed at helping people to stop smoking, it was concluded that simple advice, even on one occasion only, given by a doctor in general or family practice or in a hospital clinic to all smokers who consulted, resulted in sustained cessation of about 2% and that additional encouragement and support (additional visits, exhaled CO measurement, letters, etc.) further enhances this effect.[28] Whether similar interventions delivered by nurses are equally effective remains uncertain,[29] although there is evidence that nurse support, subsequent to doctor advice, can enhance the effect of this.[30]

This comprehensive review[25] also endorsed the use of nicotine replacement therapy but concluded that a variety of other smoking cessation interventions – hypnosis, acupuncture, aversion therapy, and pharmacologic agents other than nicotine, which are sometimes advocated – have

Table 11.2 Summary estimates of randomized controlled trials of interventions to help people to stop smoking

Intervention	% Estimate of efficacy (95% CI)	Statistical significance	Subjects (trials) (*n*)	Comment
Simple physician advice (once)	2 (1–3)	<0·001	14 438 (17)	Effective
Physician advice with additional encouragement/support	5 (1–8)	<0·01	6466 (10)	Effective
Nurse advice	1 (−1–3)	>0·10	3369 (2)	Unproven
Advice in infarct survivors	36 (23–48)	<0·001	223 (1)	Important
Advice in healthy men at high CHD risk	21 (10–31)	<0·001	13 205 (4)	Important
Hypnosis	24 (10–38)	<0·001	646 (10)	No trials with biochemical validation
Acupuncture	3 (−1–6)	>0·10	2759 (8)	No trials with biochemical validation

Adapted from Law *et al*[28]

not been shown by rigorous scientific evidence to be effective, although it must be acknowledged that the methodologic problems associated with attempts to evaluate these have yet to be overcome. A summary of estimates of effectiveness is provided in Table 11.2.

Specialist smoking cessation clinics

Specialist smoking cessation clinics have been shown to deliver effective interventions and can make a useful contribution to the provision of individual interventions, usually by providing regular group treatments. There is some evidence that they can achieve enhanced attendance and abstinence rates as high as 20% or more, but interpretation of their success should take account of the fact that they recruit widely and participants are generally highly motivated to stop, compared with the majority of those expressing an intention to do so. When available, they offer a self-referral and secondary referral service and can provide valuable opportunities for smoking cessation research.[31] However, as they are relatively few in number in relation to the huge need for such interventions, their overall contribution will inevitably be small.

Practical aspects of smoking cessation in clinical practice

The essential features of individual smoking cessation interventions in medical practice are to:

- *assess* in any medical consultation the smoking status of the patient, whether a non-smoker, smoker or ex-smoker;
- *advise* all smokers about the desirability and importance of stopping smoking because of health hazards, especially those who already have smoking-related diseases;
- *assist* smokers to stop smoking, particularly those with smoking-related diseases and especially if expressing interest to do so;
- *follow up* at subsequent consultations to assess the outcome and, if necessary, further assist those trying to stop smoking while encouraging ex-smokers to maintain their non-smoking status.[32]

Assessment

The smoking status of all patients should be recorded in medical records in such a way that the information is easily accessible in future consultations. Assessment of smoking should include a brief history of the patient's smoking, including attempts to stop and their current tobacco consumption. Assessment of nicotine addiction should also be made by inquiring how soon after waking they smoke their first cigarette and some assessment of their motivation to stop smoking.

Advice

Grade B All patients with smoking-related diseases should be advised to stop smoking and any reasons that patients put forward for wanting to stop smoking should be strongly reinforced.

Assistance

Specific help with smoking cessation should be strongly influenced by patients' preferences and patients should

themselves be active in deciding what to do. There is no set "prescription" for how to go about stopping smoking, but it is possible to provide guidance, which experience has shown to be useful. It is important to adopt an individual approach but guidance might include:

- **Grade A** setting a target date for stopping;
- some preparation for stopping, review of motivation and reasons for stopping;
- awareness of times when a particular need is felt for a cigarette, and attempts to change routines to avoid association of these times with smoking;
- eliciting support for cessation from friends and colleagues and, ideally, recruiting a fellow smoker (particularly a spouse) to join in the attempt to give up smoking.

Generally, sudden complete withdrawal is likely to be more successful than attempts to gradually reduce smoking. Strategies need to be planned for coping with withdrawal symptoms and other difficulties likely to be encountered immediately after cessation; avoidance of other smokers and smoking environments is likely to be important, particularly at "danger times", like teabreaks and after meals or when having a drink.

A number of self-help leaflets are available from a variety of sources to supplement and reinforce such simple guidance. These leaflets have particular value and effectiveness when handed out by health professionals as an adjunct to brief advice.

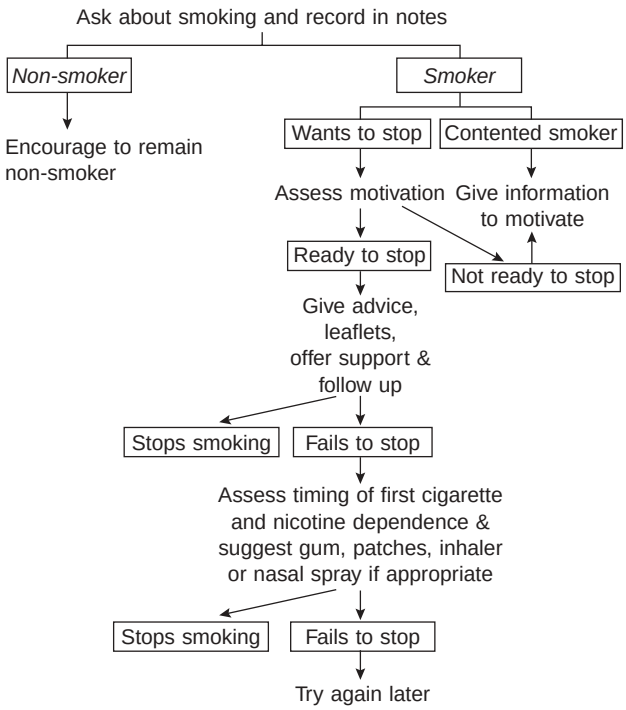

Figure 11.6 Smoking cessation protocol for doctor/nurse intervention

Use of NRT should be encouraged in all those (except perhaps the lightest smokers) for whom advice and self-help are not enough. Assessment of nicotine dependence is most simply done by asking how soon after waking the first cigarette is smoked. If this is within half an hour, this is evidence of at least moderate dependence and suggests likely benefit from using NRT.

As already indicated, although there is debate about the safety of using NRT in patients with cardiovascular disease, evidence of harm from doing this is lacking but there is some evidence that suggests that it is safe. This is likely to be so if nicotine gum or patches are used (as they should be) as a temporary substitute for smoking. A combination of smoking and nicotine replacement may well be potentially harmful and should be strongly discouraged. A simple smoking cessation protocol is illustrated in Figure 11.6.

Key points

- Tobacco smoking is a critically important, modifiable cardiovascular risk factor (especially in those with established cardiovascular disease).
- Smoking cessation attenuates cardiovascular risk and early benefits accrue (again, especially in those with established cardiovascular disease).
- There is good evidence for the effectiveness of simple, brief smoking cessation advice and the use of NRT as an adjunct to this. NRT is effective and safe.
- Smoking and smoking cessation should be routinely addressed by health professionals in any consultations with patients who smoke.
- Simple cessation advice and support should be routinely offered by healthcare professionals in any consultations with patients who smoke.
- NRT – chewing gum, transdermal patches, nasal spray, or oral inhaler – should be recommended to all smokers trying to quit. Encouragement and support should accompany this, and compliance for 2 or 3 months should be encouraged in those who achieve short-term abstinence with it.
- Bupropion (Zyban) is a proven alternative to NRT.

References

1. Peto R, Lopez AD, Boreham J, Thun M, Heath C. *Mortality from smoking in developed countries 1950–2000*. Oxford: Oxford University Press, 1994.
2. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observation on male British doctors. *BMJ* 1994;**309**:901–11.
3. *Fourth Report of Independent Scientific Committee on Smoking and Health*. London: HMSO, 1988.
4. Glanz SA, Parmley WW. Passive smoking and heart disease: mechanisms and risk. *JAMA* 1995;**273**:1047–53.
5. Darby SC, Doll R, Stratton IM. Trends in mortality from smoking-related diseases in England and Wales. In: Wald N,

Frogatt P, eds. *Nicotine, smoking and the low tar programme*. Oxford: Oxford University Press, 1989.
6. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation of British male doctors. *BMJ* 1976;**4**:1525–36.
7. Cook DG, Pocock SJ, Shaper AG *et al*. Giving up smoking and the risk of heart attacks. *Lancet* 1986;**2**:1376–80.
8. Daly LE, Mulcahy R, Graham IM, Hickey M. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *BMJ* 1983;**287**:324–6.
9. Wilhelmssen C, Vedin J, Elmfeld D *et al*. Smoking and myocardial infarction. *Lancet* 1975;**1**:415–17.
10. Rose G, Colwell L. Randomised controlled trial of antismoking advice. *J Epidemiol Community Health* 1992;**46**:75–7.
11. Pittilo RM, Woolf N. Cigarette smoking, endothelial injury and atherosclerosis. *J Smoking-related Dis* 1993;**4**:17–25.
12. Hawkins RI. Smoking, platelets and thrombosis. *Nature* 1972;**263**:450–2.
13. Meade TW, Imeson J, Sterling Y. Effect of changes in smoking on clotting factors and on risk of ischaemic heart disease. *Lancet* 1987;**ii**:986–8.
14. Marsh A, Matheson J. *Smoking attitudes and behaviour*. London: HMSO, 1993.
15. US Department of Health and Human Services. *The health consequences of smoking and nicotine addiction*. Report of Surgeon General 1988. Washington DC: DHHS, 1989.
16. RCPL. *Nicotine addiction in Britain*. London: Royal College of Physicians of London, 2000.
17. Kottke T, Battista R, DeFriese G, Brekke M. Attributes of successful smoking cessation interventions in medical practice: a meta-analysis of 39 controlled trials. *JAMA* 1988;**259**: 2883–9.
18. Prochaska JO, DiClemete C. Towards a comprehensive model of change. In: Miller WR, Heather N, eds. *Treating addictive behaviours: processes of change*. New York: Plenum, 1986.
19. Russell MAH, Wilson C, Taylor C, Bales CD. Effect of general practitioner's advice against smoking. *BMJ* 1979;**ii**:231–5.
20. Jamrozik K, Vessey M, Fowler G *et al*. Controlled trial of three different antismoking interventions in general practice. *BMJ* 1984;**288**:1499–503.
21. Russell MAH, Merrium L, Stapleton J, Taylor W. Effect of nicotine chewing gum as an adjunct to general practitioners' advice against smoking. *BMJ* 1983;**287**:1782–5.
22. Imperial Cancer Research Fund General Practice Research Group. Randomised trial of nicotine patches in general practice: results at one year. *BMJ* 1994;**308**:1476–7.
23. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis of the efficacy of nicotine replacement in smoking cessation. *Lancet* 1994;**343**:139–42.
24. Tang TL, Law M, Wald N. How effective is nicotine replacement in helping people to stop smoking? *BMJ* 1994;**308**:21–6.
25. Joseph AM, Norman SM, Ferry LH *et al*. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;**335**:1792–8.
26. Jorenby DE, Leischow SJ, Nides MA *et al*. A controlled trial of sustained-release bupropion, a nicotine patch, as both for smoking cessation. *N Engl J Med* 199;**341**:685–91.
27. Benovitz NL, Goursley SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol* 1997;**29**:422–31.
28. Law M, Tang TL, Wald N. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med* 1995;**155**:1933–41.
29. Sanders D, Fowler G, Mant D *et al*. Randomised controlled trial of anti-smoking advice by nurses in general practice. *J Roy Coll Gen Pract* 1989;**39**:273–6.
30. Hollis J, Lichenstein E, Vogt T *et al*. Nurse-assisted counselling for smokers in primary care. *Ann Intern Med* 1993;**118**:521–5.
31. Sutherland G, Stapleton J, Russell MAH *et al*. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;**340**:324–9.
32. US Department of Health and Human Services. *1996 Clinical practice guidelines no. 18: Smoking cessation*. Washington DC: DHHS, 1996.

12 Lipids and cardiovascular disease

Malcolm Law

For many years the issue of lipids and cardiovascular disease was seen as controversial and difficult to resolve, yet the high-fat diet typical of many western countries over the greater part of the 20th century has proved to be the major underlying factor in the epidemic of ischemic heart disease, and modern cholesterol lowering drugs can reduce risk more than any other single intervention.[1]

Serum total and low density lipoprotein cholesterol

Typical values of serum total and low density lipoprotein (LDL) cholesterol in western countries are high in comparison to those in agricultural and hunter–gatherer communities, because of the high saturated fat content of the western diet. Average serum cholesterol concentration (in men aged 45–60) is about 3–3·5 mmol/l in hunter–gatherer societies and rural China (where heart disease is rare), 5·0 mmol/l in Japan, 5·5 mmol/l in Mediterranean populations and a little higher in the USA, and 6 mmol/l in Britain and several other European countries.[2] Average levels of LDL cholesterol are about 2 mmol/l lower.[2] Use of the term "normal" in reference to usual or average western cholesterol values may therefore be misleading.

Of the average total serum cholesterol in western populations, two thirds is low density lipoprotein (LDL) cholesterol and one quarter is high density lipoprotein (HDL) cholesterol. The atherogenic properties lie in the LDL fraction (sometimes measured as its carrier protein, apolipoprotein B, with which it is highly correlated). Many of the large epidemiological studies and randomized trials measured only total serum cholesterol, and results based on total serum cholesterol have been taken to estimate effects of LDL cholesterol. Fortuitously, the approximation is a good one. The absolute reduction in total serum cholesterol produced by diet and by most drugs (including statins[1]) is similar to the reduction in LDL cholesterol. Observational differences in total cholesterol between individuals are close to the corresponding differences in LDL cholesterol, because HDL cholesterol is independent of total serum cholesterol.[3,4] This arises because the tendency for HDL cholesterol to be positively associated with total cholesterol (as HDL cholesterol is part of total) is offset by the small inverse association between HDL and LDL cholesterol. Much epidemiologic and clinical trial data are therefore available to estimate quantitatively the effect of lowering serum LDL cholesterol on the risk of ischemic heart disease.

Serum cholesterol and ischemic heart disease

Evidence from genetics, animal studies, experimental pathology, epidemiologic studies and clinical trials indicates conclusively that increasing serum cholesterol is an important cause of ischemic heart disease and that lowering serum cholesterol reduces the risk,[5,6] and the results of six large randomized trials of statins have ensured that this is now widely accepted.[1,7–11] Three important practical questions arise: the nature of the dose–response relationship, the size of the effect, and the speed of the reversal of risk. To answer these questions data from both observational epidemiology (cohort studies) and randomized controlled trials are necessary. The two are complementary; examining trial data alone is misleading. Table 12.1 summarizes the advantages of each. In cohort (or prospective) studies serum cholesterol is measured in a large number of individuals and subsequent heart disease mortality (or incidence of myocardial infarction) is recorded. Cohort studies are easier to conduct than trials (as there is no intervention) and can therefore be much larger. Accordingly, their statistical power is greater and they can examine the association across a wider range of serum cholesterol values and a wider range of ages than trials have done. Most of the cohort studies and trials of cholesterol and ischemic heart disease recruited men, for reasons of economy, as ischemic heart disease is more common in men. The more limited data from women indicate a similar effect as in men.[1]

The nature of the dose–response relationship: is there a threshold?

Figure 12.1 shows mortality from ischemic heart disease plotted according to quintile groups (fifths) of the ranked serum cholesterol measurements in a large cohort study of serum cholesterol and ischemic heart disease (MRFIT Screenees).[12] With ischemic heart disease plotted on a logarithmic scale, the relationship is described almost perfectly by a straight line linking the *proportional* change in

Table 12.1 Relative advantages of cohort studies and randomized trials in assessing the relation between serum cholesterol and ischemic heart disease

Objective	Advantage (comment)
Statistical power	Cohort studies (recorded about three times more ischemic heart disease events than the trials)
Dose–response relationship	Cohort studies (observation across wide range of cholesterol values)
Wide age range	Cohort studies (ischemic heart disease events at age 35–85, but mostly 55–65 in trials)
Long-term effects of cholesterol differences	Cohort studies (on recruitment the serum cholesterol was the same in intervention and control groups)
Short-term effects of cholesterol differences	Randomized trials (on recruitment serum cholesterol was the same in intervention and control groups)
Avoid bias	Randomized trials (not a major advantage – bias in cohort studies can be allowed for)

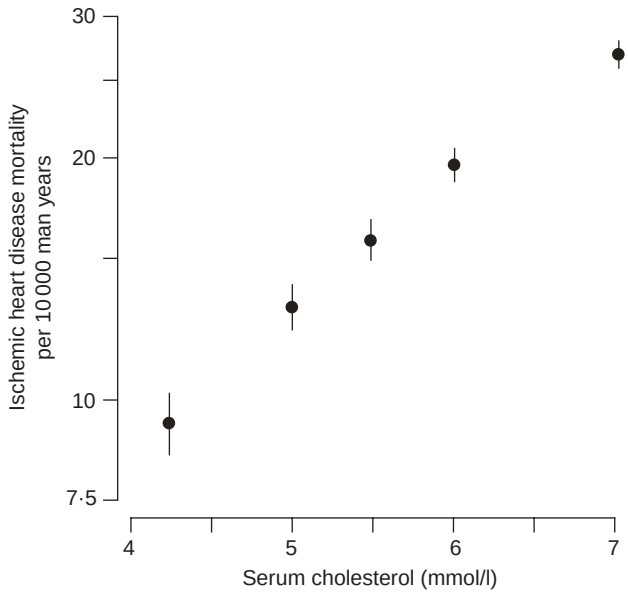

Figure 12.1 Mortality from ischemic heart disease (with 95% confidence intervals) according to serum cholesterol in a large cohort study[12]

ischemic heart disease to the *absolute* difference in serum cholesterol ($r = 0{\cdot}997$). Other cohort studies show the same relationship.[6] The 95% confidence limits of the risk estimates in each quintile group do not overlap, establishing that there is no threshold below which a further decrease in serum cholesterol is not associated with a further decrease in risk of ischemic heart disease. The exponential relationship indicated by the straight line means that a given absolute difference in serum cholesterol concentration from *any* point on the cholesterol distribution is associated with a constant proportional difference in the incidence of ischemic heart disease.

This absence of a threshold has been contentious; many published guidelines on lowering cholesterol invoke one, commonly advocating cholesterol lowering drugs only in patients whose serum cholesterol exceeds 5 mmol/l, yet the evidence is firmly against any threshold. The data in Figure 12.1 (which alone are conclusive) are supported by data from other large cohort studies,[6] including an important study from China which shows that the continuous relationship extends below serum cholesterol values of 4 mmol/l.[13] The results of a subgroup analysis in one statin trial[8] showing no reduction in coronary events in persons with the lowest serum cholesterol levels have been misinterpreted, because the confidence interval on the result was consistent both with no reduction in coronary events and with the expected reduction from the continuous association shown in cohort studies. Large randomized trials have now confirmed the result from cohort studies that the constant proportional reduction in risk extends below 5 mmol/l.[9,11,14] Experimental data on the transfer of cholesterol from the blood into atheromatous lesions exclude a threshold as low as 1 mmol/l.[15] Patients at high risk of an ischemic heart disease event (especially those with existing disease) should be offered a statin irrespective of their existing level of total or LDL cholesterol.

The size of the effect

Cohort studies provide the best estimates because they cover a wide age range and have high statistical power, and because the serum cholesterol differences between individuals recorded on entry to a cohort study will have been present on average for decades beforehand (so cohort studies show long-term associations). Trials, on the other hand, show the effect of short-term differences. Cohort studies are subject to bias, but this can be corrected. The major bias is the so-called "regression dilution bias".[3]

Table 12.2 Estimates (from 10 cohort studies) of the percentage decrease in risk of ischemic heart disease according to extent of serum cholesterol reduction and age[6]

Age (years)	Estimated percentage decrease in risk for a serum cholesterol reduction (mmol/l) of			
	0·3 (5%)	0·6 (10%)	1·2 (20%)	1·8 (30%)
40	32	54	79	90
50	22	39	63	77
60	15	27	47	61
70	11	20	36	49
80	10	19	34	47

Table 12.2 shows estimates of the long-term percentage decrease in the risk of an ischemic heart disease event according to the decrease in serum cholesterol concentration and age at event. The estimates are taken from an analysis of the 10 largest cohort studies, corrected for the regression dilution bias and for the minor distinction between differences in total and in LDL cholesterol discussed above.[6] A reduction in total or LDL cholesterol of 0·6 mmol/l (about 10%) is associated with a decrease in risk of ischemic heart disease of about 50% at age 40, 40% at 50, 30% at 60, and 20% at 70–80. The *proportional* decrease in risk decreases with age, but the *absolute* benefit increases because the disease becomes more common with age. The increasing reduction in risk with greater reduction in serum cholesterol shown in Table 12.2 follows from the exponential dose–response relationship described above. For a 0·6 mmol/l cholesterol reduction at age 60, for example, the reduction in risk is 27% and the relative risk is therefore 0·73; with a serum cholesterol reduction three times as great (1·8 mmol/l), the relative risk is $0{\cdot}73^3$ ($0{\cdot}73 \times 0{\cdot}73 \times 0{\cdot}73$) or 0·39, and the reduction in risk is 61%.

Speed of reversal and consistency of observational and trial data

Data have been analyzed from the "old generation" of 28 randomized trials in which the average serum cholesterol reduction was about 0·6 mmol/l (10%).[6] Figure 12.2 shows the reduction in incidence of ischemic heart disease in all trials combined according to time since entry. In the first 2 years there was little reduction in risk. From 2 to 5 years the average reduction in risk was 22%, and after 5 years the reduction was 25%. The ischemic heart disease events in these trials mostly occurred at an average age of about 60, and at this age the estimate of the long-term effect from the cohort studies is 27% (Table 12.2). The similarity of the estimates of effect from the cohort studies and from the trial

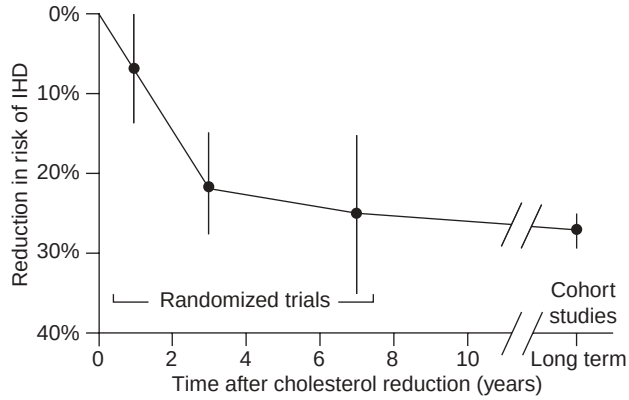

Figure 12.2 Reduction in the incidence of ischemic heart disease (IHD) per 0.6 mmol/l (about 10%) decrease in serum cholesterol, as estimated from randomized trials according to time since entry and from cohort studies (which reflect the long term association)[6]

data from the third year onwards therefore indicates that the reversal of risk is near maximal after 2 years – a surprisingly rapid effect.

The trial data show that the proportional reduction in risk from lowering serum cholesterol is similar in persons with and without previous myocardial infarction or other clinical evidence of coronary artery disease.[6]

The six large trials of statins[1,7–11] have achieved significantly larger reductions in total and LDL cholesterol. These trials too showed a relatively small reduction in ischemic heart disease events in the first 2 years, but a reduction after 2 years that is close to the maximum indicated by cohort studies. Most of these trials achieved an average reduction in total and LDL cholesterol of about 1 mmol/l in treated relative to placebo patients. The reduction in ischemic heart disease events was about 40% from the third year onwards, similar to the long-term estimate corresponding to this cholesterol reduction at age 60 (the average age at the time of the events) from the cohort studies. With relatively little reduction in risk in the first 2 years, the average reduction over the entire duration of the trials (5 years or so) was about a third. Importantly, however, the randomized trials of statins do not show their full potential for preventing ischemic heart disease events because of "contamination" – some patients allocated to the treated group leave the trial and stop taking the tablets, whereas some patients allocated to the placebo group take statins. Atorvastatin and simvastatin can reduce serum total and LDL cholesterol by about 1·8 mmol/l, but no trial has maintained this difference between all patients allocated to the treated and placebo groups over the 5 year duration of a trial. Two trials have maintained a difference of about 1·6 mmol/l – one statin trial[1] and a trial in which serum cholesterol was reduced by ileal bypass surgery.[6] A long-term reduction in ischemic heart disease events of about 55% at age 60 would be

expected from the cohort study data in Table 12.2, and this was approximately the observed reduction after 2 years in these two trials. With a serum cholesterol of 1·8 mmol/l a reduction in heart disease events of about 60% would be expected in the longer term, as Table 12.2 shows. The randomized trials therefore confirm the dose–response relationship shown in the cohort studies (the greater the cholesterol reduction the greater the reduction in heart disease events) and confirm the estimates from the cohort studies in Table 12.2 of the reduction in risk. We can therefore be confident that using atorvastatin or simvastatin in doses of around 20 mg/day to reduce cholesterol by 1·8 mmol/l will reduce risk by about 60% in the longer term.

Dietary fat and serum cholesterol

The relationship between dietary saturated fat and serum cholesterol is shown by the data from Japan and Britain in Table 12.3. This comparison is a useful one because dietary saturated fat differs greatly, yet dietary polyunsaturated fat and cholesterol are similar in the two countries. As in other situations (salt and blood pressure, for example) the size of the association varies with age, yet there has been a tendency to generalize to older age groups the results of studies conducted in younger age groups. Many dietary trials, for example, have been conducted in people under 30. The few that have been conducted in people over 50 tend to support the above Japan–Britain comparison.[6] In older people a reduction in dietary saturated fat equivalent to 10% of calories will lower serum cholesterol by about 1 mmol/l, which in turn will reduce ischemic heart disease mortality in the long term by about 40%.

The chain lengths of saturated fatty acids influence the extent to which they increase blood cholesterol. Palmitic ($C_{16:0}$) and myristic ($C_{14:0}$) acids have the major effect, lauric acid ($C_{12:0}$) some effect, and stearic acid ($C_{18:0}$) and medium chain fatty acids have little or no effect.

Table 12.3 Serum cholesterol and dietary saturated fat in Japan and Britain. Data compiled from national surveys in each country[2]

Age	Japan	Britain	Difference
Dietary saturated fat (% calories)			
All ages	6%	16%	10%
Serum cholesterol (mmol/l)			
20–9	4·5	5·0	0·5
30–9	5·0	5·6	0·6
40–9	5·1	6·0	0·9
50–9	5·2	6·2	1·0
60–9	5·0	6·2	1·2

Trans unsaturated fatty acids are also important: randomized trials show that they increase serum total and LDL cholesterol by about as much as these longer chain saturated fatty acids.[16,17] They are scanty in naturally occurring fats but are generated by the hydrogenation of vegetable oils for use as hardening agents in manufactured foods. They constitute 6–8% of dietary fat, or 2% of calories, in western diets.

Naturally occurring *cis* unsaturated fatty acids reduce serum cholesterol by approximately half as much as longer chain saturated fatty acids increase it. Reduction in dietary cholesterol has a small effect on blood cholesterol concentration.[5] Substitution of *cis* unsaturated for saturated fats in the western diet is thus the most appropriate change in lowering the high levels of blood cholesterol in western populations.

The reduction in serum total or LDL cholesterol that can easily be attained by individuals trying to alter their diet in isolation from family, friends and workmates is relatively small (about 0·3 mmol/l, or 5%). A larger serum cholesterol reduction, about 0·6 mmol/l (10%), is realistic on a community basis, as the availability of palatable low-fat food increases when other family members or the community alter their diet, and the dietary change is perceived more positively. A reduction by about 7% of calories, a realistic target for a high-fat population, would lower serum cholesterol by 0·6 mmol/l, which in turn would reduce the mortality from ischemic heart disease at age 60 by 25–30%. Reductions in serum cholesterol of about 0·6 mmol/l through dietary change have occurred in entire western communities, in the United States and Finland for example.[2] Measures that facilitate such a change include wider public education, labeling of foods sold in supermarkets, and the provision of information on the fat content of restaurant meals. Most important is the implementation of national and international policies on food subsidies that are linked to health priorities.

Serum cholesterol and circulatory diseases other than ischemic heart disease

Table 12.4 shows the death rates from all circulatory diseases according to total serum cholesterol concentration, observed in the same large cohort study (MRFIT Screenees[18]) as shown in Figure 12.1. Apart from ischemic heart disease, serum cholesterol is associated with stroke and with other circulatory diseases.

Stroke

The data from the large cohort study of the MRFIT Screenees (Table 12.4) are useful because thrombotic and hemorrhagic stroke were distinguished. For deaths from thrombotic stroke the data are consistent with a continuous dose–response relationship with serum cholesterol,

Table 12.4 Death rates per 100 000 man years (number of deaths) from circulatory diseases according to serum cholesterol in a large cohort of men[18]

Cause of death (IDC-9 code)	Serum cholesterol (mmol/l) (% of all men)				
	<4·1 (6%)	4·1–5·1 (31%)	5·2–6·1 (39%)	≥6·2 (24%)	*P* (trend)
Ischemic heart disease (410–4)	65 (160)	98 (1239)	169 (2731)	289 (2804)	<0·001
Stroke					
thrombotic (433–8)	6 (14)	6 (73)	8 (135)	13 (126)	<0·001
intracranial hemorrhage (431–2)	9 (22)	4 (55)	5 (86)	6 (57)	–
Other circulatory diseases	31 (77)	39 (483)	41 (670)	57 (556)	<0·001
All circulatory diseases (390–459)	110 (273)	147 (1850)	224 (3622)	365 (3543)	<0·001

analogous to that shown for ischemic heart disease in Figure 12.1. For hemorrhagic stroke (intracranial and subarachnoid), however, there is an *excess* risk at lower serum cholesterol levels.[18,19] Cohort studies that have distinguished thrombotic and hemorrhagic strokes are fairly consistent in showing a positive association of serum cholesterol with thrombotic stroke mortality but an inverse association with hemorrhagic stroke mortality, and cohort studies that do not distinguish the two types of stroke tend to show little or no association between cholesterol and stroke mortality, consistent with the two associations cancelling each other out.[20] Whether the inverse association is cause and effect is uncertain. It is more difficult to see how a spurious (non-causal) association with intracranial hemorrhage might arise through the disease (or predisposition to the disease) lowering serum cholesterol than is the case with depression and suicide or cancer. It is also difficult to see any mechanism by which the inverse association might be cause and effect, although experimental data lend some support to an interpretation of a causal effect of low cholesterol in that the endothelium of intracerebral arteries might be weaker at very low serum cholesterol levels.[19]

The randomized trials of serum cholesterol reduction, especially the statin trials, have shown a lower incidence of stroke (all types combined) in treated than control patients:[9–11,21] statins reduced stroke by about 26%.[21] However, these were nearly all non-fatal strokes. Thrombotic stroke has a lower case fatality than hemorrhagic stroke, so the majority of non-fatal strokes (recorded in the trials) will be thrombotic but little more than half of fatal strokes (recorded in the cohort studies) will be thrombotic. Also, the randomized trials tended to recruit patients in the upper half of the serum cholesterol distribution, where thrombotic stroke will be more common because of its positive association with serum cholesterol. These observations can probably reconcile the reduction in the incidence of stroke in trials (where most of the strokes will have been thrombotic) with the absence of an association between serum cholesterol and stroke mortality in cohort studies. **Grade A** Trials that distinguished thrombotic from hemorrhagic stroke showed that the risk of thrombotic stroke was significantly reduced by a statin,[11] but there are too few data on hemorrhagic stroke to confirm or refute the inverse association with cholesterol shown in cohort studies.

Even if the association between low cholesterol and hemorrhagic stroke is cause and effect, however, the increased mortality from hemorrhagic stroke due to very low cholesterol concentrations is small compared to the lower mortality from other vascular diseases. For example, in Table 12.4 the mortality from all circulatory diseases at the lowest serum cholesterol (<4·1 mmol/l) was 110 per 100 000 man years, lower than the rate of 147 per 100 000 man years in the next highest cholesterol group.

Patients who have had a thrombotic stroke are at high risk of a recurrent event and should receive statins, as should patients with carotid artery disease and others at high risk. Patients who have had a hemorrhagic stroke should not receive statins.

Peripheral arterial disease

Observational data show the expected association between peripheral arterial disease and serum cholesterol. In a large case–control study the association was equivalent in magnitude to an increase in risk of intermittent claudication of about 24% for a 0·6 mmol/l increase in serum cholesterol[22] (uncorrected for regression dilution bias), similar in magnitude to the association of serum cholesterol with ischemic heart disease. In the 4S trial (serum cholesterol reduction 1·8 mmol/l) the incidence of intermittent claudication was reduced by 38% (95% confidence interval 12%, 56%; 52 *v* 81 cases).[23]

Abdominal aortic aneurysm

The pathology of the condition is complex, but abdominal aortic aneurysms are associated with atheromatous disease and tend to coexist with coronary artery or peripheral arterial disease. Abdominal aortic aneurysms are associated with

a higher serum LDL cholesterol and triglyceride and a lower HDL cholesterol.

Other circulatory diseases

Table 12.4 shows a strong association between serum cholesterol and all circulatory diseases other than ischemic heart disease and stroke. Deaths from peripheral arterial disease and abdominal aortic aneurysm are too infrequent to account fully for this association. It is probably attributable also to poorly certified ischemic heart disease: deaths certified due to atrial fibrillation, heart failure, myocardial degeneration and atherosclerosis, for example, are in many cases due to ischemic heart disease.

Safety of cholesterol reduction

The uncertainty concerning the excess mortality from hemorrhagic stroke at low serum cholesterol concentrations is unresolved, as discussed above. This apart, there are no material grounds for concern about hazard. Trials of "statin" drugs, particularly informative on safety because of the large reduction in serum cholesterol that they achieve, have resolved the issue of safety because they show no excess mortality from non-circulatory causes.[1,7–11] The excess mortality from cancer and accidents and suicide at very low serum cholesterol in observational studies is attributable to cancer or depression lowering serum cholesterol, not the reverse.[19] Further reassurance on safety is provided by the condition of heterozygous familial hypobetalipoproteinemia, in which serum cholesterol levels are as low as 2–3 mmol/l. Life expectancy is prolonged because coronary artery disease is avoided, and no adverse effects from the low cholesterol are recognized[24,25] – an important natural experiment.

Statins as drugs are safe, with few adverse effects. The rare complication of rhabdomyolysis, with severe muscular pain and myoglobulinuria, has received attention with the withdrawal from the market of cerivastatin, but this is thought to affect only about one in 250 000 patients using the other statins. It is commoner with concomitant therapy with cytochrome P450 metabolized drugs, of which erythromycin and fibrates (especially gemfibrozil) are the most common.

Why was cholesterol reduction contentious?

A few years ago many clinicians regarded serum cholesterol reduction with uncertainty or suspicion. Until the early 1990s unfavorable evidence had been reported at regular intervals over the previous 30 years. The earliest trials used toxic agents to lower serum cholesterol, notably estrogen (in men) and thyroxine. Some early trials were short in duration[26] and showed no reduction in risk, because none occurs in the first year after lowering cholesterol. Cross-sectional studies of dietary saturated fat and serum cholesterol showed little or no relationship, an observation that was wrongly interpreted as indicating that lowering dietary saturated fat did not reduce cholesterol, until randomized trials established that it did. (The weak cross-sectional association arises because the inaccuracy in measuring individual dietary saturated fat is large in comparison to the small degree of variation between individuals in true saturated fat consumption.[27]) Clinicians were reluctant to accept that there was benefit in lowering average levels of serum cholesterol in high-risk patients: the notion that the average serum cholesterol in entire western populations is high appeared counterintuitive. The issue of safety caused concern, as discussed above. Lastly, it has seemed inconsistent that serum cholesterol is a poor screening test yet an important cause of heart disease, as discussed below. All these issues are now satisfactorily resolved.

Dietary fat and coagulation

Dietary fat increases blood levels of coagulation factor VII and hence increases the risk of thrombosis, myocardial infarction and cerebral thrombosis.[28,29] Saturated and unsaturated fat increase factor VII equally, and the increase appears directly related to the extent of postprandial lipemia. The importance of this effect in increasing the risk of cardiovascular death is difficult to quantify. However, analyses of differences in serum cholesterol and ischemic heart disease mortality between different populations (so-called "ecological" comparisons), such as the Seven Countries Study, yield significantly larger estimates of the relationship than obtained from the cohort studies and trials discussed above, and differences between *populations* in serum cholesterol are largely attributable to differences in dietary fat, whereas genetic differences account for over half the variation in serum cholesterol between individuals in a cohort. At age 60, for example, the ecological estimate is a 38% difference in risk for a 0·6 mmol/l cholesterol difference, compared to a 27% difference in the cohort studies (Table 12.2).[3] The difference may partly reflect the effect of dietary fat on heart disease risk.

Triglycerides

Serum triglyceride concentration was associated with the risk of ischemic heart disease in many cohort studies, but the association is subject to confounding by serum LDL and HDL cholesterol, diabetes and other factors.[4,30] The effect of dietary fat increasing factor VII will also produce an indirect association between triglycerides and heart disease mortality. Whether an independent association exists is

contentious. Very high serum levels of triglyceride caused by genetic defects (familial lipoprotein lipase deficiency, for example) are not associated with atheroma or coronary artery disease, and this observation, together with the potential for confounding in cohort studies, suggests that a material cause and effect relationship between serum triglyceride and heart disease is unlikely.

High density lipoprotein cholesterol

There is an inverse association between HDL cholesterol (or apolipoprotein A1) and ischemic heart disease. An absolute increase corresponding to 0·12 mmol/l (about 10% of the average value) is associated with about a 15% decrease in the risk of ischemic heart disease at age 60[4,30] or a 20% decrease with adjustment for the regression dilution bias.[30] The effect of alcohol in increasing HDL cholesterol is the major mechanism for the lower risk of heart disease in drinkers.[31] The effect of smoking in decreasing HDL cholesterol contributes to the excess risk of heart disease in smokers. The statin cholesterol lowering drugs increase HDL cholesterol relatively little. Certain other cholesterol lowering drugs (such as fibrates and niacin) increase HDL cholesterol more, but even in persons with relatively low HDL cholesterol the overall protective effect of these drugs is smaller because they reduce LDL cholesterol less, and so they should not be preferred to statins.

Lipids as screening tests

Serum cholesterol reduction is important in reducing the risk of ischemic heart disease, but cholesterol and other lipids are poor population screening tests for ischemic heart disease. The reason for the apparent discrepancy is that the screening potential of a factor depends not only on the strength of its relationship with disease, but also on its variation in magnitude across individuals in a community. In the case of lipids, the high average values in western societies place everyone at risk, and the variation between individuals is too small for use in population screening. By analogy, if everybody smoked between 15 and 25 cigarettes per day, cases of lung cancer would not cluster in the minority who smoked 25 cigarettes a day to the extent that those who smoked 15 or 20 could be ignored. Moreover, the Gaussian distribution of serum cholesterol means that many people have values around the average and few have relatively high values, so that most ischemic heart disease events will occur in people whose serum cholesterol is about average.

Among men aged 35–64, the 5% with the highest serum total cholesterol experience only about 12% of all deaths from ischemic heart disease – their risk is little more than double the population average.[30] The 5% of men with highest LDL cholesterol (or its carrier protein, apolipoprotein B) experience 17% of the heart disease deaths.[30] **Grade A** Including HDL cholesterol improves this poor detection by only about one percentage point. Lipids cannot identify a small minority of the population in whom the majority of future heart disease deaths will cluster.

Appropriate policy

In a small proportion of the population, notably persons with familial hypercholesterolemia, the absolute risk of death from ischemic heart disease at a young age is so great that affected persons should be identified and treated, even though the condition accounts for a fraction of all heart disease deaths in a population. **Grade A** The most appropriate screening strategy has not yet been devised; measuring lipids in relatives of known cases will not identify all cases.

Because screening cannot identify a group who would *not* benefit from a reduction in dietary fat and serum cholesterol, such measures should be directed at the entire population. Serum cholesterol reductions of 0·6 mmol/l (10%), as discussed above, have occurred in entire western communities, facilitated by health education, the wider availability of healthy food in restaurants and supermarkets, and a positive image of healthy eating. A reduction of 0·6 mmol/l is less likely when an individual attempts dietary change in isolation. The most important measures to lower cholesterol in healthy people therefore involve wider public education, encouragement of labeling of the nutrient content of foods, and the widespread availability of palatable low-fat foods.

Clinicians need to direct their activities towards high-risk patients, and the most important high-risk group (based on the proportion of all heart disease deaths that can be anticipated) are patients who have had a myocardial infarction. As a group, these patients face a risk of death from ischemic heart disease of about 5% per year (untreated), a risk that varies relatively little with age or sex. As in healthy people, serum cholesterol testing cannot identify a substantial group at either materially higher or materially lower than average risk of death. Also, the evidence strongly indicates that there is no threshold below which serum cholesterol reduction is not effective. It follows that serum cholesterol should be reduced in all survivors of myocardial infarction. Simvastatin and atorvastatin can lower serum cholesterol by 1·8 mmol/l (30%) and this, as discussed above, will reduce mortality from heart disease by about 60% after 2 years, a substantially larger reduction in risk than can be achieved by any other single intervention. Other high-risk groups include patients with angina, patients who have had a thrombotic stroke, patients with carotid artery disease, patients with peripheral arterial disease and claudication,

and diabetics. All these patients should receive statins routinely.

The "population" and "high-risk" approaches are complementary – the first primarily a public health issue aimed at altering the population diet and hence the incidence of ischemic heart disease, the second primarily a clinical activity, identifying and treating with statins patients with coronary artery disease.

Conclusions

The high levels of serum cholesterol found in western populations are a major cause of the high mortality from ischemic heart disease and, to a lesser extent, stroke and other circulatory diseases. Realistic dietary change in a community can lower serum cholesterol by 0·6 mmol/l (10%) and reduce heart disease mortality by about 25–30%. Simvastatin and atorvastatin can lower cholesterol by 1·8 mmol/l (30%) and reduce the risk of heart disease death by about 60% from the third year onwards, and should be offered to all high-risk survivors. Despite the importance of lowering cholesterol, lipids are poor screening tests of individual risk, because the average risk is high and the range across a population is relatively narrow.

Serum cholesterol and ischemic heart disease

Grade A

- The effect of serum cholesterol reduction on ischemic heart disease mortality is large and important.
- There is little reduction in risk in the first year, but the expected reduction in risk is largely attained from the third year onwards.
- There is no threshold across the range of cholesterol values in western countries below which reducing serum cholesterol reduction is not worthwhile. In particular there is no justification for withholding statins from high risk patients whose serum cholesterol is below 5 mmol/l.
- The greater the reduction in serum cholesterol, the greater the reduction in risk.
- Simvastatin and atorvastatin can lower cholesterol by 1.8 mmol/l (30%) and reduce the risk of heart disease death at age 60 by about 60% from the third year onwards; their use should be routine in high-risk patients.
- Realistic dietary change in a community can lower serum cholesterol by 0.6 mmol/l (10%) and reduce the risk of heart disease death by 25–30% at age 60. In an individual acting alone, the realistic change is half this.
- The benefits are similar in men and women.

Serum cholesterol and other circulatory diseases

- Statins reduce the risk of thrombotic stroke and peripheral arterial disease and should be used in high-risk patients.
- Cohort studies show excess mortality from hemorrhagic stroke at very low cholesterol levels. The interpretation is uncertain. The possible hazard, however, is greatly outweighed by the benefit of low mortality from heart disease at very low cholesterol levels.

Screening

- Lipids are poor screening tests for predicting heart disease death in an individual: it is not possible to identify a small minority in a community who will experience the majority of heart disease deaths.
- The 5% of men with highest total serum cholesterol experience only about 12% of heart disease deaths.
- In the extremity of the distribution, familial hypercholesterolemia is important to detect because the absolute risk of heart disease death at a young age is high, even though the condition accounts for only a small proportion of heart disease deaths.

References

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
2. Law MR, Wald NJ. An ecological study of serum cholesterol and ischaemic heart disease between 1950 and 1990. *Eur J Clin Nutr* 1994;**48**:305–25.
3. Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;**308**:363–6.
4. Pocock SJ, Shaper AG, Phillips AN. Concentrations of high density lipoprotein cholesterol, triglycerides, and total cholesterol in ischaemic heart disease. *BMJ* 1989;**298**:998–1002.
5. American Heart Association, National Heart, Lung, and Blood Institute. The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. *Circulation* 1990;**81**:1721–33.
6. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;**308**: 367–72.
7. Shepherd J, Cobbe SM, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;**333**:1301–7.
8. Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.
9. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
10. Downs JR, Clearfield M, Weis S *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 1998;**279**:1615–22.
11. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in

20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
12. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Arch Intern Med* 1992;**152**:56–64.
13. Chen Z, Peto R, Collins R *et al.* Serum cholesterol concentration and coronary heart disease in a population with low cholesterol concentrations. *BMJ* 1991;**303**:276–82.
14. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;**345**:1274–5.
15. Smith EB, Slater RS. Relationship between low-density lipoprotein in aortic intima and serum-lipid levels. *Lancet* 1972;**i**:463–9.
16. Mensink RP, Katan MB. Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* 1990;**323**:439–45.
17. Nestel P, Noakes M, Belling B *et al.* Plasma lipoprotein lipid and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res* 1992;**33**:1029–36.
18. Neaton JD, Blackburn H, Jacobs D *et al.* Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. *Arch Intern Med* 1992;**152**: 1490–500.
19. Law MR, Wald NJ, Wu T, Bailey A. Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994;**308**:373–9.
20. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995;**346**:1647–53.
21. Crouse JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis* 1998;**138**:11–24.
22. Fowkes FGR, Housley E, Riemersma RA *et al.* Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischaemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; **135**:331–40.
23. Kjekshuj J, Pedersen TR, Pyorala K, Olsson AG. Effect of simvastatin on ischaemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *J Am Coll Cardiol* 1997;**29**(Suppl A):75A.
24. Linton MF, Farese RV, Young SG. Familial hypobetalipoproteinemia. *J Lipid Res* 1993;**34**:521–41.
25. Glueck CJ, Gartside P, Fallat RW, Sielski J, Steiner PM. Longevity syndromes: familial hypobeta and familial hyperalpha lipoproteinemia. *J Lab Clin Med* 1976;**88**:941–57.
26. Frantz ID, Dawson EA, Ashman PL *et al.* Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota coronary survey. *Arteriosclerosis* 1989;**9**:129–35.
27. Jacobs DR, Anderson JT, Blackburn H. Diet and serum cholesterol. *Am J Epidemiol* 1979;**110**:77–87.
28. Miller GJ, Cruickshank JK, Ellis LJ *et al.* Fat consumption and factor VII coagulant activity in middle-aged men. An association between a dietary and thrombotic coronary risk factor. *Atherosclerosis* 1989;**78**:19–24.
29. Salomaa V, Rasi V, Pekkanen J *et al.* The effects of saturated fat and n-6 polyunsaturated fat on postprandial lipemia and hemostatic activity. *Atherosclerosis* 1993;**103**:1–11.
30. Wald NJ, Law M, Watt HC *et al.* Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994; **343**:75–9.
31. Gaziano JM, Buring JE, Breslow JL *et al.* Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993;**329**:1829–34.

13 Use of lipid lowering agents in the prevention of cardiovascular disease

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Introduction

According to the most recent data from the American Heart Association, 12 600 000 American adults have coronary heart disease (CHD).[1] CHD is the leading cause of death among US adults, responsible for one of every five deaths in the United States in 1999. Although the age adjusted death rate from CHD decreased by 24% from 1989 to 1999, the actual number of deaths decreased by only 6·8% over this same time.[1]

The associated morbidity, treatment of related conditions and preventive approaches for CHD are reviewed in other chapters of this book. Discussed here is the practical use of lipid lowering agents to prevent hypercholesterolemia – a well-established risk factor for the development of CHD.

Major trials have clearly demonstrated that decreases in low density lipoprotein cholesterol (LDL-C) are associated with reductions in total mortality,[2–4] CHD mortality,[2–4] fatal and non-fatal CHD as well as strokes.[2–5] Other major trials have also shown that lowering LDL-C can retard the progression of coronary artery atherosclerosis[6] and carotid atherosclerosis[7] and may even cause their regression, as well as slow the progression and occlusion of atherosclerosis in saphenous vein bypass grafts.[8] In both primary[3] and secondary[2,4] CHD prevention settings, decreases in total and cause-specific mortality have been demonstrated, and these benefits have been shown in both subjects with elevated,[2,3] average,[5] and normal LDL-C levels. Evidence of the benefits of statins in reducing the risk of stroke and observations concerning their pleiotropic effects are also reviewed.

This chapter's primary purpose is to review the evidence regarding plasma lipid-altering medications, their mechanisms of action, dosages and dosing schedules, effects on lipid and lipoprotein variables, adverse effects, and clinical uses. The evidence for cholesterol lowering in such subgroups as the elderly, women, diabetic patients, and those with small-dense LDL particles will also be summarized.

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor agents (statins), which are highly effective LDL-C lowering agents, are reviewed, as are niacin, bile acid sequestering agents (resins), fibrates, and ezetimibe. A brief review of the costs/1% LDL-C lowering/year and cost effectiveness concludes this chapter.

The National Cholesterol Education Program (NCEP) has been instrumental in developing and promulgating guidelines for initiating LDL-C lowering. These guidelines, developed on the basis of the patient's established baseline LDL-C and presence or absence of CHD or its risk factors, recommend treatment goals to attain desired levels of plasma LDL-C. To date, the NCEP has issued three Adult Treatment Panel (ATP) reports. ATP I emphasized primary prevention of CHD in persons with high (>160 mg/dl) or borderline-high LDL levels (130–159 mg/dl) and >2 risk factors for development of CHD. In ATP II, persons with established CHD were targeted for intensive lipid lowering therapy.

ATP III, disseminated in 2001, continues to identify elevated LDL-C as the primary target of cholesterol lowering therapy and to maintain attention on intensive treatment of patients with CHD.[9] It expands the indications for intensive therapy to lower levels of cholesterol in clinical practice. A major new feature is that intensive LDL-C lowering treatment is a primary prevention measure for persons with multiple risk factors for developing CHD, as identified by the estimated 10 year CHD risk score developed from the Framingham data. ATP III sets the optimal LDL-C level as <100 mg/dl and defines low HDL-C as <40 mg/dl (previous cutpoint was <35 mg/dl).[9]

ATP III also recommends that persons with the metabolic syndrome – a constellation of major lipid and non-lipid risk factors, life-habit risk factors, and emerging risk factors – should be targeted for intensive therapeutic lifestyle changes. Characteristics of the metabolic syndrome include abdominal obesity, elevated blood pressure, insulin resistance, and atherogenic dyslipidemia – elevated triglycerides, small LDL particles, and low HDL-C. Atherogenic dyslipidemia should be treated with lipid-altering agents.[9] Boxes 13.1–13.4 summarize the major new recommendations of ATP III and classifications of cholesterol levels.[9]

Use of individual lipid-altering agents

In this short evidence-based overview, we focus on documented activities of known lipid- and lipoprotein-altering drugs on lipid and lipoprotein variables, and their related

Box 13.1 New features of adult treatment panel III

Focus on multiple risk factors

- Raises persons with diabetes without CHD, most of whom display multiple risk factors, to the risk level of CHD risk equivalent.
- Uses Framingham projections of 10 year absolute CHD risk, (that is, the per cent probability of having a CHD event in 100 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment.
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes.

Modifications of lipid and lipoprotein classification

- Identifies LDL-C <100 mg/dl as optimal
- Raises categorical low HDL-C from <35 to <40 mg/dl
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations

Adapted from *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*[9]

Box 13.2 ATP III classification of LDL, total and HDL cholesterol

LDL cholesterol:

<100 Optimal
Near optimal/above optimal
Borderline high
High
≥190 Very high

Total cholesterol:

<200 Desirable
Borderline high
≥240 High

HDL cholesterol:

<40 Low
≥60 High

Reproduced from *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*[9]

Box 13.3 Major risk factors (exclusive of LDL cholesterol) that modify LDL goals*

- Cigarette smoking
- Hypertension (blood pressure >140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dl)†
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men >45 years; women >55 years)

* Diabetes is regarded as a coronary heart disease (CHD) risk equivalent. LDL indicates low density lipoprotein; HDL high density lipoprotein.

† HDL cholesterol <60 mg/dl counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

Adapted from *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*[9]

Box 13.4 Three categories of risk that modify LDL cholesterol goals

Risk category	*LDL goal (mg/dl)*
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
0–1 risk factor	<160

* Risk factors that modify the low density lipoprotein (LDL) goal are listed in Box 13.3. CHD indicates coronary heart disease.

Adapted from *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*[9]

adverse effects. We identify those issues that remain more speculative as such. The interested reader is referred to the excellent and more complete reviews by Lousberg *et al*,[10] as well as the recent ATP III guidelines.[9]

HMG-CoA reductase inhibitors (statins)

These agents have a powerful LDL-C lowering and those currently approved for use differ only in their dose-response curves and unit cost.

Mevastatin was first isolated in 1976 by Endo and colleagues as a natural product from *Penicillium* species. A related natural product, lovastatin, was approved by the FDA for cholesterol lowering in 1987. Subsequently, simvastatin, pravastatin, fluvastatin, atorvastatin, and cerivastatin were developed and approved for use in the US.[11] Cerivastatin was withdrawn later because of adverse effects.

Mechanism of action: lipid-altering effects

Brown and colleagues demonstrated that lovastatin inhibits HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.[12] Total body cholesterol synthesis is reduced by at least 20%. Ultimately a critical reduction in cholesterol concentration occurs in the liver cell leading to enhanced production of hepatic LDL receptors,[13] and increased cellular uptake of LDL-C. Further, reduced very(V) LDL biosynthesis occurs. Although speculative, it appears that the mechanism by which an increased removal of VLDL from the plasma occurs best fits with the upregulation of LDL receptors and an enhanced removal of VLDLs from the plasma due to an alteration in VLDL structure (specifically apo B-100).[14]

Pleiotropic effects

In addition to reducing cholesterol biosynthesis, other potential antiatherogenic mechanisms of action for the statins are under current, intense investigation. Their exact role and importance remains speculative. Inhibition of 3-HMG-CoA reductase may be pleiotropic.[15] Pleiotropic effects of statins on the vascular system and the arterial walls – affecting endothelial function, inflammation, coagulation, plaque stabilization, and smooth muscle cell migration – have been identified.[15–19] Several statins have been shown to decrease smooth muscle cell migration and inhibit cholesterol accumulation in macrophages.[15] The small GTP-binding protein, Rho, has membrane localization and activity affected by post-translational isoprenylation. Its role in mediating the direct vascular effects of statins is also under intense study.[20]

The Pravastatin Inflammation/CRP Evaluation (PRINCE) provides clinical evidence of anti-inflammatory properties of a statin.[21] In this prospective, randomized, cohort study, pravastatin lowered levels of C-reactive protein (CRP), an inflammatory biomarker that is predictive of cardiovascular risk. Decreased CRP levels were seen as early as 12 weeks in pravastatin-treated participants ($P < 0{\cdot}001$). Pravastatin lowered the median CRP level by 16·9% versus placebo ($P < 0{\cdot}001$) at 24 weeks. The decreases occurred in both the primary and secondary prevention groups and occurred regardless of sex, age, smoking, body mass index, baseline lipid levels, diabetes, and use of aspirin or hormone replacement therapy.[21]

Results of the recently completed Prospective Pravastatin Pooling (PPP) Project – a meta-analysis of three large, placebo-controlled, randomized trials including almost 20 000 patients and 102 559 person-years of follow up – provide further clinical evidence that statins may be anti-inflammatory and/or antithrombotic. In particular, statins may be beneficial in reducing strokes.[22] Pooled data from two of the trials, CARE and LIPID, involving more than 13 000 patients, showed a 22% reduction in total strokes and a 25% reduction in non-fatal stroke.[22] WOSCOPS, the third trial pooled for analysis, had a similar, but smaller, trend for reduction in total stroke. Pravastatin reduced the risk of non-hemorrhagic stroke over a wide range of lipid values in patients with documented CHD.[22] These results contrast importantly with those of a 1995 meta-analysis, which found no effect of lipid lowering on stroke in earlier non-statin clinical trials.[23]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial provides clinical evidence of an anti-ischemic effect with statins. Atorvastatin reduced early recurrent ischemic events in patients with acute coronary syndromes.[24] The statin (80 mg/day) was initiated 24 to 96 hours after an acute coronary syndrome to over 3000 adults with unstable angina or non-Q-wave myocardial infarction (MI). In the atorvastatin group, 14·8% of patients had a primary end point (death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring emergency rehospitalization) versus 17·4% in the placebo group ($P = 0{\cdot}048$).[23] The MIRACL investigators suggest that patients with acute coronary syndromes begin statin therapy before hospital discharge, regardless of baseline LDL-C levels.

Atorvastatin Versus Revascularization Treatment (AVERT) compared the efficacy of aggressive cholesterol lowering therapy versus percutaneous transluminal coronary angioplasty in low-risk, stable patients with CHD. Results favor the use of aggressive lipid lowering over angioplasty in patients with mild to moderate CHD. In addition to significantly reducing LDL-C levels, atorvastatin was associated with a 36% reduction in ischemic events and a significant delay in time to first ischemic event.[25]

Dosage

The recommended dosages of these agents have been described and are shown in Table 13.1.[11] Statins are to be

Table 13.1 Dose response lipid and lipoprotein changes (% change)

Total dose (mg/d)	5	10	20	40	80
	Total cholesterol reductions				
Lovastatin BID	19	24	29	34	
Simvastatin	19	23	28	31	36
Pravastatin		16	24	25	27
Fluvastatin			17	19	25
Atorvastatin		29	33	37	45
	LDL cholesterol reductions				
Lovastatin BID	28	34	40	42	
Simvastatin	26	30	38	41	47
Pravastatin		22	32	34	37
Fluvastatin			22	25	35
Atorvastatin		39	43	50	60
	Triglycerides				
Lovastatin BID	7	16	19	27	
Simvastatin	12	15	19	18	24
Pravastatin		15	11	24	19
Fluvastatin			12	14	19
Atorvastatin		19	26	29	37
	HDL cholesterol				
Lovastatin BID	8	9	10		
Simvastatin	10	12	8	9	8
Pravastatin		7	2	12	13
Fluvastatin			3	4	7
Atorvastatin		6	9	6	5

From *Physicians' Desk Reference*[11]

taken with the evening meal or if they are taken twice daily with the morning and evening meals. Higher dosages of both simvastatin and pravastatin have been approved by the FDA and are now on the market.

Impact on lipid levels

All of these agents except atorvastatin will lower plasma total cholesterol between 20 and 40% and LDL-C by 25 to 45% at maximum approved doses. Fluvastatin appears to lower cholesterol by up to 20% and LDL-C by 25% at maximum doses. To achieve 35–45% LDL-C lowering, daily doses of 40 mg of simvastatin or 80 mg of lovastatin are required. Triglycerides are reduced between 10 and 30%. HDL-C plasma levels are frequently increased by 5–10%, but the increases may be more modest or absent in those with inherently low levels. Lp(a) levels are not affected.[11] Statin therapy alters small dense LDL particles to a larger more buoyant form and also normalizes the responsiveness of coronary vessels to vasoactive stimulus.[26] E-selectin, a cell adhesion molecule with increased expression in atherosclerotic states, is reduced with simvastatin or atorvastatin as monotherapy or in combination with colestipol.[27]

Atorvastatin is a more powerful member of the statin class. Reductions in total cholesterol of 45–50%, LDL-C of up to 60%, and triglycerides of 35–45% are seen at 80 mg/day doses. Reductions in apo B levels of 35–40% have been observed.[11] Changes in plasma levels of Lp(a) are small, if they occur.[28] Increases in HDL-C are inconsistent but may reach 12%.[29] Table 13.1 summarizes the effects of approved statins.

Adverse reactions

Overall adverse reactions occur in less than 2% of individuals. From 1 to 3% of persons taking a statin will have dose-related, elevated, hepatic enzyme levels.[30] Most of these abnormalities are seen within the first 3 months of beginning treatment and require monitoring.[30] In patients who abuse alcohol, there is an increased risk of hepatic toxicity. An extremely low incidence of adverse events (not significantly different from placebo) has been documented over 5·5 years in the Heart Protection Study (HPS),[4] to be discussed in more detail below.

Statins compete with other drugs for specific metabolic pathways of the cytochrome P450 system,[31] whose enzymes act as a major catalyst for drug oxidation in the liver.[32] Lovastatin and simvastatin undergo extensive first-pass metabolism by CYP3A4, and caution is urged in using them with cyclosporin (a known inhibitor of CYP3A4), particularly when other inhibitors of the cytochrome P450 system, such as azole-derived antifungal drugs, erythromycin and clarithromycin, are in use, as well as nefazodone and many HIV protease inhibitors. Atorvastatin is also at least partially metabolized by CYP3A4 but inhibitors of this enzyme only mildly increase serum concentrations.

Fluvastatin is metabolized mostly by CYP2C9 and few drug–drug interactions have been noted. Pravastatin has less potential for drug interaction with other substrates, inhibitors, or inducers of the CYP3A4 and CYP2C9 systems than the other statins because it is metabolized by sulfation, not the cytochrome system.[32]

From 5 to 10% of individuals taking statins may develop muscle enzyme elevations. However, one should consider discontinuing statin therapy if CPK increases by more than threefold. Rare (less than 0·1%) and reversible increases of greater than 10-fold in CPK levels have been described. The causes of CPK elevation remain unexplained. Statin monotherapy or combination therapy can cause myopathy, which, although rare, can progress to rhabdomyolysis.[33] This effect can be seen with any statin; however, cerivastatin was voluntarily withdrawn from the world market in 2001 because of an increased rate of rhabdomyolysis compared with other statins. Rhabdomyolysis occurred more often in patients taking full-dose cerivastatin (0·8 mg/day) and with concomitant gemfibrozil, and it led to kidney failure and death in 52 cases.[34]

Clinical use

Although the biggest proportional reduction in LDL-C levels occurs at low doses, the clinical response to statins is dose-dependent, and it appears to be independent of patient characteristics, such as age, gender, smoking status and initial lipid and lipoprotein levels.[35] ATP III calls for LDL-C lowering drug therapy in persons with CHD and CHD risk equivalents when the LDL-C is $\geqslant$130 mg/dl.[9] In persons with two or more risk factors for the development of CHD, ATP III suggests that lipid lowering drug therapy also begin at LDL-C levels $\geqslant$130 mg/dl.[9]

ATP III also recommends that LDL-C be measured, either at admission or within 24 hours, in all patients hospitalized with a major coronary event.[9] Lipid lowering drug therapy should be initiated at hospital discharge in a person with a coronary event or procedure if LDL-C is $\geqslant$130 mg/dl.[9] Treatment initiation at hospital discharge takes advantage of patients' likely higher motivation to comply with therapy at that time and may avoid the "treatment gap" that can occur if outpatient follow up is less consistent. ATP III still recommends lifestyle changes, including reduced cholesterol and saturated fat diets, weight loss if overweight, and physical activity in hyperlipidemic patients.[9]

Novel agents

The newest statin, rosuvastatin, has been submitted for approval to both the FDA and regulatory authorities in Europe. Called a superstatin because of its potency, rosuvastatin

rapidly lowers total C and LDL-C while increasing levels of HDL-C.[36] A long half life (20 hours) and lack of metabolism via the cytochrome P4503A4 isoenzyme have also been demonstrated.[37] In a phase II study, rosuvastatin across a dose range of 1–80 mg lowered LDL-C by 34–65%. Phase III trials demonstrated greater reductions in LDL-C for rosuvastatin versus atorvastatin as well as greater increases in HDL-C. A starting dose of 10 mg will reduce LDL-C by approximately 50%. The drug appears to be well tolerated at doses up to 80 mg/day.

Nicotinic acid

In the early 1950s Attschult noted profound reductions in plasma total cholesterol and triglyceride levels in association with use of nicotinic acid. Nicotinic acid has the most marked clinical effect on triglycerides and HDL,[38] and is the only lipid-altering agent to consistently lower Lp(a) plasma levels.[39] It also can alter small, dense LDL particles to larger, more buoyant forms.[39]

Mechanism of action

Nicotinic acid's predominant effect on plasma lipid levels is to reduce production of very low-density lipoprotein (VLDL) particles[40] with subsequently reduced production of intermediate density lipoprotein (IDL) and LDL particles. Nicotinic acid's major effect on VLDL metabolism results from an inhibition of hormone-sensitive, lipase-induced lipolysis in adipose tissue, and decreased triglyceride esterification in the liver. HDL-C increases, to a greater extent with niacin than with other drugs, and appears to be related to reduced apo A-I clearance and increased production of apo A-II. How Lp(a) levels are reduced is unknown, but early nicotinic acid induced hepatotoxicity may play a role.

Dosage

Crystalline nicotinic acid is available in 0·1 and 0·5 g tablets. There is a sustained-release form in dosages of 0·125, 0·25 and 0·5 g. The maximum daily dose is usually 3 g (Table 13.2).[41] A new extended-release form of niacin, available since 2000, has relatively mild hepatic effects and can be taken at bedtime to lessen cutaneous flushing.[42] Extended-release niacin is essentially equivalent to immediate-release niacin in increasing HDL-C.[43]

Results

Regardless of the patient's clinical lipoprotein abnormality, dose-dependent reductions in total and LDL-C and plasma triglycerides have been achieved with use of nicotinic acid. HDL-C levels may increase 15–40%; the average increase is 25%, with increases commonly plateauing at a dosage between 1·5 and 3·0 g/d. Reductions in Lp(a) of 25–30% are achieved.[44] As noted above, small-dense LDL particles become larger and more buoyant during nicotinic acid therapy.[45] In certain patients, optimal responses may be formulation- and dosing regimen-dependent.[46]

Adverse reactions

Even at very low doses (0·05–0·10 g), nicotinic acid often causes cutaneous flushing (>80%) and pruritus (50%). Other frequently noted adverse effects are gastrointestinal symptoms (5–20%), liver enzyme elevations (3–10%), and uric acid increases (5–10%). Liver enzyme elevations occur more commonly with slow-release preparations and rapid dose increases. The clinical picture of mild liver function abnormalities usually resolves with continued therapy or reduced doses.

Some 5 to 10% of patients who are taking nicotinic acid will have abnormal glucose tolerance tests or fasting blood sugar levels. A flu-like syndrome that can include hepatitis-like findings on liver biopsy, a secretory defect with profound decreases in LDL-C, decreases in HDL-C and a prothrombin time abnormality may occur. This clinical picture is dose-dependent and resolves when the agent is stopped.[47] Blurred vision with macular edema occurs very rarely. Prednisone is contraindicated for use with nicotinic acid; co-administration can result in patients manifesting clinical diabetes.

Clinical use

Many prescription and non-prescription forms of nicotinic acid are available in the US. Although non-prescription forms are usually less expensive, bioavailability may be a problem. Niaspan, Nicolar and Rugby brands are highly effective prescription nicotinic acids, and the latter is also available as an over-the-counter formulation. The larger crystalline-form tablets are scored, which allows easy tailoring of the therapeutic regimen starting with a single low dose of either 0·1 or 0·25 g/d. Dosing with the crystalline form requires three or four administrations a day. No preparation or dosing regimen has been shown to be superior to multiples of 0·1 g crystalline tablets administered four times a day. Many patients will have little or no effect from two administrations a day, unless using sustained-release preparations. Increases in the dosage are implemented only every few days.[46] Clinicians commonly reduce the number of administrations to three times per day and use 0·5 g tablets starting with 0·25 g qd for the first week. Sustained-release preparations should be used only in those patients with a documented response to immediate-release forms.

Nicotinic acid should always be taken with food. Hot drinks and alcoholic beverages should be avoided at time of administration and dosages should be reduced or perhaps restarted if several successive doses are missed. Cutaneous

Table 13.2 Summary of effects of non-statin lipid-altering agents

Agent	Lipid/ lipoprotein indication	Dosage and dosing	Response expected	Common adverse effects	Comments
Nicotinic acid	↑ Triglyceride (TGs) ↑ LDL-C ↓ HDL-C ↑ Lp(a)	1–3 g/d 6–8 g/d maximum dose 3–4 admin/d	↓ TGs 20–80% ↓ LDL-C 25–40% ↑ HDL-C 25% ↓ Lp(a) 10–30%	Cutaneous flushing, pruritis, GI symptoms, "Flu-like" syndrome	Start low dose Advance slowly Relative contraindications: ↑ FBS, ↑ Liver function test (LFTs)
Bile acid sequestrants	↑ LDL-C	4–24 g cholestyramine 5–30 g colestipol	↓ LDL-C 25–35% at maximum dose ↑ TGs 15–20% ↑ HDL-C 4–7%	GI symptoms	Premix, slow admin Alters absorption of other drugs, for example, glycosides, warfarin, etc.
	↓ HDL-C	2 admin/d,1 at major meal			Contraindicated in hypertriglyceridemia
Fibric acid derivatives	↑ TGs	Clofibrate 1 g bid	↓ LDL-C 10–20% ↓ TGs 40–55% ↓ HDL-C 15–20%	GI symptoms	Will ↑ LDL-C in hypertriglyceridemic patients
		Gemfibrozil 0·6 g/bid Fenofibrate 0·4 g qd			Contraindicated in those with gall stones Marked dose alteration in those with chronic renal failure
Selective cholesterol absorption inhibitor	↓ LDL-C ↑ HDL-C	Ezetimibe 5 mg/d 10 mg/d	↓ LDL-C 16–19% ↑ HDL-C 3–3·5%	No common AEs shown to date	

flushing and pruritus will occur routinely if these precautions are not followed. If symptoms occur, they are the most severe during the first administration. Pretreatment with aspirin or ibuprofen may lessen cutaneous reactions.

Although nicotinic acid may profoundly alter glucose metabolism in some, many diabetic patients have had their lipid disorders successfully managed with this agent. A fasting blood sugar >115 mg/dl predicts subjects who will lose the acute insulin response with an intravenous glucose tolerance test.[48] A fasting blood sugar level <100 mg/dl should identify those patients who can take nicotinic acid without development of clinical diabetes.

Bile acid sequestering agents (resins)

(Table 13.2)

This class of agents was first developed for the treatment of cholestasis-related pruritus by Carey and Williams in 1960. Hashim and Van Itallie subsequently demonstrated that cholestyramine lowered plasma cholesterol and it has been in clinical use for 30 years. Other agents in this class are colestipol and the recently approved colesevelam.

Mechanism of action

The enterohepatic circulation of bile acids allows for only 6 or 7% of them to be excreted each day. These polymers with a molecular weight of over 10^6 are not absorbed and function by binding bile acids in the gastrointestinal lumen. Since an increase in bile acid excretion from the body and an increased production in the liver occur, relative depletion of cholesterol from the liver cells occurs inducing an increased level of hepatic LDL-receptor activity.[49,50] The net effect is an increase in the catabolism of LDL-C and decreased plasma levels.

Dosage

Resins are dispensed in individual packets and are also available in a cost effective bulk formulation. Scoops, equivalent

in size to the number of grams in one packet, are used to dispense from the parent container. The newest resin, colesevelam, has a hydrogel tablet formulation.

Results

Resins are associated with significant reductions in plasma total and LDL-C and with small increases in plasma HDL-C levels.[51] Plasma triglycerides are inconsistently affected, but substantial increases may occur, if used in those with already elevated plasma triglyceride levels.[52] In familial dysbetalipoproteinemia (type III or remnant removal disease) plasma triglyceride levels may increase by more than threefold.

Adverse reactions

No long-term adverse effects have been demonstrated.[51] Drugs that are highly charged, including the cardiac glycosides, the anticoagulant warfarin, diuretic agents, as well as thyroid hormone, will have their absorption affected[53] if taken in close proximity to resin administration. Concomitant warfarin and resin therapy may be extremely challenging.

If a resin's effect on the absorption of a specific medication is not known, the resin should be taken at least 4 hours before or 2 hours after other medications. In clinical situations of existing gastrointestinal malabsorption, the absorption of fat-soluble vitamins may also be reduced.

Clinical use

The biggest proportional reduction in lipid levels occurs at low doses and in those who have moderately elevated levels of cholesterol.[54] Careful selection of the vehicle and logistics used in resin administration will promote long-term patient adherence. Premixing with cold water (taking advantage of the resin's hygroscopic nature) and drinking the preparation slowing is by far the most frequent and successful method of administration. Still, some patients prefer mixing with a heavily textured juice. Pre-existing gastrointestinal symptoms should be addressed before resin therapy is started. Bloating, belching and increased flatus are related to rapid ingestion. Dyspepsia and increased stool consistency or frank constipation can be managed with increases in fluids or dietary fiber intake.

The newest agent in the resin class is colesevelam, available for use in the US since 2000. It is a polymeric, high-potency, water-absorbing hydrogel with a non-systemic mechanism of action.[55] Based on data from approximately 1400 subjects, colesevelam reduced LDL-C by a median of 20%; the reduction is dose-dependent. When combined with lovastatin, simvastatin, or atorvastatin, colesevelam will reduce LDL-C levels by 8 to 16% over that seen with the statin alone.[55] Colesevelam has also been shown to increase HDL-C up to 9%; however, increases in triglycerides, as much as 25%, have also been reported.[56] Colesevelam does not cause constipation, which is likely to improve patient adherence,[55] and is formulated as a tablet, which should eliminate the palatability problems that some patients have with resin powders.[56] In drug-interaction studies, colesevelam was coadministered with digoxin, warfarin, sustained-release metoprolol and verapamil, quinidine and valproic acid, and no clinically significant effects on absorption were reported.[57]

Fibric acid derivatives (Table 13.2)

The fibrates currently marketed in the US are clofibrate, gemfibrozil, and fenofibrate. Fibrates available in other countries include bezafibrate, fenofibrate, ciprofibrate, beclafibrate, etiofibrate and clinofibrate. In a WHO study clofibrate was shown to reduce modestly ($P < 0{\cdot}05$) all cardiovascular events. However, increases in non-cardiovascular morbidity and mortality and total mortality occurred.[58] In the Helsinki Heart Study, gemfibrozil was associated with a 35% reduction in MIs, particularly in those with elevated levels of plasma LDL-C and triglycerides and low levels of plasma HDL-C. Increases in non-cardiovascular deaths and no reduction in total mortality was observed,[59] leading to concerns about the use of fibrates. No fibrate trial has yet shown a significant decrease in total mortality. These agents are approved for use primarily in those with hypertriglyceridemia. Clofibrate can be toxic; in some early studies there was a high mortality rate from malignancy and gastrointestinal disease in association with its use. Therefore, its use should be restricted to patients with severe hypertriglyceridemia unresponsive to other fibrates, niacin, or a combination of niacin and fibrate.

Gemfibrozil has been shown to lower the risk of CHD and stroke in men with previous CHD, and low HDL-C and low LDL-C levels. In the Veterans Affairs HDL Intervention Trial (VA-HIT),[60] 2531 men with CHD (mean HDL-C 31·5 mg/dl and mean LDL-C 111 mg/dl) were randomized to receive gemfibrozil 1200 mg/day or placebo. There was a 22% reduction in CHD over 5 years.[60] A more recent VA-HIT study describes the effect of therapy on stroke. There were 134 confirmed strokes (90% ischemic), 76 and 58 in the placebo and gemfibrozil groups, respectively ($P = 0{\cdot}03$). Risk reduction was evident after 6 to 12 months of gemfibrozil use. Adjusted for baseline variables, the relative risk reduction with gemfibrozil was 31%.[61] Attributing the reduction in CHD to a change in HDL-C levels has been questioned by some. Clearly the reduction in CHD may more properly be associated with changes in other lipoprotein particles[62] than with modest changes in HDL-C levels. Although the number of strokes in the study are modest,[61] this is the first suggestion that stroke can be reduced with a form of lipid-altering therapy that has little effect on LDL-C.

Mechanism of action

Decreased synthesis of VLDL with more efficient lipolysis and increased VLDL triglyceride catabolism has long been speculated as the mechanism of action of fibrates on lipid metabolism. Schoonjans *et al* in 1996 offered direct evidence that fibrates and fatty acids work as ligands for a class of compounds called peroxisome proliferator-activated receptors, of the nuclear receptor superfamily.[63] Peroxisome proliferator-activated receptor alpha partially mediates the inductive effects of fibrates on HDL-C levels by regulating the transcription of HDL apolipoproteins, apo A-1 and apo A-II. Four specific actions are noted:

1. increased hydrolysis of plasma triglycerides due to induction of LPL and reduction of apo-CIII expression
2. stimulation of cellular fatty acid uptake and conversion to acyl-CoA derivatives due to increased expression of genes for fatty acid transport protein and acyl-CoA synthetase
3. increased peroxisomal and mitochondrial beta-oxidation
4. decreased synthesis of fatty acids and triglycerides with a concomitantly decreased production of VLDLs.

Gemfibrozil was associated with a greater reduction in clinical events than the amount of cholesterol lowering or increase in HDL would predict.[64] This suggests that its effects on CHD are mediated by a different mechanism, possibly related to its effects on triglycerides or other lipoprotein particles and HDL. Fibrates also shift the size of LDL particles from smaller, denser forms to larger, more buoyant forms, which could be less atherogenic.

Dosage

Table 13.2 lists dosing information for the three fibrates marketed in the US. Bezafibrate, 0·2 g, is given tid. (0·4 g, sustained-release qd), fenofibrate, 0·3–0·4 g, is given qd, and ciprofibrate, 0·1–0·2 g, is given qd.

Results

In patients with familial combined hyperlipidemia, LDL-C levels may be reduced by fibrates, but, particularly in those with elevated baseline levels of plasma triglycerides there will almost uniformly be an increase in LDL-C levels as VLDL-C levels decrease.[65] Gemfibrozil and clofibrate had similar impact on lipids and lipoproteins in a double-blind crossover study.[66] In patients with moderate to severe forms of hypertriglyceridemia, reductions in plasma triglycerides of 40–60% may occur with concomitant increases of 12–30% in HDL-C levels, but 100% increases in LDL-C may occur.[67]

Adverse reactions

Fibrates are associated with adverse effects in 5–10% of patients. GI side effects (5%) are the most common, but only rarely are these sufficient to warrant discontinuation of the medication. The increased incidence of hepatobiliary disease (particularly gallstones) occurs with all agents in this class.[68] Minor alterations in several plasma biochemical values may occur, but these are dose-dependent and usually transient. The effective non-toxic dose-range is narrow, and at high doses fibrates cause myositis. They may potentiate the effects of oral anticoagulants and oral hypoglycemics and might also interact with statins to raise the risk of rhabdomyolysis.

Clinical use

The primary indication for the use of these agents has shifted to treatment of severe hypertriglyceridemia and more specifically for familial dysbetalipoproteinemia, or remnant removal disease. They are preferred by those who are less experienced in the use of nicotinic acid in clinical circumstances with increases in both plasma LDL-C and reductions in HDL-C levels. Because of the long-term adverse effects on hepatobiliary function and the potential for increases in LDL-C levels, liver function tests and LDL-C levels must be monitored closely. Chronic renal failure requires a 50% reduction in gemfibrozil dose.[69]

Novel agents

Cholesterol lowering agents with different mechanisms of action are in development. Ezetimibe is a novel cholesterol absorption inhibitor that selectively and potently inhibits intestinal absorption of dietary and biliary cholesterol.[70] In phase II clinical trials, ezetimibe at 10 mg/day reduced LDL-C by ≥15% in 68% of patients and by ≥25% in 22% over 12 weeks. HDL-C increased by 3·5% and the drug was well tolerated.[70] Ezetimibe may have additive effects if given in combination with a statin. When given in a fixed combination tablet with simvastatin, LDL-C was reduced by 52%.[71] Policosanol is a phytochemical that is a mixture of higher primary aliphatic alcohols isolated from sugar cane wax.[72] At dosages of 10 to 20 mg/day, it decreased total-C by 17 to 21% and LDL-C by 21 to 29%, while raising HDL-C by 8 to 15%.[72] Policosanol appears to have an acceptable safety/tolerability profile.

Combination therapy

Combination drug therapy should be used when diet and single drug therapy do not reduce LDL-C levels to the desired levels. Verification of adherence to and the efficacy of a prescribed regimen should be made on at least two occasions at monthly intervals before adding to the regimen. Table 13.3 describes a stepped approach to combination therapy depending on the lipid or lipoprotein variable(s) that are the therapeutic objective. Recall that reduction in LDL-C is the only alteration in lipid(s) or lipoprotein(s) that has been unequivocally demonstrated to reduce risks for CHD

Table 13.3 Stepped approach to lipid medication altering therapies

Elevated LDL-C	Elevated TG/LDL decreased HDL-C	Elevated Lp(a)	Markedly elevated TGs
1. Statin	Niacin	Niacin	Fibrate/ niacin
2. Statin+ resin	Niacin+resin		
3. ↑ Statin+ resin	↑ Niacin+resin		
4. ↑ Statin+ resin+ niacin or ezetimibe	↑ Niacin+statin or Statin+fibrate		

in clinical trials. Epidemiologic data demonstrate an increased risk associated with reduced levels of HDL-C,[64] increased plasma Lp(a) (usually in association with increased LDL-C levels), and, to a lesser extent, increased plasma triglyceride levels (usually in association with other risk factors). Intervention studies demonstrating reduction in CHD risk with changes in other lipid and lipoprotein particles have yet to be done.

Guidelines for selecting combination therapy

Practitioners should review four questions before adding other agents to initial diet and lipid-altering drug therapy regimens.[73]

1. Has adherence to and efficacy of the initial regimen been verified?
2. Does the patient have fasting hypertriglyceridemia? (Bile acid sequestering agents should be used as second or third agent only.)
3. What contraindications are present mitigating addition of other lipid-altering agents? (Other diseases or clinical conditions, or other lipid-altering agents.)
4. What are the total costs of additional drug therapy to the patient?

Efficacy of various combinations

Selected examples of maximum lipid and lipoprotein alterations are given in Table 13.4. Prior to the development of atorvastatin the maximum lowering of LDL-C was demonstrated with a combination of lovastatin (40 mg/day), colestipol (30 g/day) and nicotinic acid (5·5 g/day) at 70%. Triglyceride reductions of 80% can be effected with nicotinic acid alone with little to be gained in efficacy by adding another agent. Lp(a) levels are affected substantially only by nicotinic

Table 13.4 Efficacy of selected combination of hyperlipidemic drug therapy in modifying plasma concentrations of total, LDL and HDL cholesterol levels

Drug combination	% change			Reference
	Total	LDL	HDL	
Cholestyramine				
+niacin	−26	−32	+23	Angelin *et al*, 1986
+lovastatin	−51	−61	+21	Leren *et al*, 1988
+pravastatin	−36	−43	+18	Jacob *et al*, 1993
Colestipol				
+niacin	−41	−48	+25	Packard *et al*, 1980
+lovastatin	−45	−54	−2	Illingworth *et al*, 1981
+niacin	−55	−66	+32	Malloy *et al*, 1987
+simvastatin	−41	−50	+9	Simons *et al*, 1992
+fenofibrate	−39	−54	+15	Heller *et al*, 1981
Lovastatin				
+gemfibrozil	−34	−40	+7	Illingworth *et al*, 1989
Simvastatin				
+gemfibrozil	−54	−58	+18	Feussner *et al*, 1992
Atorvastatin				Hunninghake *et al*, 2001
+colesevelam	−31	−48	+11	
Ezetimibe				
+fenofibrate	−27	−36	−1·9	Bays *et al*, 2001
+atorvastatin	−38	−55	−1·1	Bays *et al*, 2001

acid. HDL-C can be consistently raised by 25% with nicotinic acid alone with little further gain by adding other agents.

Adverse effects

The important adverse effects of the single agents are described in Table 13.2. As noted previously, the most serious interaction is seen when a statin drug is used in combination with cyclosporin and myopathy develops. While cessation of the statin allows symptomatic myopathy and elevated muscle enzymes to resolve, continued therapy at the same dose may lead to frank rhabdomyolysis necessitating hemodialysis. Statins have also been associated with myopathic syndromes in patients using erythromycin, niacin and gemfibrozil. Reduced levels of any statin should be used in transplant patients in association with niacin and gemfibrozil with careful monitoring of muscle enzyme levels. Erythromycin use should be absolutely contraindicated in transplant patients already on cyclosporin and a statin. If erythromycin is used the statin must be temporarily discontinued.

Clinical use

Although single-drug therapy offers a simple regimen, combination therapy with low-dose statin and low-dose bile acid sequestrant has been investigated.[74,75] Since the largest portion of lipid alteration is effected at low doses of both of these classes of agents and they work by very different mechanisms, an additive or synergistic response may occur. Low-dose combinations provide a good clinical alternative for patients who have symptoms at higher statin dosages and for organ transplant patients. They also appear to be more cost effective than using a statin as a single agent.

The newest resin, colesevelam, has been studied in combination with statins. Low-dose colesevelam and low-dose lovastatin were given in a double-blind, placebo-controlled study to 135 hypercholesterolemic patients.[76] The combination lowered LDL-C by 34% and 32% (the agents were either taken at the same time or colesevelam was taken at dinner, lovastatin at bedtime). Both combinations were superior to either agent alone, and both decreased total-C by 21%. Neither combination treatment significantly changed HDL-C or triglycerides. All treatments were well tolerated.[76] The resin was also studied alone or in combination with low-dose atorvastatin in hypercholesterolemic men and women. Combination therapy reduced LDL-C by 48%, statistically different from either low-dose atorvastatin or colesevelam alone, but did not affect triglycerides.[77] All treatment groups had similar frequency of adverse effects and the combination was well tolerated.[77] Colesevelam was also given in combination with simvastatin to 251 hypercholesterolemic patients in a randomized, double-blind, placebo-controlled format. All groups, including the placebo-treated patients, had decreased LDL-C levels versus baseline. Among all combination treatment groups (given different dosages of colesevelam and simvastatin), the mean decrease in LDL-C was 42%; this exceeded the decrease with either simvastatin or colesevelam alone.[78] Combination therapy was not significantly different from simvastatin monotherapy in effects on HDL-C and triglycerides. Side effects were similar among all treatment groups.[78]

Informed decisions about "gray zones"

Data have now accumulated on the use of lipid lowering drugs in previously less-well-studied subgroups such as the elderly, women, and diabetic patients. How and when should we use lipid lowering drugs in the following groups?

The elderly

If one lives until age 80 in the US, the average additional life expectancy is 8 years. Older individuals appear to be at least as responsive to cholesterol lowering agents as those in younger age groups. While some have suggested that risk attenuates for those who have hypercholesterolemia at older age, the absolute risk for developing CHD outcomes in the elderly over a short time interval is much higher than it is in younger individuals.

ATP III notes that most new CHD events and most coronary deaths occur in persons older than 65 and that a high LDL-C/low HDL-C level still has predictive power for development of CHD in an older person.[9]

WOSCOPS,[3] (primary intervention, or PI) included patients up to the age of 64 years, 4S[2] (secondary intervention, or SI) up to the age of 70 years, Post-CABG[8] (SI) up to 74 years and CARE[5] (SI) previously provided limited data for those up to 75 years. All except Post-CABG showed benefit on CHD and CVD mortality. WOSCOPS and 4S showed benefit on total mortality, although statistical significance of the data from WOSCOPS was marginal. All of these studies included limited analyses by age group. When data from WOSCOPS were pooled in the PPP, pravastatin significantly reduced relative risk of coronary events in older patients.[79]

More recently, the Heart Protection Study (HPS) enrolled over 20 000 participants – including 5082 women, 3982 type 2 diabetic patients and 1263 elderly patients between the ages of 75 and 80 years. It also enrolled 3421 subjects with low baseline LDL-C levels, and follow up lasted for 5·5 years.[4] Recently reported results show that a dose of 40 mg simvastatin once daily yielded striking results in terms of reduced events: 12% reduction in total mortality, 17% reduction in vascular mortality, 22% reduction in CHD events, 27% reduction in all strokes, and 16% reduction in non-coronary revascularizations.[4] Statin therapy appeared to be beneficial at all cholesterol levels – even in participants

whose baseline levels were well below the currently recommended target levels of 100 mg/dl.[4,80]

Other ongoing trials that will provide needed information on lipid therapy in the elderly are the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Disease Trial (ALLHAT) and the Women's Health Initiative (WHI).[81] Complete ALLHAT results, involving 10 000 participants without an upper age limit, are expected in 2002.[81] WHI will evaluate the effects of diet and lowering of fats in 48 000 female participants, aged 79 or younger, with completion expected in 2007.[81]

According to ATP III, "hard-and-fast" age restrictions do not appear to apply to the use of lipid lowering drugs in elderly persons with established CHD.[9] For primary prevention, ATP III recommends therapeutic lifestyle changes, including low-fat diet, exercise, and weight loss if overweight, and LDL lowering drugs if older persons are at increased risk because of multiple risk factors or advanced subclinical atherosclerosis.[9]

Women

Women were not included in early cholesterol lowering trials because of concerns about confounding hormonal effects on lipids, specifically in premenopausal women. Yet the relationship between increases in plasma cholesterol and CHD exists for women at all ages.

Based on recent secondary and primary prevention trials that did not convincingly show that hormone replacement therapy reduced CHD risk in postmenopausal women and did show benefits with statins, ATP III recommends a cholesterol lowering drug over hormone replacement for CHD risk reduction in women.[9] The later onset of CHD in women should be factored into clinical decision making regarding cholesterol lowering drugs.[9]

Of the "older" major clinical trials, CARE (Cholesterol and Recurrent Events) enrolled a fairly high percentage of women, 14%. It reported a 46% reduction in major coronary events among women participants versus a 20% commensurate risk reduction in men.[4] In the PPP, which included analysis of pooled data from CARE, pravastatin significantly reduced relative risk of coronary events in women.[22]

The first CHD primary prevention trial of statins to include women was the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[82] Among 997 postmenopausal women who received either placebo or lovastatin (20 to 40 mg/day), statin therapy showed consistent numerical decreases in first acute coronary major events and in all prespecified secondary end points (for example coronary revascularization, MI). The study was insufficiently powered, however, to detect significant differences between treatment groups.[82]

In HPS, 34% of participants enrolled were women, and benefits were consistent regardless of sex.[4] Male and female participants experienced similar reductions in risk.

Diabetic patients

Although aggressive control of blood glucose levels in type 2 diabetic patients reduces microvascular clinical outcomes, its effect on macrovascular disease outcomes remains unknown. Other traditional CHD risk factors are believed to increase dramatically the risk for clinical CHD events in these patients. Inherent in the diabetic disease process is an abnormality of lipoprotein lipase activity that is partially but not completely corrected by optimal glucose control. Any additional lipid and lipoprotein disorder(s) present in diabetic patients because of either inherited or secondary causes (obesity, alcohol consumption, etc.), accelerate atherosclerotic progression and increase the risk of clinical CHD events. Treatment of lipid disorders in diabetic patients with commensurate lowering of blood cholesterol levels suggests a similar treatment benefit in diabetic as in non-diabetic patients.[2,3,5]

The use of niacin in diabetic patients has traditionally not been recommended because of concerns about adverse effects on glycemic control. In the Arterial Disease Multiple Intervention Trial (ADMIT), however, niacin was given to diabetic patients in a prospective, randomized, placebo-controlled study enrolling 468 subjects, 125 of them with diabetes and diagnosed peripheral arterial disease.[83] Niacin was given at 3000 mg/day or to maximally tolerated dose, for up to 60 weeks. Niacin significantly increased HDL-C and decreased triglycerides and LDL-C in all participants ($P < 0{\cdot}01$: niacin *v* placebo for all). It modestly raised glucose levels in all participants while HbA_{1c} was unchanged from baseline through follow up.[83] ADMIT investigators conclude that lipid-modifying doses of niacin can be safely used in patients with diabetes and that niacin may be considered an alternative therapy in such patients who do not tolerate statins or in whom statins do not correct hypertriglyceridemia or low HDL-C levels.[83]

In CARE, 586 normocholesterolemic diabetic patients with CHD (14% of total sample) were given pravastatin or placebo for 5 years. In the diabetic patients given pravastatin, there were 8% and 25% reductions respectively in absolute and relative risks of coronary events.[84] Pravastatin also reduced the risk for revascularization procedures among diabetic patients by 32%. In subjects who were not diabetic but who had impaired glucose tolerance, pravastatin also substantially lowered the risk of recurrent coronary events.[84] According to the pooled data in PPP, pravastatin significantly reduced relative risk of coronary events in diabetic patients.[79]

The HPS trial included 3980 persons with diabetes and 2930 of these had no CVD. As noted above, the event reductions seen with simvastatin occurred in diabetic patients as well. There was a 24% decrease in CVD and a 25% decrease in total CHD.[4]

Peripheral vascular disease

In the Rancho Bernardo studies, patients with peripheral vascular disease had a several-fold increased risk of dying of

CHD. Greater than 80% of these individuals have CHD although some will manifest few symptoms. It is reasonable, but unsubstantiated, to treat these individuals as if they have CHD.

Small dense LDL-C particles (phenotype B)

The entire population may be generally divided into two categories on the basis of predominant LDL species present in plasma. People with a predominance of smaller, more dense LDL particles exhibit an increased propensity for oxidative susceptibility of these species.[85] These individuals have a higher risk for CHD, which may be associated to interrelated changes in plasma lipids, specifically an increase in triglycerides and reduced plasma levels of HDL. Alternatively, this pattern may be related to the insulin resistance syndrome, or syndrome X, which consists of impaired glucose tolerance, increased insulin levels, hypertension and abnormalities of coagulation factors. No trial of clinical outcomes and intervention of LDL subspecies has been done.

Key points

Lipid and lipoprotein alteration for prevention of coronary heart disease

1. Plasma LDL cholesterol lowering is effective in both men and women. **Grade A1a**
2. Plasma LDL cholesterol lowering is cost effective above the age of 35 years. **Grade A1a**
3. Plasma LDL cholesterol lowering is effective for ages at least to age 80 years. **Grade A1a**
4. Plasma LDL cholesterol lowering extends the patency survival of coronary artery saphenous vein grafts. **Grade A1a**
5. The variables (NIDDM, hypertension, increased plasma triglycerides, low plasma HDL-C, small-dense LDL and increased PAI-1 levels) that are components of the so-called "insulin resistance syndrome" appear to be a marker for individuals with small-dense LDLs. **Grade B2**
6. Alteration of plasma lipids (triglycerides) beyond total plasma cholesterol and LDL-C has not been demonstrated to affect CHD-cause specific morbidity or mortality. **Grade A1a**
7. Therapeutic increases in HDL-C may be associated with reductions in CHD. Associated changes in VLDL-triglyceride-rich particles appear to have an important role in CHD prevention. **Grade A1a**
8. Since it is effective even in high risk individuals with low initial LDL levels, consider initiation of appropriate therapy without initial determination of plasma lipid and lipoprotein levels. **Grade A1a** Best medical practice supports monitoring LDL-C levels during treatment. **Grade C5**

Costs and cost effectiveness of lipid alterations for CHD prevention

True benefits for individuals and the public health have only been demonstrated for alteration of plasma LDL-C. One method for comparing the costs of cholesterol lowering is shown in Table 13.5 where the cost of the various statins is given in terms of the number of dollars per per cent of LDL-C lowering per year.

Table 13.5 Comparative cost, dose and LDL-C lowering of statins

Agent	Dose (mg)	LDL-C ↓ (%)[b]	AWP ($/day)[c]	Cost/1%/ LDLR ($/yr)
Lovastatin	10[a]	−21	1·49	11·45
	20	−24	2·63	23·09
Simvastatin	10[a]	−30	2·52	27·66
	80	−47	4·40	75·27
Pravastatin	20[a]	−32	2·78	32·47
	80	−37	4·34	58·61
Fluvastatin	20[a]	−22	1·47	11·80
	40	−24	1·47	12·87
Atorvastatin	10[a]	−39	2·30	32·87
	80	−60	3·64	79·71

[a] *Common starting dose, qd.*
[b] From *Physicians' Desk Reference*[11]
[c] From *Red Book Update*. Montvale, NJ: Medical Economics Company; 2002
Cost/1%/LDLR was derived as cost/year/1% LDL reduction.

Until the release of results from the 4S study, reductions in CHD morbidity from plasma cholesterol-related CHD had been modest and reductions in CHD and total mortality had not been demonstrated. Since elevated plasma cholesterol is a major risk factor for CHD and is prevalent in Western countries, evaluation of the cost effectiveness of plasma cholesterol lowering is important because of the size of the potential population for intervention and the associated healthcare costs of what can be lifelong medical therapy. In a sensitivity analysis,[86] data from 4S demonstrate cost effectiveness of intervention for both men and women from 35–70 years and at plasma cholesterol levels above 213 mg/dl. The estimates of treatment costs for benefits observed in the 4S study, indicate that treatment is cost effective, among both men and women and at all plasma cholesterol levels between 213 and 309 mg/dl and with evidence of vascular disease.

A WOSCOPS economic analysis, comparing pravastatin with dietary changes alone, showed the economic efficiency of therapeutic intervention with a statin.[87] Caro *et al* used a generalized model of cardiovascular disease prevention and followed hypercholesterolemic men over a given time period to quantify the effect on cardiovascular diseases

avoided. Over a broad range of inputs and regardless of country, cost effectiveness ratios are below $35 000 per life-years gained. Pravastatin is cost-efficient in preventing CHD.[87] Based on US medical price levels and the clinical trial evidence up to 1998, Hay *et al* concluded that statin therapy is cost effective (that is, cost less than $50 000/year of life saved) in any patient with an annual CHD risk >1%, including those with previous CHD or diabetes.[88]

In a recent cost-effectiveness analysis of the VA-HIT trial, the cost per year of life gained with gemfibrozil was estimated. Using the prices for gemfibrozil negotiated by the VA, gemfibrozil was cost-saving.[89] Using prices for gemfibrozil paid outside the VA system, the cost of a quality-adjusted life-year saved by gemfibrozil ranged from $6300 to $17 000. The VA-HIT investigators concluded that gemfibrozil reduced cardiovascular events in men with CHD and low levels of HDL-C and LDL-C at annual drug cost-savings of $100 or less in 1998 dollars. Even at higher drug prices, the cost of a life-year saved is well below the threshold considered cost effective.[89]

Malik *et al*[90] provide a graphic demonstration of how cost effective statin therapy is versus other widely used therapies for CHD, such as ACE inhibitors, β blockers, and non-CV interventions, such as driver's side air bags (Figure 13.1). The cost effectiveness threshold here is £25 000/year of life saved (US $35 000/year of life saved).

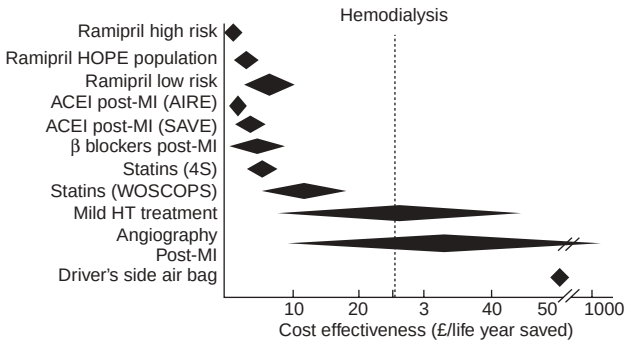

Figure 13.1 Comparison* of cost effectiveness of different strategies in prevention

*Estimates from previous studies are in 1994–1995 UK pounds. Adapted from: Malik IS, *et al Heart*, 2001;**85**:539–43

Future directions

The benefits of statins beyond the coronary vascular bed are now being intensively investigated. In addition to their lipid lowering properties, statins demonstrate pleiotropic effects on many aspects of atherosclerosis, such as plaque thrombogenicity, cellular migration, endothelial function, and thrombotic tendency.[18] Whether or not these effects can be related to a decrease in progression of atherosclerosis or to reductions in acute coronary syndromes remains to be seen. Another area for more study is the benefit of moderate versus aggressive LDL lowering. For example what are the risks and benefits of lowering LDL-C to 75 mg/dl compared to about 100 mg/dl? The exact role of manipulation of other lipoprotein particles also remains to be demonstrated.

Summary

The HMG-CoA reductase inhibitors are an important advance in the treatment of CHD and there is compelling evidence that LDL-C lowering with these agents can decrease the risk of CHD events and total mortality in both primary and secondary prevention. In addition to their effects on LDL-C, statins have pleiotropic effects, which may affect the development and the occurrence of clinical events of atherosclerosis. Lipid lowering therapy benefits the elderly, women, and diabetic patients, even if these individuals have normal LDL-C levels. Effective single- and combination-agent regimens for intervention for other plasma lipid and lipoprotein variables are also available.

Key points

Cardinal issues for using lipid altering agents

1. Is the diagnosis of hyperlipidemia certain?
2. Are there currently medications in the patient's regimen that cause dyslipidemia or offer the potential for drug interactions with hypolipidemic therapy?
3. ALWAYS start the therapeutic regimen with diet and other lifestyle modifications. **Grade A**
4. The statins act as a class of agents, but possess different dose response curves. Some may have substantial levels of adverse effects. **Grade A**
5. The currently approved statins have powerful lipid-altering effects and a very low order of adverse effects. **Grade A**
6. Nicotinic acid is a powerful agent which can be effective in many people including some diabetic patients when used carefully. **Grade A**
7. Nicotinic acid is the most effective of any agent on HDL-C levels and the only one with a possible effect on Lp(a). **Grade A**
8. Resin therapy can be effective for lowering LDL-C plasma levels with careful attention to details of dosing and administration, particularly when added to low-dose statin or low-dose niacin. **Grade A**
9. Fasting hypertriglyceridemia is a relative contraindication to primary or combination resin therapy. **Grade A**
10. Fibrates are effective agents for lowering triglyceride particularly when extremely high and moderately raising HDL-C levels, but changes in LDL-C levels need to be monitored. **Grade A**
11. Are there contraindications to the specific hypolipidemic drug combinations?
12. Consider the direct and indirect costs before initiating primary lipid-altering therapy and with the addition of each agent to the combined regimen.

References

1. American Heart Association. *2002 Heart and Stroke Statistical Update*. Dallas, TX: The American Heart Association, 2001.
2. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;**344**:1383–9.
3. Shepherd J, Cobbe SM, Ford I *et al* for the West of Scotland Coronary Prevention study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;**333**:1301–7.
4. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
5. Sacks FM, Pfeffer MA, Moye LA *et al* for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**: 1001–9.
6. Brown G, Albers JJ, Fisher LD *et al.* Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;**323**:1289–98.
7. Furberg CD, Adams HP, Applegate WB *et al* for the Asymptomatic Carotid Plaque Study (ACAPS) Research Group. Effect of lovastatin and warfarin on early carotid atherosclerosis and cardiovascular events. *Circulation* 1994;**90**:1670–87.
8. The Post Coronary Artery Bypass Graft Trial investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;**336**:153–62.
9. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*. Executive summary. NIH Publication No. 01-3670 May 2001.
10. Lousberg TR, Denham AM, Rasmussen JR. A comparison of clinical outcome studies among cholesterol-lowering agents. *Ann Pharmacother* 2001;**35**:1599–607.
11. *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co; 2002.
12. Brown MS, Faust JR, Goldstein JL. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in human fibroblasts incubated with compactin (ML-236B), a competitive inhibitor of the reductase. *J Biol Chem* 1978;**253**:1121–8.
13. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Scienc*e 1986:**232**:34–47.
14. Berglund LF, Beltz WF, Elam RL, Witztum JL. Altered apolipoprotein B metabolism in very low density lipoprotein from lovastatin-treated guinea pigs. *J Lipid Res* 1994;**35**: 956–65.
15. Corsini A, Bellosta S, Baetta R, Faumgalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999;**84**: 413–28.
16. Gotto AM Jr, Farmer JA. Pleiotropic effects of statins: do they matter? *Curr Opin Lipidol* 2001;**12**:391–4.
17. Farmer JA. Pleiotropic effects of statins. *Curr Atheroscler Rep* 2002;**2**:208–17.
18. Vaughan CJ, Gotto AM Jr, Basson CT. The evolving role of statins in the management of atherosclerosis. *J Am Coll Cardiol* 2000;**35**:1–10.
19. Faggiotto A, Paoletti R. State-of-the-art lecture. Statins and blockers of the renin-angiotensin system: vascular protection beyond their primary mode of action. *Hypertension* 1999;**34**: 987–96.
20. Laufs U, Liao JK. Direct vascular effects of HMG-CoA reductase inhibitors. *Trends Cardiovasc Med* 2000;**10**:143–8.
21. Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE Investigators. Effects of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;**286**:64–70.
22. Byington RP, Davis BR, Plehn JF *et al.* Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation* 2001;**103**:387–92.
23. Hebert PR, Gaziano JN, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Ann Intern Med* 1995;**155**:50–5.
24. Schwartz GG, Olsson AG, Ezekowitz MD *et al.* Myocardial Ischemia Reductions with Aggressive Cholesterol Lowering (MIRACL) Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–18.
25. Waters DD. Medical therapy versus revascularization: the atorvastatin versus revascularization treatment AVERT trial. *Can J Cardiol* 2000 Jan;**16**(Suppl. A):11A–13A.
26. Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995; **332**:488–93.
27. Hackman A, Yasunori A, Insull W Jr, Pownall H, Smith L, Dunn K, Gotto AM Jr, Ballantyne CM. Levels of soluble cell adhesion molecules in patients with dyslipidemia. *Circulation* 1996; **93**:1334–8.
28. Nawrocki JW, Weiss SR, Davidson MH *et al.* Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;**15**:678–82.
29. Bakker-Arkema RG, Davidson MH, Goldstein RJ *et al.* Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 1996;**275**: 128–33.
30. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Saf* 2000;**23**:197–213.
31. Neuvonen PJ, Jalava K-M. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996;**60**:54–61.
32. Beaird SL. HMG-CoA reductase inhibitors: assessing differences in drug interactions and safety profiles. *J Am Pharm Assoc (Wash)* 2000;**40**:637–44.
33. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;**35**:1096–107.
34. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med* 2001;**2**:205–7.
35. Shear CL, Franklin FA, Stinnett S *et al.* Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. *Circulation* 1992;**85**:1293–303.

36.Hanefeld M. Clinical rationale for rosuvastatin, a potent new HMGCoA reduction inhibitor. *Int J Clin Pract* 2001;**55**: 399–405.
37.McTaggart F, Buckett L, Davidson R *et al.* Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor. *Am J Cardiol* 2001;**87**:28B–32B.
38.Alderman JD, Pasternak RC, Sacks FM, Smith HS, Monrad S, Grossman W. Effect of modified, well tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. *Am J Cardiol* 1989;**64**:725–9.
39.Carlson LA, Hampsten A, Asplund A. Effects of hyperlipidemic drugs on serum levels of lipoprotein Lp(a) in hyperlipidemic subjects treated with nicotinic acid. *J Int Med* 1989; **226**:271–6.
40.Grundy SM, Mok HYI, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res* 1981;**22**:24–36.
41.Illingworth DR, Stein EA, Mitchel YB *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia. *Arch Intern Med* 1994;**154**:1586–95.
42.White Robinson A, Sloan HL, Arnold G. The antilipidemic effects of plain and extended-release niacin. *Prev Cardiol* 2000;**3**:131–5.
43.Knopp RH. Evaluating niacin in its various forms. *Am J Cardiol* 2000;**86**:51L–56L.
44.Superko HR, Krauss RM. Differential effects of nicotinic acid in subjects with different LDL subclass patterns. *Atherosclerosis* 1992;**95**:69–76.
45.Zambon A, Brown BG, Hokanson JE, Brunzell JD. Hepatic lipase changes predict coronary artery disease progression/ regression in Familial Atherosclerosis Treatment Study (FATS). *Circulation* 1997;**94**:1–539.
46.Probstfield JL, Hunninghake DB. Nicotinic acid as a lipoprotein-altering agent: therapy directed by the primary physician. *Arch Intern Med* 1994;**154**:1557–9.
47.Patterson DJ, Dew EW, Gyorkey F, Graham DY. Niacin hepatitis. *South Med J* 1983;**76**:239–41.
48.Brunzell JD, Robertson RP, Lerner RL *et al.* Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 1976;**42**:222–9.
49.Shepherd J, Packard CJ, Bicker S, Lawrie TD, Morgan HG. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. *N Engl J Med* 1980;**302**:1219–22.
50.Kovanen PT, Bilheimer DW, Goldstein JL, Jaramillo JJ, Brown MS. Regulatory role for hepatic low density lipoprotein receptors *in vivo* in the dog. *Proc Natl Acad Sci* 1981; **78**: 1194–8.
51.Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in the incidence of coronary heart disease. *JAMA* 1984;**251**:351–64.
52.Levy RI (Moderator). Discussants: Dietary and drug treatment of primary hyperlipoproteinemia, NIH Conference. *Ann Intern Med* 1972;**77**:267–94.
53.Hunninghake DB. Bile acid sequestrants. In Rifkind BM, ed. *Drug treatment of hyperlipidemia*. New York: Marcel Dekker, Inc., 1991.
54.Superko HR, Greenland P, Manchester RA. Effectiveness of low dose colestipol therapy in patients with moderate hypercholesterolemia. *Am J Cardiol* 1992;**70**:135–40.
55.Davidson MH, Dicklin MR, Maki KC, Kleinpell RM. Colesevelam hydrochloride: a non-absorbed, polymeric cholesterol-lowering agent. *Expert Opin Investig Drugs* 2000; **9**:2663–71.
56.Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother* 2001;**35**:898–907.
57.Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000; **14**: 681–90.
58.Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischemic heart disease with clofibrate to lower serum cholesterol: mortality follow-up. *Lancet* 1980;**2**: 279–385.
59.Frick MJ, Elo O, Haapa K *et al.* Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317**:1237–45.
60.Bloomfield Rubin H, Robins S *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *N Engl J Med* 1999;**341**:410–18.
61.Bloomfield Rubins H, Davenport J, Babikiam V *et al.* for the VA-HIT Study Group. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 2001;**103**:2828–33.
62.Robins SJ, Collins D, Wittes JT *et al.* VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;**285**:1585–91.
63.Schoonjans K, Staels B, Auwrex J. Role of the peroxisome proliferator-activated receptors (PPAR), in mediating the effects of fibrates and fatty acids on gene expression. *J Lipid Res* 1996;**37**:907–25.
64.Gordon DJ, Probstfield JL, Garrison RJ, *et al.* High density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 1989; **79**:8–15.
65.Hokanson JE, Austin ME, Zambon A, Brunzell JD. Plasma triglyceride and LDL heterogeneity in familial combined hyperlipidemia. *Arterioscler Thromb* 1993;**13**:427–34.
66.Illingworth DR. Fibric acid derivatives. In Rifkind BM, ed. *Drug treatment of hyperlipidemia*. New York: Marcel Dekker, Inc., 1991.
67.Rabkin SW, Hayden M, Frohlich J. Comparison of gemfibrozil and clofibrate on serum lipids in familial combined hyperlipidemia. A randomized placebo-controlled, double-blind, crossover clinical trial. *Atherosclerosis* 1988;**73**: 233–40.
68.Palmer RH. Effects of fibric acid derivatives on biliary litogenicity. *Am J Med* 1987;**83**(Suppl. 5B):37–43.
69.Goldberg AP, Sherrard DJ, Hass LB, Brunzell JD. Control of clofibrate toxicity in uremic triglyceride. *Clin Pharmacol Ther* 1977;**21**:317–25.
70.Bays HE, Moore PB, Drehobl MA *et al.* Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with

primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001;**23**:1209–30.
71. Meng CQ. Ezetimibe (Schering-Plough). *Curr Opin Invest Drugs.* 2001;**2**:389–92.
72. Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* 2002;**143**:356–65.
73. Hoeg JM. Combination drug therapy. In Rifkind BM, ed. *Drug treatment of hyperlipidemia*. New York: Marcel Dekker, Inc., 1991.
74. Simons LA, Simons J, Parfitt A. Successful management of primary hypercholesterolaemia with simvastatin and low-dose colestipol. *Med J Aust* 1992;**15**:455–59.
75. Jacob BG, Richter WO, Schwandt P. Long-term treatment (2 years) with the HMG CoA reductase inhibitors lovastatin or pravastatin in combination with cholestyramine in patients with severe primary hypercholesterolemia. *J Cardiovasc Pharmacol* 1993;**22**:396–400.
76. Davidson MH, Toth P, Weiss S *et al.* Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decrease low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. *Clin Cardiol* 2001;**24**: 467–74.
77. Hunninghake D, Insull W Jr, Toth Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001;**158**:407–16.
78. Knapp JJ, Schrott H, Ma P *et al.* Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. *Am J Med* 2001;**110**:352–60.
79. Sacks FM, Tonkin AM, Shepherd J, *et al.* Effects of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation* 2000;**102**:1893–1900.
80. Fox R. American Heart Association 2001 scientific sessions: late-breaking science – statins: the new aspirin? *Circulation* 2001;**104**:E9051–2.
81. The Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *Am J Cardiol* 1995;**75**:1130–4.
82. Clearfield M, Downs JR, Weis S *et al.* Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women. *J Womens Health Gender Based Med* 2001; **10**: 971–81.
83. Elam MB, Hunninghake DB, Davis KB *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial Disease Multiple Intervention Trial. *JAMA* 2000;**284**:1263–70.
84. Goldberg RB, Mellies MJ, Sacks FM *et al.* Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The CARE Investigators. *Circulation* 1998;**98**:2513–19.
85. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med* 1993;**94**:350–6.
86. Weinstein MC, Stason WB. Foundations of cost effectiveness analysis for health and medical practices. *N Engl J Med* 1977;**296**:716–21.
87. Caro J, Klittich W, McGuire A, Ford I, Pettitt D, Norrie J, Shepherd J. International economic analysis of primary prevention of cardiovascular disease with pravastatin in WOSCOPS. West of Scotland Coronary Prevention Study. *Eur Heart J* 1999;**20**:263–8.
88. Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics* 1999;**15**:47–74.
89. Nyman JA, Martinson MS, Nelson D, the VA-HIT Study Group. Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol: the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial. *Arch Intern Med* 2002;**162**:177–82.
90. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. *Heart* 2001; **85**:539–43.

14 Blood pressure and cardiovascular disease

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Definition

A new classification of elevated blood pressure (BP) that places greater emphasis on systolic BP was introduced in the 1993 *Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V)*[1] and slightly modified in the 1997 *JNC VI*.[2] Hypertension is defined as systolic blood pressure (SBP) 140 mmHg or greater and/or diastolic blood pressure (DBP) 90 mmHg or greater (Table 14.1). The new classification addresses the issue of severity or increased risk by defining three stages of hypertension, ranging from stage 1 (SBP 140–159 mmHg and/or DBP 90–99 mmHg) to stage 3 (SBP ≥180 mmHg and/or DBP ≥110 mmHg).

In middle-aged populations, the most common type of elevated BP is combined systolic-diastolic hypertension. A second type, isolated systolic hypertension, generally occurs in older persons, probably as a result of age-related stiffening of the arteries. A recent Clinical Advisory Statement[3] recommends that SBP should be the principal measure for the detection, evaluation, and treatment of hypertension in both middle-aged and older individuals.

Hypertension is also classified as complicated or uncomplicated according to the presence or absence of target organ manifestations. These manifestations, which can be cardiac, cerebrovascular, peripheral vascular, renal, or retinal, represent complications of hypertension, and they also increase the risk of other hypertension-related complications (Box 14.1).

Thus, hypertension is classified by its type (combined systolic-diastolic or isolated systolic hypertension), its

Table 14.1 Classification of blood pressure for adults aged 18 years and older[a]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal[b]	<120	and	<80
Normal	<130	and	<85
High normal	130–139	or	85–89
Hypertension			
Stage 1[c]	140–159	or	90–99
Stage 2[c]	160–179	or	100–109
Stage 3[c]	≥180	or	≥110

[a] Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mmHg should be classified as stage 2 hypertension and 174/120 mmHg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as SBP ≥140 mmHg and DBP <90 mmHg and staged appropriately (for example 170/82 mmHg is defined as stage 2 isolated systolic hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment.

[b] Optimal blood pressure with respect to cardiovascular risk is <120/80 mmHg. However, unusually low readings should be evaluated for clinical significance.

[c] Based on the average of two or more readings taken at each of two or more visits after an initial screening.

Adapted from *JNC VI*[2]

Box 14.1 Components for cardiovascular risk stratification in patients with hypertension

Major risk factors

- Smoking
- Dyslipidemia
- Diabetes mellitus
- Age older than 60 years
- Gender (men and postmenopausal women)
- Family history of cardiovascular disease: women under age 65 or men under age 55

Target organ damage/clinical cardiovascular disease

- Heart diseases
  - Left ventricular hypertrophy
  - Angina/prior myocardial infarction
  - Prior coronary revascularization
  - Heart failure
- Stroke or transient ischemic attack
- Nephropathy
- Peripheral arterial disease
- Retinopathy

Adapted from *JNC VI*[2]

severity (stage 1–3), and by coexisting target organ manifestations (if present, complicated, or uncomplicated). These classifications are clinically important, since they have risk as well as treatment implications.

Prevalence

In cohort analysis,[4] mean SBP increases gradually with age, regardless of initial BP (Figure 14.1). Mean DBP also increases until the age of 55–60 years, when it levels off.[4] Later in life there is a reduction in mean DBP, especially in those with high initial levels (Figure 14.1). The age-related changes in BP explain the increase in overall prevalence of hypertension with age and the increase in the prevalence of isolated systolic hypertension with advanced age. The prevalence of target organ manifestations also increases with age, as a result of the increasing prevalence and the longer duration of hypertension.

The prevalence of hypertension is greater for African-Americans than for non-Hispanic Whites and Mexican-Americans,[5] and for less educated than more educated people.

Natural history

Hypertension is one of the major risk factors for cerebrovascular disease (stroke), coronary heart disease (acute myocardial infarction [MI]), congestive heart failure (both systolic and diastolic dysfunction), and renal dysfunction. The risk is directly associated with the BP level and with the presence of target organ manifestations and other cardiovascular risk factors. Ferrucci *et al.*[6] calculated the cardiovascular risk score for each participant of the Systolic Hypertension in the Elderly Program (SHEP) using the Multiple Risk Factor Assessment Equation.[7] The simple risk score is based on age, sex, total and HDL-cholesterol, SBP, smoking, and diabetes. In the placebo group, the 5 year rates of MI, stroke, and heart failure were progressively higher with higher quartiles of risk score in those who were free of cardiovascular disease at baseline. The *relative* event protection conferred by chlorthalidone-based treatment was similar across quartiles of risk. Thus, the *absolute* risk reduction increased by quartile of risk. This was reflected in a 2- to 10-fold lower "number needed to treat" (NNT) to prevent hypertensive complications in the highest-risk quartile (Figure 14.2). The authors concluded that hypertensive patients with additional cardiovascular risk factors should be the prime candidates for antihypertensive treatment.

Disease burden

Hypertension is one of the most common medical conditions in the developed world. It has been estimated that as many as 43 million adult non-institutionalized Americans have hypertensive BP levels or are taking antihypertensive medications. Another seven million persons may be controlling their hypertension using non-pharmacologic methods.[5]

Over the last two decades, the National High Blood Pressure Education Program has markedly raised the population's awareness concerning the high prevalence and complications of hypertension.[1] The number of patients taking

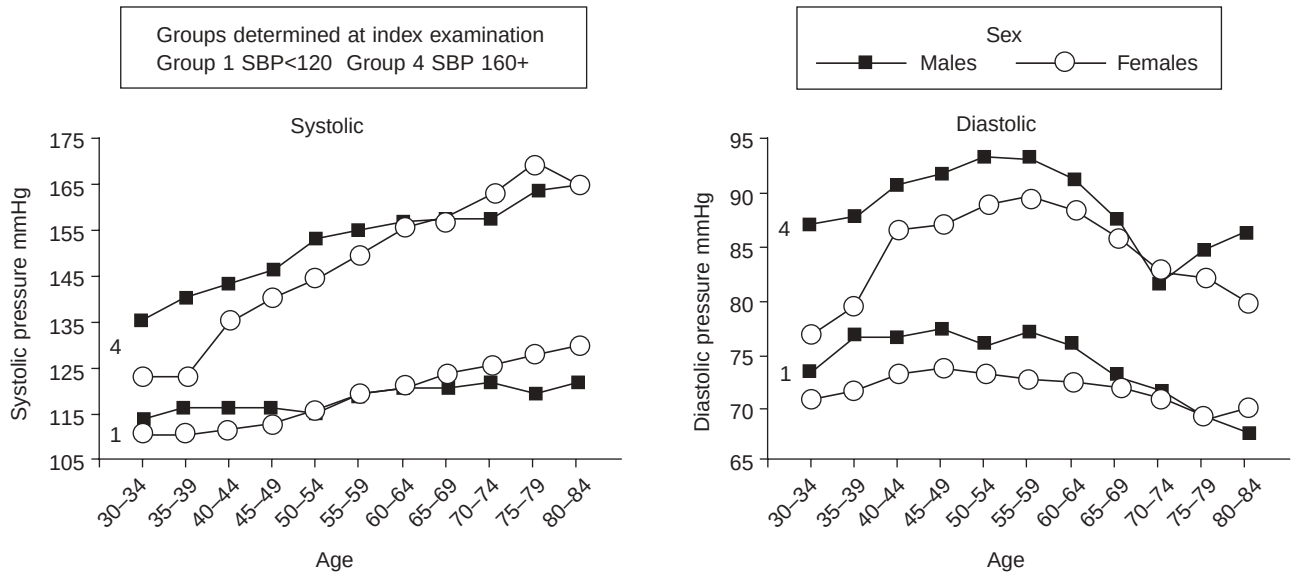

Figure 14.1 Arterial pressure components by age: group averaged data by sex. Averaged blood pressure levels from all available data for each subject with 5 year age intervals (30–34 through 80–84) by SBP groupings 1 *v* 4. (Adapted from Franklin *et al.*[4])

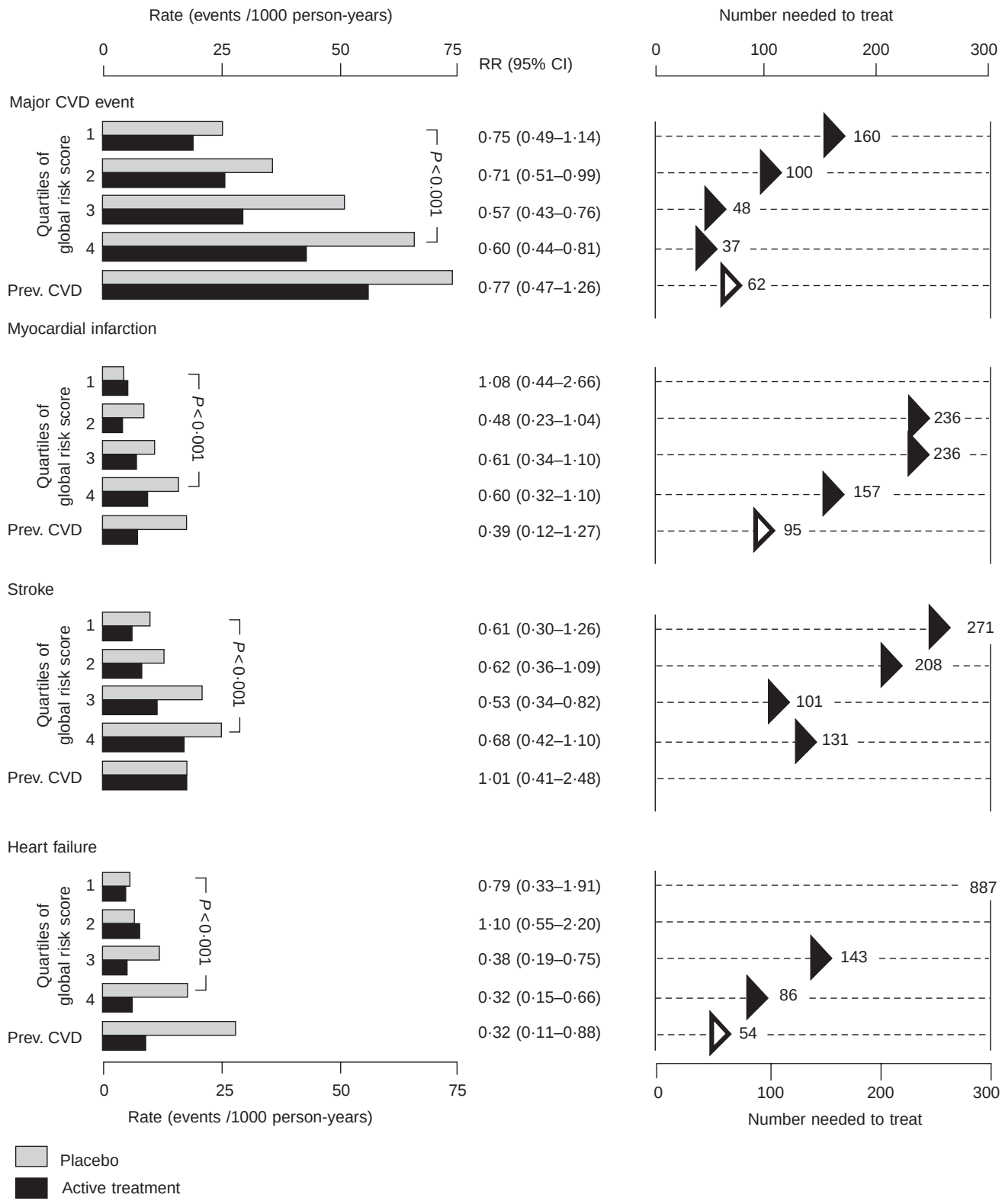

Figure 14.2 Rates of new cardiovascular events, relative risks (RR), and 95% confidence intervals and estimates of NNTs by quartile of global risk score for SHEP participants free of cardiovascular disease (CVD). The fifth group of bars in each panel shows data for subjects with prevalent (prev.) CVD at baseline. (Adapted from Ferrucci *et al.*[6])

antihypertensive medications and having their elevated BP controlled has increased dramatically. The rates of awareness, treatment, and control for hypertension for the new definition of ≥140/90 mmHg in a US population sample in 1991–1994 were 68%, 54%, and 27%, respectively.[2]

The cost of antihypertensive drugs in the USA alone in 2001 has been estimated as high as $12·3 billion.[8] Since as many as half of all hypertensives (defined as ≥140/90) remain untreated, the annual drug costs could easily double, unless we can change lifestyles more successfully or can be more efficient in allocating resources. During the late 1980s and early 1990s, the shift away from the less expensive, often generic diuretics and β blockers (with proven efficacy) to the newer, generally more expensive, ACE inhibitors, calcium antagonists, α blockers and angiotensin II blockers (with unproven efficacy) has been costly to society.[9]

Prevention of hypertension

Despite the established benefits of antihypertensive treatment, concerns are often raised about the prospect of use of antihypertensive drugs over decades by 20% or more of the adult population. All drugs have adverse effects and the cost of medical care for hypertension is considerable. Also, the 12 year follow up of approximately 350 000 middle-aged men screened for the Multiple Risk Factor Intervention Trial shows that 32% of the CHD deaths related to elevated BP occurred below the level at which drug treatment would be considered.[10] Therefore, the prevention of hypertension is a desirable goal.

The multifactorial etiology of hypertension is reflected by the large number of non-pharmaceutical approaches that have been tested.[11–13] Two types of populations have been examined. In individuals with above optimal but non-hypertensive BP levels, lifestyle interventions have been tested to determine their effect on BP. The outcome has been either BP reduction in short-term trials or prevention of BP elevation with age and reduction in the incidence of hypertension in long-term trials. Trials have also been conducted in hypertensive patients with the objective of determining the BP-lowering effects of various non-pharmacologic interventions. One rationale has been that the findings are likely to be generalizable to non-hypertensive individuals. Another rationale has been to determine the efficacy of lifestyle modifications as definitive first-line or adjuvant therapy for hypertension. All treatment guidelines recommend lifestyle modifications as the first therapeutic approach in newly diagnosed less severe hypertensive patients, with pharmacologic treatment to follow only in those who fail to respond adequately.

Cross-sectional or longitudinal observational studies have found the following factors to be associated with BP and prevalence or incidence of hypertension: adiposity, physical inactivity, alcohol consumption, high intake of sodium, low intake of potassium, magnesium, calcium, and certain types of dietary fiber, intake of certain macronutrients, and chronic stress.

Most of the 100+ published randomized clinical trials evaluating hypertension prevention and treatment were small and short term, had follow up periods of weeks or months, and focused on a single intervention. The interventions required varying amounts of involvement by the patients. Lifestyle modifications such as weight loss, exercise, or reduced alcohol or sodium intake require substantial counseling and commitment on the part of patients. Short-term changes may be accomplished, but whether these are sustained is often unknown. Other interventions have been based on supplementation (potassium, magnesium, calcium, fish oil, or fiber) by taking pills, capsules, or various forms of wheat bran, although some dietary trials have been conducted.

Trial results on the efficacy of interventions for prevention of hypertension are summarized in Table 14.2. Based on literature reviews, including meta-analysis, evidence of efficacy is conclusive for weight loss, exercise, diets high in fruits and vegetables, and reduction in alcohol and sodium intake, and potassium supplementation. **Grade A** A weight reduction of 10 lb (4·5 kg) can be expected to lower the BP by approximately 4/3 mmHg. Since exercise, as part of efforts to achieve caloric balance, influences weight, distinguishing an exercise effect on BP from the effect of weight loss can be difficult, but there is good evidence of BP reduction from fitness training.[14] Low intensity/high frequency activity appears as effective as or more effective than high intensity exercise. A sodium reduction of 80–100 mmol/day induces an average BP reduction of 5/3 mmHg in hypertensives and 2/1 mmHg in non-hypertensives.[12] Similar BP effects were observed in trials that accomplished alcohol reductions of about 85% (a mean consumption of three drinks/day reduced to three drinks/week).[15]

The BP effects of lifestyle modifications are modest, but they appear to be additive under some circumstances.[16] A short-term study recently reported substantial BP reductions in adults given a diet rich in fruits, vegetables, and low fat dairy foods, and reduced saturated and total fat.[17] A further reduction of SBP was observed when the sodium intake was reduced to below 100 mmol per day.[18] However, counseling, if required on an indefinite basis through a traditional clinical setting, may not be more cost effective than drugs. Therefore, interventions (such as reducing salt intake by modifying processed foods) that can potentially be accomplished on a population basis are attractive. The efficacy of supplementation with magnesium, fiber, fish oil, or calcium has been judged to be limited or unproven at this time.[11] The trial findings are discordant and the effect sizes small. Potassium supplementation (50–100 mmol KCl or equivalent increase from food) moderately reduces BP, especially in those who have a high sodium intake.[13]

Table 14.2 Trial results on efficacy of interventions for primary prevention of hypertension

Intervention	References	Duration (months)	Change in targeted factors	Change in BP, mmHg (systolic/diastolic)
Sodium reduction	16	6	−50 mmol/day	−2·9/−1·6
	16	18	−43 mmol/day	−2·0/−1·2
	16	36	−40 mmol/day	−1·2/−0·7
	12	0·5–36	−76 mmol/day	−1·9/−1·1
Weight loss	16	6	−4·5 kg	−3·7/−2·7
	16	18	−2·7 kg	−1·8/−1·3
	16	36	−1·9 kg	−1·3/−0·9
Exercise	14	1–16	To 65% maximum exercise capacity	−2·1/−1·6
Alcohol reduction	15	1·5	−2·6 drinks/day	−3·8/−1·4
Potassium increase	13	0·3–36	+46 mmol/day	−1·8/−1·0
Dietary pattern	17, 18	2	Increased fruit, vegetables, low fat dairy, protein, lower saturated fat, dietary cholesterol	−3·5/−2·1

Long-term trials in individuals with high-normal BP have documented that the incidence of hypertension can be reduced by as much as 50%. **Grade A** The most impressive results are from a 5 year trial of a multifactorial intervention.[19] The cumulative incidence of hypertension was 19·2% in the control group and 8·8% in the intervention group. The main factors contributing to this BP reduction were weight loss and sodium reduction.[16] Overweight adults with high-normal BP appear to be prime candidates for this intervention.

Lifestyle modification is an integral part of management of hypertension. The BP-lowering effects are on average modest. Some patients do not respond or are unable to modify their lifestyles, while others respond well. As a consequence, many patients do not have to be placed on antihypertensive drugs and, if they are, lower drug doses or fewer drugs may be required. The challenge is to sustain the lifestyle modifications.

Drug treatment

Placebo-controlled trials

Despite efforts at lifestyle modifications, many patients require pharmacologic treatment. In the USA, almost 23 million civilian non-institutionalized adults are currently taking antihypertensive medications.[5] This high level of drug use to treat an asymptomatic condition has been justified by the high population burden of major morbidity and mortality causally related to untreated hypertension, and by strong evidence of treatment efficacy and safety from large, long-term clinical trials. In SHEP,[20] which enrolled older adults with isolated systolic hypertension, the 5 year event rates for the combined end points of CHD and stroke per 100 patients were 13·6 in the placebo group and 9·4 in the active group. The risk difference of 4·2% means that about 24 older adults need to be treated for 5 years in order to prevent one coronary or cerebrovascular event. It must be recognized that calculating the number needed to treat in this manner from randomized clinical trials produces an underestimate for several reasons, chiefly the selection or self-selection of lower-risk patients into trials and the dilution of effects due to drop-in to active treatment by patients in the control group. For middle-aged populations, who are at lower risk, the number needed to treat would be much higher. Because many people must receive therapy so that a few will benefit, even uncommon adverse effects may minimize or eliminate the BP-lowering benefits of antihypertensive therapy. Only with large, long-term trials such as SHEP can we be assured that the health benefits actually outweigh the health risks of particular therapies.

In a recent meta-analysis,[21] the evidence from large, long-term, controlled clinical trials of antihypertensive therapy was reviewed. **Grade A** The 18 randomized trials included 48 220 patients followed for an average of about 5 years. Clinical trials were classified according to the primary treatment strategy. While most studies used more than one drug, the agents were generally used in a stepwise fashion, and it was usually easy to identify the first-line therapy.

Compared with controls, β blocker therapy was effective in preventing stroke and congestive heart failure (Table 14.3). Similarly, high-dose diuretic therapy, which typically started with the equivalent of 50 mg/day of hydrochlorothiazide and often went to 100 mg/day, was associated with a reduced risk of stroke and heart failure. Despite lowering BP

Table 14.3 Meta-analysis of randomized, placebo-controlled clinical trials in hypertension according to first-line treatment strategy

Outcome drug regimen	Dose	Trials (*n*)	Events, active treatment/ control	RR (95% CI)	RR (95% CI) 0·4 0·7 1·0 Treatment better / Treatment worse
Stroke					
Diuretics	High	9	88/232	0·49 (0·39–0·62)	
Diuretics	Low	4	191/347	0·66 (0·55–0·78)	
β blockers		4	147/335	0·71 (0·59–0·86)	
HDFP	High	1	102/158	0·64 (0·50–0·82)	
Coronary heart disease					
Diuretics	High	11	211/331	0·99 (0·83–1·18)	
Diuretics	Low	4	215/363	0·72 (0·61–0·85)	
β blockers		4	243/459	0·93 (0·80–1·09)	
HDFP	High	1	171/189	0·90 (0·73–1·10)	
Congestive heart failure					
Diuretics	High	9	6/35	0·17 (0·07–0·41)	
Diuretics	Low	3	81/134	0·58 (0·44–0·76)	
β blockers		2	41/175	0·58 (0·40–0·84)	
Total mortality					
Diuretics	High	11	224/382	0·88 (0·75–1·03)	
Diuretics	Low	4	514/713	0·90 (0·81–0·99)	
β blockers		4	383/700	0·95 (0·84–1·07)	
HDFP	High	1	349/419	0·83 (0·72–0·95)	
Cardiovascular mortality					
Diuretics	High	11	124/230	0·78 (0·62–0·97)	
Diuretics	Low	4	237/390	0·76 (0·65–0·89)	
β blockers		4	214/410	0·89 (0·76–1·05)	
HDFP	High	1	195/240	0·81 (0·67–0·97)	

Trials indicate number of trials with at least 1 end point of interest. Abbreviations: RR, relative risk; CI, confidence interval; HDFP, Hypertension Detection and Follow-up Program Study (5484 subjects in stepped care and 5455 in referred care). For these comparisons, the numbers of participants randomized to active therapy and placebo were 7768 and 12 075 for high-dose diuretic therapy; 4305 and 5116 for low-dose diuretic therapy; and 6736 and 12 147 for β blocker therapy. Because the Medical Research Council trial included two active arms, the placebo group is included twice in these totals, once for a diuretic comparison and again for a β blocker comparison. The total number of participants randomized to active therapy and control therapy were 24 294 and 23 926, respectively.
Adapted from Psaty *et al.*[21]

by an average of about 5–6 mmHg, neither β blocker therapy nor high-dose diuretic therapy demonstrated significant reduction of coronary disease events (Table 14.3).

Compared with controls, low-dose diuretic therapy prevented not only stroke and heart failure but also CHD and cardiovascular and total mortality (Table 14.3). In contrast to high-dose diuretic therapy, the adverse metabolic effects of low-dose diuretic therapy are minimal. The safety and proven effectiveness make low-dose diuretic therapy the logical first-line pharmacologic treatment for hypertension. β blockers, which clearly prevent stroke and heart failure in hypertensive patients, are an alternative. The current US guidelines[2] appropriately identify low-dose diuretics and β blockers as preferred first-line agents in the treatment of hypertension.

It is not clear why low-dose diuretic therapy prevents CHD, but neither high-dose diuretic therapy nor β blocker therapy is associated with a reduced risk of coronary disease. The low-dose trials (see reference 21 for references) were conducted mainly in older adults while the high-dose trials were conducted largely in middle-aged adults. Evidence from observational studies suggests that, compared with low-dose diuretic therapy, high-dose diuretic therapy is associated with an increased risk of sudden

death.[22] For high-dose diuretics, the most likely explanation for this increased risk of sudden death is the dose of the diuretics rather than the age of patients. Abrupt withdrawal of β blocker therapy is associated with an increased risk of MI in patients with high BP.[23] It is possible that withdrawal reactions from non-compliance with β blockers may have minimized the drugs' ability to prevent CHD in hypertensive patients, who generally represent a low-risk population group.

The findings for β blocker and high-dose diuretic therapy provide direct evidence that BP lowering alone is not adequate to predict the effect of an antihypertensive medication on important health outcomes. "In light of all previous cardiovascular trials…" Topol and colleagues remark, "surrogate end points cannot be considered authentic measures of true clinical efficacy and safety."[24] Evidence from individual comparative trials and meta-analyses of comparative trials strongly indicates that it matters how elevated BP is lowered (see below). Although average BP reductions are similar across different classes of drugs, important differences exist between these classes in terms of their effects on major morbid events, especially heart failure and acute MI.[25] Yet drug regulatory agencies currently approve antihypertensive medications primarily on the basis of their ability to lower BP.

Results from several long-term, placebo-controlled trials of the newer classes of antihypertensive agents have been published since 1997 (Table 14.4). A placebo-controlled trial of nitrendipine, which is not available in the USA, in isolated systolic hypertension (Syst-Eur) found a statistically significant reduction in stroke risk and showed trends for reductions in risks of acute MI and congestive heart failure.[26] Two placebo-controlled trials in patients with type 2 diabetes and nephropathy, the Irbesartan Diabetic Nephropathy Trial (IDNT)[27] and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study,[28] investigated two different angiotensin II receptor blockers. The primary end point in both trials was a composite renal outcome defined as a doubling of serum creatinine, development of end stage renal disease, or death from any cause. The primary results were very similar: the composite renal outcome was lowered by 20% in IDNT by irbesartan and by 16% in RENAAL by losartan ($P=0{\cdot}02$ in both trials). IDNT also evaluated the effect of amlodipine, a calcium-channel blocker, that did no better than placebo for the renal outcome (RR 1·04). In neither trial did the active treatments significantly reduce the risk of a composite cardiovascular outcome in comparison to the placebo controls.

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) recently reported that ACE inhibitor-based treatment reduced the risk of stroke by 28% and the risk of total major vascular events by 26%.[29] Those receiving the combination of perindopril and the diuretic indapamide (56% of the population) benefitted the most. In this subgroup, the mean reduction in BP was 12/5 mmHg and the reduction in stroke risk was 43%. Those assigned to perindopril alone experienced a small reduction in blood pressure, 5/3 mmHg, with no significant reduction in stroke risk.

In conclusion, placebo-controlled trials conducted through the early 1990s documented conclusively that low-dose diuretics and β blockers used as first-line drugs markedly reduce the devastating cardiovascular complications experienced by hypertensive patients. **Grade A** This achievement had two important consequences. First, it established low-dose diuretics as the proper control group for comparative trials. Second, it limited the opportunity for conducting

Table 14.4 Clinical effects of newer antihypertensive agents from recent placebo-controlled trials

Trial	Study population	First-line treatment	Outcome	RR (95% CI)
Syst-Eur[26]	ISH	nitrendipine	Stroke	0·58 (0·40–0·83)
			AMI	0·70 (0·44–1·09)
			Heart failure	0·71 (0·47–1·10)
IDNT[27]	Diabetic nephropathy	irbesartan	Composite renal	0·80 (0·66–0·97)
			Composite CV	0·91 (0·72–1·14)
		amlodipine	Composite renal	1·04 (0·86–1·25)
			Composite CV	0·88 (0·69–1·12)
RENAAL[28]	Diabetic nephropathy	losartan	Composite renal	0·84 (0·72–0·98)
			Composite CV	0·90 (NA)
PROGRESS[29]	Stroke, TIA	perindopril alone	Stroke	0·95 (0·77–1·19)
			Major vascular	0·96 (0·80–1·15)
		perindopril + indapamide	Stroke	0·57 (0·46–0·70)
			Major vascular	0·60 (0·51–0·71)

Abbreviations: CV, cardiovascular; TIA, transient ischemic attack

long-term, placebo-controlled trials, since withholding active treatment generally became ethically unacceptable. Only in specific subgroups of hypertensive patients – for example, those with major comorbidity such as nephropathy and cerebrovascular disease – were placebo-controlled designs considered acceptable. The focus of clinical research in hypertension has shifted from answering the question, "Is blood pressure lowering beneficial?" to asking, "Does it matter how elevated blood pressure is lowered?" The latter question requires comparative or active-controlled trials.

Active-controlled trials

ALLHAT, initiated in 1994,[30] is one of the first major active-controlled or comparative outcome trial to examine whether the type of drug used to lower high BP matters. While the study hypotheses are formally two-sided, the primary interest is a test of superiority, with the overall objective being to determine whether each of three drugs from newer drug classes (ACE inhibitors, calcium-channel blockers, and α blockers), when used as first-line therapy, are superior to low-dose diuretics in reducing the risk of cardiovascular events. The α blocker (doxazosin) arm was terminated early in 2000[31] for two reasons – a 25% excess of major cardiovascular events, primarily congestive heart failure, and a very small likelihood of observing that it is superior to low-dose diuretics in reducing major coronary events (Table 14.5). The fact that excess cardiovascular events with doxazosin occurred despite BP reduction that was similar to the diuretic group points to the importance of drug selection in the treatment of hypertension.

A meta-analysis of nine randomized comparative clinical trials of intermediate- and long-acting calcium-channel blockers (CCB) was recently published.[32] The comparators were mostly low-dose diuretics, β blockers, and ACE inhibitors. The mean BP reduction was almost identical in the CCB and non-CCB groups. In the database that included nearly 120 000 person-years of treatment, use of CCBs was associated with approximately 25% excess rates of both congestive heart failure and acute MI ($P < 0{\cdot}005$) (Table 14.5). No differences were observed between the groups for stroke or all-cause mortality. When the database from a second meta-analysis[33] was used to examine the same question – CCBs versus non-CCBs – the results were similar and statistically significant.[34]

In a similar type of meta-analysis, the benefit of ACE inhibitors was compared to that of non-ACE inhibitors, primarily CCBs in patients with diabetes.[35] The pooled analysis, supported subsequently by another trial,[36] strongly suggested that ACE inhibitors have advantages over

Table 14.5 Clinical effects of newer antihypertensive agents from recent active-controlled trials

Study	Study population	Treatment		Outcome	RR (95% CI)
		Study	Control		
ALLHAT[31]	Elderly, high-risk	doxazosin	chlorthalidone	CHD	1·03 (0·90–1·17)
				Mortality	1·03 (0·90–1·15)
				Stroke	1·19 (1·01–1·40)
				Combined CVD	1·25 (1·17–1·33)
				CHF	2·04 (1·79–2·32)
				Angina	1·16 (1·05–1·27)
				Coronary revasc	1·15 (1·00–1·32)
Pahor *et al.*[32]		CCBs	non-CCBs	CHF	1·25 (1·07–1·46)
				AMI	1·26 (1·11–1·43)
				Stroke	0·90 (0·80–1·02)
				Mortality	1·03 (0·94–1·13)
Pahor *et al.*[35a]	Diabetics	Non-ACEIs, Mostly CCBs	ACEIs	AMI	1·45 (1·12–1·89)
				Stroke	1·08 (0·80–1·43)
				CV event	1·20 (1·00–1·45)
				Mortality	1·08 (0·86–1·35)
AASK[37]	Non-diabetic nephropathy	amlodipine	ramipril	Composite renal	1·61 (1·15–2·27)
IDNT[27]	Diabetic nephropathy	amlodipine	irbesartan	Composite renal	1·32 (1·09–1·58)
				Composite CV	0·97 (0·76–1·23)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; CCBs, calcium-channel blockers; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease
[a] Updated to include reference 36.

non-ACE inhibitors in reducing the risk of acute myocardial infarction and major cardiovascular events, in spite of similar BP reduction (Table 14.5).

The fourth source of evidence concerning the relevance of how elevated BP is lowered comes from two very recent trials with similar design in patients with nephropathy (Table 14.5). The achieved BP levels were similar for the two therapies – amlodipine versus a drug blocking the renin– angiotensin system. In the AASK trial,[37] among patients with non-diabetic nephropathy, the amlodipine group was terminated early owing to a more rapid decline in renal function and a 60% higher risk of a composite renal outcome – renal disease progression, end stage renal disease, or death compared to the ramipril group. Amlodipine was also inferior to irbesartan in patients with diabetic nephropathy in IDNT.[27] The risk of the composite renal outcome was 32% higher in the amlodipine group compared to the irbesartan group. There was no group difference for a composite cardiovascular outcome.

In conclusion, these reports document that in certain circumstances it matters how elevated BP is lowered. It appears that two types or classes of drugs, α blockers and CCBs, are as effective as other antihypertensive agents in reducing SBP and DBP in the reviewed trials, but less effective in reducing the risk of heart failure (both classes) and MI (CCBs). In elderly high-risk hypertensive patients, doxazosin was less effective than chlorthalidone in reducing risk of congestive heart failure and stroke. **Grade A** There was no difference in risk of major coronary events. It is likely that these observations from ALLHAT apply to all α blockers. Two thirds of the heart failure cases were either hospitalized or fatal. Several sources of data[32–37] show that CCBs are inferior to other agents in reducing the hypertensive complications of congestive heart failure and acute MI. These findings may be especially relevant in patients with type 2 diabetes.[35,36] Since diuretics, β blockers and ACE inhibitors are effective in the treatment and prevention of heart failure and most CCBs are contraindicated in patients with this condition, these observations should not be surprising. Similarly, β blockers and ACE inhibitors are beneficial in the prevention of CHD while the CCBs are not. Additionally, recent trials have reported that amlodipine is inferior to drugs blocking the renin–angiotensin system.[27,37] In these small trials, there was no difference in cardiovascular events.

Genetics, hypertension, and some potential drug–gene interactions

The phenotype of high BP represents a complex trait influenced by both genes and environment.[38–40] While behavioral factors such as obesity and physical inactivity are clearly important in the etiology, family studies and twin studies suggest that about 30% of the variation in levels of BP can be attributed to genetic factors.[39] Several monogenic forms of high BP have been identified, and they include, for instance, glucocorticoid-remediable aldosteronism and Liddle's syndrome.[38,39] These monogenic forms of hypertension, though sometimes associated with profound elevations of BP, are rare and do not contribute measurably to the burden of hypertensive disease in humans.

Essential hypertension, generally mild to moderate elevations of BP in the population, has been associated with several genetic polymorphisms. Halushka and colleagues have identified 874 single nucleotide polymorphisms in 75 candidate genes for BP homeostasis.[41] Not surprisingly, the literature on genetics and hypertension is vast. This section will illustrate the findings for several leading candidate genes, including variations in the genes coding for angiotensinogen,[42] the β-2 adrenergic receptor,[43] and α adducin,[44] with special attention to potential drug–gene interactions that may in the future affect treatment choices. The genetic studies of hypertension are immensely important for understanding the biologic and molecular etiologies of high BP and, potentially, for the design of new drugs. The public health importance of variations in candidate genes for hypertension remains to be determined. While this work has enhanced our knowledge of molecular biology, the polymorphisms associated with essential hypertension, though some are common, tend to have small effects. As Corvol has aptly observed, "Most molecular variants lead to a low attributable risk in the population or a low individual effect at the individual level."[45]

Angiotensinogen gene (*AGT*)

Polymorphisms in the *AGT* gene, especially the *Met235Thr*, have been associated with hypertension.[46,47] The *Met235Thr* variant, which is associated with elevated plasma levels of *AGT*, is in linkage disequilibrium with the *A-6G* promoter polymorphism, and the *-6G* variant is associated with increased gene transcription[46,48] and aldosterone production.[49] In response to sodium restriction, patients with the *Thr235* variant and the *-6A* promoter variant have larger reductions in level of BP than persons with the corresponding wild type allele.[50,51] Patients with the *Thr235* variant also have more pronounced responses to ACE inhibitors than those with the *Met235* allele.[52] In one study,[46] the *AGT* polymorphism predicted the BP response to treatment with ACE inhibitors. The largest fall in BP was associated with the *T235* allele of *AGT*, which is also associated with higher levels of *AGT*.[46] Since subjects with the *Thr235* and *-6A* variant alleles appear to be more salt sensitive, and since diuretics are more effective in salt-sensitive hypertension, diuretics may be especially effective in subjects with these variant alleles.[50,51]

β-2 adrenergic receptor (*β2AR*)

Adrenergic receptors are members of a large family of receptors linked to guanine-nucleotide-binding proteins

(G proteins). Recent studies in molecular biology have contributed to our understanding of the structure, function and regulation of adrenergic receptors,[53] including their interaction with G-proteins in the heart.[54–56] In a series of studies, Liggett and colleagues identified several polymorphisms in the β-2 receptors and their functional and clinical consequences.[57] Four of the nine point mutations resulted in changes in the *β2AR* amino acid sequence, and several appear to affect agonist-promoted downregulation of the *β2AR*.

The β-2 adrenergic receptors are important in BP regulation. Genetic variation in these receptors may account in part for variation in the risk of hypertension or variation in the response to drug treatment.[58] In normotensive African-Americans compared to White Americans, dilation of forearm resistance vessels in response to the infusion of a β-2 adrenergic agonist is decreased.[59] These findings suggest that alterations in the response to β-2 adrenergic stimulation may be important in the development of hypertension in African-Americans. A polymorphism in the β-2 adrenergic receptor gene detected by a restriction fragment length polymorphism (RFLP) is associated with hypertension, both in Whites and Blacks.[60] In African-Americans, this β-2-related RFLP is associated with a salt-sensitive form of hypertension.[61] In African-Caribbeans, the *Arg16Gly* polymorphism of the β-2 adrenergic receptor is associated with hypertension[58] (OR = 2·74; 95% CI 1·72–4·36).

In one recent study, Dishy and colleagues describe the association between several *β2AR* variants and responses to isoproterenol with particular attention to the desensitization that normally occurs with prolonged exposure.[43] For the *Arg16Gly* polymorphism, subjects homozygous for the *Gly16* variant were more resistant to the agonist-mediated desensitization than subjects homozygous for the *Arg16* as measured by sustained venodilatation. For the *Gln27Glu* polymorphism, subjects homozygous for the *Glu27* variant had higher maximal venodilatation in response to isoproterenol than those who were homozygous for *Gln27*.[43]

Taken together, these findings suggest that genetic variation in the β-2 adrenergic receptor may be important in hypertension, and that the risk may vary in subgroups according to ethnicity or salt sensitivity. High-salt diets produce hypertension in part by downregulating the β-2 receptors.[62] Thus, genetic variation in these β-2 receptors may influence not only the development of hypertension but also the response to diuretics as well as β blockers.

α adducin

α adducin is the first example of molecular genetic research in the rat to provide key insights to human hypertension.[40] A series of elegant experimental comparisons between the Milan Hypertensive Strain (MHS) and the Milan Normotensive Strain identified *α adducin* as a candidate gene.[63,64] Adducin, a heterodimer of alpha and beta subunits, modifies the cell cytoskeleton and thereby modulates the cell-surface exposure of the transmembrane proteins.[65,66] This interaction between cytoskeletal proteins and transmembrane proteins helps to regulate ion transport. In the MHS, the number of Na^+/K^+ pump units and their activity are increased, and Na-K ATPase activity is upregulated.[66]

In humans, a *Gly460Trp* polymorphism of *α adducin* was recognized and investigated.[67] The variant *Trp460* allele is associated with the prevalence of hypertension in Italians and French (OR = 1·6, 95% CI 1·3–1·9).[44] The variant *Trp460* allele also modifies the response to 2 months of treatment with thiazide diuretics and to acute salt-sensitivity testing.[44] Subjects with one copy of the *Trp460* variant allele had a larger BP response to thiazide treatment than those with the wild type (decrease of mean arterial pressure of 14·7 for *Trp460* versus 6·8 mmHg for the wild type). Similarly, subjects with the *Trp460* variant also had a more pronounced response to the acute salt-sensitivity testing (change in MAP of 15·9 *v* 7.4 mmHg). These findings are consistent with role of *α adducin* in controlling renal transepithelial ion transport in humans.[68] The association with hypertension has been confirmed in some[69] but not all clinic-based studies.[70–72] In the only population-based study, the OR for the association of adducin with hypertension was 1·67 (P = 0·02).[73] The response of subjects with the variant *Trp460* allele to diuretic therapy is pronounced even in populations where the variant allele is not associated with the risk of hypertension.[74]

The *α adducin* polymorphism is strongly associated with the salt-sensitive form of hypertension, and individuals with one or two copies of the variant allele display an increased rate of renal tubular sodium reabsorption after sodium depletion or loading.[75] In one large clinical trial of antihypertensive therapy,[76] it was observed that there was a reduction in cardiovascular events, particularly stroke, in the treatment group – a reduction that could not be completely accounted for by the attained BP reduction. Among participants with the adducin variant in a recent case–control study, diuretics were compared with other antihypertensive drugs. It was found that in those participants the use of diuretics was associated with a 50% reduction in the risk for MI or stroke.[77] Treatment with thiazides in people with salt-sensitive hypertension may decrease the incidence of cardiovascular events through other mechanisms than the direct lowering of BP.

Pharmacogenetics

Over centuries and across communities, large numbers of polymorphisms have appeared in what are now called drug receptors, drug effector pathways, and drug-metabolizing enzymes. Indeed, some variant alleles have become common in the absence of any exposure to most modern medications. For instance, the allele frequencies in various

populations are 11–57% for *α adducin*, 42–72% for the *β2AR* variants at positions 16 and 27, and 36–52% for angiotensinogen. Interest in pharmacogenetics is often inspired by the point of view of drug development. Identifying the genes responsible for variation in or regulation of BP may provide opportunities to design new drugs.[78] While some studies suggest the possibility of drug–gene interactions on the outcome of level of BP, no studies have examined the potential for drug–gene interactions on the occurrence of cardiovascular events. Another perspective is the point of view of drug safety.[79] Thousands of prescription medications are already on the market. In 1994, 2·2 million hospitalized persons experienced serious adverse drug reactions, and 106 000 had fatal adverse drug reactions.[80] Work in pharmacogenetics can perhaps also improve the safety profile of medications already commonly used in the USA.

The studies in molecular biology and genetics are occurring at a breathtaking pace. The identification of polymorphisms at once answers questions about genetic variation and, at the same time, raises questions about their clinical applications in medical practice – important questions that need to be answered before these genetic studies can begin to benefit the health of the public. Many of these genetic variants are exceedingly common. If screening for genetic variants such as the *Trp460* allele of *α adducin* identifies patients for whom diuretics are particularly effective in preventing cardiovascular events, then genetic screening for selected polymorphisms might become as useful as renal function tests in the initial work up of patients with high BP. Much work needs to be done before genetic screening is indicated.

Cost effectiveness

It has been estimated that medications account for 50–90% of the direct cost of hypertensive treatment.[81] The 1996 wholesale prices for starting doses of antihypertensive drugs may vary by at least 40-fold. Thus, the choice of drug(s) has a major effect on direct treatment costs.

The direct costs of routine outpatient physician visits and laboratory tests are also substantial. If one assumes three annual office visits (at $70 each) and two serum chemistry panels (at $29), these non-drug costs of hypertension management amount to $268 per patient per year. For every one million of the 20 million untreated patients in the USA started on drug treatment, the total cost could be as low as $450 million or as high as $1 billion annually. The question from a cost-effectiveness viewpoint is not whether treatment is effective, but whether the benefits justify the costs in light of competing healthcare needs.

Formal cost-effectiveness analyses are not possible for the newer antihypertensive agents because of the lack of data on effectiveness. One has to make assumptions about the magnitude of effectiveness. **Grade A** If we assume that the newer agents are as effective as low-dose diuretics, the wholesale medication costs to prevent a fatal or non-fatal coronary event, a fatal or non-fatal stroke, a death from any cause, and any of these complications among patients with uncomplicated mild to moderate hypertension are as shown in Table 14·6. The costs are given for low-dose diuretics and a prototype of the newer unproven agents, nifedipine GITS. Recent cost data based on smallest tablet size available show that retail prices currently vary approximately 20-fold.[82]

In the context of healthcare systems in which priorities are being established (fixed budgets), the prime candidates for antihypertensive drug treatment are:

- elderly patients
- patients with moderate to severe hypertension
- patients with other cardiovascular risk factors, target organ manifestations.

These patient groups (among others) are at a higher risk of clinical hypertensive complications. Since clinical trials have demonstrated similar relative reductions in risk of stroke, acute MI, congestive heart failure, and mortality in

Table 14.6 Costs (US$) in wholesale medication prices to prevent a fatal or non-fatal CHD event, a fatal or non-fatal stroke, a death of any cause or any of these events in patients with uncomplicated mild to moderate hypertension assuming similar efficacy[a]

Event	Hydrochlorothiazide		Nifedipine GITS	
	Middle-aged	Elderly	Middle-aged	Elderly
CHD	21 374	3822	1 571 809	281 025
Stroke	7413	2453	545 141	180 372
Mortality	14 826	3931	1 090 281	289 078
Any of above	4730	1588	347 859	116 758

[a] The relative efficacy of calcium blockers compared to diuretics has not been reliably evaluated. These estimates assume similar impact of the two agents.
Adapted from Pearce *et al*[80]

low-risk compared to high-risk patients, the absolute benefit expressed as number needed to treat to prevent one event or as number of events prevented per 100 patients treated is substantially greater in the high-risk groups described above.

Unanswered questions

- In terms of clinical efficacy and safety, how do the newest agents compare with the proven treatments, low-dose diuretics, β blockers and ACE inhibitors? Are they superior, the same, or inferior? This question and the following one are the key clinical questions today. The answer to this question depends on large, long-term trials that include an actively treated control group. ALLHAT is an excellent example.[30]
- Compared to the older proven drugs, are the newer agents cost effective? Regrettably, formal analysis to date has been limited by a lack of efficacy data for the newer agents. If, in ongoing trials, they turn out to be superior, we have to decide whether the degree of superiority justifies the price differential and, if so, whether the newer drugs deserve to be considered as first-line agents. If the newer agents are the same or inferior, their use should be restricted to second- or third-line agents, and be limited to patients who do not respond to low-dose diuretics, β blockers, and ACE inhibitors, or who cannot tolerate them or to specific targeted populations.
- What is the best method for risk stratification? How can we implement feasible and acceptable risk stratification in the clinical setting, thus, allowing treatment decisions to be based on an individual's overall cardiovascular risk?
- What is the optimal level of treated BP? Should the treatment goals be even lower than 140 mmHg (systolic) or 90 mmHg (diastolic) for certain high-risk subpopulations?
- What are the optimal method(s) for long-term lifestyle modifications?
- How can we best reduce the incidence of hypertension?
- Will genetic information improve the efficacy and safety of drug treatment with specific antihypertensive agents?

Key points

- Hypertension should be classified by its type (diastolic/combined *v* isolated systolic hypertension), its severity (stage 1–3) and by coexisting target organ manifestations (complicated *v* uncomplicated). **Grade A**
- If choices must be made, high-risk hypertensive patients – that is, elderly patients, those with moderate to severe hypertension and those with target organ manifestation – ought to be the prime candidates for treatment owing to more favorable benefit–risk and cost-effectiveness ratios. **Grade A**

Key points Continued

- Lifestyle modification – primarily weight control and sodium reduction – is an integral part of management of hypertension. Good evidence on efficacy also exists for increased physical activity, moderation of alcohol intake, and ensuring adequate potassium intake. **Grade A**
- Low-dose diuretics should be the first-line drugs because of proven efficacy and safety; β blockers and ACE inhibitors are alternatives. In patients with type 2 diabetes, ACE inhibitors appear to be the drugs of choice. **Grade A** Emerging evidence suggests that angiotension II receptor blockers convey benefit similar to that of ACE inhibitors. The use of calcium antagonists, and α blockers ought to be restricted to patients who do not respond to low-dose diuretics, β blockers and ACE inhibitors or who cannot tolerate them.
- Major differences in direct drug cost between low-dose diuretics and the newer and heavily promoted agents ought to be a strong incentive to enhance use of the former. **Grade A**

References

1. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;**153**:154–83.
2. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;**157**:2413–46.
3. Izzo JL, Jr, Levy D, Black HR. Importance of systolic blood pressure in older Americans. *Hypertension* 2000;**35**: 1021–4.
4. Franklin SS, Gustin IVW, Wong ND *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997;**96**:308–15.
5. Burt VL, Whelton P, Roccella EJ *et al.* Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;**25**:305–13.
6. Ferrucci L, Furberg CD, Penninx BWJH *et al.* Treatment of isolated hypertension is most effective in older patients with high-risk profile. *Circulation* 2001;**104**:1923–6.
7. Grundy SM, Pasternak R, Greenland P, Smith S, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;**100**: 1481–92.
8. American Heart Association. *2001 Heart and stroke statistical update*. Dallas, Texas: American Heart Association, 2000.

9. Manolio TA, Cutler JA, Furberg CD *et al.* Trends in pharmacologic management of hypertension in the United States. *Arch Intern Med* 1995;**155**:829–37.
10. Stamler J, Stamler R, Neaton J. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med* 1993;**153**:598–615.
11. Cutler JA, Psaty BM, MacMahon S, Furberg CD. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, eds. New York: Raven Press, 1995.
12. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997;**65**: 643S–51S.
13. Whelton PK, He J, Cutler JA *et al.* Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997;**277**:1624–32.
14. Fagard RH. Prescription and results of physical activity. *J Cardiovasc Pharm* 1995;**25**(Suppl. 1):S20–S27.
15. Puddey IB, Beilin LJ, Vandongen R, Rouse IL, Rogers P. Evidence for a direct effect of alcohol consumption on blood pressure in normotensive men: a randomized controlled trial. *Hypertension* 1985;**7**:707–13.
16. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. *Arch Intern Med* 1997;**157**:657–67.
17. Appel LJ, Moore TJ, Obarzanek E *et al.*, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;**336**: 1117–24.
18. Sacks FM, Svetkey LP, Vollmer WM *et al.* Effects of blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001; **344**:3–10.
19. Stamler R, Stamler J, Gosch FC *et al.* Primary prevention of hypertension by nutritional-hygienic means: final report of a randomized, controlled trial. *JAMA* 1989;**262**:1801–7.
20. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**:3255–64.
21. Psaty BM, Smith NS, Siscovick DS *et al.* Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 1997; **277**:739–45.
22. Siscovick DS, Raghunathan TE, Psaty BM *et al.* Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;**330**:1852–7.
23. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. *JAMA* 1990;**263**: 1653–7.
24. Topol EJ, Califf RM, van de Werf F *et al.* Perspectives on large-scale cardiovascular clinical trials for the new millenium. *Circulation* 1997;**95**:1072–82.
25. Furberg CD, Psaty BM, Pahor M, Alderman MH. Clinical implications of recent findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and other studies of hypertension. *Ann Intern Med* 2001;**135**:1074–8.
26. Staessen JA, Fagard R, Thijs L *et al.*, for the Systolic Hypertension – Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with systolic hypertension. *Lancet* 1997;**350**:757–64.
27. Lewis EL, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60.
28. Brenner BM, Cooper ME, Zeeuw DD *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9.
29. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033–41.
30. Davis BR, Cutler JA, Gordon DJ *et al.* Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 1996; **9**:342–60.
31. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;**283**: 1967–75.
32. Pahor M, Psaty BM, Alderman MH *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000;**356**:1949–54.
33. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of angiotensin-converting-enzyme inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 2000;**356**:1955–64.
34. Pahor M, Psaty BM, Alderman MH *et al.* Blood-pressure-lowering treatment. *Lancet* 2001;**358**:152–3.
35. Pahor M, Psaty BM, Alderman MH *et al.* Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care* 2000;**23**:888–92.
36. Lindholm LH, Hansson L, Ekbom T *et al.*, for the STOP Hypertension-2 Study Group. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. *J Hypertens* 2000;**18**:1671–6.
37. Agodoa LY, Appel L, Bakris GL *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis. A randomized controlled trial. *JAMA* 2001;**285**:2719–28.
38. Lifton RP. Molecular genetics of human blood pressure variation. *Science* 1996;**272**:676–80.
39. O'Byrne S, Caulfield M. Genetics of hypertension: therapeutic implications. *Drugs* 1998;**56**:203–14.
40. Luft FC. Molecular genetics of human hypertension. *J Hypertens* 1998;**16**:1871–8.
41. Salomaa V, Matei C, Aleksic N *et al.* Soluble thrombomodulin as a predictor of incident coronary heart disease and symptomless

carotid artery atherosclerosis in the Atherosclerosis Risk in Communities (ARIC) Study: a case-cohort study. *Lancet* 1999;**353**:1729–34.
42. Jeaunemaitre X, Soubreir, Kotelevtsev Y *et al.* Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992; **71**:169–80.
43. Dishy V, Sofowora GG, Xie HG *et al.* The effect of common polymorphisms of the beta-2-adrenergic receptor on agonist-mediated vascular desensitization. *N Engl J Med* 2001;**345**: 1030–5.
44. Cusi D, Barlassina C, Azzani T *et al.* Polymorphism of alpha-adducin and salt sensitivity in patients with essential hypertension. *Lancet* 1997;**349**:1353–7.
45. Corvol P, Persu A, Gimenez-Roqueplo AP, Jeunemaitre X. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. *Hypertension* 1999;**33**:1324–31.
46. Inoue I, Nakajima T, Williams CS *et al.* A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription in vitro. *J Clin Invest* 1997;**99**:1786–97.
47. Kato N, Sugiyama T, Morita H *et al.* Angiotensinogen gene and essential hypertension in the Japanese: extensive association study and meta-analysis on six reported studies. *J Hypertens* 1999;**17**:757–63.
48. Jeunemaitre X, Inoue I, Williams C *et al.* Haplotypes of angiotensinogen in essential hypertension. *Am J Hum Genet* 1997;**60**:1448–60.
49. Fardella C, Zamorano P, Mosso L *et al. A-6G* variant of angiotensinogen gene and aldosterone levels in hypertensives. *Hypertension* 1999;**34**:779–81.
50. Hunt SC, Geleijnse JM, Wu LL, Witteman JCM, Williams RR, Grobee DE. Enhanced blood pressure response to mild sodium reduction in subjects with the 235T variance of the angiotensinogen gene. *Am J Hypertens* 1999;**12**:460–6.
51. Hunt SC, Cook NR, Oberman A *et al.* Angiotensinogen genotype, sodium retention, weight loss and prevention of hypertension: Trials of Hypertension Prevention, Phase II. *Hypertension* 1998;**32**:393–401.
52. Hingorani AD, Jia H, Stevens PA *et al.* Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. *J Hypertens* 1995;**13**:1602–9.
53. Insel PA. Adrenergic receptors – evolving concepts and clinical implications. *N Engl J Med* 1996;**334**:580–5.
54. Steinberg SF. The molecular basis for distinct beta-adrenergic receptor subtype action in cardiomyocytes. *Circ Res* 1999;**85**: 1101–11.
55. Xiao RP, Cheng H, Zhou YY, Kuschel M, Lakatta EG. Recent advances in cardiac beta2-adrenergic signal transduction. *Circ Res* 1999;**85**:1092–100.
56. Cross HR, Steenbergen C, Lefkowitz RJ, Koch WJ, Murphy E. Overexpression of the cardiac beta2-adrenergic receptor and express of a beta-adrenergic receptor kinase-1 (BARK1) inhibitor both increase myocadial contractility but have differential effects on susceptibility to ischemic injury. *Circ Res* 1999;**85**:1077–84.
57. Green SA, Turki J, Halls JP, Liggett SB. Implications of genetic variability of human B2-adrenergic receptor structure. *Pulm Pharmacol* 1995;**8**:1–10.
58. Kotanko P, Binder A, Tasker J *et al.* Essential hypertension in African Caribbeans associates with a variant of the beta-2-adrenoceptor. *Hypertension* 1997;**30**:773–76.
59. Lang CC, Stein CM, Brown M *et al.* Attenuation of isoproterenol-mediated vasodilatation in blacks. *N Engl J Med* 1995;**333**:155–60.
60. Svetkey LP, Timmons PZ, Emovon O *et al.* Association of hypertension with beta-2-and alpha-2c10-adrenergic receptor genotype. *Hypertension* 1996;**27**:1210–15.
61. Svetkey LP, Chen YT, McKeown SP, Preis L, Wilson AF. Preliminary evidence of linkage of salt sensitivity in black Americans at the beta-2-adrenergic receptor locus. *Hypertension* 1997;**29**:918–22.
62. Skrabal F, Kotanko P, Luft FC. Inverse regulation of alpha-2 and beta-2 adrenoceptors in salt-sensitive hypertension: an hypothesis. *Life Sci* 1989;**45**:2061–76.
63. Cusi D, Bianchi G. A primer on the genetics of hypertension. *Kidney Int* 1998;**54**:328–42.
64. Ferrari P. Pharmacogenomics: a new approach to individual therapy of hypertension? *Curr Opin Nephrol Hypertens* 1998;**7**:217–22.
65. Lin B, Nasir J, McDonald H *et al.* Genomic organization of the human adducin gene and its alternately spliced isoforms. *Genomics* 1995;**25**:93–9.
66. Manunta P, Barlassina C, Bianchi G. Adducin in essential hypertension. *FEBS Lett* 1998;**430**:41–4.
67. Casari G, Barlassina C, Cusi D *et al.* Association of the alpha-adducin locus with essential hypertension. *Hypertension* 1995;**25**:320–6.
68. Manunta P, Burnier M, D'Amico M *et al.* Adducin polymorphism affects renal proximal tubule reabsorption in hypertension. *Hypertension* 1999;**33**:694–7.
69. Tamaki S, Iwai N, Tsujita Y, Nakamura Y, Kinoshita M. Polymorphism of alpha-adducin in Japanese patients with essential hypertension. *Hypertens Res* 1998;**21**:29–32.
70. Ishikawa K, Katsuya T, Sato N *et al.* No association between alpha-adducin 460 polymorphism and essential hypertension in a Japanese population. *Am J Hypertens* 1998; **11**:502–6.
71. Kato N, Sugiyama T, Nabika T *et al.* Lack of association between the alpha-adducin locus and essential hypertension in the Japanese population. *Hypertension* 1998;**31**:730–3.
72. Kamitani A, Wong ZYH, Fraser R *et al.* Human alpha-adducin gene, blood pressure, and sodium metabolism. *Hypertension* 1998;**32**:138–43.
73. Castellano M, Barlassina C, Muiesan ML *et al.* Alpha-adducin gene polymorphism and cardiovascular phenotypes in a general population. *J Hypertens* 1997;**15**:1707–10.
74. Glorioso N, Manunta P, Filigheddu F *et al.* The role of alpha-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. *Hypertension* 1999;**34**:649–54.
75. Manunta P, Cusi D, Barlassina C *et al.* Alpha-adducin polymorphism and renal sodium handling in essential hypertensive patients. *Kidney Int* 1998;**53**:1471–8.
76. Ekbom T, Dahlof B, Hansson LH *et al.* The stroke preventive effect in elderly hypertensives cannot fully be explained by the reduction in office blood pressure – insights from the Swedish Trial in Old Patients with Hypertension (STOP- Hypertension). *Blood Press* 1992;**1**:168–72.

77.Psaty BM, Smith NL, Heckbert SR *et al.* Diuretic therapy, the alpha-adducin gene variant, and the risk for myocardial infarction or stroke in persons with treated hypertension. *JAMA* 2002;**287**:1680–9.
78.Housman D, Ledley FD. Why pharmacogenomics? Why now? *Nat Biotechnol* 1998;**16**:492– 3.
79.Moore TJ, Psaty BM, Furberg CD. Time to act on drug safety. *JAMA* 1998;**279**:1571–3.
80.Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**:1200–5.
81.Pearce KA, Furberg CD, Psaty BM, Kirk J. Cost-minimization and the number needed to treat in uncomplicated hypertension. *Am J Hypertens* 1998;**11**:618–29.
82.Drugs for hypertension. *Med Letter* 2001;**43**:17–22.

15 Glucose abnormalities and cardiovascular disease: "dysglycemia" as an emerging cardiovascular risk factor

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Large epidemiologic studies have consistently shown that patients with diabetes mellitus (DM) have a two-to fourfold increased risk of cardiovascular disease relative to non-diabetic patients.[1–3] Patients with both type 1 and type 2 diabetes are at increased risk. For patients with type 1 diabetes, who present soon after the disease develops, this increased risk is not apparent until 20 to 30 years after the diagnosis is made. For patients with type 2 diabetes, who constitute over 90% of all patients with diabetes, this increased risk is apparent right at the time of diagnosis and is independent of the duration of diagnosed diabetes.[4–6] For these patients, this observation may be due to a 5–10 year antecedent history of undiagnosed diabetes, preceded by an indeterminate period of elevated glucose levels that are below the diabetic cut off.[7]

Recent studies suggest that in patients with diabetes, the degree of glucose elevation is directly related to the risk of cardiovascular disease. For non-diabetic patients, a critical overview of the available epidemiologic studies suggests that this continuous relationship extends below the diabetic threshold and includes mildly elevated glucose levels that are generally considered to be normal. There may or may not be a lower glucose threshold to this risk. Thus, like total cholesterol or diastolic hypertension, glucose appears to be a continuous cardiovascular risk factor. Whether or not modification of this risk factor by interventions that lower glucose levels will also prevent cardiovascular disease remains an important and unanswered question.

Definition and epidemiology of diabetes and impaired glucose tolerance

The diagnosis of DM applies to a heterogeneous group of disorders that are all characterized by high levels of glucose in the blood.[8] This hyperglycemia is due either to absent or minimal insulin secretion from insulin-producing β cells of the pancreas, or to insufficient insulin secretion to overcome a variable degree of "insulin resistance" that is present in a large proportion of the general population. As insulin is the primary hormone that prevents hyperglycemia, both by inhibiting hepatic glucose production and facilitating glucose clearance by muscle, insufficient insulin quickly results in an elevated glucose level. The clinical classification of diabetes and the associated characteristics and suspected causes of each type are listed in Table 15.1.

For many years it was apparent that patients with diabetes had a high risk of developing eye disease, kidney disease, peripheral nerve disease, and cardiovascular disease (that is, coronary heart disease, cerebrovascular disease, and peripheral vascular disease). In 1979 and 1980 it was also recognized that these complications were occurring in patients with both diagnosed diabetes and asymptomatic, undiagnosed diabetes.[9] On the basis of epidemiologic studies of the risk of eye and kidney disease according to the 2 hour glucose level (during a 75 g oral glucose tolerance test) in populations at high risk for diabetes, specific glucose thresholds were defined for the diagnosis of diabetes (Table 15.2). These specific levels were those above which patients were at high risk of diabetic retinopathy and nephropathy; patients with levels below this threshold had a very low risk for these diabetic complications.[7,8,10] The fact that these thresholds were not chosen to reflect the risk of cardiovascular disease is apparent from many studies demonstrating a high risk of cardiovascular disease in patients with much lower glucose levels (see below).

At the time that these thresholds were established, it was clear that a large number of people had glucose levels that fell below the diabetic threshold but that were nevertheless still elevated. This led to the classification of Impaired Glucose Tolerance (IGT), which was defined on the basis of the glucose level (Table 15.2) and not on the basis of any particular clinical characteristics.[8,9] Although people with IGT were at low risk for diabetic retinopathy and nephropathy, they had a higher risk for developing diabetes than people with normal glucose tolerance (defined by

Table 15.1 Etiologic classification of diabetes mellitus[a]

Name	Characteristics	Etiology	Epidemiology
Type 1	Primarily due to pancreatic islet β-cell destruction; prone to ketoacidosis	Autoimmune or idiopathic; genetics play a role	~10% of patients with diabetes; 0·2% of the general population
Type 2	Results from insulin resistance with an insulin secretory defect	Genetics play a key role	~90% of patients with diabetes; up to 10% of the adult population
Gestational diabetes	Diabetes with onset or first recognition during pregnancy	Usually a result of hormonal changes in pregnancy; usually resolves after delivery	Complicates ~4% of pregnancies in USA
Other specific types	Related to a genetic, congenital, pancreatic, endocrine, or infectious acquired disease, or drug-induced	Examples include hemochromatosis, pancreatitis, hypercortisolemia	Other forms of diabetes account for ~2% of all patients with diabetes

[a] Adapted from reference 8. Note that patients with any form of diabetes may require treatment with insulin at some stage of their disease. Use of insulin does not in itself classify the patient.

Table 15.2 Diagnostic thresholds for diabetes, impaired glucose tolerance, and impaired fasting glucose[a]

Classification	Random plasma glucose	Fasting plasma glucose	2 hour post-load (75 g glucose) plasma glucose
Diabetes mellitus	≥11·1 mmol/l and classical signs and symptoms of hyperglycemia[b]	≥7·0 mmol /l[b]	≥11·1 mmol/l[b]
Impaired glucose tolerance	N/A	<7·0 mmol/l	≥7·8 and <11·1 mmol/l
Impaired fasting glucose	N/A	≥6·1 and <7·0 mmol/l	N/A

[a] The diagnostic criteria for diabetes recommended by the Expert Committee of the American Diabetes Association have been modified from those previously recommended by the National Diabetes Data Group (that is, fasting plasma glucose ≥7·8 mmol/l on at least two occasions, or plasma glucose ≥11·1 mmol/l at 2 hours and at one other point in the test in an oral glucose tolerance test) and the World Health Organization (that is, fasting plasma glucose ≥7·8 mmol/l, 2 hour plasma glucose ≥11·1 mmol/l in a 75 g oral glucose tolerance test, or both).
[b] Must be confirmed on a subsequent day by any one of the three methods.

a fasting and 2 hour plasma glucose <6·1 and 7·8 mmol/l respectively[8]).

Prevalence estimates

Data from both Canada[11,12] and the USA[13] suggest that approximately 3–5% of all adults have a known diagnosis of diabetes. A large survey completed in 1994 in the USA also showed that one third of all cases of diabetes were undiagnosed.[14] Thus up to 8% of all adults in North America have diabetes. This prevalence varies with age, approaching 15–20% of all people over the age of 64 in the USA.[13] It also varies with race and ethnicity, and is higher in aboriginal populations throughout the world, in East Indians, American Blacks and Hispanics, and in Chinese and Indian migrant communities.[15] The prevalence of impaired glucose tolerance varies in a similar pattern; in most populations it is approximately equal to the prevalence of diabetes (both diagnosed and undiagnosed);[15] thus in the USA the prevalence of IGT and diabetes exceeds 20% of people aged 40–74.[14]

Relationship between the glucose level and retinopathy, nephropathy, and peripheral neuropathy

In patients with diabetes, the risk of retinopathy, nephropathy, and neuropathy is highly correlated with various measures of glycemia including fasting plasma glucose, 2 hour postprandial plasma glucose (after a 75 g oral glucose load), and glycated hemoglobin level.[10,16,17] For example, the risk of retinal and renal disease is very low below a fasting and 2 hour plasma glucose of 7·0 mmol/l or 11·1 mmol/l respectively, and increases as these measures increase within the diabetic range.

Therefore, the plasma glucose level is a continuous risk factor for these complications in patients with diabetes. It is also a modifiable risk factor. The Diabetes Control and Complications Trial[16] clearly showed that for patients with type 1 diabetes, dramatic reductions of the risk of retinopathy (63% risk reduction [RR]), laser therapy (51% RR), microalbuminuria (39% RR), clinical proteinuria (54% RR), and neuropathy (60% RR) can be achieved by "tight" glucose control. "Tight" glucose control also led to reductions in the risk of any diabetes end point and microvascular end points in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) (for example, there was a 25% RR for the combined end point of renal failure or death, vitreous hemorrhage, or photocoagulation).[18] Thus achieving and maintaining normoglycemia in patients with diabetes is beneficial regardless of the etiology of the diabetes.

Relationship between the glucose level and the risk of cardiovascular disease

Risk of cardiovascular disease in patients with diabetes

As noted above, diabetes is an independent risk factor for cardiovascular disease.[2] People with diabetes have a two- to fourfold higher risk of coronary, cerebrovascular, and peripheral vascular disease than non-diabetic people.[1] The relative risk is greater for women than for men.[1,19] Diabetes is also a poor prognostic factor post myocardial infarction (MI); diabetic patients have a higher inhospital mortality, and post-discharge mortality than non-diabetic patients, and a higher risk of infarct-related complications.[20,21]

Just as the risk of eye, kidney, and nerve disease increases with the degree of glycemia, a growing number of studies of diabetic patients suggest that the risk of cardiovascular disease also rises with the degree of glycemia. For example, the Wisconsin Epidemiologic Study of Diabetic Retinopathy followed a population-based sample of 1210 patients with diabetes presenting before the age of 30 and 1780 patients with diabetes presenting at or after the age of 30.[22] In both groups of subjects 10 year mortality increased with the baseline glycated hemoglobin quartile. After controlling for other risk factors, a 1% increase in glycated hemoglobin was associated with a 10% (older onset subjects) to 18% (younger onset subjects) increase in the hazard of dying from ischemic heart disease.[22] In addition, at least two other smaller population-based epidemiologic studies noted a higher rate of CHD[23] or total mortality[24] in subjects with higher glucose levels than in those with better glucose control. In the UKPDS, every 1% increase in hemoglobin A (HbA_{1c}) in subjects with type 2 diabetes increased the risk of death by 14%, myocardial infarction by 14%, and stroke by 12%.[25]

Glucose levels and the risk for cardiovascular disease in non-diabetic patients

Many prospective studies have consistently showed that the relationship between glucose levels and the subsequent risk of cardiovascular disease extends well below the diabetic threshold. For example, after 10 years of follow up in the Whitehall study of 18 050 non-diabetic male civil servants, there was up to a twofold increase in coronary heart disease and stroke mortality in subjects whose 2 hour postload capillary glucose value was greater than 5·4 mmol/l compared to those with lower glucose levels. This increase was independent of age, smoking, blood pressure, cholesterol, and occupation.[26,27] The relationship of non-diabetic-range hyperglycemia and cardiovascular disease was also clearly noted after 14 years in the Rancho Bernardo study.[28] In this prospective study of 3458 non-diabetic men and women aged 40–70 with a fasting plasma glucose $<7{\cdot}8$ mmol/l, the age-adjusted ischemic heart disease mortality rates approximately doubled in men as the fasting glucose rose from 5 to 7 mmol/l, and tripled in women as the fasting glucose rose from 6 to 7·2 mmol/l.

Despite these, and other large cohort and cross-sectional studies[29–32] that showed a graded relationship between non-diabetic, and even non-impaired glucose tolerance levels of hyperglycemia and cardiovascular disease, some studies did not support such a relationship, especially with only moderate degrees of glucose elevation.[33–35] A systematic overview and meta-analysis of all published cohort studies of mainly non-diabetic populations was therefore done in 1998 to resolve these discrepancies, and to characterize the relationship between glucose levels and cardiovascular disease.[36] This analysis of studies describing more than one million person-years of follow up found that the risk of cardiovascular disease increased continuously with glucose levels above 4.2 mmol/l (75 mg/dl). This finding was supported by a recent prospective, population-based study of 4662 men aged 45–79, followed for up to 4 years, which found a continuous relationship between all-cause, cardiovascular, and ischemic heart disease mortality and HbA_{1c} throughout the entire population distribution, with the lowest rates in those with $HbA_{1c} < 5\%$.[37]

Hyperglycemia occurring at the time of an acute stress may also increase the risk of mortality in non-diabetic individuals. Two meta-analyses of prospective studies concluded that "stress" hyperglycemia increased the risk of mortality in non-diabetic patients with acute MI (RR 3·9)[38] and stroke (RR 3·1).[39]

Therefore, glucose appears to be a continuous cardiovascular risk factor, similar to cholesterol or blood pressure in its dose-response relationship.[40] We have suggested that the term *dysglycemia*[41] may be useful for describing this continuous relationship between glucose and cardiovascular disease. Thus people with dysglycemia alone are at risk for cardiovascular disease, people with dysglycemia and impaired glucose tolerance (IGT) are at higher risk for cardiovascular disease as well as DM, and people with DM are at even higher risk for cardiovascular disease as well as eye, kidney, and nerve disease (Figure 15.1).

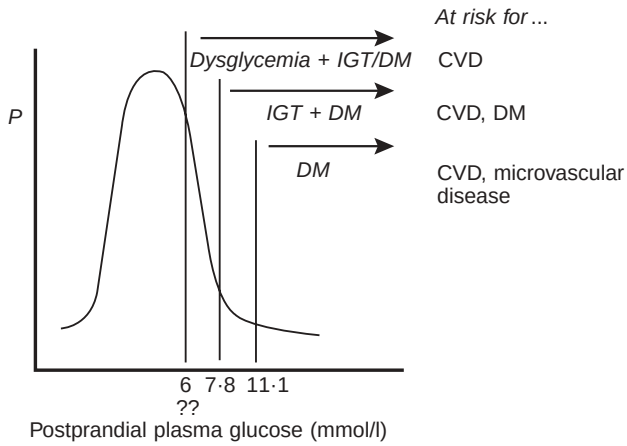

Figure 15.1 *Frequency distribution of glucose levels in the general population.* The significance of glucose as a risk factor for chronic disease depends on the level. Glucose levels above the diabetic threshold are associated with an increasing risk of cardiovascular and microvascular disease, levels above the IGT threshold are associated with an increasing risk of diabetes, and elevated levels above some as yet undefined "dysglycemic" threshold are associated with an increasing risk of cardiovascular disease. CVD, cardiovascular disease; DM, diabetes mellitus; IGT, impaired glucose tolerance.

Mechanisms relating hyperglycemia to cardiovascular disease

Possible explanations for a glucose–cardiovascular disease relationship include:

- direct toxic effects of glucose on cell function and structure
- indirect effects owing to insufficient insulin secretion to maintain normoglycemia
- a long history of insulin resistance and hyperinsulinemia prior to glucose elevations
- an association of dysglycemia with other recognized and unrecognized risk factors for cardiovascular disease, including dyslipidemia, hypertension, abdominal obesity, renal damage, and coagulation abnormalities.

Direct toxic effects of glucose

Glycation of a variety of proteins may directly promote cardiovascular disease.[42–45] Glycated albumin promotes albuminuria and endothelial cell dysfunction; glycated red cell membranes are less deformable; glycated LDL apoproteins are more susceptible than non-glycated LDL uptake by scavenger cells (which would increase foam cell formation), oxidation, and increase platelet aggregation; glycated HDL is less able to transport cholesterol, and glycated fibrin and platelet membranes adversely affect vascular homeostasis. AGE (advanced glycation end product) proteins also accumulate on vessel walls and in the vessel matrix, and may adversely affect endothelial cell function and promote atherosclerosis.[44–46]

Glucose metabolism also results in the formation of reactive oxygen species directly,[47] and indirectly through activation of the polyol pathway and AGE formation.[48] Any increased glucose metabolism owing to higher ambient glucose levels therefore presents an oxidative stress.[48] Finally, increased glucose metabolism to diacylglycerol may promote vascular cell growth, altered vascular permeability, smooth muscle contraction, and synthesis of various prostaglandins through protein kinase C activation.[49]

Insufficient insulin production

Glucose is the major stimulus for insulin secretion, which in turn prevents rises in glucose levels. Therefore an elevated glucose level implies a lack of sufficient insulin to maintain normoglycemia. Such a lack of *sufficient* insulin may occur in the presence of both low and high absolute levels of insulin, depending on the degree of insulin resistance.

A number of observations support the possibility that insufficient insulin secretion may be related to cardiovascular disease.

- Patients with both type 1 diabetes (with no endogenous insulin secretion) and type 2 diabetes (who are not able to make sufficient insulin to prevent hyperglycemia) are at high risk for cardiovascular disease. Intensified insulin therapy may decrease this risk, and certainly does not seem to worsen it (see below).
- Patients with hypertension and other cardiovascular risk factors are resistant to the antilipolytic effects of insulin;[50] any decrease in the secretory capacity of insulin would accentuate this and promote free fatty acid transport to the liver. The ensuing hypertriglyceridemia may promote atherosclerosis.[51]

- Patients with cardiovascular disease have increased levels of proinsulin and split products[52,53] – a possible biochemical marker of a failing β cell.[54]
- Many patients with atherosclerosis and/or cardiovascular disease are insulin resistant,[55] and require high insulin levels to prevent hyperglycemia. Such a prolonged demand may increase the risk of subsequent β cell failure and diabetes.[56,57]

Hyperinsulinemia

In non-diabetic people, fasting and 2 hour postload insulin levels rise with fasting and 2 hour glucose levels.[58,59] Thus even mildly hyperglycemic patients have higher levels of insulin than normoglycemic controls. Moreover, hyperinsulinemia is associated with coronary heart disease,[60,61] and many other cardiovascular risk factors including hypertension,[62] left ventricular hypertrophy,[63] elevated levels of triglyceride,[64–66] fibrinogen, von Willebrand factor-related antigen, factor VIII activity, plasminogen activator inhibitor-1 (PAI-1) antigen, and PAI-1 activity,[64] and depressed levels of HDL[65,66] and tPA.[64,67] Insulin may promote hypertension and atherosclerosis by stimulating renal sodium, water retention,[65] smooth muscle proliferation, and vascular growth factor production,[65] and sensitizing smooth muscle to the pressor effects of angiotensin II,[68] and increasing norepinephrine release through activation of the sympathetic nervous system.[69]

Despite these associations, the role of hyperinsulinemia in cardiovascular disease remains unclear.

- Hyperinsulinemia is not a consistent risk factor in large epidemiologic studies of non-diabetic patients with cardiovascular disease.[70]
- Patients with insulinomas who are insulin resistant, hyperinsulinemic, and *hypoglycemic* have normal lipid profiles and blood pressure, and no clinical evidence of cardiovascular disease.[71]
- Studies of intensified insulin therapy in patients with type 1 diabetes taking multiple daily doses of insulin suggest a reduced, and not an increased risk for the biochemical changes associated with atherosclerosis.[72]
- The fact that non-diabetic insulin levels are correlated with glucose levels suggests that the association of cardiovascular disease with insulin levels may reflect an association with glucose. The independent contribution of insulin and glucose, and any interaction of the two, to the risk of cardiovascular disease remains unclear despite multivariate analyses.

Association with other risk factors

Hyperglycemia commonly clusters with hypertension, insulin resistance, increased visceral fat, hypertriglyceridemia, and microalbuminuria.[66] It is also associated with obesity, poor socioeconomic status, and low birth weight. As such, the observed association between glucose and cardiovascular disease may be due to one of these other risk factors or to a common antecedent, and not because of any direct causal connection.[73,74]

Is glucose a modifiable cardiovascular disease risk factor?

To date, several randomized controlled trials of intensive versus conventional glucose lowering therapy have been completed in people with type 1 diabetes (in which different insulin regimens were used to lower glucose levels) and people with type 2 diabetes (in which different regimens of oral agents and/or insulin were used to lower glucose levels). None of these trials was designed or powered to determine whether or not glucose lowering reduced cardiovascular events. Nevertheless, several trials did report a non-significant trend in favor of a beneficial cardiovascular effect.

For people with type 1 diabetes, randomized trials of different levels of insulin-mediated glycemic control were designed to determine the impact of glycemic control on eye, kidney, and nerve disease (that is, microvascular disease). As such, they included mainly young people who had a low annual rate of cardiovascular events. Nevertheless, an exploratory analysis of results from the Diabetes Control and Complications trial (DCCT)[72] suggested that insulin-mediated glucose lowering may be cardioprotective. Moreover, in a recent meta-analysis that included this and other randomized trials, there was a significant 45% reduction in the total number of cardiovascular events and a non-significant 28% reduction in the risk of a first event.[75]

Clinical trials of different levels of glycemic control in people with type 2 diabetes also support the hypothesis that glucose lowering may reduce cardiovascular events (Tables 15.3 and 15.4). The strongest evidence was reported in a Swedish study of 620 diabetic MI patients randomized to conventional coronary care unit (CCU) therapy versus an insulin infusion followed by intensified insulin therapy for at least 3 months.[76] Total mortality in the treatment group was reduced by 31% (95% CI 4–51, $P = 0{\cdot}028$) at 1 year, and 28% at 3 years.[77] *This study needs to be replicated. Nevertheless, it supports the use of insulin in diabetic patients with myocardial infaction.* **Grade A1c** All of the other trials were done in ambulatory populations. The largest dataset relevant to whether or not glycemic control is cardioprotective was collected during the United Kingdom Prospective Diabetes Study (UKPDS), in which MI, stroke, and total mortality were recorded as secondary outcomes.[18] The main UKPDS study included 3867 people with newly diagnosed type 2 diabetes who were assigned to either conventional glycemic control or to intensive glycemic

Table 15.3 Glucose-lowering trials and cardiovascular events in type 2 diabetes trials

Study	Follow up (years)	HbA_{1c} difference (%)	Drugs	Event	Relative risk reduction (95% CI)	
					Reported (%)	Per 1% HbA_{1c} difference (%)
UKPDS[18]	10	0·9	Insulin/SU	MI	16 (0–29)	18
				Stroke	−11 (−51–9)	12
UKPDS[78]	10.7	0·6	Metformin	MI	39 (11–55)	65
				Stroke	41 (−18–71)	68
Kumamoto[79]	6	2·3	Insulin	CV event	46	20
VACSDM[80]	2·3	2·2	Insulin/SU	CV event	−40	−18
DIGAMI[77]	3	0·8	Insulin	Death	28 (8–45)	35

Abbreviations: CI, confidence interval; CV, cardiovascular; DIGAMI, Diabetes Mellitus, Insulin Glucose Infusion in Myocardial Infarction; MI, myocardial infarction; SU, sulfonylurea; VACSDM, Veterans Administration Cooperative Study in Diabetes Mellitus; UKBS, United Kingdom Prospective Diabetes Study

Table 15.4 Glucose lowering and cardiovascular events in the United Kingdom Prospective Diabetes Study

Participants	HbA_{1c} difference (%)	Initial drugs	Event	Relative risk reduction	
				Reported (%)	Per 1% HbA_{1c} difference
All ($n = 3867$)[18]	0·9	Insulin/SU	MI	16	17·7
			Stroke	−11	−12·2
			Death	8	8·9
Obese ($n = 1704$)[78]	0·6	Metformin	MI	39[a]	65
			Stroke	41	68·3
			Death	36[a]	60
		Insulin/SU	MI	21	35
			Stroke	−14	−23·3
			Death	8	13·3
		Metformin/insulin/SU	MI	22·5	37·5
			Stroke	0	0
			Death	14·3	23·8

[a] Statistically significant.
Abbreviations: CV, cardiovascular; MI, myocardial infarction; SU, sulfonylurea

therapy starting with either insulin or a sulfonylurea. Participants assigned to the intensive policy had a median HbA_{1c} over 10 years of 7·0%, and had a non-significant 16% relative risk reduction for MI compared to participants whose median HbA_{1c} was 7·9% ($P = 0·052$). A small obese subgroup of these participants was also assigned to either conventional therapy or intensive therapy with either metformin ($n = 342$), insulin or a sulfonylurea ($n = 951$). The group assigned to metformin experienced a 39% risk reduction in MI compared to the conventional group.[78]

These studies, as well as a 6 year Japanese study of intensified versus conventional insulin therapy in patients with type 2 diabetes,[79] and one small pilot study of 153 men with type 2 diabetes[80] are summarized in Tables 15.3 and 15.4. Taken together they suggest, but do not prove, that glycemic control may lower the risk of cardiovascular disease in patients with DM. No large intervention studies of the impact of reducing glucose levels in patients with elevated glucose levels that are below the diabetic cut off have been reported to date, and no studies have studied whether or not targeting postprandial glucose is more or less important than targeting fasting glucose levels.

Conclusion

There are a number of direct and indirect biologic pathways linking dysglycemia to cardiovascular disease. Similar to dyslipidemia, in which ongoing studies are continuing to

show the therapeutic value of reducing even minimally elevated lipid levels,[81] dysglycemia may be a continuous modifiable cardiovascular disease risk factor: therapies that reduce elevated glucose levels may reduce the risk of cardiovascular disease.

A number of ongoing studies will address this issue. These include the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, which is testing whether intensive control of blood glucose and associated risk factors can reduce cardiovascular disease in people with type 2 diabetes.[82] It also includes the VA Diabetes Trial, which will study the effect of intensive glucose therapy on cardiovascular outcomes in people with poorly controlled type 2 diabetes.[83] The BARI II (Bypass and Angioplasty Revascularization Investigation) trial is testing the effect of revascularization plus aggressive medical therapy versus aggressive medical therapy alone for patients with type 2 diabetes and stable coronary artery disease. Patients in BARI II are also randomized to an insulin-providing versus and insulin-sensitizing strategy of glucose control.[82] For patients with impaired glucose tolerance, strategies to prevent diabetes may also lead to a reduction in cardiovascular disease. The Diabetes Prevention Program showed that healthy lifestyle changes (which included 5–7% weight loss through a low fat diet and at least 150 minutes of exercise per week) prevented diabetes in obese adults with impaired glucose tolerance. The drug metformin was also effective to a lesser extent.[84] Cardiovascular disease is a secondary outcome in this trial. Other strategies to prevent diabetes are being tested in ongoing clinical trials, in which cardiovascular disease is a documented secondary outcome. These strategies include ramipril and rosiglitazone (being tested in the DREAM [Diabetes Reduction Assessment with ramipril and rosiglitazone Medications] study[85]); and acarbose (being tested in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus[86]). These studies are likely to shed new light on the relationship between glucose and cardiovascular disease and may provide ways of preventing cardiovascular disease in many individuals.

References

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. the Framingham study. *JAMA* 1979;**241**:2035–8.
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diab Care* 1993;**16**:434.
3. Goldbourt U, Yaari S, Medalie JH. Factors predictive of long-term coronary heart disease mortality among 10059 male Israeli civil servants and municipal employees. A 23 year mortality follow-up in the Israeli Ischemic Heart Disease Study. *Cardiology* 1993;**82**:100–21.
4. Jarrett RJ, Shipley MJ. Type 2 (non-insulin-dependent) diabetes mellitus and cardiovascular disease – putative association via common antecedents; further evidence from the Whitehall study. *Diabetologia* 1988;**31**:737–40.
5. Herman JB, Medalie JH, Goldbourt U. Differences in cardiovascular morbidity and mortality between previously known and newly diagnosed adult diabetics. *Diabetologia* 1977;**13**: 229–34.
6. Jarrett RJ. Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease – chicken, egg or neither? *Diabetologia* 1984;**26**:99–102.
7. Harris MI. Undiagnosed NIDDM: clinical and public health issues. *Diab Care* 1993;**16**:642–52.
8. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diab Care* 2001;**24**(Suppl. 1):S5–S20.
9. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;**28**:1039–57.
10. McCance DR, Hanson RL, Charles M *et al.* Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 1994;**308**:1323–8.
11. Young TK, Roos NP, Hammerstrand KM. Estimated burden of diabetes mellitus in Manitoba according to health insurance claims: a pilot study. *Can Med Assoc J* 1991;**144**:318–24.
12. Tan MH, MacLean DR. Epidemiology of diabetes mellitus in Canada. *Clin Invest Med* 1995;**18**:240–6.
13. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MS, Boyko EJ, Reiber GE, Bennett PH, eds. *Diabetes in America*. National Institutes of Health, NIH Publication No. 95-1468, 1995.
14. Harris MI, Flegal KM, Cowie CC *et al.* Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. *Diab Care* 1998;**21**:518–24.
15. King H, Rewers M, WHO Ad Hoc Diabetes Reporting Group. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diab Care* 1993;**16**: 157–77.
16. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**: 977–86.
17. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1995;**332**:1251–5.
18. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**: 837–53.
19. Barrett-Connor E, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991;**265**:627–31.
20. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol* 1993;**22**:1788–94.

21. Granger CB, Califf RM, Young S *et al.* Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. *J Am Coll Cardiol* 1993;**21**:920–5.
22. Moss SE, Klein R, Klein BEK, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 1994;**154**:2473–9.
23. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 1994;**43**:960–7.
24. Andersson DKG, Svardsudd K. Long-term glycemic control relates to mortality in type II diabetes. *Diab Care* 1995;**18**: 1534–43.
25. Stratton IM, Adler MI, Neil AW *et al.* on behalf of the UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405–12.
26. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycemia: the Whitehall study. *Br Med J Clin Research Ed* 1983;**287**:867–70.
27. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. *Lancet* 1980;**8183**:1373–6.
28. Scheidt-Nave C, Barrett-Connor E, Wingard DL, Cohn BA, Edelstein SL. Sex differences in fasting glycemia as a risk factor for ischemic heart disease death. *Am J Epidemiol* 1991; **133**:565–76.
29. Singer DE, Nathan DM, Anderson KM, Wilson PWF, Evans JC. Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham heart study. *Diabetes* 1992;**41**:202–8.
30. Wilson PWF, Cupples A, Kannel WB. Is hyperglycemia associated with cardiovascular disease? The Framingham study. *Am Heart J* 1991;**121**:586–90.
31. Donahue RP, Abbott RD, Reed DM, Yano K. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu heart program. *Diabetes* 1987; **36**:689–92.
32. Jackson CA, Yudkin JS, Forrest RD. A comparison of the relationships of the glucose tolerance test and the glycated hemoglobin assay with diabetic vascular disease in the community. The Islington Diabetes Survey. *Diab Res Clin Pract* 1992;**17**: 111–23.
33. Pyorala K, Savolainen E, Lehtovirta E, Punsar S, Siltanen P. Glucose tolerance and coronary heart disease: Helsinki Policemen Study. *J Chron Dis* 1979;**32**:729–45.
34. Ohlson LO, Svardsudd K, Welin L *et al.* Fasting blood glucose and risk of coronary heart disease, stroke, and all-cause mortality: a 17-year follow-up study of men born in 1913. *Diabetic Med* 1986;**3**:33–7.
35. Stamler R, Stamler J, Lindberg HA *et al.* Asymptomatic hyperglycemia and coronary heart disease in middle-aged men in two employed populations in Chicago. *J Chron Dis* 1979;**32**: 805–15.
36. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95 783 individuals followed for 12.4 years. *Diab Care* 1999; **22**: 233–40.
37. Khaw KT, Wareham N, Luben R *et al.* Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 2001;**322**:15–20.
38. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;**355**:773–8.
39. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients. A systematic overview. *Stroke* 2001; **32**:2426–32.
40. Neaton JD, Wentworth D, MRFIT Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316 099 white men. *Arch Int Med* 1992;**152**: 56–64.
41. Gerstein HC, Yusuf S. Dysglycaemia and risk of cardiovascular disease. *Lancet* 1996;**347**:949–50.
42. Lyons TJ. Glycation and oxidation: a role in the pathogenesis of atherosclerosis. *Am J Cardiol* 1993;**71**:26B–31B.
43. Lyons TJ. Lipoprotein glycation and its metabolic consequences. *Diabetes* 1992;**41**:67–73.
44. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. *Lab Invest* 1994;**70**:138–51.
45. Brownlee M. Glycation and diabetic complications. *Diabetes* 1994;**43**:836–41.
46. Hogan M, Cerami A, Bucala R. Advanced glycosylation endproducts block the antiproliferative effect of nitric oxide. *J Clin Invest* 1992;**90**:1110–5.
47. Baynes JW. Role of oxidative stress in development of complications of diabetes. *Diabetes* 1991;**40**:405–12.
48. Giugliano D, Ceriello A, Paolisso G. Diabetes mellitus, hypertension and cardiovascular disease: which role for oxidative stress? *Metabolism* 1995;**44**:363–8.
49. Kreisberg JI. Hyperglycemia and microangiopathy. Direct regulation by glucose of microvascular cells. *Lab Invest* 1992;**67**: 416–26.
50. Hennes MM, O'Shaughnessy IM, Kelly TM, LaBelle P, Egan BM, Kissebah AH. Insulin-resistant lipolysis in abdominally obese hypertensive individuals. Role of the renin-angiotensin system. *Hypertension* 1996;**28**:120–6.
51. Austin MA, Hokanson JE. Epidemiology of triglycerides, small dense low-density lipoprotein, and lipoprotein(a) as risk factors for coronary heart disease. [Review]. *Med Clin North Am* 1994;**78**:99–115.
52. Bavenholm P, Proudler A, Tornvall P *et al.* Insulin, intact and split proinsulin, and coronary artery disease in young men. *Circulation* 1995;**92**:1422–9.
53. Nordt TK, Schneider DJ, Sobel BE. Augmentation of the synthesis of plasminogen activator inhibitor type-1 by precursors of insulin. A potential risk factor for vascular disease. *Circulation* 1994;**89**:321–30.
54. Haffner SM, Mykkanen L, Valdez RA *et al.* Disproportionately increased proinsulin levels are associated with the insulin resistance syndrome. *J Clin Endocrinol Metab* 1994;**79**: 1806–10.

55.Stern MP. Do non-insulin dependent diabetes mellitus and cardiovascular disease share common antecedents? *Ann Int Med* 1996;**124**:110–16.
56.Bogardus C. Agonist: the case for insulin resistance as a necessary and sufficient cause of type II diabetes mellitus. *J Lab Clin Med* 1995;**125**:556–8.
57.Taylor SI, Accili A, Imai Y. Insulin resistance or insulin deficiency. Which is the primary cause of NIDDM? *Diabetes* 1994;**43**:735–40.
58.Welborn TA, Wearne K. Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diab Care* 1979;**2**:154–60.
59.Barrett-Connor E, Schrott HG, Greendale G *et al.* Factors associated with glucose and insulin levels in healthy postmenopausal women. *Diab Care* 1996;**19**:333–40.
60.Fontbonne A, Charles MA, Thibult N *et al.* Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15 year follow-up. *Diabetologia* 1991;**34**:356–61.
61.Pyorala K. Hyperinsulinemia as predictor of atherosclerotic vascular disease: epidemiologic evidence. *Diab Metab* 1991; **17**:87–92.
62.Denker PS, Pollock VE. Fasting serum insulin levels in essential hypertension. A meta-analysis. *Arch Intern Med* 1992; **152**:1649–51.
63.Sasson Z, Rasooly Y, Bhesania T, Rasooly I. Insulin resistance is an important determinant of left ventricular mass in the obese. *Circulation* 1993;**88**:1431–6.
64.Juhan-Vague I, Thompson SG, Jespersen J. Involvement of the hemostatic system in the insulin resistance syndrome. A study of 1500 patients with anfina pectoris. The ECAT Angina Pectoris Study Group. *Artersiosclerosis Thromb* 1993;**13**:1865–73.
65.Elliott TG, Viberti G. Relationship between insulin resistance and coronary heart disease in diabetes mellitus and the general population. *Bailliere's Clin Endocrinol Metab* 1993;**7**: 1079–103.
66.Laws A, Reaven GM. Insulin resistance and risk factors for coronary heart disease. *Bailliere's Clin Endocrinol Metab* 1993;**7**:1063–78.
67.Eliasson M, Asplund K, Evrin PE, Lindahl B, Lundblad D. Hyperinsulinemia predicts low tissue plasminogen activator activity in a healthy population: the northern Sweden MONICA study. *Metab Clin Exp* 1994;**43**:1579–86.
68.Gaboury CL, Simonson DC, Seely EW, Hollenberg NK, Williams GH. Relation of pressor responsiveness to angiotensin II and insulin resistance in hypertension. *J Clin Invest* 1994;**94**: 2295–300.
69.Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 1991; **87**:2246–52.
70.Wingard DL, Barrett-Connor E, Ferrara A. Is insulin really a heart disease risk factor? *Diab Care* 1995;**18**:1299–304.
71.Leonetti F, lozzo P, Giaccari A, Buongiorno A, Tamburrano G, Andreani D. Absence of clinically overt atherosclerotic vascular disease and adverse changes in cardiovascular risk factors in 70 patients with insulinoma. *J Endocrinol Invest* 1993;**16**: 875–80.
72.Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the diabetes control and complications trial. *Am J Cardiol* 1995;**75**:894–903.
73.Stern MP. Diabetes and cardiovascular disease: the "common soil" hypothesis. *Diabetes* 1995;**44**:369–74.
74.Jarrett RJ. The cardiovascular risk associated with impaired glucose tolerance. *Diabetic Med* 1996;**13**(3 Suppl. 2): S15–S19.
75.Lawson M, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis. *Diab Care* 1999;22(Suppl. 2):B35–B39.
76.Malmberg K, Ryden L, Efendic S *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57–65.
77.Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 1997;**314**:1512–15.
78.UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854–65.
79.Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diab Res Clin Pract* 1995;**28**:103–17.
80.Abraira C, Colwell JA, Nuttall F *et al.* Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. *Arch Intern Med* 1997;**157**:181–8.
81.Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.
82.http://apps.nhlbi.nih.gov/clinicaltrials/
83.Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diab Care* 2001;**24**:942–5.
84.Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl J Med* 2002;**346**:393–403.
85.Yusuf S, Gerstein H, Hoogwerf B *et al.* for HOPE Study Investigators. Ramipril and the development of diabetes. *JAMA* 2001;**286**:1882–5.
86.Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diab Care* 1998;**21**: 1720–5.

16 Physical activity and exercise in cardiovascular disease prevention and rehabilitation

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Introduction

The goal of this chapter is to review the scientific evidence regarding the benefits and safety of physical activity and exercise with respect to a series of health outcomes. Brief coverage within this review is aimed at the adult American population in order to acquaint the physician with the latest recommendations for primary prevention. The major focus, however, is on the coronary population with a minor focus on elderly people, women, and those who are physically disabled. Existing evidence-based reviews and consensus documents are used to support the evidence. The recommendations are deliberately kept very brief, but the necessary references are cited to assist the primary care physician, internist or cardiologist in obtaining such documents.

Evidence for benefits of regular exercise in adults

An accumulation of scientific evidence provides consistent substantiation to the assertion that light to moderate physical activity in healthy adults reduces the risk for all-cause mortality and cardiovascular disease (CVD) in men and women.[1–3] However, approximately 60% of US adults are not regularly physically active and 25% are inactive.[4] Physical inactivity is a serious, nationwide problem. It poses a major public health challenge with a national burden of unnecessary illnesses and premature death. Physical activity and exercise are pivotal in health promotion and disease prevention, especially now that the evidence for the hazards of being physically inactive are clear.[5] These statistics, representing low levels of exercise in the US population, call for urgent action by health professionals. Primary care physicians, internists, and cardiologists in particular need to provide evidence-based physical activity recommendations to their patients.

Additionally, the Surgeon General's Report[5] urges healthcare providers to counsel their patients to do the following.

Box 16.1 Benefits and adverse effects in adults[5]
Grade A/B

Physical activity improves health in the following ways:

- reduces risk of dying prematurely;
- reduces risk of dying from heart disease;
- reduces risk of developing diabetes;
- reduces risk of developing high blood pressure;
- helps reduce blood pressure in people who already have high blood pressure.

Other documented health benefits include:

- reduces the risk of developing colon cancer;
- reduces feelings of depression and anxiety;
- helps control weight;
- helps build healthy bones, muscles, and joints;
- helps older adults become stronger and better able to move about without falling;
- promotes psychological wellbeing.

Adverse effects of physical activity

Types of adverse effects:

- musculoskeletal injuries
- metabolic abnormalities
- hematologic and body organ abnormalities
- hazards
- infection, allergic, and inflammatory conditions
- precipitation of cardiac events.

1. Most skeletal muscular events are preventable by gradually working up to a desirable level, avoiding excessive amounts of activity.
2. Serious cardiovascular events can occur with physical exertion. Net effect is lower risk of mortality from cardiovascular disease.

Recommendations for adults

Recent recommendations for physical activity from the Centers for Disease Control (CDC) and National Institutes of Health (NIH) suggest that American adults should engage in physical activity at a level appropriate to their capacity, needs, and interests. Regular exercise is recommended, preferably daily, of at least 30–45 minutes of brisk walking (3 mph), bicycling or working around the house or yard.

Activities may include formal exercise such as walking or jogging or intermittent types of activity that include stair climbing, gardening or housework.[5]

A well-rounded exercise program should include both muscular strength training and joint flexibility exercises in order to improve one's ability to perform tasks and to reduce the potential for injury.[3,5] Upper extremity and resistance (strength) training can improve muscle function and evidence suggests that there may be cardiovascular benefit in older patients and those with underlying CVD. This area, however, is rather new and further evidence is needed before recommendations can be made to the public. While these recommendations are especially important for elderly people, persons who have been deconditioned due to recent inactivity or illness may benefit as well. People who are already physically active will benefit even more by increasing intensity or duration of their activity. These recommendations are intended primarily for the healthy sedentary population.[5]

Box 16.2 Essentials of physical activity counseling

- All subjects should be asked about their physical activity status. Questions should address leisure and recreational activities (that is, sports and exercise), as well as intermittent activity (walking, stair climbing, household and yard work).
- Assess whether activities meet the current activity recommendation guidelines (that is, activity should be at least of moderate intensity or equivalent intensity to a brisk walk at 3 mph on most or all days).
- Patients should be assisted in planning an appropriate program of physical activity.

Evidence for benefits from regular exercise in the coronary population

A recent comprehensive evidence-based review has been completed on the benefits of exercise in the coronary population.[6] For brevity, this consensus document will be used as a source of evidence along with other consensus documents. The major focus of this review was on coronary patients (including myocardial infarction (MI), coronary artery bypass surgery (CABG), and percutaneous transluminal coronary angioplasty (PTCA)), with a lesser focus on heart failure and cardiac transplantation literature and special populations such as elderly people, women, and those with physical disabilities (see Figure 16.1 for the criteria guiding this review).

Clinical and physiologic outcomes in the coronary population

A comprehensive review by the Agency for Health Care Policy and Research[6] provides consistent scientific evidence of the benefits of exercise training on a number of outcomes that include morbidity, mortality, exercise tolerance, and symptoms (see summary below). The evidence is less consistent for the benefit of reduced blood lipids, smoking cessation, psychological wellbeing, social adjustment and functioning, reduction in excess body weight, and a series of physiologic measures.

Morbidity and safety issues

Forty-two studies – 15 randomized controlled trials (RCTs), 14 non-randomized studies, and 13 observational studies – provide evidence that exercise training does not change the rate of non-fatal re-infarction. The safety of exercise rehabilitation is well established; rates of infarction and cardiovascular complications are very low.[6] No study documented increased morbidity when comparing patients in the intervention group to the control group, with 4578 patients included in the controlled trials (randomized and non-randomized reviewed).[6]

Reduced mortality

Thirty-one studies – 17 RCTs, eight non-randomized studies, and six observational studies – provide evidence that exercise training programs significantly reduce total and cardiovascular mortality in patients following myocardial infarction (MI).[6]

Exercise tolerance

A total of 114 studies – 46 RCTs, 25 non-randomized studies, and 43 observational studies – demonstrated that exercise training consistently improved objective measures of exercise tolerance, without significant cardiovascular complications or other adverse outcomes. Therefore, appropriately prescribed exercise training is recommended as an integral component of cardiac services, particularly for patients with decreased exercise tolerance. Maintenance of continued exercise training is required to sustain improved exercise tolerance.[6] A minimum duration and frequency of exercise has not been definitively determined and more study is needed in this area.

Strength training (resistance training)

Seven studies – four RCTs and three non-randomized studies – have shown that strength training improves skeletal muscle strength and endurance in clinically stable coronary patients.[6] In the majority of these studies, weight training was added as a strength training component to the exercise regimens of coronary patients, who had already participated in aerobic exercise training for 3 months or more. Documented benefits occurred with both low and high resistance training. Weight carrying tolerance (time) or

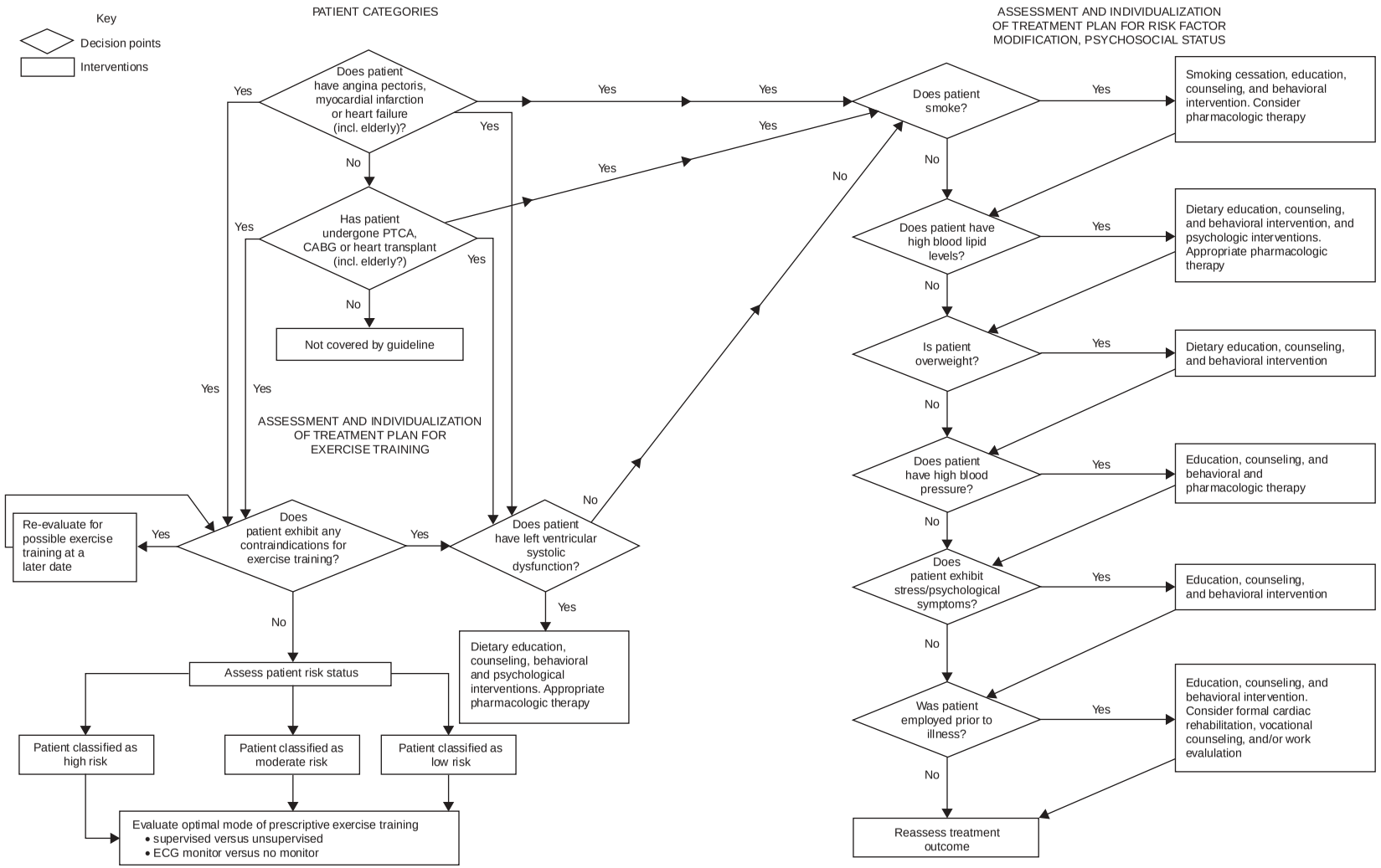

Figure 16.1 Decision tree for cardiac rehabilitation services (From Wenger *et al.*[6])

Source: Adapted from material provided by Health Economics Research, Inc., Waltham, MA.

Summary of evidence for cardiac rehabilitation outcomes:[a] effects of exercise training

Outcome	Evidence base				
	Total number of studies	Randomized studies	Non-randomized studies	Observational studies	Grading of evidence
Exercise tolerance	114	46	25	43	**Grade A**
Exercise tolerance (strength training)	7	4	3	0	**Grade B**
Exercise habits	15	10	2	3	**Grade B**
Symptoms	26	12	7	7	**Grade B**
Smoking	24	12	8	4	**Grade B**
Lipids	37	18	6	13	**Grade B**
Body weight	34	11	7	16	**Grade C**
Blood pressure	18	9	6	3	**Grade B**
Psychological wellbeing	20	9	8	3	**Grade B**
Social adjustment and functioning	6	2	2	2	**Grade B**
Return to work	28	10	9	9	**Grade A**
Morbidity	42 (+2 survey reports)	15	14	13	**Grade A**
Mortality	31 (+2 survey reports)	17	8	6	**Grade B**
Pathophysiologic measures: changes in atherosclerosis	9	5	1	3	**Grade A/B**
Changes in hemodynamic measurements	5	0	0	5	**Grade B**
Changes in myocardial perfusion/myocardial ischemia	11	6	2	3	**Grade B**
Changes in myocardial contractility, ventricular wall motion abnormalities, and/or ventricular ejection fraction	22	9	5	8	**Grade B**
Changes in cardiac arrhythmias	5	4	0	1	**Grade B**
Heart failure patients	12	5	3	4	**Grade A**
Cardiac transplantation patients	5	0	1	4	**Grade B**
Elderly patients	7	0	1	6	**Grade B**

[a] Number of studies from scientific literature by type of study design.

increases in skeletal muscle strength after completion of resistance training was reported by all studies. Five of the seven strength training studies demonstrated that submaximal and peak resistance exercise, using a variety of resistance training devices, resulted in significantly lower peak heart rate, pressure rate products, and oxygen consumption responses than did maximal treadmill exercise testing.[6] Moreover, angina, ventricular arrhythmias, and ischemic ST-segment depression occurred less frequently during resistance testing than during aerobic exercise testing to the point of fatigue.[7–9] These studies therefore provide indirect evidence of the effectiveness of resistance exercise training in selected patients with coronary disease.

A meta-analytic review by Buchner[10] concluded that high intensity exercise programs reported much more gain in strength than did low intensity training. High intensity

training was well tolerated by older adults, even those who were frail. Improvements in muscle strength can improve patients' performance of activities of daily living.[11] However, most of the studies involved small numbers of "low-risk" male patients, aged 70 years and younger, with good left ventricular function; also, training was of relatively short duration (less than or equal to 12 weeks). Hence the application of this intervention to women coronary patients is at this time based on an extrapolation.

Recommendation for strength training exercises

The strength training exercise sessions were typically started 4–6 weeks after MI or coronary artery bypass graft (CABG) and were carried out each week. The intensity ranged from 25% to 80% of the one repetition maximal; the most typical format consisted of three 30–60 minute strength training exercise sessions per week for 6–26 weeks.

Safety of strength training exercises in coronary patients

The lack of cardiovascular and orthopedic complications in the 3 year follow up of strength training was largely attributed to strict preliminary screening and careful supervision.[12] It is unclear if safety can be extrapolated to other populations of coronary or cardiac patients (for example, women, older men and women patients with low aerobic conditioning, patients at moderate to high cardiovascular risk) and this requires study. However, regimens designed to increase skeletal muscle strength can safely be included in exercise programs of clinically stable coronary patients when appropriate instruction and surveillance are provided.

Symptoms

Twenty-six studies – 12 RCTs, seven non-randomized studies, and seven observational studies – showed that exercise training decreases both angina pectoris in patients with coronary heart disease (CHD) and symptoms of heart failure in patients with left ventricular (LV) systolic dysfunction. Therefore, exercise training is recommended as an integral component of symptom management for these patients.[6]

Return to work

Twenty-eight studies – 10 RCTs, nine non-randomized studies, and nine observational studies – provide evidence that does not support an improved rate of return to work as a result of exercise training alone. A likely explanation may be that exercise training exerts less influence on return to work than many non-exercise variables including employer attitudes, prior employment status, economic incentives, and the like.[6]

Blood lipid levels

Thirty-seven studies – 18 RCTs, six non-randomized studies, and 13 observational studies – suggest that exercise training is not recommended as a sole intervention for lipid modification because of inconsistent effects on lipid and lipoprotein levels. Optimal lipid management requires specific dietary and medically indicated pharmacologic management in addition to exercise training.[6]

Smoking cessation

Twenty-four studies – 12 RCTs, eight non-randomized studies, and four observational studies – conclude that exercise training has little or no effect on smoking cessation. Smoking cessation is achieved primarily by targeted smoking cessation strategies.[6] The smoking cessation guidelines developed by an AHCPR evidence guideline panel provide detailed guidance on the optimum strategies for smoking cessation.[13]

Psychological wellbeing

Twenty studies – nine RCTs, eight non-randomized studies, and three observational studies – found that exercise training – with or without other cardiac rehabilitation services – generally results in decrease in anxiety and depression and improved physical function.[6] Exercise is therefore recommended to enhance psychological wellbeing, particularly when it is one component of a multifactorial rehabilitation program. Studies of exercise training in a supervised group setting as a sole intervention do not show consistent improvement in anxiety and depression. Studies of exercise training as a sole intervention are confounded by the consequences of group interactions, formation of social support networks, peer and professional support, and counseling and guidance, all of which may affect depression, anxiety, and self-confidence.

Blood pressure

Eighteen studies – nine RCTs, six non-randomized studies, and three observational studies – allow the conclusion that exercise training as a sole intervention had no demonstrable effect in lowering blood pressure levels. A multifactorial education, counseling, behavioral, and pharmacologic approach is the recommended strategy for the management of hypertension according to the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1993).[14]

Social adjustment and functioning

Six studies – two RCTs, two non-randomized studies, and two observational studies – provide evidence that exercise

training improves social adjustment and functioning and is therefore recommended in the care of cardiac patients. The social benefits from participation in exercise and cardiac rehabilitation are a favorable result. More research is needed to evaluate the impact of cardiac rehabilitation on social adjustment and functioning.[6]

Body weight

Thirty-four studies – 11 RCTs, seven non-randomized studies, and 16 observational studies – provide evidence that exercise training alone has inconsistent effects on controlling excess body weight and is not recommended as a sole intervention for this risk factor. Optimal management of overweight patients requires multifactorial intervention including intensive nutritional education, counseling and behavioral modification as an adjunct to exercise training. The panel[6] concluded that after a review of behavioral therapy literature involving obese patients, state of the art weight loss programs were shown to be successful. Results of a meta-analysis of 70 studies indicated that weight reduction through dieting can also help normalize plasma lipids and lipoprotein levels in overweight individuals.[15] It is essential to note that the comprehensive use of exercise, education, counseling, and behavioral interventions as a multifactorial approach has consistently yielded much stronger evidence, in terms of health outcomes, than exercise programs alone.

Pathophysiologic measures

Atherosclerosis

Nine studies – five RCTs, one non-randomized study, and three observational studies – provide convincing evidence that exercise training as a sole intervention does not result in regression, limitation or progression of angiographically documented coronary atherosclerosis. But regression or limitation in progression of atherosclerosis may occur when exercise training is combined with intense dietary intervention, with or without lipid lowering drugs.[6]

Hemodynamic measurement

Five observational studies provide evidence that exercise training has no effect on development of coronary collateral circulation and produces no consistent changes in cardiac hemodynamic measurements during cardiac catheterization. Exercise training in patients with heart failure and depressed ventricular ejection fraction produces favorable hemodynamic changes in the skeletal musculature. Therefore, cardiac rehabilitation exercise training is recommended to improve skeletal muscle function; however, it does not enhance cardiac hemodynamic function or promote development of collateral coronary circulation.[6]

Myocardial perfusion/myocardial ischemia

Eleven studies – six RCTs, two non-randomized studies, and three observational studies – provide evidence that exercise training decreases myocardial ischemia as measured by exercise ECG testing, ambulatory ECG recording, and radionuclide perfusion imaging. Exercise training is recommended to improve the measures of myocardial ischemia.[6]

Myocardial contractility, ventricular wall motion abnormalities, and/or ventricular ejection fraction

Twenty-two studies – nine RCTs, five non-randomized studies, and eight observational studies – document that exercise training has little effect on ventricular ejection fraction and regional wall motion abnormalities. The effect of exercise training on left ventricular function in patients after anterior wall Q wave MI with LV dysfunction is inconsistent. Exercise training is not recommended to improve measures of ventricular systolic function.[6]

Other clinical populations

Heart failure and cardiac transplantation

Heart failure patients

Twelve studies – five RCTs, three non-randomized, and four observational studies – provide evidence for the benefit of exercise training in the heart failure population. Exercise training in patients with heart failure and moderate to severe LV dysfunction improves functional capacity and symptoms, without changes in LV function. Exercise training is recommended in these patients to attain functional and symptomatic improvement but there is a potentially higher likelihood of adverse events. In summary, although these studies had small numbers and populations of young patients, predominantly male, and CAD was the major etiology of heart failure, exercise training in patients with heart failure and diminished ventricular systolic dysfunction resulted in documented improvement in functional capacity. The benefits are thought to be due predominantly to adaptation in peripheral circulation and skeletal musculature.[6]

Cardiac transplantation patients

Seven studies – one non-randomized study and six observational studies – suggest that exercise training following cardiac transplantation improves exercise tolerance and is recommended for this purpose. These trials demonstrated

that participation in an exercise program produced physiological training responses that included: increased peak oxygen uptake, resting heart rate, decreased peak exercise heart rate, increased resting blood pressure, and decreased peak systolic blood pressure compared with normal controls. No change was observed in peak systolic blood pressure or pressure rate product. However, these studies were uncontrolled and therefore these changes could be either the result of spontaneous improvement or a treatment effect. While there are few studies in this area and no RCTs, initial observations demonstrate efficacy of this intervention. In addition, it is believed that strength training before the transplantation may help enhance recovery after the operation. However, more research is needed in this area to identify the extent of spontaneous recovery versus the added benefit from exercise intervention.[6]

Changes in cardiac arrhythmias

Five studies – four RCTs and one observational study – provide evidence for the role of exercise in patients with arrhythmias. Two of the four RCTs showed that exercising patients, but not the controls, had a reduction in ventricular arrhythmias.[17,18] One demonstrated no statistically significant difference between exercise patients and controls when monitoring ventricular arrhythmia frequency or severity with 24 hour ambulatory ECG.[19] One RCT reported more malignant premature ventricular contractions (PVCs) on 24 hour ambulatory ECG monitoring during exercise training days in exercise patients compared to control patients.[20] The one observational study showed no difference in PVCs at baseline versus after exercise training. Exercise training has inconsistent effects on ventricular arrhythmias.

Special populations

Elderly patients

Elderly patients constitute a high percentage of those with MI, CABG, and PTCA and are also at high risk of disability following a coronary event. Seven studies – one non-randomized study and six observational studies – provide the evidence for this review.[6] Also, the Surgeon General's report[5] concludes that physical activity, including strength training (resistance) exercise, appears to be protective against falling and fractures among elderly people, probably by increasing muscle strength and balance. Elderly coronary patients have exercise trainability comparable to younger patients participating in similar exercise rehabilitation. Elderly female and male patients show comparable improvement, but referral to and participation in exercise rehabilitation is less frequent for elderly patients,[5] especially females. Physical activity need not be strenuous to achieve health benefits.[11] No complications or adverse outcomes of exercise training in elderly subjects were described in any study. Although few studies and no randomized controlled trials specifically addressed the efficacy and safety of exercise training and multifactorial rehabilitation in elderly people, the available studies provide important new information of beneficial functional improvement from exercise training for current clinical practice. Elderly patients of both genders should be strongly encouraged to participate in exercise-based cardiac rehabilitation and special effort should be taken to overcome the obstacles to entry and participation in cardiac rehabilitation services for elderly patients.

Women

The scientific evidence was either lacking altogether or small numbers of women were included in RCTs, making separate analyses for benefit impossible. This practice resulted in lack of information at best and confusion at worst. If indeed women do experience differing responses than men in exercise training then the effects are likely to be diluted for men and non-informative for women. The consensus of the expert panel[6] was that in most instances women can benefit from exercise training. However, women have unique considerations that require special attention. In studies of CAD patients women tend to be older, live alone more often (they are widowed or divorced), and have fewer economic and social resources. These circumstances require that women be given special attention to minimize the barriers to enrollment in exercise programs and to continuation with the program.

The Center for Women's Health at the National Institutes of Health has as its primary goal compensation for this scientific deficit regarding women's health. Until these new initiatives have been completed and reported in the literature, only scant scientific evidence exists to guide the physician regarding specific recommendations for women.[21] Many studies are now in progress or have already been completed since the formulation of the Center for Women's Health in 1980.

People with physical disabilities

With the passing of the Americans with Disabilities Act (1990), physicians in the USA are now required to address the special exercise training needs of patients with a variety of physical disabilities. People with physical disabilities are advised to see a physician before starting a program of physical activity that is new to them.[11] In particular, physically disabled patients with CVD should be referred to the cardiologist for physical therapy or exercise prescription. A recent comprehensive review is available for the reader who requires greater detail than is possible here.[22,23]

General safety issues

Patients with chronic health problems, such as heart disease or diabetes, should first obtain medical clearance before beginning a new exercise program. Skeletal muscle and other injury can be avoided by beginning exercises slowly and gradually building up to the desired amount of exercise (duration, frequency, and intensity) to give skeletal muscles and the cardiovascular system time to adapt. It is recommended that men over 40 and women over 50 consult a physician prior to beginning a vigorous physical activity program. This is to ensure that the patient does not have undiagnosed heart disease or other health problems that may place them at increased risk and that may require special modification in the exercise prescription or the monitoring of their response to the exercise.[5] The ACSM,[24] AHA,[25] and AACVPR[26] have issued guidelines for assessment of an exercise facility prior to beginning an exercise program. A medical evaluation, including an exercise test, is recommended for individuals with known coronary risk factors or a strong family history of CVD. Exercise testing is recommended for persons over 40 years of age, especially if they have two or more risk factors for CVD. But it is not recommended for apparently healthy individuals less than 40 years due to the relatively low predictive value of a positive test.[25]

Other organizational and clinical issues

Adherence to exercise

The evidence for exercise interventions for cardiovascular risk reduction has been provided in the preceding pages. However, the extent to which exercise is effective may depend in large part on adherence.[27] Burke and colleagues,[27] in their comprehensive review on adherence, further concluded that non-adherence, whether it occurs early or late in the treatment course, is one mediator of clinical outcomes. Hence, specific attention is given to adherence here. Barriers to exercise are twofold: the lack of physicians' exercise prescription and patient non-adherence. Since physicians have had limited clear evidence on reduction of "hard events" until recently, coronary patients have not consistently received physician recommendations regarding exercise or have received suggestions that were too general to be beneficial. Cardiac rehabilitation programs are available for referral by the physician in virtually every major city throughout the USA.

Much of the information on adherence is derived from multifactorial cardiac rehabilitation studies that were designed *not* to evaluate or enhance adherence but to determine the effects of rehabilitation services on other outcomes. These studies demonstrate a progressive decline with longer treatment duration, with 20–25% of patients dropping out within the first 3 months, 40–50% between 6 and 12 months, and little further change occurring during the next 3–4 years.[28] Although not confirmed, this trend for high early dropout rates may relate to several factors: cost of the exercise program, insurance reimbursement, convenience associated with program scheduling and facility location, return to work or family demands or simply poor motivation. Alternatively, patients may have mastered their skills and dropped out because of adequate self-care. There are differences in adherence with different modes of delivery of exercise services; what is known about adherence to cardiac rehabilitation is based largely on studies conducted when cardiac rehabilitation content, duration, delivery, and goals were considerably different from what they are at present.

Recommendations to improve adherence

Adherence may be enhanced if the physician understands the factors that affect exercise behavior and accordingly devises an exercise program that is tailored to the needs, preferences, and health status of a given person.[29] Patients, in general, wish to be partners in healthcare decisions that affect them or their families and improving communication may be a potent adherence enhancing strategy. Attention to the interpersonal relationships between patient and provider can result in greater cooperation and greater patient and provider satisfaction, as well as improved adherence.[30] For example, increased involvement by the patient in clinical decision making has been shown to improve patient satisfaction,[27] patient adherence, and patient outcomes.[28] In addition, limited evidence supports the importance of involving family members in promoting adherence to cardiac rehabilitation services.[35] If the objective of patient counseling is to permit the patient to make informed decisions about treatments, then a patient may decide to disregard some or all professional advice. This suggests that what is inappropriate behavior from the clinician's perspective (that is, not following recommendations) may in fact be rational decision making from the patient's perspective. Many patients make the best decisions they can without considering the importance or even the implications of adherence and carry out their own risk–benefit analysis for each treatment they are offered.[36]

Other factors that may influence patient adherence include: emotional support; understanding the patient's (and family's) values, viewpoints, and preferences; integration of the intervention into the patient's lifestyle, as well as patient characteristics and demographic characteristics; aspects of treatment regimens including complexity, duration, and convenience (such as cost, facility location, time of day); and disease factors such as severity of symptoms, among others. Patient perceptions, as well as personal and

social circumstances, determine patient decisions about following recommendations.

Adherence to exercise is in general lower than that for pharmacologic interventions; Burke *et al*[27] suggest that the increased behavioral requirements for maintaining an exercise program may account for this. In general, adherence to the exercise program was better in the home exercise programs than the community-based rehabilitation programs.[27] Most likely, the convenience factor can account for these improved rates of adherence.[27]

Strategies to improve adherence

Improving patient–provider communication with more information about CVD and its treatments would likely result in more informed decision making by the patient; providing culturally sensitive care may also improve adherence and perhaps patient outcomes and is likely to improve patient and clinician satisfaction.[37,38] Successful strategies for adherence include:

- Clear communication between patient (family) and provider.
- Emotional support and alleviation of fears and anxieties.
- Understandable and practical explanations about regimens that are compatible with the patient's values, preferences, and expressed needs, acknowledging the patient's social and cultural needs.
- Integration and coordination of patient care to provide continuity of care between transitions.[6]

Alternatives to monitored exercise training

Eleven studies – seven RCTs and four non-randomized studies – informed this question. The evidence suggests that alternative approaches to the delivery of cardiac rehabilitative services, other than traditional supervised group interventions, can be implemented effectively and safely for carefully selected clinically stable patients. Transtelephonic and other means of monitoring and surveillance of patients can extend cardiac rehabilitative services beyond the setting of supervised, structured, group-based rehabilitation (see Box 16.3 for guide to ECG monitoring). These alternative approaches have the potential to provide cardiac rehabilitation services to low- and moderate-risk patients, who comprise the majority of patients with stable coronary disease, most of whom do not currently participate in supervised, structured rehabilitation. (For risk stratification guidelines, see Box 16.4.)

Box 16.3 Criteria for electrocardiographic monitoring[39]

- Two or more MIs
- New York Heart Association class 3 or greater
- Exercise capacity less than 6 METs
- Ischemic horizontal or downsloping ST depression of 4 mm or more or angina during exercise
- Fall in systolic blood pressure with exercise
- A medical problem that the physician believes may be life-threatening
- Previous episode of primary cardiac arrest
- Ventricular tachycardia at a workload of less than 6 METs

Note: MET, metabolic equivalent units

Box 16.4 Minimal guidelines for risk stratification

Risk level	*Characteristics*
Low	No significant left ventricular dysfunction (that is, ejection fraction ≥50%)
	No resting- or exercise-induced myocardial ischemia manifested as angina and/or ST-segment displacement
	No resting- or exercise-induced complex arrhythmias
	Uncomplicated myocardial infarction, coronary artery bypass surgery, angioplasty or atherectomy
	Functional capacity ≥6 METs on graded exercise test 3 or more weeks after clinical event
Intermediate	Mild to moderately depressed left ventricular function (ejection fraction 31–49%)
	Functional capacity >5–6 METs on graded exercise test 3 or more weeks after clinical event
	Patients who consistently exceed the intensity of their exercise prescription
	Exercise-induced myocardial ischemia (1–2 mm ST-segment depression) or reversible ischemic defects (echocardiographic or nuclear radiography)
High	Severely depressed left ventricular function (ejection fraction ≤30%)
	Complex ventricular arrhythmias at rest or appearing or increasing with exercise
	Decrease in systolic blood pressure of >15 mmHg during exercise or failure to rise with increasing exercise workloads
	Survivor of sudden cardiac death
	Myocardial infarction complicated by congestive heart failure, cardiogenic shock, and/or complex ventricular arrhythmias
	Severe coronary artery disease and marked exercise-induced myocardial ischemia (>2 mm ST-segment depression)

MET, metabolic equivalent units

Source: From *Guidelines for rehabilitation programs* (p. 14) by the American Association of Cardiovascular and Pulmonary Rehabilitation, Champaign, IL: Human Kinetics Books. Copyright 1995 by American Association of Cardiovascular and Pulmonary Rehabilitation. Reprinted by permission.

Recent studies have explored new approaches to deliver cardiac rehabilitation services, with the goals of increasing availability and decreasing costs, while preserving efficacy and safety. Case management approaches to exercise training, smoking cessation, and diet drug management of hyperlipidemia that rely on telephone contact can be provided to appropriately selected patients with coronary disease.

Guidelines for participation in supervised and unsupervised exercise training programs are published by the American College of Sports Medicine.[24] In brief, supervision is recommended for patients with two or more major CAD risk factors and patients with known CAD with less than 8 MET functional capacity. Supervision is not suggested in apparently healthy individuals or persons who have equal or more than 8 MET functional capacity. The generalizability of these case management systems to other treatment settings – including university centers, public and community hospitals, and clinics – will depend largely on formulas for reimbursement for services and the extent of physician support for this approach, as well as the state regulations regarding medical and health practices. Within each of these settings, managed care programs seeking optimal methods for coronary risk factor reduction and exercise rehabilitation may favor case management systems that provide convenient, individualized health care at low cost.

Risk stratification

Appropriate risk stratification is recommended to minimize any adverse effects that patients might experience. This practice is also valuable in aiding the healthcare provider in deciding the type and intensity at which an exercise regimen will be started and the degree of monitoring and supervision. Furthermore, careful risk stratification also identifies the frequency of surveillance needed for a given patient, alerts the practitioner to respond promptly to changes in patient status, and promotes the safety of exercise training in any delivery system.[6]

Focus of further scientific study

Scientific studies should address the following areas:[6]

- Evaluate exercise training in special populations, including elderly people, women, members of different ethnic groups, and those of low educational and socioeconomic status.
- Evaluate exercise therapy following contemporary therapies, including thrombolysis and acute angioplasty.
- Evaluate effects of exercise training using return to work as a primary outcome.
- Identify factors that promote adherence.
- Identify the optimum degree of supervision and monitoring for high-risk groups, such as those with heart failure, elderly patients, and those with complex medical problems.
- Evaluate the safety and benefit of exercise training in patients with compensated heart failure and impaired ventricular systolic function.
- Evaluate a variety of different delivery models of exercise therapy.
- Evaluate the safety and specific added benefits of resistance training on cardiac patient outcomes.

Summary

Clear evidence exists for the recommendation of exercise for all individuals for primary preventive purposes. The evidence for patients with CAD is also well substantiated. Further research is indicated to verify how exercise recommendations are best delivered given the current rapid change in healthcare practice.

References

1. Blair SN, Kohl HW, Paffenbarger RS *et al.* Physical fitness and all cause mortality. A prospective study of healthy men and women. *JAMA* 1989;**262**:2395–401.
2. Blair SN, Kampert JB, Kohl HW *et al.* Influences of cardiovascular fitness and other precursors on cardiovascular disease and all cause mortality in men and women. *JAMA* 1996;**276**:205–10.
3. National Institutes of Health. Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. *JAMA* 1996;**276**:241–6.
4. Powell KE, Thompson PD, Caspers CJ, Kendricks JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Publ Health* 1987;**8**:253–87.
5. US Department of Health and Human Services. *Physical activity and health: a report of the Surgeon General.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Centers for Chronic Disease Prevention and Health Promotion, 1996.
6. Wenger MK, Froelicher ES, Smith LK *et al. Cardiac rehabilitation.* Clinical Practice Guideline No. 17. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, 1995.
7. Faigenbaum AD, Skrinar GS, Cesare WF, Kraemer WJ, Thomas HE. Physiologic and symptomatic responses of cardiac patients to resistance exercise. *Arch Phys Med Rehabil* 1990;**71**:395–8.
8. Featherstone JF, Holly RG, Amsterdam EA. Physiologic response to weight lifting in coronary artery disease. *Am J Cardiol* 1993;**71**:287–92.
9. Sheldahl M, Wilke NA, Tristani FE, Kalbfleisch JH. Responses of patients after myocardial infarction to carrying a graded series of weight loads. *Am J Cardiol* 1983;**52**:689–703.

10.Buchner DM. Understanding variability in studies of strength training in older adults: meta-analytic perspective. *Top Geriatric Rehabil* 1993;**8**:1–21.
11.Leon AS, ed. *Physical activity and cardiovascular health. A national consensus*. Champaign, IL: Human Kinetics, 1997.
12.Stewart AL, Greenfield S, Hays RD *et al.* Functional status and well-being of patients with chronic conditions: results from the medical outcomes study. *JAMA* 1989;**262**:907–13.
13.Fiori MC, Bailey WC, Cohen SJ *et al. Smoking cessation*. Clinical Practice Guideline No. 18. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1996.
14.National High Blood Pressure Education Program. *The fifth report of the Joint National Committee on detection, evaluation and treatment of high blood pressure*. NIH publication no. 93–1088. Bethesda, MD: National Institutes of Health, National Heart, Lung and Blood Institute, 1993.
15.Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoprotein: a meta-analysis. *Am J Clin Nutr* 1992;**56**:320–8.
16.Shephard JR. Responses of the cardiac transplant patient to exercise and training. *Exerc Sports Sci Rev* 1992;**20**:297–320.
17.DeBusk RF, Houston N, Haskell W, Fry F, Parker M. Exercise training soon after myocardial infarction. *Am J Cardiol* 1979; **44**:1223–9.
18.Hamalainen H, Luurila OJ, Kallio V, Astrila M, Hakkila J. Long-term reduction in sudden deaths after a multifactorial intervention programme in patients with myocardial infarction: 10-year results of a controlled follow-up study. *Eur Heart J* 1989;**10**:55–62.
19.Todd IC, Ballantyne D. Effects of exercise training on the total ischaemic burden: an assessment by 24 hour ambulatory electrocardiographic monitoring. *Br Heart J* 1992;**68**:560–6.
20.Hogberg E, Schuler G, Kunze B *et al.* Silent myocardial ischemia as a potential link between lack of premonitoring symptoms and increased risk of cardiac arrest during physical strain. *Am J Cardiol* 1990;**65**:853–9.
21.Healy B. Narrowing the gender gaps in biomedical research. *J Myocardial Ischemia* 1992;**4**:14–24.
22.Fletcher BJ, Dunbar SB, Felner JM *et al.* Exercise testing and training in physically disabled men with clinical evidence of coronary artery disease. *Am J Cardiol* 1994;**73**:170–4.
23.Heath GW, Fentem PH. Physical activity among persons with disabilities – a public health perspective (Review). *Exerc Sports Sci Rev* 1997;**25**: 195–234.
24.American College of Sports Medicine (ACSM). *ACSM's guidelines for exercise testing and prescription*. Baltimore, MD: Williams and Wilkins, 1995.
25.American Heart Association. *Strategic plan for promoting physical activity*. Dallas: American Heart Association, 1995.
26.American Association of Cardiovascular and Pulmonary Rehabilitation. *Guidelines for cardiac rehabilitation programs, 2nd edn*. Champaign, IL: Human Kinetics, 1995.
27.Burke LE, Dunbar-Jacob JM, Hill MN. Compliance with cardiovascular disease prevention strategies: a review of the research. *Ann Behav Med* 1997;**19**:239–63.
28.Oldridge NB. Compliance and dropout in cardiac rehabilitation. *J Cardiac Rehab* 1984;**4**:166–77.
29.Blumenthal JA, Gullette ED, Napolitano M, Szczepanski R. Behavioral and psychological issues of cardiac rehabilitation. In Leon AS, ed. *Physical activity and cardiovascular health. A national consensus*. Champaign, IL: Human Kinetics, 1997.
30.Ewart CK, Stewart KL, Gillilan RE, Kelemen MH. Self-efficacy mediates strength gains during circuit weight training in men with coronary artery disease. *Med Sci Sports Exerc* 1986; **18**:531–640.
31.Gould KL. Reversal of coronary atherosclerosis: clinical promise as a basis of noninvasive management of coronary artery disease. *Circulation* 1994;**90**:1558–71.
32.Andrew GM, Oldridge NB, Parker JO *et al.* Reasons for dropout from exercise programs in post-coronary patients. *Med Sci Sports Exerc* 1981;**13**:164–8.
33.Roter DL. Patient participation in patient–provider interaction: the effects of patient questions asking on the quality of interaction, satisfaction, and compliance. *Health Educ Monogr* 1977; **5**:281–315.
34.Kaplan FH, Greenfield S, Ware JE Jr. Assessing the effect of physician–patient interaction on the outcome of chronic disease. *Med Care* 1989;**27**:S110–27.
35.Sotile WM, Sotile MO, Ewen GS, Sotile LJ. Marriage and family factors relevant to effective cardiac rehabilitation: a review of risk factor literature. *Sports Med Training Rehabil* 1993;**4**: 115–28.
36.Donavan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making? *Soc Sci Med* 1992;**34**: 507–13.
37.Epstein LH, Cluss PA. A behavioral medicine perspective on adherence to long-term medical regimens. *J Consult Clin Psychol* 1982;**50**:950–71.
38.Morris LS, Schulz RM. Patient compliance – an overview. *J Clin Pharm Ther* 1992;**17**:283–95.
39.Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. *Circulation* 1996;**86**:340–4.

17 Psychosocial factors in the primary and secondary prevention of coronary heart disease: an updated systematic review of prospective cohort studies

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Key points

There is widespread belief among the general public, fostered by the media, that psychologic and social factors influence the risk of disease. Over the last three decades the scientific community has picked up this interest in psychosocial factors – that is, those factors (such as work characteristics, depression, and social support) that link psychologic phenomena to the social environment. Much of this research has focused on the effect of psychosocial factors on health, in particular coronary heart disease (CHD), in part because they may mediate the association between social class and health. Our previous systematic review of prospective studies published up until 1997 investigated the association between psychosocial factors and CHD etiology and prognosis.[1] Here, in updating this review to June 2001, we have used better search methods (and identified 71 new papers), improved summaries of the results and discussed the findings in an explicit framework of causality. Our objective for this review is to assess the relative strength of the epidemiologic evidence for causal links between psychosocial factors and CHD incidence among healthy populations, and prognosis among CHD patients.

Psychosocial factors as coronary risk factors

Over time there have been improvements in the measurement of psychosocial factors, moving away from the general idea of "stress" to concepts based on theoretical models that can be tested. These psychosocial factors may relate to personality factors, such as type A behavior and psychological disorders (for instance, depression and anxiety), and to factors more explicitly involving the social environment, including work characteristics and social support. The validity and reliability of the questionnaire-based instruments used to measure the psychosocial factors has been improved through the use of psychometric techniques; increasingly studies use identical measurement scales. However, such standardization is more apparent for some factors, such as depression, than others, such as work characteristics.

Two aspects of the association between CHD and psychosocial factors have been researched intensively. The first aspect is the effect of psychosocial factors on CHD incidence, or newly diagnosed CHD. The second aspect is the impact of psychosocial factors on survival among people with CHD. Despite the large literature that has accumulated, the question of whether psychosocial factors are causally related to risk of, and survival from, CHD remains open for debate. This systematic review aims to highlight key issues in ascribing causal status to one or more psychosocial factor.

Are psychosocial CHD associations causal?

An initial question to ask of an epidemiologic association between psychosocial factors and CHD is, Can it be explained by bias? Most attention has been paid to bias intrinsic to study design as reported within a publication. One example is self-report bias that may arise if study participants tend to report adversely on both the psychosocial exposures and symptoms of heart disease. Our review addresses this issue by emphasizing death and non-fatal myocardial infarction (MI) as outcomes rather than softer end points, such as angina, which may be more prone to reporting bias. However, for a systematic review, a potentially more important set of biases lies extrinsic to individual published reports in the stages between hypothesis specification and communication to the scientific community. Of all the existing psychosocial CHD data, an unknown amount remains unreported. Positive studies may be more likely to be published than negative studies; and, once published, positive studies may have greater impact than negative studies.

However, notwithstanding these potential biases, Bradford Hill[2] outlined a set of interrelated criteria for judging an association to be causal. This is used as a framework for discussing the results of the studies.

- *Consistency*. Finding the same association in different studies, in different populations and under different circumstances – that is, consistency – strengthens the evidence for causation. As an example, depression is related to risk for CHD in Finland,[3] the USA[4] and the Netherlands,[5] as well as in both men and women.[6] However, as our review shows, studies are not unanimous for any psychosocial factor. These inconsistencies in the data may arise from, *inter alia*, differences in study designs or ways of measuring the psychosocial factors.
- *Temporal association*. In order to address the requirement that exposure should precede the disease, we limited our review to prospective cohort studies. However, the presence of effects in shorter term follow up studies, which are not found in longer term follow up, raises the possibility that early manifestations of disease might have caused the psychosocial exposure.
- *Confounders, mediators, and biologic mechanisms*. Demonstration of biologic pathways linking psychosocial factors and CHD might strengthen the evidence for a causal association. There are three plausible biologic pathways by which psychosocial factors could be linked to the incidence of CHD. These have been reviewed elsewhere.[7,8] First, psychosocial factors may influence health-related behaviors, such as smoking, diet, alcohol consumption, and exercise, which in turn have pathophysiologic consequences.[9,10] If this is true, then studies that treat health behaviors as potential confounders may be underestimating the effect of psychosocial factors. Nearly all studies do this in our review; we are therefore summarizing the direct effect of psychosocial factors on CHD events, net of lifestyle variables, and we are not assessing potential mediation of the association between psychosocial factors and CHD by health behaviors. Psychosocial factors themselves may contribute to the pathway by which social position is inversely associated with CHD. However, a minority of studies in the review considered social position. Second, psychosocial factors, including social support or depression, may produce real or apparent hurdles to help-seeking behavior and access to quality medical care, so that the progression of subclinical to clinical disease is more rapid in people with poor psychosocial characteristics. This possibility awaits adequate investigation. Third, psychosocial factors may produce direct or chronic physiologic changes that increase the risk for CHD.[11] Adverse psychosocial characteristics can induce biologic arousal through neuroendocrine mechanisms affecting blood lipids, blood fibrinogen, and blood pressure, or neuroendocrine mechanisms that increase catecholamines and cortisol.
- *Strength*. Stronger associations are more likely to be causal. This means that larger relative risks (RR) give stronger evidence for causality than smaller relative risks, so an RR of 2·86 (95% CI 1·19–6·89)[12] is more indicative of an association between type A behavior and CHD than a RR of 1·43 (95% CI 0·63–3·26).[13]
- *Dose response*. The existence of a dose-response relationship between the exposure and disease also supports causation, and an example of this is the higher relative risks for the association between major depression, than minor depression, and mortality in people with CHD.[14,15]
- *Reversibility*. Ultimately the purpose of cardiologic practice is to intervene and reduce the risk associated with psychosocial factors.

Methods of systematic review

The methods of this review, which updates our review of publications to 1997,[1] are similar to the first review in terms of qualitative data analysis, but are improved as regards searching for papers and summarizing data. A methodologic quality filter was used to determine inclusion of papers in the systematic review, so that the strength of evidence could be compared across psychosocial factors. For inclusion, papers had to meet four quality criteria relating to design, size, psychosocial variable specification, and outcomes.

Study design

Since cross-sectional and retrospective case–control studies are subject to recall bias, we limited the review to prospective cohort studies. Nested case–control studies were not included in this review, because our search methods may not distinguish nested and retrospective case–control studies.

Study size

This review was limited to studies that included at least 500 participants (etiologic studies in healthy populations) or 100 participants (prognostic studies in populations of patients with CHD). The number of participants included was taken as the total number reported after exclusion of ineligible subjects. Therefore, we do not report the restriction of the cohort for subgroup analyses, which was occasionally substantial.

Psychosocial variable specification

Psychosocial factors were included if they were used in at least two eligible study populations. Unspecified "stress" was not considered a valid psychosocial factor, since it was too vague to be informative.[16,17] Papers had to specify precisely which measurement scale was used.

Outcomes

Valid outcomes were limited to fatal CHD, sudden cardiac death, incident non-fatal MI, incident angina, incident heart failure, and, for prognostic studies only, all-cause mortality.

Searching for eligible papers

The principal method of identifying new papers for updating the review was through the Science Citation Index (accessed on the web of science at www.webofscience.com). In June 2001 the Science Citation Index was used to identify papers that cited any of the 65 papers included in our original review. This search method yielded more eligible papers, and missed none, compared to searches on PubMed. Abstracts of over 280 new papers identified with potentially relevant titles were extracted and those papers obviously not eligible were eliminated. Next, two independent researchers assessed full text versions of over 100 potentially relevant papers for inclusion criteria, as well as all the papers included in the first review. Finally, the bibliographies of all retrieved articles were manually searched to identify further studies, which lead to the inclusion of four more studies. Multiple papers from the same study were included if they met the eligibility criteria. Our search produced 71 new papers in total for this review, of which 41 were published from 1998 to June 2001.

Summary of effect (Box 17.1)

We used relative risks, where available, to summarize the association between the psychosocial factor and the outcome, and this included incidence rate ratios, cumulative incidence ratios, hazard ratios, and odds ratios (occasionally these were calculated). Unless otherwise stated, we took relative risks comparing the top (highest risk) versus bottom (lowest risk) category of exposure and statistical significance was inferred at P value of $\leq 0{\cdot}05$, and, unlike the earlier review, we report confidence intervals (CI). Where several effect estimates were reported, we took the most highly adjusted estimate, but avoided effect estimates that adjusted for other psychosocial factors, as this may reflect overadjustment. Effect estimates were reported separately for men and women and for different outcomes, data allowing.

Box 17.1

The extent to which the paper supports the hypothesis that adverse psychosocial characteristics increase risk of, or mortality from, CHD, is summarized in a single symbol (−, 0, + or ++). The description of the summary symbols is as follows:

− Relative risk <0·75
"*finding counter to hypothesis*"
Example: One SD increase on the Bortner type A behavior scale was protective for risk of mortality post MI (RR = 0·70, 95% CI 0·51–0·96)[18]

0 Relative risk 0·75–1·50
"*lack of clear association*"
Example: Low social support was unrelated to risk of fatal CHD (RR = 1·42, 95% CI 0·72–2·81) or risk of non-fatal MI (RR = 1·00, 95% CI 0·58–1·71)[19]

+ Relative risk ≥1·50 and <2·00
"*moderate association in line with hypothesis*"
Example: Depression increased risk for fatal and non-fatal MI (RR = 1·70, 95% CI 1·23–2·34)[15]

++ Relative risk ≥2·00
"*strong association in line with hypothesis*"
Example: Job strain substantially increased the risk of fatal CHD and non-fatal CHD (RR = 4·95, P value = 0·03)[20]

Number of citations per paper

In order to explore the extent to which the scientific influence of each study might relate to the degree of study positivity, we recorded the number of times that each paper was cited as of September 2001 using the Science Citation Index. From this the mean number of citations across studies by the strength of the reported association was calculated separately for different years of publication.

Results

Type A behavior pattern (TABP) and hostility (Table 17.1)

TABP is a personality trait characterized by hard driving and competitive behavior, excessive job involvement, impatience, hostility, and vigorous speech stylistics and psychomotor activity. Early positive findings for the effect of TABP on CHD risk, reported by the Western Collaborative Group's Study and the Framingham Study,[21–23] led to the National Institutes of Health declaring type A to be an independent risk factor for CHD and to the implementation of intervention trials.[24] As more data accumulated, however, the early positive findings were not confirmed and interest grew in hostility as the toxic component of TABP.

In the current review 18 etiologic studies were included. As mentioned above, the three early studies provided moderate support for the hypothesis,[21–23] although two of these studies were published from the Western Collaborative Group Study,[21,22] and this association disappeared with extended follow up.[25] Subsequently, 12 studies that did not show a clear effect were published, including two very large studies (MRFIT[26] and the Scottish Heart Health Study[27]), one of which showed evidence for a protective effect of TABP on CHD risk in women.[27] Last, the three smallest studies strongly supported the hypothesis,[12,28,29] although for one the association was found only in women[29] and for the other only with respect to angina incidence.[28]

For the prognostic studies, 10 were not supportive of the underlying hypothesis that TABP worsened prognosis in patients with CHD. Three studies actually showed a

Table 17.1 Studies of type A behavior pattern and hostility and coronary heart disease

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Etiologic studies									
Jenkins, 1974, USA, Western Collaborative Group Study[21]	2750 (0)	39–59 –	Type A (JAS)	4 (mx)	NF MI and angina (120)	None	1·8 (ss)	N/A	+
Rosenman, 1976, USA, Western Collaborative Group Study[22]	3154 (0)	39–59	Type A (SI)	8·5 (mx)	Fatal CHD, NF MI, angina (257)	Age, smoking, blood pressure, cholesterol, schooling (age 39–49: corneal arcus, parental CHD, β/α lipoprotein ratio) (age 50–59: BMI, exercise)	Whole group aged 39–49: 1·87 Men aged 50–59: 2·16	N/A	+
Haynes, 1980, USA, Framingham Heart Study[23]	1674 (57)	45–77	Type A (Framingham)	8 (mx)	Fatal CHD, NF MI, coronary insufficiency and angina (170)	Age, smoking, blood pressure, cholesterol, (men: number of promotions in past 10 years, anger-out) (women: glucose intolerance, anger-discuss)	Standardized coefficient Men: CHD = 0·380 ($P < 0·01$) MI = 0·544 ($P < 0·01$) Women: CHD = 0·453 ($P < 0·01$) Angina = 0·668 ($P < 0·01$)	N/A	+
Shekelle, 1983, USA, Western Electric Study[80]	1877 (0)	40–55	Hostility (MMPI)	10 (mx) (incidence) 20 (mx) (mortality)	10 year fatal CHD and NF MI (139) 20 year coronary death (220)	Age, smoking, blood pressure, cholesterol, alcohol	10 year fatal CHD and NF MI: 1·47 ($P = 0·04$) 20 year CHD mortality: 1·27 (P = ns)	344	0
Cohen, 1985, USA, Honolulu Heart Program[81]	2187 (0)	57·8 (me)	Type A (JAS)	8 (mx)	Fatal CHD, NF MI and angina (190)	Smoking, blood pressure, cholesterol, BMI, alcohol, and other biologic factors	1·43 (ns) Associated with prevalence, not incidence or post-mortem findings	43	0
Shekelle, 1985, USA, MRFIT[26]	12 772 (0)	35–57	Type A (JAS) and SI on subset (3110)	7·1 (me)	Fatal CHD and NF MI (554 in total group, 129 in subgroup)	Age, smoking, blood pressure, cholesterol, alcohol, education	Regression coefficient for point increase in TAB score: −0·006 (−0·015–0·003) In subgroup: 0·87 (0·59–1·28)	208	0
Appels, 1987, the Netherlands, Kaunas-Rotterdam Intervention Study[82]	3171 (0)	45–59	Type A (JAS)	9·5 (me)	Fatal CHD and NF MI (269), angina and coronary graft surgery without MI (75)	None	Fatal CHD/NF MI: 0·90 (ns) Angina and coronary graft surgery without MI: 1·11 (ns)	17	0
Johnston, 1987, UK, British Regional Heart Study[83]	5936 (0)	40–59	Type A (Bortner)	6·2 (me)	Fatal CHD and NF MI (254)	Age and social class	0·89 (ns)	25	0

Koskenvuo, 1988, Finland, Finnish Twin Cohort[84]	3750 (0)	40–59	Hostility	3 (mx)	Fatal CHD and hospital discharge with CHD (29)	Age	0·77 (0·10–6·13)	91	0
Ragland, 1988, USA, Western Collaborative Group Study[25]	3154 (0)	39–59	Type A (SI)	22 (mx) (8·5 (mx) (for incidence)	Fatal CHD (214), incidence data: MI, SCD, angina pectoris (257)	Age, smoking, blood pressure, cholesterol	Mortality: 0·98 (0·85–1·12) Incidence: 1·38 (1·20–1·47)	69	0
Eaker, 1989, USA, Framingham Heart Study[28]	1289 (56)	45–64	Type A (Framingham)	20 (mx)	Fatal CHD and NF MI (188), and uncomplicated angina (125)	Age, smoking, blood pressure, cholesterol, BMI, diabetes, occupation, education	Men: Fatal CHD/NF MI: 1·0 (0·7–1·5) Angina: 2·2 (1·2–4·0) Women: Fatal CHD/NF MI: 1·0 (0·5–1·7) Angina: 2·6 (1·4–4·9)	16	Fatal CHD/ NF MI: 0 Angina: ++
Hollis, 1990, USA, MRFIT[85]	12 772 (0)	35–57	Type A (JAS)	6 (mx)	Fatal CHD and NF MI (635), angina (not stated)	Age, smoking, blood pressure, cholesterol, life events, study group	Cox regression coefficients: Fatal CHD/NF MI: −0·04 (ns) Fatal CHD: −0·31 (ns) Angina: no association	20	0
Barefoot, 1995, Denmark, Glostrup[29]	730 (44)	50	Hostility (Cook Medley)	27	NF MI (122)	Age, sex, smoking, blood pressure, triglycerides, sedentary work and sedentary leisure	Men: 1·26 (0·78–2·03) Women: 2·95 (1·37–6·35)	46	Men: 0 Women: ++
Bosma, 1995, Lithuania and the Netherlands, Kaunas-Rotterdam Intervention Study[86]	5817 (0)	45–60	Type A (JAS)	9·5 (me)	Fatal CHD and NF MI (394)	Age	No association	N/A	0
Everson, 1997, Finland, Kuopio Ischemic Heart Disease Risk Factor Study[13]	1599 (0)	42–60	Cynical hostility (Cook Medley)	9 (mx)	MI (60)	Age, smoking, blood pressure, cholesterol, BMI, alcohol, exercise, prevalent disease, social support, income	1·43 (0·63–3·26)	34	0
Tunstall-Pedoe, 1997, Scotland, Scottish Heart Health Study[27]	11 629 (51)	40–59	Type A (Bortner)	7·6 (me)	Fatal CHD (206) and NF MI and coronary artery surgery (581)	Age	HR for trend: Men: Fatal CHD: 0·98 (0·87–1·10) CHD: 0·98 (0·91–1·05) Women: Fatal CHD: 0·77 (0·60–0·99) CHD: 0·82 (0·73–0·93)	68	Men: 0 Women: −

Table 17.1 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Whiteman, 1997, UK, Edinburgh Artery Study[64]	1592 (49)	55–74	Hostility (Bedford-Foulds Personality Deviance Scales)	5 (mx)	Fatal CHD and NF MI (114), and angina (89)	Age, smoking, blood pressure, cholesterol, triglycerides, BMI, alcohol, degree of baseline vascular disease, social class	1 SD increase in score: Men: Total MI: 1·13 (0·89–1·41) Angina: 1·00 (0·74–1·35) Women: Total MI: 1·03 (0·70–1·39) Angina: 1·06 (0·74–1·53)	18	0
Kawachi, 1998, USA, Normative Aging Study[12]	1305 (0)	40–90	Type A (MMPI-2)	7·0 (me)	Fatal CHD (20), MI (30), angina (60)	Age, smoking, blood pressure, cholesterol, BMI, alcohol, family history of CHD	Fatal CHD/NF MI: 2·86 (1·19–6·89) Angina pectoris: 2·07 (1·00–4·27)	11	++
Prognostic studies									
Case, 1985, USA, Multicenter Post-Infarction Program[87]	516 (18) patients <14 days post-MI	<70	Type A (JAS)	2 (me)	Fatal CHD (38)	Age, sex, hard-driving, job involvement, speed and impatience, education, rales, ejection fraction, New York Association functional class, ventricular premature beats	Type A continuous: 0·8 (0·5–1·5)	176	0
Shekelle, 1985, USA, Aspirin Myocardial Infarction Study[88]	2314 (11) patients post-MI	30–69	Type A (JAS)	3 (mi)	Fatal CHD and NF MI (294)	Smoking, previous MI, angina, fasting glucose	Partial regression coefficient: Men: −0·004 (se = 0·007) Women: −0·0216 (se = 0·0240)	122	0
Brackett, 1988, USA, Recurrent Coronary Prevention Project[89]	1012 (8) patients 42 months (mean) post-MI	53 (me)	Type A (SI)	4·5 (mx)	SCD (23), non-SCD (32), NF MI (87)	None	Mean type A score (*P* value for difference compared to no recurrence): No recurrence: 30 SCD: 36 (*P* = 0·02) Non-SCD: 28 (ns) NF MI: 30 (ns)	50	SCD: + Non-SCD and NF MI: 0
Eaker, 1988, USA Framingham Heart Study[31]	204 (29) patients post-MI	45–77	Type A	5·5 (me)	All cause mortality (67), fatal CHD (32), recurrent MI (31)	Age, smoking, blood pressure, cholesterol	Recurrent MI: Men: 0·6 (0·3–1·5) Women: 0·8 (0·1–5·0) CHD death: Men: 0·5 (0·2–1·3) Women: 0·9 (0·2–4·3)	7	Women: 0 Men: −

							Total mortality: Men: 0·7 (0·3–1·3) Women: 0·8 (0·3–2·3)		
Koskenvuo, 1988, Finland, Finnish Twin Cohort[84]	104 (0) with hypertension and/or previous IHD	40–59	Hostility	3 (mx)	Fatal CHD and hospital discharge with CHD (26)	Age and dyspnea	21·10 (1·59–282)	91	++
Ragland, 1988, USA, Western Collaborative Group Study[30]	257 (0) with MI or angina	39–70	Type A (SI)	22 (mx)	Fatal CHD (91)	Age, smoking, blood pressure, cholesterol (long-term only: type of initial event)	Mortality within 24 hours of follow up: 0·96 (0·37–2·50) Mortality after 24 hours of follow up: 0·58 (0·35–0·96)	182	<24 hours: 0 ≥24 hours: –
Barefoot, 1989, USA, Duke Medical Center[90]	1467 (18) patients with angiographic disease	52 (me)	Type A (SI) and hostility (Cook-Medley)	9·2 (mx)	Fatal CVD and NF MI (315)	Stratified on clinical prognostic factors	Type A: no association ($\chi^2 = 1·76$) No association between hostility and mortality	29	0
Ahern, 1990, USA, Cardiac Arrhythmia Pilot Study[18]	353 patients 6–60 days post-MI	<75	Type A (Bortner)	1(mx)	All-cause mortality and NF MI	Baseline ejection fraction, β blocker or digitalis use, presence of transmurality in qualifying MI, runs of ventricular premature complexes	0·70 (0·51–0·96) for 1 sd increase in measure of TABP	177	–
Palmer, 1992, Australian, Sydney[70]	170 (25) patients 2–10 days after admission with MI	29–81	Type A (SI)	1 (mx)	Fatal CHD and NF MI (21)	Age	No significant multivariate association ($P = 0·85$)	4	0
Jenkinson, 1993, UK, Anglo-Scandinavian Study of Early Thrombolysis[91]	1376 (22) with 7 days post-MI	25–84	Type A	3 (me)	All-cause mortality (247)	Age, sex, hypertension previous MI, hospital complications, diabetes, car ownership	No significant multivariate association Survival at 3 years 83% in type A and 82% in non-type A group	17	0
Friedman, 1995, USA, Cardiac Arrhythmia Suppression Trial ancillary study[74]	369 (15) patients after acute MI with ventricular arrhythmias	63 (me)	Type A (JAS)	1 (mx)	All-cause mortality (20)	Diabetes, left ventricular ejection fraction, runs of ventricular premature beats, pet ownership, social support, anxiety, optimism	No significant multivariate association	17	0
Carinci, 1997, Italy, GISSI-2 Psychological Study[77]	2449 (12) patients post-MI	3·7% > 70	Type A (JAS)	0·6 (me)	All-cause mortality (63)	Age, sex, hypertension, exercise test ineligibility, ventricular failure, recovery phase LV dysfunction, previous MI, exercise test positivity, electrical instability, extroversion	No significant multivariate association Unadjusted analyses: Type A: 1·4 (0·8–2·4)	7	0

Table 17.1 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Irvine, 1999, Canada, Canadian Amiodarone MI Arrhythmia Trial[92]	671 (17) patients 6–45 days post-MI	32–89	Hostility (Cook-Medley)	2 (mx)	SCD (34)	Previous MI, previous CHF, depression, social network, social participation, dyspnea/fatigue	No significant multivariate association	9	0
Kaufmann, 1999, USA, Pennsylvania[93]	331 (34) patients 3–15 days post-MI	28–92	Hostility (Cook-Medley)	1 (mx)	All-cause mortality (33)	Left ejection fraction, history of chronic heart failure, previous stroke, diabetes	No significant multivariate association ($\chi^2 = 41{\cdot}41$) Unadjusted analyses: Prevalence of hostility at 6 months 93·3% in non-survivors and 90·5% in survivors	8	0
Welin, 2000, Sweden, Gothenburg[48]	275 (16) patients 3–6 days post first MI	30–65	Type A (JAS)	10 (mx)	All-cause mortality (67), fatal CHD (41), NF MI (55)	None	No association with fatal CHD ($P = 0{\cdot}99$), all cause mortality or NF MI	1	0

Abbreviations: 0, lack of clear association; +, moderate association (RR ≥1·50 and <2·00); ++, strong association (RR ≥2·00); BDI, Beck Depression Inventory; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CES-D, Centre for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CHF, congestive heart failure; DIS, Diagnostic Interview Schedule; GHQ, General Health Questionnaire; HDL, high density lipoprotein; IHD, ischemic heart disease; JAS, Jenkins Activity Survey; LDL, low density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; me, mean or median; MI, myocardial infarction; MMPI, Minnesota Multiphasic Personality Inventory; mx, maximum; N/A, not available; NF, non-fatal; ns, non-significant; PTCA, percutaneous transluminal coronary angioplasty; PVC, premature ventricular contractions; QOL, quality of life; RR, relative risk; SCD, sudden cardiac death; SCL, symptoms checklist; sd, standard deviation; SI, structured interview; ss, statistically significant; SMR, Standardized Mortality Ratio; TAB, type A behavior

significantly protective effect of TABP on prognosis after CHD, one of which was the Western Collaborative Group Study,[30] although for the Framingham Heart Study the effect was limited to men.[31] There was only one small study that showed a strong effect of hostility on prognosis, and one study that showed a moderate increase in sudden cardiac death among patients post-MI with TABP. Therefore there was little overall support for an association between TABP and CHD risk, nor was there evidence, as had been hypothesized, that hostility alone predicted CHD.

Depression (Table 17.2)

The association between depression and CHD has attracted a great deal of research interest in recent years, with 29 studies published from 1998 to 2001 meeting our inclusion criteria. Depression, and anxiety (Table 17.3), differ from the other psychosocial factors reported here, since they are defined psychiatric disorders and are amenable to drug intervention. Furthermore, depression is a frequent result of CHD and, moreover, depression and CHD may share a common antecedent (for example, social support or environmental stressors), so that elucidation of the cause and effect association becomes particularly difficult.

Table 17.2 shows the results from the 22 prospective studies that investigated the role of depression in the etiology of CHD. Eight of these studies found a lack of clear association, five studies were moderately and four studies were strongly supportive of the hypothesis. The remaining five studies all reported strong effects of depression on CHD incidence limited to men,[32,33] angina incidence[34,35] or major depression.[36] Interestingly, the three studies that separated angina from other outcomes reported stronger effects of depression on angina,[34–36] suggesting the existence of reporting bias as angina is the CHD event least amenable to objective corroboration. Both studies that focused on the degree of depression found that risk of CHD was higher among people seriously depressed than among those who were only moderately depressed,[4,5] suggesting a dose-response association.

There were 34 studies that investigated the effect of depression on prognosis for patients with CHD. Of these studies 16 found a lack of clear association, seven were moderately supportive, and 11 were strongly supportive studies. There was, therefore, no evidence that the association between depression and events differed between prognostic and etiologic studies, although where associations were observed they were generally of greater magnitude for the prognostic studies. It is of note that for several prognostic studies depression is predictive of prognosis in the unadjusted analyses, but adjusting for traditional coronary risk factors and markers of disease severity explained much of the relationship, hence the association between depression and prognosis might be mediated by lifestyle factors, disease severity, and pharmacologic interventions. Five studies looked separately at the effect of moderate and severe depression on prognosis; one found a lack of clear association,[37] three showed a higher risk among patients with major depression,[5,14,15] and the last found a lower risk of fatal CHD in patients with major depression compared to those with depressive symptoms.[38]

Anxiety and distress (Table 17.3)

Of the eight etiologic studies identified, four studies showed a lack of clear effect. Two papers, both published from the Israeli civil servant cohort, reported strong or moderate association between anxiety and the incidence of angina.[39,40] The remaining two studies gave evidence for an association between phobic anxiety and fatal CHD, but did not show a clear effect on non-fatal CHD or of free-floating anxiety.[41,42] Furthermore, the studies with longer follow up were less likely to find a positive association than the studies with less extended follow up. This is exemplified by the Northwick Park Heart Study where the association between anxiety and fatal CHD found after 10 years of follow up,[41] disappeared when the follow up was extended by another decade.[43] Hence, anxiety may be a result of preclinical CHD rather than a cause of fatal CHD.

Of the 18 prognostic studies, half found a lack of clear association and one reported results significantly contrary to the hypothesis. Four studies showed a strong association between anxiety and prognosis and the remaining four studies showed moderate support for an association, either in the entire group or in relation to a specific subgroup, exposure or outcome.

Psychosocial work characteristics (Table 17.4)

The belief that stress at work has a deleterious effect on health is common among the general public. To combat the lack of precision in defining job stress, various constructs have been made to explain how the interaction between a worker and the job environment causes stress, and how this affects health. The Karasek and Theorell "job strain" model[44,45] proposes that high demands at work (the need to work quickly and hard), in combination with low job control, produces stress. Thus, workers cannot moderate the pressure caused by high job demands by organizing their time, making new decisions or learning new skills, and this stress has deleterious effects on health. Another model for psychosocial work characteristics is Siegrist's effort-reward imbalance model.[46] Here the mismatch between high workload and low payback (in terms of money, esteem, promotion prospects, and job security) produces a condition of emotional distress, which increases risk for CHD.

Despite these models, work characteristics have been measured with a lesser degree of standardization than, for

Table 17.2 Studies of depression and coronary heart disease

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Etiologic studies									
Ostfeld, 1964, USA, Western Electric Company[94]	1885 (0)	40–55	Depression (MMPI)	4·5 (mx)	MI (38), angina (50)	None	Mean (sd) depression score: MI group: 57·4 (9·5) Angina group: 60·9 (11·4) Non-coronary group: 58·0 (10·7)	N/A	0
Hallstrom, 1986, Sweden, Gothenburg[34]	795 (100)	38, 46, 50 and 54	Depression (DIS and Hamilton Rating Scale)	12 (mx)	MI (11), angina pectoris (25), ischaemic changes on ECG (39)	Age, social class, marital status, conventional risk factors	Angina significantly related, but other outcomes not Age adjusted only: Angina: 5·4 (ss)	27	Angina: ++ Other outcomes: 0
Haines, 1987, UK, Northwick Park Heart Study[41]	1457 (0)	40–64	Depression (Crown-Crisp experiential index)	10 (me)	Fatal CHD (56) and NF MI (57)	None	Mean depression score (lower quartile, upper quartile): Survivors: 2·2 (0·8, 4·1) Fatal CHD: 3·3 (0·9, 5·6) NF MI: 2·2 (0·8, 5·6)	88	0
Anda, 1993, USA, National Health Examination Follow-up Study[61]	2832 (52)	45–77	Depressed affect (General Well-Being Schedule)	12·4 (me)	Fatal CHD (189) and NF CHD (205)	Age, sex, smoking, blood pressure, cholesterol, BMI, alcohol, exercise, race, education, marital status	Fatal CHD: 1·5 (1·0–2·3) NF CHD: 1·6 (1·1–2·4)	145	+
Aromaa, 1994, Finland, Mini-Finland Health Survey[3]	5355 (55)	40–64	Depression (GHQ-36 and PSE)	6·6 (me)	Fatal CHD (91)	Age	1·95 (ss) In those with no pre-existing CVD: 3·36 (ss)	5	++
Vogt, 1994, USA, Kaiser Permanente[95]	2573 (54)	≥18	Depression (Langner Mental Health Index)	15 (mx)	Fatal and NF CHD (not stated)	Age, sex, smoking, self-reported health, social class, duration of health plan membership	0·94 (0·70–1·28)	40	0
Barefoot, 1996, Denmark, Glostrup[96]	730 (44)	50 or 60	Depression (Obvious Depression Scale of MMPI)	27 (mx)	Fatal and NF MI (122)	Age, sex, smoking, blood pressure, triglycerides, exercise	1·70 (1·23–2·34)	146	+
Pratt, 1996, USA, Baltimore cohort of the Epidemiologic Catchment Area Study[4]	1551 (62)	18–64	Major depressive episode (DIS), dysphoria (>2 weeks of sadness)	13 (mx)	NF MI (64)	Age, sex, hypertension, marital status, phobia, panic disorder, alcohol abuse/dependence, psychotropic medicine use, mutually	Compared to people with neither disorder: Major depression: 4·14 (1·48–11·62) Dysphoria: 2·06 (1·15–3·72)	103	++

Wassertheil-Smoller, 1996, USA, Systolic Hypertension in the Elderly Program[97]	4367 (53)	≥60	Depression (CES-D)	4·5 (me)	Fatal and NF (126)	Age, sex, smoking, randomization group, history of MI, stroke and diabetes, ADL, race, education	No significant multivariate association Univariate RR = 0·9	68	0
Mendes de Leon, 1998, USA, Established Population for the Epidemiologic Study of the Elderly[98]	2391 (66)	65–99	Depression (CES-D)	9 (mx)	Fatal CHD and NF MI (391)	Age, smoking, blood pressure, diabetes, exertional angina, physical functioning, education	Trend across five categories: Fatal CHD: Men: 0·98 (0·95–1·01) Women: 1·02 (0·99–1·05) Total CHD events: Men: 0·98 (0·95–1·01) Women: 1·01 (0·99–1·03)	12	0
Ford, 1998, USA, The Precursor Study[99]	1190 (0)	26 (me)	Depression (self-report and treatment)	37 (me)	All CHD (MI, sudden death, angina, chronic IHD, CAB surgery, PTCA) (163), MI (MI and sudden death) (103)	Age, smoking, cholesterol, exercise, hypertension, premature parental MI, diabetes	MI: 2·12 (1·11–4·06) CHD: 2·12 (1·24–3·63)	61	++
Penninx, 1998, USA, Established Population for the Epidemiologic Study of the Elderly[32]	3701 (66)	70–103	Depression (CES-D)	4·0 (me)	CHD events (537)	Age, sex, smoking, blood pressure, BMI, alcohol, history of stroke, diabetes or cancer, physical disability, region	Compared to never depressed: Men: Newly depressed: 2·03 (1·28–3·24) Chronically depressed: 1·19 (0·58–2·46) Women: Newly depressed: 1·22 (0·83–1·80) Chronically depressed: 1·12 (0·76–1·65)	22	Men newly depressed: ++ Women newly depressed: 0 Chronically depressed: 0
Sesso, 1998, USA, Normative Aging Study[35]	1305 (0)	21–80	Depression (MMPI-2D, MMPI-2DEP, SCL-90)	7·0 (me)	Fatal CHD and NF MI (50), and angina (60)	Age, smoking, blood pressure, cholesterol, BMI, alcohol, family history	Fatal CHD and NF MI: MMPI-2 D: 1·69 (0·70–4·05) MMPI-2 DEP: 1·88 (0·77–4·59) SCL-90: 0·67 (0·26–1·76) Angina: MMPI-2 D: 1·34 (0·63–2·82) MMPI-2 DEP: 2·30 (1·00–5·28) SCL-90: 3·33 (1·48–7·49)	13	Fatal CHD/ NF MI: + Angina: ++
Chen, 1999, USA, Established Population for the Epidemiologic Study of the Elderly[100]	1749 (59)	65–99	Depression (CES-D)	7·9 (me)	Heart failure (173)	Age, sex, blood pressure, BMI, diabetes, MI during follow up	No significant multivariate association Unadjusted analysis: 1·10 (0·72–1·69)	6	0

Table 17.2 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Cole, 1999, USA, College Alumni Health Study[65]	5053 (0)	65 (me)	Physician-diagnosed depression	12 (mx)	Fatal CHD (222)	Age, smoking, BMI, exercise, alcohol, hypertension, diabetes, hours of sleep, insomnia, use of sleeping pills or tranquilizers, mutually	1·20 (0·53–2·71)	1	0
Ariyo, 2000, USA, Cardiovascular Heart Study[36]	4493 (61)	65–98	Depression (CES-D)	6 (me)	CHD (fatal CHD, MI, angioplasty, CABG, angina) (606), MI (270), angina without MI (298)	Age, sex, smoking, cholesterol, alcohol, exercise, triglycerides, hypertension, diabetes, angina, CHF, race, education, marital status	5 unit increase in baseline depression score: MI: 1·12 (0·97–1·29) CHD: 1·11 (1·01–1·22) Angina: 1·13 (0·99–1·29)	4	+
Cohen, 2000, USA, 1199 National Benefit Fund Cohort[101]	54 997 (68)	43 (me)	Documented antidepressant medication use	3·6 (me)	Fatal or NF MI (207)	Age, sex, hypertension, hyperlipidemia, diabetes, heart disease, anxiety, cancer	1·8 (1·1–3·1)	5	+
Ferketich, 2000, USA, First National Health and Nutrition Examination Study[33]	7893 (63)	55 (me)	Depression (CES-D)	8·3 (me)	Fatal CHD (129 in women and 137 in men) NF CHD (187 in women and 187 in men)	Age, smoking, BMI, hypertension, diabetes, poverty (men: race also) Fatal: also adjust for NF CHD events	Men: Fatal CHD: 2·34 (1·54–3·56) NF CHD: 1·71 (1·14–2·56) Women: Fatal CHD: 0·74 (0·40–1·48) NF CHD: 1·73 (1·11–2·68)	8	Fatal CHD: Men: ++ Women: − NF CHD: +
Chang, 2001, USA, National Health and Nutrition Examination Study and Epidemiologic Follow-up Study[102]	10 766 (57)	35–74	Depression (General Well-Being Schedule)	21 (mx)	Fatal CHD (1401)	Age, smoking, cholesterol, BMI, exercise, hypertension, diabetes, replacement hormones, education	No significant association in multivariate analyses Unadjusted analyses: White men: 1·4 (1·0–2·0) Black men: 1·9 (0·9–4·0) White women: 1·3 (0·9–1·8) Black women: 0·8 (0·3–2·0)	0	0
Cohen, 2001, USA, New York[6]	5564 (36)	53 (me)	History of treatment for depression	4·9 (me)	MI (112), Cardiac events (138), IHD events (192)	Age, sex, smoking, blood pressure, cholesterol, BMI, alcohol, hypertension, diabetes, blood sugar, history of CVD, left ventricular hypertrophy, school, race, marital status	Men: MI: 2·03 (0·87–4·74) Cardiac event: 2·35 (1·13–4·91) IHD event: 1·86 (0·94–3·71) Women: MI: 2·42 (0·70–8·37)	1	++

							Cardiac event: 2·69 (0·90–8·05) IHD event: 2·66 (1·10–6·46)		
Haines, 2001, UK, Northwick Park Heart Study[43]	1408 (0)	40–64	Depression (Crown-Crisp experiential index)	20·9 (me)	Fatal CHD (127)	Age, smoking, blood pressure, cholesterol, BMI, fibrinogen, factor VIIc, social class	One point increase: 1·07 (0·99–1·15)	0	+
Penninx, 2001, the Netherlands, Longitudinal Aging Study Amsterdam[5]	2397 (55)	55–85	Major depression (DIS) and minor depression (CES-D)	4·2 (me)	Cardiac mortality (91) and CHD mortality (45)	Age, sex, smoking, BMI, alcohol, hypertension, diabetes, stroke, lung disease, cancer, education	Cardiac mortality: Minor depression: 1·5 (0·9–2·6) Major depression: 3·9 (1·4–10·9) CHD mortality: Minor depression: 1·3 (0·6–3·1) Major depression: 5·2 (1·5–17·7)	1	Minor depression: 0 Major depression: ++
Prognostic studies									
Barefoot, 1989, USA, Duke Medical Center[90]	1467 (18) patients with angiographic disease	52 (me)	Depression (MMPI)	9·2 (mx)	Fatal CVD and NF MI (315)	Stratified on clinical prognostic factors	No association between depression and mortality	29	0
Schleifer, 1989, USA, New York[17]	283 (36) patients 8–10 days post-MI	64 (me)	Depression (Schedule for Affective Disorders and Schizophrenia, Hamilton Depression Rating Scale)	0·33 (mx)	All-cause mortality and reinfarction (25)	None	Minor depression: 0·83 (0·33–2·04) Major depression: 0·79 (0·28–2·29)	216	0
Ahern, 1990, USA, Cardiac Arrhythmia Pilot Study[18]	353 patients 6–60 days post-MI	<75	Depression (BDI)	1 (mx)	All-cause mortality and NF MI	Baseline ejection fraction, β blocker or digitalis use, presence of transmurality in qualifying MI, runs of ventricular premature complexes	1 sd increase in measure of depression: 1·38 (0·99–1·93)	177	+
Ladwig, 1991, Germany, Post-Infarction Late Potential Study[14]	560 (0) patients 3weeks post-MI	29–65	Depression (PSYCHIS-Munchen)	0·5 (mx)	Fatal CHD (12)	Age, recurrent infarction, late potentials, dyspnoea, long-term ECG	Medium depressive disorder: 2·8 Major depressive disorder: 4·9 $P = 0·07$	105	++
Berkman, 1992, USA, Established Population for the Epidemiologic Study of the Elderly[103]	194 (48) hospitalized with acute MI	≥65	Depression (CES-D)	0·5 (mx)	All-cause mortality (76)	None	1·08 (0·46–2·51)	157	0
Frasure-Smith, 1993, Canada, Montreal Heart Institute[104]	222 (22) patients 5–15 days post-MI	24–88	Depression (DIS)	0·5 (mx)	All-cause mortality (12)	Warfarin, lack of close friends, Killip class, previous MI	3·44 (2·25–4·63)	460	++

Table 17.2 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Jenkinson, 1993, UK, Anglo-Scandinavian Study of Early Thrombolysis[91]	1376 (22) within 7 days post-MI	25–84	Depression	3 (me)	All-cause mortality (247)	Age, sex, previous MI, hospital complications, diabetes, hypertension, car ownership	No association in multivariate analyses Survival at 3 years is 84% in depressed and 83% in non-depressed group	17	0
Ladwig, 1994, Germany, Post-Infarction Late-Potential Study[105]	377 (0) patients 17–21 days post-MI	29–65	Depression (interview)	0·5 (mx)	Angina (not stated)	Age, social class, recurrent infarction, rehabilitation, cardiac events, adherence to anti-anginal medication, pre-MI angina, helplessness	Severe depression: 2·31 (1·11–4·80)	78	++
Denollet, 1995, Belgium, Antwerp[106]	105 (0) less 3–6 weeks post-MI	45–60	Depression (Zung)	3·8 (me)	All-cause mortality (15), fatal CHD (11)	Age, smoking, low exercise tolerance, previous or anterior MI	Depression not significantly related total and cardiac mortality Unadjusted analyses: Total mortality: 4·57 (1·37–15·26) Fatal CHD: 5·38 (1·22–23·67)	21	0
Frasure-Smith, 1995, Canada, Montreal Heart Institute[38]	222 (22) patients 5–15 days post-MI	24–88	Depressive symptoms (BDI) and major depression (DIS)	1·5 (mx)	Fatal CHD (19)	Age, previous MI, PVCs, Killip class	Depressive symptoms: 6·64 (1·76–25·09) Major depression: 2·68 (0·77–9·31)	278	++
Frasure-Smith, 1995, Canada, Montreal Heart Institute[73]	222 (22) patients 5–15 days post-MI	24–88	Depressive symptoms (BDI) and major depression (DIS)	1 (mx)	Recurrent cardiac events (arrhythmic death, fatal and NF MI, survived cardiac arrest and unstable angina) (48)	Previous MI, prescription of ACE inhibitors, anxiety	Depressive symptoms: 1·99 (0·92–4·31) Previous depression: 1·82 (0·85–3·90)	58	+
Friedman, 1995, USA, Cardiac Arrhythmia Suppression Trial ancillary study[74]	369 (15) patients after acute MI with ventricular arrhythmias	63 (me)	Depression (Zung)	1 (mx)	All-cause mortality (20)	Diabetes, left ventricular ejection fraction, runs of ventricular premature beats, pet ownership, social support, anxiety, optimism	No association	17	0
Hoffmann, 1995, Switzerland, Gais, Seewis and Le Noirmont[75]	222 (0) patients 7 weeks (mean) after first MI	30–60	Depression	1 (mx)	Poor medical outcome (death, re-infarction, New York Heart association	Age, exercise, severity of MI, overprotection by friends, external locus of control	No association with poor medical outcome Associated with angina incidence ($P < 0·01$)	9	Poor medical outcome: 0 Angina: +

					Class ≥ III, exercise capacity <100 W) (19)				
Oxman, 1995, USA, Dartmouth-Hitchcock Medical Center[107]	232 (0) patients after elective open heart surgery	≥55	Depression (Hamilton Rating Scale for Depression)	0.5 (mx)	All-cause mortality (21)	Age, previous cardiac surgery, severe impairment, social support	No significant association Unadjusted 2·20 (0·94–5·11)	83	0
Barefoot, 1996, USA, Duke Medical Center[15]	1250 (18) patients with angiographic disease	46–59	Depression (Zung)	15·2 (me)	All-cause mortality (604) and fatal CHD (488)	Disease severity	Total mortality: Severe depression: 1·78 Mild depression: 1·57 Fatal CHD: Severe depression: 1·69 Mild depression: 1·38	93	+
Denollet, 1996, Belgium, Antwerp Cardiac Rehabilitation Programme[108]	303 (12) patients with angiographic CHD	31–79	Depression (Millon Behavioral Health Inventory)	7·9 (me)	All-cause mortality (38)	Left ventricular function, number of diseased vessels, low exercise tolerance, lack of thrombolytic therapy, type D personality	No significant multivariate association Unadjusted association: 2·38 (1·28–4·41)	59	0
Lesperance, 1996, Canada, Montreal Heart Institute[109]	222 (22) patients 5–10 days post-MI	24–88	Depression (DIS and BDI)	1·5 (mx)	All-cause mortality (21)	None	3·96 (1·50–10·5)	73	++
Carinci, 1997, Italy, GISSI-2 Psychological Study[77]	2449 (12) patients post-MI	3·7% > 70	Depression (Cognitive Behavioral Assessment Hospital Form)	0·6 (me)	All-cause mortality (63)	Age, sex, hypertension, exercise test ineligibility, ventricular failure, recovery phase LV dysfunction, previous MI, exercise test positivity, electrical instability, extroversion	No significant multivariate association Unadjusted analysis: 1·7 (0·9–3·1)	7	0
Krumholz, 1998, USA, Established Population for the Epidemiologic Study of the Elderly[110]	292 (57) patients hospitalized with heart failure	80 (me)	Depression (CES-D)	1 (mx)	CVD death or re-admission (142)	Age, sex, LVEF, physiology score, MI at current admission, hypertension, Rosow-Breslau or Nagi impairment, social support	No significant multivariate association Unadjusted analysis: 1·13 (0·87–1·48)	24	0
Frasure-Smith, 1999, Canada, Montreal Heart Attack Readjustment Trial and Emtions and Prognosis Post-Infract Study[78]	896 (32) patients 7 days after MI	24–88	Depression (BDI)	1 (mx)	Fatal CHD (37)	Age, sex, smoking, Killip class, non-Q wave MI, LVEF	3·66 (1·68–7·99)	31	++

Table 17.2 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Irvine, 1999, Canada, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial[92]	671 (17) patients 6–45 days post-MI	32–89	Depression (BDI)	2 (mx)	SCD (34)	Previous MI, previous CHF, social participation, social network contacts, dyspnea/fatigue	Amiodarone group: 0·47 (0·13–1·65) Placebo group: 1·73 (0·75–3·98)	9	0
Kaufman, 1999, USA, Pennsylvania[93]	331 (34) patients 3–15 days post-MI	28–92	Depression (DIS)	1 (mx)	All-cause mortality (33)	LVEF, history of chronic heat failure, previous stroke, diabetes	Depression not significant in multivariate analyses Unadjusted: 2·33 (1·16–4·65)	8	0
Murberg, 1999, Norway, Stavanger[111]	119 (29) patients with congestive heart failure 61 months after diagnosis (mean)	66 (me)	Depression (Zung)	2 (mx)	Fatal CHD (20)	Age, sex, disease severity (proANF)	Moderately depressed: 2·08 (ss)	5	++
Barefoot, 2000, USA, Duke Medical Center[79]	1250 (18) patients with significant CAD	46–58	Depression (Zung)	15·2 (me)	Fatal CHD (488)	Age, sex, hazard scores, treatment status, income	2 sd increase in score: 1·37 ($P < 0·001$)	0	+
Denollet, 2000, Belgium, Antwerp[112]	319 (8) patients in a cardiac rehabilitation program	35–70	Depression (Zung)	5 (mx)	Fatal CHD and NF MI (22)	Age, LVEF	Depression not significant in multivariate analyses Unadjusted analyses: Depression: 2·6 (1·1–6·3)	3	0
Herrmann, 2000, Germany, Gottingen[113]	5057 (26) patients referred to cardiology department for exercise testing	54 (me)	Depression (Hospital Anxiety and Depression Scale)	5·7 (me)	All-cause mortality (457)	Age, sex, cardiac history, exercise performance and mutually	1 sd increase in score: 1·16 (1·01–1·30)	1	+
Horsten, 2000 Sweden, Stockholm Female Coronary Risk Study[114]	292 (100) 3–6 months post hospitalization for acute CHD	30–65	Depression (Pearlin)	4·8 (me)	CVD mortality, recurrent MI, revascularization (81)	Age, smoking, blood pressure, HDL, BMI, exercise, diagnosis at index event, heart failure, diabetes, hypertension, angina severity	1·8 (0·86–3·6)	4	+
Lane, 2000, UK West Midlands[115]	288 (25) patients within 15 days post-MI	63 (me)	Depression (BDI)	0·33 (mx)	Fatal CHD (22)	None	1·31 (0·53–3·24)	1	0

Lane, 2000, UK, West Midlands[116]	288 (25) patients within 15 days post-MI	63 (me)	Depression (BDI)	1 (mx)	Recurrent CHD event (fatal and NF) requiring hospitalization (82)	Peel index score, previous MI, hypertensive, angina, Killip class, thrombolyzed, hypercholesterolemia, diabetes, hospital stay	No multivariate association Unadjusted analyses: 0·97 (0·55–1·70)	1	0
Lesperance, 2000, Canada, Montreal Heart Institute[117]	430 (29) patients mean 5 days after hospitalization with unstable angina	31–87	Depression (BDI)	1 (mx)	Fatal CHD and NF MI (28)	Electrocardiagraphic evidence of ischemia, LVEF, number of diseased vessels	6·73 (2·43–18·64)	1	++
Welin, 2000, Sweden, Gothenburg[48]	275 (16) patients 3–6 days post first MI	<65	Depression (Zung)	10 (mx)	All-cause mortality (67), fatal CHD (41), NF MI (55)	Sex, left ventricular failure, ventricular dysrhythmia, social support	Total mortality: 1·75 (1·02–2·99) Fatal CHD: 3·16 (1·38–7·25) Depression unrelated to NF MI	1 +	Total mortality: + Fatal CHD: ++ NF MI: 0
Baker, 2001, Australia, Adelaide[118]	158 (26) patients undergoing CABG surgery	65 (me)	Depression (Depression Anxiety Stress Scale)	2·1 (me)	>30 day all-cause mortality (6)	None	6·24 (1·18–32·98)	0	++
Lane, 2001, UK, West Midlands[119]	288 (25) patients within 15 days post-MI	31–89	Depression (BDI)	1 (mx)	Fatal CHD (27)	None	1·15 (0·49–2·67)	2	0
Penninx, 2001, the Netherlands, Longitudinal Aging Study Amsterdam[5]	450 (38) subjects with diagnosis of cardiac disease	55–85	Major depression (DIS) and minor depression (CES-D)	4·2 (me)	Cardiac mortality (93) and CHD mortality (63)	Age, sex, smoking, BMI, alcohol, hypertension, diabetes, stroke, lung disease, cancer, education	Cardiac mortality: Minor depression: 1·6 (1·0–2·7) Major depression: 3·0 (1·1–7·8) CHD mortality: Minor depression: 2·1 (1·1–3·8) Major depression: 3·9 (1·3–11·8)	1	++

Abbreviations: ADL, activities of daily living; MMPI 2-D, Minnesota Multiphasic Personality Inventory 2-D; MMPI-2 DEP, Minnesota Multiphasic Personality Inventory 2-Dep; for other abbreviations see Table 17.1

Table 17.3 Studies of anxiety and distress and coronary heart disease

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Etiologic studies									
Medalie, 1973, Israel, Israeli Ischemic Heart Disease Study[39]	8538 (0)	≥40	Anxiety (Anxiety Index)	5 (mx)	Angina (300)	Age and area	2·2	N/A	++
Medalie, 1976, Israel, Israeli Ischemic Heart Disease Study[40]	8166 (0)	≥40	Anxiety (Anxiety Index)	5 (mx)	Angina (234)	Age, blood pressure cholestrol, BMI, diabetes, ECG abnormalities, psychosocial problems	β coefficient: 0·29 ($P < 0·01$)	N/A	+
Haines, 1987, UK, Northwick Park Heart Study[41]	1457 (0)	40–64	Free floating anxiety and phobic anxiety (Crown-Crisp experimental index)	10 (me)	Fatal CHD (56) and NF MI (57)	Age, smoking, blood pressure, cholesterol, factor VII activity, fibrinogen, social class, shift work	Fatal CHD: High phobic anxiety: 3·77 (1·64–8·64) NF MI: High phobic anxiety: 1·26 (0·62–2·54) Free-floating anxiety unrelated	88	Phobic anxiety: Fatal CHD: ++ NF MI: 0 Free-floating anxiety: 0
Eaker, 1992, USA, Framingham Heart Study[60]	749 (100)	45–64	Anxiety (Somatic Strain Scale)	20 (mx)	Fatal CHD and NF MI (69)	Age, smoking, blood pressure, cholestrol, HDL, BMI, diabetes	Unrelated for total women Homemakers ($n = 353$): 7·8 (2·00−32·3)	67	0
Kawachi, 1994, USA, Health Professionals Follow-up Study[42]	33 999 (0)	42–77	Phobic anxiety (Crown-Crisp experiential index)	2 (mx)	Fatal CHD (40) and NF MI (128)	Age, smoking BMI, alcohol, exercise, hypertension, diabetes, hypercholesterolemia, parental history of MI	Fatal CHD: 2·45 (1·00–5·96) NF MI: 0·89 (0·45–1·79)	114	Fatal CHD: ++ NF MI: 0
Vogt, 1994, USA Kaiser Permanente[95]	2573 (54)	≥18	Worries (Bradburn Worries Index)	15 (mx)	Fatal CHD and NF CHD (not stated)	Age, sex, smoking, self-reported health, social class, duration of health plan membership	Worries: 1·18 (0·85–1·63)	40	0
Kubzansky, 1997, USA, Normative Aging Study[120]	1759 (0)	21–80	Worry (Worries Scale)	13·7 (me)	Fatal CHD (86), NF MI (113), and angina (124)	Age, smoking, blood pressure, cholestrol, BMI,	Per point increase in scale of worry	36	NF MI: Worry about social conditions: +

						alcohol, family history of CHD	Fatal CHD: Social conditions: 0·94 (0·71–1·26) Health: 1·17 (0·82–1·66) Financial: 1·21 (0·86–1·70) Self-definition: 0·97 (0·74–1·29) Aging: 1·05 (0·67–1·62) NF MI: Social conditions: 1·49 (1·16–1·93) Health: 0·86 (0·63–1·17) Financial: 1·17 (0·87–1·56) Self-definition: 0·97 (0·74–1·26) Aging: 1·06 (0·71–1·59) Angina: Social conditions: 1·17 (0·92–1·50) Health: 1·39 (1·04–1·87) Financial: 1·20 (0·91–1·58) Self-definition: 1·11 (0·86–1·42) Aging: 1·28 (0·89–1·85)		Angina: Work about health: + Others: 0
Haines, 2001, UK, Northwick Park Heart Study[43]	1408 (0)	40–64	Free-floating anxiety, phobic anxiety (Crown-Crisp experiential index)	20·9 (me)	Fatal CHD (127)	Age, smoking, blood pressure, cholesterol, BMI, fibrinogen, factor VIIc, social class	One point increase: Anxiety: 1·04 (0·99–1·10) Phobic anxiety: 1·07 (0·99–1·15)	0	0
Prognostic studies									
Ahern, 1990, USA, Cardiac Arrhythmia Pilot Study[18]	353 patients 6–60 days post-MI	<75	Anxiety (STAI)	1 (mx)	All-cause mortality and NF MI	None	Mean (sd) trait anxiety: Survivors: 38·8 (8·0) Non-survivors: 39·5 (10·8) Mean (sd) state anxiety: Survivors: 35·7 (10·8) Non-survivors: 36·1 (11·2)	177	0
Allison, 1995, USA, Mayo Clinic[121]	381 (18) patients with CAD referred for cardiac rehabilitation	25–85	Psychologic distress (SCL-90-R)	0·5 (mx)	Cardiovascular rehospitalization (49) and recurrent cardiovascular event (fatal CHD, NF MI, cardiac arrest, cardiac operation, angiographic progression of CAD, CHF, embolic stroke, pulmory embolus) (39)	Smoking, diabetes, ejection fraction, previous cardiac event, β blockers, bypass surgical procedure or coronary angioplasty at index hospitalization	Cardiovascular rehospitalization: Distress: 3·05 ($P = 0·01$) Recurrent cardiovascular event: Distress: 4·39 ($P = 0·003$)	46	++

Table 17.3 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Denollet, 1995, Belgium, Antwerp[106]	105 (0) patients 3–6 weeks post-MI	45–60	Distressed personality (STAI Heart Patients Psychological Questionnaire)	3·8 (me)	All-cause mortality (15), fatal CHD (11)	Age, smoking, low exercise tolerance, previous or anterior MI	Distressed personality significantly predicted total and fatal CHD Unadjusted analyses: Total mortality: 7·56 (2·62–21·82) Fatal CHD: 5·61 (1·80–17·55)	21	++
Frasure-Smith, 1995, Canada, Montreal Heart Institute[73]	222 (22) patients 5–15 days post-MI	24–88	Anxiety (STAI)	1 (mx)	Recurrent cardiac events (arrhythmic death, fatal and NF MI, survived cardiac arrest and unstable angina) (48)	Previous MI, prescription of ACE inhibitors, depression	2·52 (1·15–5·55)	58	++
Friedmann, 1995, USA, Cardiac Arrhythmia Suppression Trial ancillary study[74]	369 (15) patients after acute MI with ventricular arrhythmias	63 (me)	Anxiety (STAI)	1 (mx)	All-cause mortality (20)	Ejection fraction, diabetes, runs of ventricular premature beats, pet ownership, social support, optimism	Low state anxiety improved survival ($P = 0·09$)	17	0
Hoffman, 1995, Switzerland, Gais, Seewis and Le Noirmont[75]	222 (0) patients 7 weeks (mean) after first MI	30–60	Anxiety (MAS)	1 (mx)	Poor medical outcome (death, re-infarction, New York Heart Association Class ≥III, exercise capacity <100W) (19)	Age, severity of MI, exercise, overprotection by friends, external locus of control	No association with poor medical outcome Associated with angina incidence ($P < 0·01$)	9	Poor medical outcome: 0 Angina: +
Denollet, 1996, Belgium, Antwerp Cardiac Rehabilitation Programme[108]	303 (12) patients with angiographic CHD	31–79	Type D personality (suppression of emotional distress) (STAI and HPPQ)	7·9 (me)	All-cause mortality (38)	Left ventricular function, number of diseased vessels, low exercise tolerance, lack of thrombolytic therapy	4·1 (1·9–8·8)	59	++
Carinci, 1997, Italy, GISSI-2 Psychological Study[77]	2449 (12) patients post-MI	3·7% > 70	Anxiety (Cognitive Behavioural Assessment Hospital Form)	0·6 (me)	All-cause mortality (63)	Age, sex hypertension, exercise test ineligibility, ventricular failure, recovery phase LV	No significant association in multivariate Unadjusted analyses: Anxiety: 1·3 (0·8–2·1)	7	0

						dysfunction, previous MI, exercise test positivity, electrical instability, extroversion			
Perski, 1998, Sweden, Stockholm[122]	171 (17) patients post-CABG surgery	43–80	Emotional distress (Nottingham Health Profile)	3 (mx)	Cardiac events (11) (fatal CHD, NF MI, revascularization, unstable angina)	Blood pressure, LDL/HDL ratio	1·89 (1·04–3·55)	3	+
Frasure-Smith, 1999, Canada, Montreal Heart Attack Readjustment Trial and Emotions and Prognosis Post-Infarct Study[78]	896 (32) patients 7 days after MI	24–88	Anxiety (Spielberger's STAI)	1 (mx)	Fatal CHD (37)	Smoking, non-Q wave MI at baseline, LVEF	Men: 2·58 (1·06–6·30) Women: 0·63 (0·20–2·04)	31	Men: ++ Women: −
Irvine, 1999, Canada, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial[92]	671 (17) patients 6–45 days post-MI	32–89	Psychologic distress (Symptom Check List)	2 (mx)	SCD (34)	Previous MI, previous CHF, social participation, social network contacts, dyspnea/ fatigue	Psychologic distress not associated	9	0
Denollet, 2000, Belgium, Antwerp[112]	319 (8) patients in a cardiac rehabilitation program	35–70	Anxiety (State Anxiety Scale), Type D personality (DS16)	5 (mx)	Cardiac events (fatal CHD or NF MI) and impaired QOL(22)	Age, LVEF	Type D: 8·9 (3·2–24·7) Anxiety not significant Unadjusted analyses: Type D: 7·6 (2·9–20·2) Anxiety: 2·0 (0·8–4·8)	3	Type D: ++ Anxiety: 0
Herrmann, 2000, Germany, Gottingen[113]	5057 (26) patients referred to cardiology department for exercise testing	54 (me)	Anxiety (Hospital Anxiety and Depression Scale)	5·7 (me)	All-cause mortality (457)	Age, sex, cardiac history, exercise performance, and mutually	1 sd increase in score: Survival: 1·19 (1·08–1·28)	1	−
Lane, 2000, UK, West Midlands[115]	288 (25) patients within 15 days post-MI	63 (me)	Anxiety (STAI)	0·33 (mx)	Fatal CHD (22)	None	1 unit increase in: State anxiety: 0·99 (0·96–1·03) Trait anxiety: 0·98 (0·93–1·02)	1	0
Lane, 2000, UK, West Midlands[116]	288 (25) patients within 15 days post-MI	63 (me)	Anxiety (STAI)	1 (mx)	Recurrent CHD event (fatal and NF) requiring hospitalization (82)	Peel index score, previous MI, hypertension, angina, Killip class, thrombolyzed, hypercholesterolemia diabetes, hospital stay	No multivariate association Unadjusted 1 unit increase in: State anxiety: 1·00 (0·98–1·02) Trait anxiety: 0·98 (0·95–1·01)	1	0

Table 17.3 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk	Citations (*n*) (Sept 2001)	Summary
Mayou, 2000, UK, Oxford Myocardial Infarction Incidence Study[123]	344 (27) patients <3 days after hospitalization for suspected MI	30–79	Distress (HAD)	1·5 (mx)	All-cause mortality (28)	All significant unadjusted predictors of mortality (not stated which variables)	No association	5	0
Welin, 2000, Sweden, Gothenburg[48]	275 (16) patients 3–6 days post first MI	<65	Anxiety (Trait Anxiety Inventory)	10 (mx)	All-cause mortality (67), fatal CHD (41), NF MI (55)	None	Total mortality: 0·91 (0·56–1·50) Fatal CHD: 1·08 (0·59–2·00)	1	0
Lane, 2001, UK, West Midlands[119]	288 (25) patients within 15 days post-MI	31–89	Anxiety (STAI)	1 (mx)	Fatal CHD (27)	None	Anxiety unrelated to NF MI 1 point increase State anxiety: 0·99 (0·96–1·03) Trait anxiety: 0·98 (0·94–1·02)	2	0

Abbreviations: DS16, Type-D Scale-16; HAD, Hospital Anxiety and Depression Scale; HPPQ, Heart Patients Psychological Questionnaire; STAI, State Trait Anxiety Inventory; for other abbreviations see Table 17.1

Table 17.4 Studies of psychosocial work characteristics and coronary heart disease

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Etiologic studies									
Theorell, 1977, Sweden, Building Construction Workers[124]	5187 (0)	41–61	Workload index	2 (mx)	Fatal CHD and NF MI (31)	Age	1·98 (ss)	N/A	++
La Croix, 1984, USA, Framingham Heart Study[125]	876 (37)	45–64	Job control and demands (individual and ecologic)	10 (mx)	Fatal CHD, NF MI, coronary insufficiency and angina (not stated)	Age, smoking, blood pressure, cholesterol	Women: 2·9 (ss) Men: no association Ecologic exposure was associated with risk in men and women	20	Individual: Women: ++ Men: 0 Ecologic: +
Alfredsson, 1985, Sweden, 5 Swedish counties[126]	958 096 (51)	20–64	Hectic work, few chances to learn new things, and monotonous work (ecologic)	1 (mx)	NF MI hospitalizations (1201)	Age, smoking, 10 socio-demographic factors, heavy lifting	Men: Hectic work + non-learning: SMR = 128 (109–148) Hectic monotonous work: SMR = 118 (102–135) Women: Hectic monotonous work: SMR = 164 (112–233)	120	Men: 0 Women: +
Haan, 1988, Finland, Study of Metal Workers[20]	902 (33)	17–65	Job strain (physical strain, variety and control) (individual)	10 (mx)	Fatal CHD and NF CHD (60)	Age, sex, smoking, blood pressure, cholesterol, relative weight, alcohol	Strain (low control, low variety, high physical strain) 4·95 ($P = 0·03$)	26	++
Reed, 1989, USA, Honolulu Heart Program[127]	4737 (0)	45–65	Strain (decision latitude and psychologic demands) (ecologic)	18 (mx)	Fatal CHD and NF MI (359)	Age, smoking, blood pressure, cholesterol, exercise, glucose	Job strain inversely associated with CHD incidence ($P = 0·07$) No significant effect of either job control or demand	73	0
Netterstrom, 1993, Denmark, Urban Bus Drivers[128]	2045 (0)	21–64	Job variety and satisfaction (individual)	10 (mx)	Fatal CHD (59)	Age	Choose same job: 2·2 (1·2–4·0) Not looking for new job: 6·5 (1·6–27·0) Job is special: 1·9 (1·1–3·1) Cannot use skills: 1·5 (0·9–2·5) High work pace: 0·9 (0·5–1·6) Passengers complain: 0·6 (0·4–1·2) Job varied: 1·6 (0·9–1·9) Job very varied: 2·5 (1·4–4·5)	22	Job satisfaction: ++ Job variety: + Others: 0

Table 17.4 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Suadicani, 1993, Denmark, Copenhagen Male Study[129]	1638 (0)	59·7 (me)	Job influence, monotony, pace, satisfaction, ability to relax (individual)	4 (mx)	Fatal CHD and NF MI (46)	Age, smoking, blood pressure, cholesterol, HDL, triglycerides, BMI, alcohol, exercise hypertension, selenium, social class	Only inability to relax after work associated with CHD 2·9 (1·3–6·1)	14	Inability to relax: ++ Others: 0
Alterman, 1994, USA, Western Electric Study[130]	1683 (0)	38–56	Job strain (decision latitude and psychologic demands) (ecologic)	25 (mortality – mx) 10 (incidence – mx)	Fatal CHD (283) and NF CHD (115)	Age, smoking, blood pressure, cholesterol, alcohol, family history of CVD, education	Per tertile increase in exposure: Fatal CHD: Job control: 0·76 (0·59–1·00) Job demands: 0·78 (0·48–1·26) Job strain: 1·40 (0·92–2·14) NF CHD: Job control: 0·87 (0·57–1·31) Job demands: 1·07 (0·54–2·12) Job strain: 1·54 (0·85–2·80)	47	Control: + Demands: 0 Job strain: +
Bosma, 1997, UK, Whitehall II study[131]	10 308 (33)	35–55	Job control, job demands, social support at work (individual and ecologic)	5·3 (me)	Diagnosed CHD (166), angina (328)	Age, sex, smoking, blood pressure, cholesterol, BMI, drugs for hypertension	Low job control: CHD: 1·26 (0·67–2·39) Angina: 2·02 (1·22–3·34) Job demands and social support at work not related Ecologic and individual measures similar	99	Control: Angina: ++ CHD: 0 Others: 0
Lynch, 1997, Finland, Kuopio Ischemic Heart Disease Risk Factor Study[132]	1727 (0)	42, 48, 54 or 60	Job demands, resources, income (individual)	10·8 (mx)	Fatal CHD and NF MI (89)	Age, behavioral, biologic and psychosocial covariates	Demands/resources/ income: (compared to low/ high/high) High/low/low: 1·57 (0·78–3·18)	22	+
Steenland, 1997, USA, NHANES1[133]	3575 (0)	25–74	Job strain (job control and job demand) (ecologic)	16 (mx)	Fatal CHD and NF MI (519)	Age, smoking, blood pressure, cholesterol, BMI, diabetes, education	High control: 0·71 (0·54–0·93) High demands: 0·81 (0·61–1·09) Job strain: 1·08 (0·81–1·49)	15	0
Bosma, 1998, UK, Whitehall II study[134]	10 308 (33)	35–55	Job control (also ecologic), job demands,	5·3 (me)	Angina pectoris and doctor diagnosed	Age, sex, smoking, cholesterol, BMI,	Effort reward imbalance: 2·15 (1·15–4·01) Low control (individual):	47	Effort reward imbalance: ++

			social support at work, effort-reward imbalance (individual)		ischemia (413)	hypertension, employment grade, negative affectivity, and mutually	2·38 (1·32–4·29) Low job control (ecologic): 1·56 (1·08–2·27) Job demands and social support at work unrelated		Job control: ++ Others: 0
Moore, 1999, Canada, Quebec[135]	869 (0)	42–60	Occupational stress (individual)	10 (mx)	Fatal CHD, NF MI or angina (79)	None	Dissatisfied with: Work environment: 1·16 (0·62–1·15) Work schedule: 1·30 (0·73–2·29) Job context: 1·01 (0·52–1·97) Work responsibility: 0·89 (0·44–1·80) Support at work: 1·06 (0·61–1·86) Frequent stress at work: 1·19 (0·70–2·02)	3	0
Prognostic studies									
Hlatky, 1995, USA, Duke Medical Center[136]	1489 (24) employed patients undergoing coronary angiography	41–59	Job strain, (decision latitude and psychological demands) (individual)	4 (me)	Fatal CHD (42) and NF MI (70)	Ejection fraction, extent of coronary atherosclerosis, myocardial ischemia	Job strain Fatal CHD: 1·01 (0·51–2·01) Total CHD: 0·96 (0·62–1·46)	40	0
Hoffmann, 1995, Switzerland Gasis, Seewis and Le Noirmont[75]	222 (0) patients 7 weeks (mean) after first MI	30–60	Job work load	1 (mx)	Poor medical outcome (death, re-infarction, New York Heart Association Class ≥ III, exercise capacity <100 W) (19)	Age, severity of MI, exercise, overprotection by friends, external locus of control	High workload was positively associated with outcome ($P = 0·01$)	9	+
Orth-Gomer, 2000, Sweden, Stockholm Female Coronary Risk Study[137]	292 (100) women post acute coronary event	30–65	Job strain (job demands, job control) (Karasek)	4·8 (me)	Fatal CHD, NF MI, revascularization procedure (81)	Age, smoking, blood pressure, HDL, triglycerides, estrogen status, diabetes, diagnosis at index event, symptoms of heart failure, education	Severe work stress: 1·67 (0·64–4·32) Age adjusted only Low control: 1·62 (0·84–3·01) High demands: 1·21 (0·63–2·32)	2	+
Welin, 2000, Sweden, Gothenburg[48]	275 (16) patients 3–6 days post first MI	<65	Extra work, mental strain at work	10 (mx)	All-cause mortality (67), fatal CHD (41), NF MI (55)	None	No association between fatal CHD and extra work ($P = 0·26$), mental stress at work ($P = 0·99$) No association with total mortality of NF MI	1	0

For abbreviations see Table 17.1.

instance, depression and anxiety. Because of the lack of consistency in measuring psychosocial work characteristics, it was difficult to compare the strength of evidence for the two theoretical models – a challenge when evaluating this literature and for future researchers. Moreover, work characteristics can be measured either through self-report or ecologic measurements (assigning a score on the basis of job title). Self-reports may be biased by early manifestations of disease, and ecologic measurements may lack precision.

There were 13 etiologic studies investigating the effect of work characteristics on CHD that were included in this review. Of these, three studies found a lack of clear association between work characteristics and CHD, and five were either moderately supportive, or supportive only for a subset of the population, a particular outcome, or a particular exposure. The final five papers showed strong evidence for an effect of work stress on CHD incidence, although in three of these studies the effect was limited either to particular psychosocial work characteristics or to women. There is some evidence that CHD incidence was more closely related to individually, rather than ecologically, measured work characteristics. This could suggest either that there is more non-differential misclassification, and therefore bias towards the null, for ecologic than individual measures, or that preclinical CHD influences subjective reporting of work characteristics. Of the four prognostic studies, two found a lack of clear association between work characteristics and prognosis, and two were moderately supportive of an association.

Social support (Table 17.5)

Social supports and networks relate to both the number and quality of a person's social contacts, and this includes emotional and confiding support. Social relationships may improve health through the emotional and instrumental support they provide; friends and family may encourage health-seeking behavior and discourage an unhealthy lifestyle. Furthermore, isolation itself may induce an unfavorable mental state, and conversely the presence of social contacts could reduce physiologic arousal and buffer the effect of environmental stressors. Reverse causation cannot be discounted: lack of social participation could be the result of subclinical coronary disease. Despite the interest in social support, there is little consensus on how it is measured, therefore variables ranging from "high love and support from wife", to "social network index" to "social isolation" were included.

Nine studies were included that used social support as the etiologic agent. Three studies showed no clear association, including the Health Professionals Follow-up Study.[19] Four studies, using a range of different measures of social support, were moderately supportive of the hypothesis that social support is etiologically linked to CHD. Finally, two studies were strongly supportive of an association between social support and risk of CHD.

Of the 21 prognostic studies, 10 were strongly supportive of the hypothesis, four were moderately supportive and seven showed no consistent effect. The strongly supportive studies included one of the largest studies[47] and two with extended follow up,[47,48] and they were generally highly adjusted for potential confounders, including lifestyle behaviors and indicators of disease severity. The stronger effect of social support on prognosis for people with CHD than on risk for CHD could potentially be explained if patients with CHD with high levels of social support are better taken care of or are more likely to seek medical care.

Modification of psychosocial factors

What are the implications of these findings for cardiologic practice? Box 17.2 summarizes the main points. When judged on the criteria used for drug interventions, the evidence for psychosocial intervention supports "options to be considered" rather than firm recommendations. There are two ways in which such criteria may not be entirely appropriate when psychosocial factors are considered. First, psychosocial interventions – unlike drug and invasive interventions – have few if any adverse effects (and may be less costly). Second, psychosocial factors may be interrelated and the quest for a single "toxic component" on which to intervene may not be as fruitful as in the case of, say, serum cholesterol. Few studies have investigated this interrelatedness; instead researchers have tended to emphasize one factor over others.

Box 17.2

Implications for cardiologic practice: options to consider

- Psychosocial components of cardiac rehabilitation (B/C)
- Detect and treat depression in CHD patients (B/C)
- Mobilize social support (B/C)
- Use socioeconomic status and psychosocial factors to risk-stratify patients (B/C)

A, strong evidence
(at least one well-designed RCT or effects strong and consistent across observational studies)

B, moderate evidence
(RCT[s] suggest effect despite methodological concerns or observational studies suggest an effect but conflicting data or observational studies alone)

C, limited evidence
(published research evidence available but not B or C)

A meta-analysis of randomized controlled trials (RCT) by Linden and colleagues[49] has suggested that psychosocial interventions are associated with a 41% reduction in mortality and a 46% reduction in non-fatal events in the first 2 years of follow up after MI. These RCTs – overwhelmingly in secondary prevention – have tended to be small, without prolonged follow up, and they have involved a diverse range

Table 17.5 Studies of social support and coronary heart disease

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Etiologic studies									
Medalie, 1976, Israel, Israeli Ischemic Heart Disease Study[40]	8166 (0)	≥40	Perceived love and support from wife	5 (mx)	Angina (234)	None	High love and support from wife: 0·64 (0·43–0·96)	N/A	+
House, 1982, USA, Tecumseh Community Health Study[138]	2754 (52)	35–69	Social relationships and activities (SI)	9–12	Fatal CHD	Age, baseline CHD, forced expiratory volume at 1 second	Social relationships protective for fatal CHD, significantly so in women	N/A	+
Berkman, 1983, USA, Alameda County Residents[139]	4725 (53)	30–69	Social network index	9 (mx)	Fatal CHD (120)	Age	2·13 (ss)	N/A	++
Reed, 1983, USA, Honolulu Heart Program[140]	4653 (0)	52–71	Conceptual social networks score, factor derived social networks score	8 (mx)	Fatal MI (76), NF MI (95) and angina (47)	Age, smoking, blood pressure, cholesterol, BMI, alcohol, exercise, complex carbohydrate, glucose, uric acid, forced vital capacity, SES and mutually	Standardized logistic coefficients: Conceptual social network: Fatal MI: −0·0505 (ns) NF MI: −0·0576 (ns) Angina: −0·1348 (ns) Factor-derived social network: Fatal MI: −0·0504 (ns) NF MI: −0·2146 (ns) Angina: −0·0851 (ns) Non-significant protective effect of social network	85	0
Kaplan, 1988, Finland, Kuopio and North Karelia[141]	13 301	39–59	Social connections index	5 (mx)	Fatal CHD (223)	Age, smoking, blood pressure, cholesterol, BMI, family history of CHD, education, residence	Men only: 1·72 (0·77–3·84)	105	+
Vogt, 1992, USA, Northwest Kaiser Permanente[142]	2603 (54)	≥18	Network scope, frequency, and size (Household Interview Survey)	15 (mx)	Fatal CHD and NF CHD (not stated)	Age, sex, smoking, SES, and baseline subjective health status	Network scope: 1·5 (1·0–2·3) Network frequency: 1·1 (0·8–1·5) Network size: 1·2 (0·9–1·6)	63	Network scope: + Others: 0
Orth-Gomer, 1993, Sweden, Men Born in Gothenburg in 1933[143]	736 (0)	50	Attachment and social integration	6 (mx)	Fatal CHD and NF MI (25)	Smoking, cholesterol, BMI, exercise, hypertension, diabetes	Low social integration: 3·8 (1·1–13·9) Low attachment: 3·1 (1·3–7·6)	77	++
Kawachi, 1996, USA, Health Professionals Follow-up Study[19]	32 624 (0)	42–77	Social Networks index (Berkman-Syme)	4 (mx)	Fatal CHD (128) and NF MI (275)	Age, smoking, cholesterol, BMI, alcohol, exercise, hypertension, diabetes, angina, family history of MI, time period	Low social support: Fatal CHD: 1·42 (0·72–2·81) NF MI: 1·00 (0·58–1·71)	39	0

Table 17.5 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Chen, 1999, USA, Established Population for the Epidemiologic Study of the Elderly[100]	1749 (59)	≥65	Emotional support	7·9 (me)	Heart failure (173)	Age, sex, blood pressure, BMI, diabetes, MI during follow up	No significant multivariate association Unadjusted analysis: No emotional support: 1·48 (1·05–2·10)	6	0
Prognostic studies									
Ahern, 1990, USA, Cardiac Arrhythmia Pilot Study[18]	353 patients 6–60 days post-MI	<75	Social support	1 (mx)	All-cause mortality and NF MI	None	Mean (sd) social support Survivors: 22·8 (3·2) Non-survivors: 23·3 (2·6)	177	0
Berkman, 1992, USA, Established Population for the Epidemiologic Study of the Elderly[103]	194 (48) hospitalized with acute MI	≥65	Emotional support from social network and social network structure	0·5 (mx)	All-cause mortality (76)	Age, sex, Killip class, ejection fraction, re-infarction, comorbidity, functional disability, previous MI, ventricular tachycardia	No emotional support: 2·9 (1·2–6·9) Network support measure shows similar but less powerful or consistent trends (data not presented in paper)	157	++
Hedblad, 1992, Sweden, Men born in 1914[144]	98 (0) patients with ischemic 24 hour ECG	68	Social anchorage, contact frequency, social participation, emotional support, informational support, material support, and social influence	4·5 (me)	Fatal CHD or NF MI (17)	Smoking, cholesterol, BMI, alcohol, exercise, triglycerides, previous CHD, hypertension, marital status, and mutually	Social anchorage: 1·8 (0·4–8·5) Contact frequency: 1·2 (0·3–4·9) Social participation: 0·5 (0·1–2·2) Emotional support: 4·1 (1·0–17·0) Informational support: 5·8 (1·4–24·5)	16	Support : ++ Social anchorage: + Others: 0
Williams, 1992, USA, Duke Medical Center[47]	1368 (18) people with angiographic disease	52 (me)	Structural social support (marital status) and functional social support	9 (me)	Cardiovascular mortality (237)	Age, sex, LVEF, non-invasive myocardial damage index, conduction disturbance on ECG, pain/ ischemia index, mitral regurgitation, number of diseased vessels, % stenosis of left main stem and left anterior descending artery, year	Unmarried without a confidant compared to either married or confidant: 3·34 (1·84–6·20)	175	++
Gorkin, 1993, USA, Cardiac Arrhythmia Suppression Trial-1[145]	1322 (17) with previous MI and ventricular premature complexes	61 (me)	Perceived social support, social functioning index, social integration index	0·8 (me)	All-cause mortality (not stated)	Sex, treatment, history of MI, ejection fraction, congestive heart failure, thrombolysis	No multivariate association for any social network score Unadjusted analyses: Social function: 0·82 ($P = 0·02$) Significant protective	16	0

							effect in placebo only group		
Jenkinson, 1993, UK, Anglo-Scandinavian Study of Early Thrombolysis[91]	1376 (22) within 7 days post-MI	25–84	Social isolation	3 (me)	All-cause mortality (247)	Age, sex, previous MI, hospital complications, diabetes, hypertension, car ownership	1·33 (0·89–1·98)	17	0
Frasure-Smith, 1995, Canada, Canadian Signal-Averaged ECG Trial[73]	222 (22) patients 5–15 days post-MI	24–88	Social Support Scale (Blumenthal)	1 (mx)	Recurrent cardiac events (arrhythmic death, fatal and NF MI, survived cardiac arrest and unstable angina) (48)	Previous MI, prescription of ACE inhibitors, anxiety, and depression	No association Unadjusted analyses: Low social support: 1·46 (0·70–3·07)	58	0
Friedmann, 1995, USA, Cardiac Arrhythmia Suppression Trial ancillary study[74]	369 (15) patients after acute MI with ventricular arrhythmias	63 (me)	Social support (SSQ6), social readjustment (social readjustment rating scale)	1 (mx)	All-cause mortality (20)	Diabetes, left ventricular ejection fraction, runs of ventricular premature beats, pet ownership	Social support significantly increased survival $R = 0·06$, $P = 0·05$, Exp (β) = 0·94	17	+
Greenwood, 1995, UK, Anglo-Scandinavian Study of Early Thrombolysis[146]	1283 (22) patients post-MI who survived 7 days	55–59 (me)	Social contact	5·6 (me)	All-cause mortality (302)	Age, sex, previous infarct, hospital complications, diabetes, β blockers, heart rate, hypertension, discharge diagnosis of MI, car owner	1·14 (0·78–1·67)	11	0
Oxman, 1995, USA, Dartmouth-Hitchcock Medical Center[107]	232 (28%) patients after elective open heart surgery	≥55	Social network (SNQ and ISSB), perceived social support (MSPSS), and religion	0·5 (mx)	All-cause mortality (21)	Age, previous cardiac surgery, severe impairment, and mutually	No participation in groups: 4·26 (1·15–15·73) No strength/comfort from religion: 3·25 (1·09–9·72)	83	++
Denollet, 1996, Belgium, Antwerp Cardiac Rehabilitation Programme[108]	303 (12) patients with angiographic CHD	31–79	Social alienation (Millon behavioral health inventory)	7·9 (me)	All-cause mortality (38)	Left ventricular function, number of diseased vessels, low exercise tolerance, lack of thrombolytic therapy, type D personality	No significant multivariate association Unadjusted association: 2·33 (1·24–4·38)	59	0
Farmer, 1996, USA, Corpus Christi Heart Project[147]	596 (35) patients 4–5 days post-MI	25–74	Social support (social support scale)	3·6 (me)	All-cause mortality >28 days post-MI (115)	Age, sex, smoking, diabetes, hypertension, hypercholesterolemia, ethnicity, education, employment	Low social support: 1·89 (1·20–2·97)	5	+
Woloshin, 1997, Canada, Manitoba[148]	820 (35) patients 8–22 months post-MI	67 (me)	Perceived adequacy of tangible support	1 (mx)	Total mortality (31)	Age, baseline PCS score, baseline MCS score, dyspnea	Comparing those needing much more help to patients with no perceived need: 6·5 (2·0–21·6)	5	++

Table 17.5 Continued

Author, year, country, study	Total sample (% women)	Age at entry	Exposure	Follow up (years)	Type of events (*n*)	Adjustments	Relative risk (95% CI)	Citations (*n*) (Sept 2001)	Summary
Herlitz, 1998, Sweden, Gothenburg[149]	1290 (18) patients 3 months (mean) prior to CABG	32–86	Social isolation	5 (mx)	All-cause mortality (173)	Age, smoking, LVEF, CHF, diabetes, renal dysfunction, previous CVD, intermittent claudication	1·78 (1·17–2·71)	6	+
Krumholz, 1998, USA, Established Population for the Epidemiologic Study of the Elderly[110]	292 (57) patients hospitalized with heart failure	≥65	Emotional support, instrumental support, social ties count	1 (mx)	CVD death or readmission (142)	Age, sex, LVEF, acute physiology score, MI at current admission, hypertension, Rosow-Breslau or Nagi impairment, and mutually	No social ties: 2·08 (0·95–4·54) No source of emotional support: 2·69 (1·22–5·94)	24	++
Frasure-Smith, 1999, Canada, Montreal Heart Attack Readjustment Trial and Emotions and Prognosis Post-Infarct Study[78]	896 (32) patients 7 days post-MI	24–88	Social support (Perceived Social Support Scale)	1 (mx)	Fatal CHD (37)	None	Perceived social support: 1·25 (0·59–2·66)	31	0
Irvine, 1999, Canada, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial[92]	671 (17) patients 6–45 days post-MI	32–89	Social network contacts and social participation (Health and Daily Living Form)	2 (mx)	SCD (34)	Previous MI, previous CHF, depression, dyspnea/fatigue, treatment group, and mutually	Point increase in score: Social network contacts: 1·04 (1·01–1·07) Social participation: 0·98 (0·96–1·01)	9	Network contacts: + Participation: 0
Horsten, 2000, Sweden, Stockholm Female Coronary Risk Study[114]	292 (100) 3–6 months after hospitalization for acute coronary event	30–65	Attachment and social integration (ISSI)	4·8 (me)	Cardiovascular mortality, NF MI revascularization procedure (81)	Age, smoking, blood pressure, HDL, BMI, exercise, diagnosis at index event, symptoms of heart failure, diabetes, hypertension, severity of angina symptoms	Low attachment: 1·4 (0·89–2·3) (age adjusted only) Low social integration: 2·3 (1·2–4·5)	4	Attachment: 0 Integration: ++
Orth-Gomer, 2000, Sweden, Stockholm Female Coronary Risk Study[137]	292 (100) women post acute coronary event	30–65	Marital stress (Stockholm Marital Stress Scale)	4·8 (me)	Fatal CHD, NF MI, revascularization procedure (81)	Age smoking, blood pressure, HDL, triglycerides, estrogen status, diagnosis at index event, symptoms of heart failure, diabetes, education	Severe marital stress: 2·92 (1·30–6·54)	2	++

Welin, 2000, Sweden, Gothenburg[48]	275 (16) patients 3–6 days post first MI	<65	Social relationships (ISSI, Broadhead questionnaire, social activities questionnaire)	10 (mx)	All-cause mortality (67), fatal CHD (41), NF MI (55)	Sex, left ventricular fatigue, ventricular dysrhythmia, depression	Social support: Total mortality: 1·67 (0·97–2·89) Fatal CHD: 2·75 (1·29–5·89) Unadjusted analyses for social activities: Total mortality: 2·07 (1·07–3·98) Fatal CHD: 1·89 (1·12–3·20) No association with NF MI	1	Fatal CHD: ++ Total mortality: + NF MI: 0
Brummett, 2001, USA, Mediators of Social Support Study[150]	430 (33) patients with angiographic disease	64 (me)	Network social support (Mannheim Social Support Interview)	4 (me)	Fatal CHD (120)	Age, number of diseased vessels, LVEF, CHF, comorbidity	≤3 network members: 2·43 (1·52–3·89)	1	++

Abbreviations: ISSB, Inventory of Socially Supportive Behavior; ISSI, Interview Schedule for Social Interaction; MCS, Mental Component Score; MSPSS, Multidimensional Scale of Perceived Social Support; PCS, Physical Component Score; SES, Socio-Economic Status; SNQ, Social Network Questionnaire; SSQ6 Social Support Questionnaire 6; for other abbreviations see Table 17.1

of interventions (relaxation, stress management, counseling), differing in duration and professional setting. Separate analyses including the larger but *non*-randomized Recurrent Coronary Prevention Project[50] should be viewed with caution.

An appealing target for intervention among post-MI patients is low social support and depression. Information on patients' families, friends, and colleagues is commonly available to clinicians, and this may help to risk-stratify the patient. Might improved detection and treatment of depression among CHD patients improve outcome? Frasure-Smith[51] randomized 453 male post-MI survivors to monthly monitoring of minor psychiatric morbidity (general health questionnaire) or usual care. The stress management intervention was given to participants whose psychiatric morbidity rose above a critical level; at 1 year the mortality was 4·4% in the intervention group and 8·9% in the control group ($P = 0{\cdot}05$).

However, despite this positive trial there have been three large randomized trials that have failed to show improved survival associated with psychosocial interventions among post-MI patients. In Wales, a large RCT of psychologic rehabilitation post-MI found no difference in anxiety and depression, and this may in part explain the lack of effect on mortality.[52] The Montreal Heart Attack Readjustment Trial randomized 903 men and 473 women to psychosocial support or usual care.[53] Among men there was no difference in cardiac or all-cause mortality between the intervention and control groups. By contrast, among women there was an excess of cardiac deaths among the intervention group (22/234) compared with the control group (12/239) ($P = 0{\cdot}06$). The reason for this finding – in the opposite direction to that hypothesized – awaits elucidation. A multicenter trial of 3000 patients after MI (ENRICHD – enhancing recovery in CHD) has recently been completed in the USA.[54] This trial targeted patients at high psychosocial risk (those who were depressed or socially isolated) and included large numbers of women and ethnic minorities. The results, reported at the American Heart Association in November 2001, suggest no survival benefit of the intervention of cognitive behavioral therapy.

Some trials investigated the contribution of psychosocial intervention in addition to conventional rehabilitation or other lifestyle advice post-MI. Thus, for example, Ornish[55] randomized 53 patients with coronary artery disease (CAD) to stress management, low fat diet, smoking cessation, and moderate exercise, and 43 patients to usual care. However, only 28 patients in the experimental group and 20 patients in the control group agreed to take part – a potential source of selection bias. Although quantitative coronary angiography demonstrated regression of CAD in 82% of the experimental group at 12 month follow up, it is not possible to attribute this to the stress management or any other component of the intervention.

The potential for primary prevention in relation to psychosocial factors clearly lies outside the remit of cardiologists. Psychosocial factors themselves are determined largely by social, political, and economic factors and it is therefore policymakers who influence the structure and function of communities – in the public and private domains – who may have scope for primary prevention.

Challenges in improving this systematic review

Much of the literature used for this review was based on secondary analyses of data collected for other primary purposes; only a minority of studies were set up to investigate psychosocial factors in relation to CHD. A comparison with the systematic review of randomized trials is informative. Unlike trials, few, if any, studies reported in our review had published their hypotheses detailing primary exposure, confounder, and outcome relationships prior to reporting results. This is of concern given the possibility of multiple comparisons between numerous psychosocial variables and CHD outcomes within one study. Unlike the situation with randomized trials, there is no register of studies that are testing or could test psychosocial hypotheses. Such a register provides a "denominator of hypotheses", which can then be tracked through the stages of analysis, manuscript preparation, submission, publication, and scientific impact, to determine the extent of any bias.

Study size could potentially influence the likelihood of achieving a strongly positive result. This effect was investigated by calculating the mean number of study participants in studies reporting null or negative, moderate or strong associations in line with the hypothesis, separately for each psychosocial factor. In etiologic studies on depression, the mean number of participants per study was largest for those studies that reported a moderate ($n = 8805$) compared to those reporting a strong ($n = 2993$) or null/negative ($n = 3780$) association. This pattern was the same for etiologic studies on anxiety (null/negative: 1577; moderate: 11 345; strong: 8538) and work characteristics (null/negative: 3060; moderate: 139 496; strong: 5466). However, for type A behavior (null/negative: 5521; moderate: 1919; strong: 1305) and social support (null/negative: 13 009; moderate: 6706; strong: 2730), the largest studies were more likely to show null or negative results. This supports the argument that depression, anxiety, and work characteristics are predictive of CHD occurrence, whereas for type A behavior and social support the associations are produced by the biasing effect of study size. The patterns for depression and social support, but not type A behavior, anxiety, or work characteristics, were similar among prognostic studies.

Furthermore, a number of psychosocial factors were examined in only a small number of studies, and these included anger, aggression, cynicism, dominance,

Table 17.6 Summary of prospective studies investigating psychosocial factors and CHD

	Number of reports of etiological studies ($n = 70$)				Number of reports of prognostic studies ($n = 92$)			
	−	0	+	++	−	0	+	++
Type A behavior/hostility	1	11	5	1	3	10	1	1
Depression	0	8	5	9	0	16	7	11
Anxiety	0	4	1	3	1	9	4	4
Work characteristics	0	3	5	5	0	2	2	0
Social support	0	3	4	2	0	7	4	10

−, finding counter to hypothesis; 0, lack of clear association; +, moderate association (RR ≥ 1·50 and <2·00); ++, strong association (RR ≥ 2·00)

hopelessness, neurosis, submissiveness, and vital exhaustion.[12,18,23,34,48,56–79] These less commonly used psychosocial factors tended to report strong associations with the etiology and prognosis of CHD, which is consistent with a role for publication bias.

A further bias may occur after publication. Positive studies may be more influential than studies in which there is a lack of clear association. We attempted to evaluate the effect of such an influence bias, using the number of citations on the Science Citation Index. Figure 17.1 suggests that the frequency of citation was highest for strongly positive studies, intermediate for moderately positive studies and lowest for those lacking a clear association. In the first period of assessment, studies not showing a clear association were cited most frequently, and this result is strongly influenced by the high frequency of citing the two major null studies on the TABP–CHD association.[26,80] This suggests that selective citing of positive studies, rather than using systematic reviews, may be used in specifying hypotheses. Moreover, it is clear from the tables that multiple reporting of results from the same study is an important issue and that it is not always apparent that the same study has been used for several papers. This further increases the opportunity for influence bias.

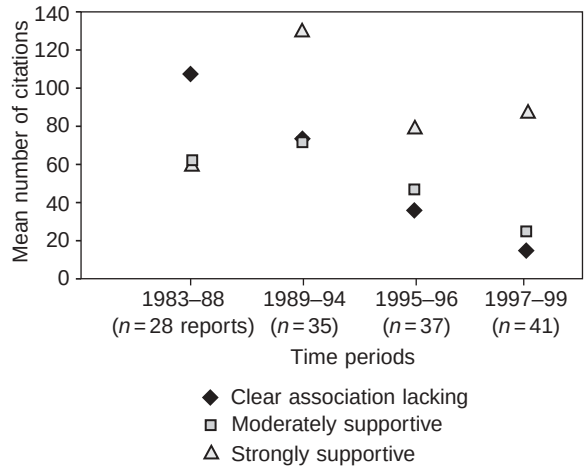

Figure 17.1 The association between the size of the effect estimate and number of citations: an indicator of influence bias

Conclusion

Our systematic review of prospective studies published up until 2001 identified 70 reports of etiologic effects and 92 reports of prognostic effects by psychosocial factors (Table 17.6). Based on prospective epidemiologic data, there was evidence for an association between depression, social support, and psychosocial work characteristics with CHD etiology and prognosis. However, the randomized trial data suggesting that psychosocial interventions reduce mortality post-MI are conflicting: three large trials to date have been negative. The field of psychosocial factors and CHD has grown over the last decade: a key challenge in terms of cardiologic practice in the next decade is to clarify the role, if any, of psychosocial factors in secondary prevention.

We should be grateful for information on any eligible studies that we may have missed.

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References

1. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ* 1999;**318**:1460–7.

2. Hill AB. The environment and disease: association or causation? *Proc Roy Soc Med* 1965;**58**:295–300.
3. Aromaa A, Raitasalo R, Reunanen A *et al.* Depression and cardiovascular diseases. *Acta Psychiatr Scand Suppl* 1994;**377**: 77–82.
4. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* 1996;**94**:3123–9.
5. Penninx BW, Beekman AT, Honig A *et al.* Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001;**58**:221–7.
6. Cohen HW, Madhavan S, Alderman MH. History of treatment for depression: risk factor for myocardial infarction in hypertensive patients. *Psychosom Med* 2001;**63**:203–9.
7. Stansfeld SA, Marmot MG (eds). *Stress and the heart.* London: BMJ Books, 2002.
8. Hemingway H, Malik M, Marmot M. Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function. *Eur Heart J* 2001;**22**: 1082–101.
9. Horsten M, Wamala SP, Vingerhoets A, Orth-Gomer K. Depressive symptoms, social support, and lipid profile in healthy middle-aged women. *Psychosom Med* 1997;**59**: 521–8.
10. Brisson C, Larocque B, Moisan J, Vezina M, Dagenais GR. Psychosocial factors at work, smoking, sedentary behavior, and body mass index: a prevalence study among 6995 white collar workers. *J Occup Environ Med* 2000;**42**:40–6.
11. Brunner E. Stress and the biology of inequality. *BMJ* 1997; **314**:1472–6.
12. Kawachi I, Sparrow D, Kubzansky LD, Spiro A III, Vokonas PS, Weiss ST. Prospective study of a self-report type A scale and risk of coronary heart disease: test of the MMPI-2 type A scale. *Circulation* 1998;**98**:405–12.
13. Everson SA, Kauhanen J, Kaplan GA *et al.* Hostility and increased risk of mortality and acute myocardial infarction: the mediating role of behavioural risk factors. *Am J Epidemiol* 1997;**146**:142–52.
14. Ladwig KH, Kieser M, Konig J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction. Results from the post-infarction late potential study. *Eur Heart J* 1991;**12**:959–64.
15. Barefoot JC, Helms MJ, Mark DB *et al.* Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* 1996;**78**:613–17.
16. Frasure-Smith N. In-hospital symptoms of psychological stress as predictors of long-term outcome after acute myocardial infarction in men. *Am J Cardiol* 1991;**67**:121–7.
17. Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. *Am J Cardiol* 1991;**68**:1171–5.
18. Ahern DK, Gorkin L, Anderson JL *et al.* Biobehavioural variables and mortality/cardiac arrest in the cardiac arrhythmia pilot study. *Am J Cardiol* 1990;**66**:59–62.
19. Kawachi I, Colditz GA, Ascherio A *et al.* A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA. *J Epidemiol Community Health* 1996;**50**:245–51.
20. Haan MN. Job strain and ischaemic heart disease: an epidemiologic study of metal workers. *Ann Clin Res* 1988;**20**: 143–5.
21. Jenkins CD, Rosenman RH, Zyzanski SJ. Prediction of clinical coronary heart disease by a test of the coronary-prone behaviour pattern. *N Engl J Med* 1974;**290**:1271–5.
22. Rosenman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in Western Collaborative Group study. *Am J Cardiol* 1976; **37**:903–9.
23. Haynes SG, Feinleib M, Kannel WB. The relationship of psychosocial factors to coronary heart disease in the Framingham study: 3. Eight year incidence of coronary heart disease. *Am J Epidemiol* 1980;**111**:37–58.
24. Sebregts EH, Falger PR, Bar FW. Risk factor modification through nonpharmacological interventions in patients with coronary heart disease. *J Psychosom Res* 2000;**48**:425–41.
25. Ragland DR, Brand RJ. Coronary heart disease mortality in the Western Collaborative Group study: follow-up experience of 22 years. *Am J Epidemiol* 1988;**127**:462–75.
26. Shekelle RB, Hulley SB, Neaton JD *et al.* The MRFIT behavior pattern study. II. Type A behavior and incidence of coronary heart disease. *Am J Epidemiol* 1985;**122**:559–70.
27. Tunstall-Pedoe H, Woodward M, Tavendale R, Brook RA, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. *BMJ* 1997;**315**:722–9.
28. Eaker ED, Abbott RD, Kannel WB. Frequency of uncomplicated angina pectoris in type A compared with type B persons (the Framingham study). *Am J Cardiol* 1989;**63**: 1042–5.
29. Barefoot JC, Larsen S, von der Lieth L, Schroll M. Hostility, incidence of acute myocardial infarction and mortality in a sample of older Danish men and women. *Am J Epidemiol* 1995;**142**:477–84.
30. Ragland DR, Brand RJ. Type A behaviour and mortality from coronary heart disease. *N Engl J Med* 1988;**318**:65–9.
31. Eaker ED, Castelli WP. Type A behavior and mortality from coronary disease in the Framingham study. *N Engl J Med* 1988;**319**:1480–1.
32. Penninx BW, Guralnik JM, Mendes de Leon CF *et al.* Cardiovascular events and mortality in newly and chronically depressed persons >70 years of age. *Am J Cardiol* 1998; **81**:988–94.
33. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. *Arch Intern Med* 2000;**160**: 1261–8.
34. Hallstrom T, Lapidus L, Bengtsson C, Edstrom K. Psychosocial factors and risk of ischaemic heart disease and death in women: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *J Psychosom Res* 1986;**30**:451–9.
35. Sesso HD, Kawachi I, Vokonas PS, Sparrow D. Depression and the risk of coronary heart disease in the Normative Aging Study. *Am J Cardiol* 1998;**82**:851–6.
36. Ariyo AA, Haan M, Tangen CM *et al.* Depressive symptoms and risks of coronary heart disease and mortality in elderly

Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation* 2000;**102**:1773–9.
37. Schleifer SJ, Macari-Hinson MM, Coyle DA *et al.* The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989;**149**:1785–9.
38. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18 month prognosis after myocardial infarction. *Circulation* 1995;**91**:999–1005.
39. Medalie JH, Snyder M, Groen JJ, Neufeld HN, Goldbourt U, Riss E. Angina pectoris among 10 000 men. 5 year incidence and univariate analysis. *Am J Med* 1973;**55**:583–94.
40. Medalie JH, Goldbourt U. Angina pectoris among 10 000 men. II. Psychosocial and other risk factors as evidenced by a multivariate analysis of a five year incidence study. *Am J Med* 1976;**60**:910–21.
41. Haines AP, Imeson JD, Meade TW. Phobic anxiety and ischaemic heart disease. *BMJ* 1987;**295**:297–9.
42. Kawachi I, Colditz GA, Ascherio A *et al.* Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation* 1994;**89**:1992–7.
43. Haines A, Cooper J, Meade TW. Psychological characteristics and fatal ischaemic heart disease. *Heart* 2001;**85**:385–9.
44. Karasek RA. Job demands, job decision latitude and mental strain: implications for job design. *Admin Sci Q* 1979;**24**: 285–308.
45. Karasek, Theorell T. *Healthy work: stress productivity and reconstruction of working life*. New York, NY: Basic Books, 1990.
46. Siegrist J, Peter R, Junge A, Cremer P, Seidel D. Low status control, high effort at work and ischemic heart disease: prospective evidence from blue-collar men. *Soc Sci Med* 1990;**31**:1127–34.
47. Williams RB, Barefoot JC, Califf RM *et al.* Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. *JAMA* 1992;**267**:520–4.
48. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. *J Intern Med* 2000;**247**:629–39.
49. Linden W, Stossel C, Maurice J. Psychosocial interventions in patients with coronary artery disease: a meta-analysis. *Arch Intern Med* 1996;**156**:745–52.
50. Friedman M, Thoresen CE, Gill JJ *et al.* Alteration of type A behavior and its effect on cardiac recurrences in post myocardial infarction patients: summary results of the recurrent coronary prevention project. *Am Heart J* 1986;**112**: 653–65.
51. Frasure-Smith N, Prince R. Long-term follow-up of the Ischemic Heart Disease Life Stress Monitoring Program. *Psychosom Med* 1989;**51**:485–513.
52. Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicenter randomised controlled trial. *BMJ* 1996;**313**:1517–21.
53. Frasure-Smith N, Lesperance F, Prince RH *et al.* Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. *Lancet* 1997; **350**:473–9.
54. Blumenthal JA, O'Connor C, Hinderliter A *et al.* Psychosocial factors and coronary disease. A national multicenter clinical trial (ENRICHD) with a North Carolina focus. *N C Med J* 1997;**58**:440–4.
55. Ornish D, Brown SE, Scherwitz LW *et al.* Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet* 1990;**336**:129–33.
56. Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. *Eur Heart J* 1988;**9**:758–64.
57. Appels A, Mulder P. Fatigue and heart disease. The association between "vital exhaustion" and past, present and future coronary heart disease. *J Psychosom Res* 1989;**33**:727–38.
58. Appels A, Schouten E. Waking up exhausted as risk indicator of myocardial infarction. *Am J Cardiol* 1991;**68**:395–8.
59. Almada SJ, Zonderman AB, Shekelle RB *et al.* Neuroticism and cynicism and risk of death in middle-aged men: the Western Electric Study. *Psychosom Med* 1991;**53**:165–75.
60. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham study. *Am J Epidemiol* 1992;**135**:854–64.
61. Anda R, Williamson D, Jones D *et al.* Depressed affect, hopelessness, and the risk of ischaemic heart disease in a cohort of US adults. *Epidemiol* 1993;**4**:285–94.
62. Everson SA, Goldberg DE, Kaplan GA *et al.* Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. *Psychosom Med* 1996;**58**:113–21.
63. Kawachi I, Sparrow D, Spiro A 3rd, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. *Circulation* 1996;**94**:2090–5.
64. Whiteman MC, Deary IJ, Lee AJ, Fowkes FG. Submissiveness and protection from coronary heart disease in the general population: Edinburgh Artery Study. *Lancet* 1997;**350**: 541–5.
65. Cole SR, Kawachi I, Sesso HD, Paffenbarger RS, Lee IM. Sense of exhaustion and coronary heart disease among college alumni. *Am J Cardiol* 1999;**84**:1401–5.
66. Gallacher JE, Yarnell JW, Sweetnam PM, Elwood PC, Stansfeld SA. Anger and incident heart disease in the Caerphilly study. *Psychosom Med* 1999;**61**:446–53.
67. Appels A, Kop WJ, Schouten E. The nature of the depressive symptomatology preceding myocardial infarction. *Behav Med* 2000;**26**:86–9.
68. Siegman AW, Kubzansky LD, Kawachi I, Boyle S, Vokonas PS, Sparrow D. A prospective study of dominance and coronary heart disease in the Normative Aging Study. *Am J Cardiol* 2000;**86**:145–9.
69. Williams JE, Paton CC, Siegler IC, Eigenbrodt ML, Nieto FJ, Tyroler HA. Anger proneness predicts coronary heart disease risk: prospective analysis from the atherosclerosis risk in communities (ARIC) study. *Circulation* 2000;**101**:2034–9.
70. Palmer KJ, Langeluddecke PM, Jones M. The relation of the type A behaviour pattern, factors of the structured interview, and anger to survival after myocardial infarction. *Aus J Psych* 1992;**44**:13–19.
71. Kop WJ, Appels A, de Leon CF, de Swart HB, Bar FW. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med* 1994;**56**:281–7.
72. Appels A, Kop W, Bar F, de Swart H, Mendes de Leon C. Vital exhaustion, extent of atherosclerosis, and the clinical course after successful percutaneous transluminal coronary angioplasty. *Eur Heart J* 1995;**16**:1880–5.

73. Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol* 1995;**14**: 388–98.
74. Friedmann E, Thomas SA. Pet ownership, social support and one-year survival after acute myocardial infarction in the cardiac arrhythmia suppression trial (CAST). *Am J Cardiol* 1995; **76**:1213–17.
75. Hoffmann A, Pfiffner D, Hornung R, Niederhauser H. Psychosocial factors predict medical outcome following a first myocardial infarction. Working Group on Cardiac Rehabilitation of the Swiss Society of Cardiology. *Coron Artery Dis* 1995;**6**:147–52.
76. Mendes de Leon CF, Kop WJ, de Swart HB, Bar FW, Appels AP. Psychosocial characteristics and recurrent events after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1996;**77**:252–5.
77. Carinci F, Nicolucci A, Ciampi A *et al.* Role of interactions between psychological and clinical factors in determining 6-month mortality among patients with acute myocardial infarction. Application of recursive partitioning techniques to the GISSI-2 database. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. *Eur Heart J* 1997; **18**:835–45.
78. Frasure-Smith N, Lesperance F, Juneau M, Talajic M, Bourassa MG. Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom Med* 1999;**61**: 26–37.
79. Barefoot JC, Brummett BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. *Psychosom Med* 2000;**62**: 790–5.
80. Shekelle RB, Gale M, Ostfeld AM, Paul O. Hostility, risk of coronary heart disease and mortality. *Psychosom Med* 1983;**45**:109–14.
81. Cohen JB, Reed D. The type A pattern and coronary heart disease among Japanese men in Hawaii. *J Behav Med* 1985; **4**:343–52.
82. Appels A, Mulder P, van 't Hof M, Jenkins CD, van Houtem J, Tan F. A prospective study of the Jenkins Activity Survey as a risk indicator for coronary heart disease in the Netherlands. *J Chronic Dis* 1987;**40**:959–65.
83. Johnston DW, Cook DG, Shaper AG. Type A behaviour and ischaemic heart disease in middle-aged British men. *BMJ* 1987;**295**:86–9.
84. Koskenvuo M, Kaprio J, Rose RJ *et al.* Hostility as a risk factor for mortality and ischemic heart disease in men. *Psychosom Med* 1988;**50**:330–40.
85. Hollis JF, Connett JE, Stevens VJ, Greenlick MR. Stressful life events, Type A behavior, and the prediction of cardiovascular and total mortality over six years. MRFIT Group. *J Behav Med* 1990;**13**:263–80.
86. Bosma H, Appels A, Sturmans F. Psychosocial factors in the aetiology of coronary heart disease: follow-up to the Kaunas-Rotterdam intervention study (KRIS). *Cardiology* 1995;**2**:54–9.
87. Case RB, Heller SS, Case NB, Moss AJ. Type A behavior and survival after acute myocardial infarction. *N Engl J Med* 1985;**312**:737–41.
88. Shekelle RB, Gale M, Norusis M. Type A score (Jenkins activity survey) and risk of recurrent coronary heart disease in the aspirin myocardial infarction study. *Am J Cardiol* 1985;**56**: 221–5.
89. Brackett CD, Powell LH. Psychosocial and physiological predictors of sudden cardiac death after healing of acute myocardial infarction. *Am J Cardiol* 1988;**61**:979–83.
90. Barefoot JC, Peterson BL, Harrell FEJ. Type A behavior and survival: a follow-up study of 1467 patients with coronary artery disease. *Am J Cardiol* 1989;**64**:427–32.
91. Jenkinson CM, Madeley RJ, Mitchell JR, Turner ID. The influence of psychosocial factors on survival after myocardial infarction. *Public Health* 1993;**107**:305–17.
92. Irvine J, Basinski A, Baker B *et al.* Depression and risk of sudden cardiac death after acute myocardial infarction: testing for the confounding effects of fatigue. *Psychosom Med* 1999; **61**:729–37.
93. Kaufmann MW, Fitzgibbons JP, Sussman EJ *et al.* Relation between myocardial infarction, depression, hostility, and death. *Am Heart J* 1999;**138**:549–54.
94. Ostfeld AM, Lebovits BZ, Shekelle RB, Paul O. A prospective study of the relationship between personality and coronary heart disease. *J Chronic Dis* 1964;**17**:265–76.
95. Vogt T, Pope C, Mullooly J, Hollis J. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. *Am J Public Health* 1994;**84**:227–31.
96. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction and total mortality in a community sample. *Circulation* 1996;**93**:1976–80.
97. Wassertheil-Smoller S, Applegate WB, Berge K *et al.* Change in depression as a precursor of cardiovascular events. SHEP Cooperative Research Group (Systoloc Hypertension in the elderly). *Arch Intern Med* 1996;**156**:553–61.
98. Mendes de Leon CF, Krumholz HM, Seeman TS *et al.* Depression and risk of coronary heart disease in elderly men and women: New Haven EPESE, 1982–1991. Established Populations for the Epidemiologic Studies of the Elderly. *Arch Intern Med* 1998;**158**:2341–8.
99. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch Intern Med* 1998;**158**: 1422–6.
100. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med* 1999;**106**: 605–12.
101. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: Association with use of tricyclic agents. *Am J Med* 2000;**108**:2–8.
102. Chang M, Hahn RA, Teutsch SM, Hutwagner LC. Multiple risk factors and population attributable risk for ischemic heart disease mortality in the United States, 1971–1992. *J Clin Epidemiol* 2001;**54**:634–44.
103. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. *Ann Intern Med* 1992;**117**:1003–9.

104.Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993;**270**:1819–25.
105.Ladwig KH, Roll G, Breithardt G, Budde T, Borggrefe M. Post infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* 1994;**343**:20–3.
106.Denollet J, Sys SU, Brutsaert DL. Personality and mortality after myocardial infarction. *Psychosom Med* 1995;**57**: 582–91.
107.Oxman TE, Freeman DH Jr, Manheimer ED. Lack of social participation or religious strength and comfort as risk factors for death after cardiac surgery in the elderly. *Psychosom Med* 1995;**57**:5–15.
108.Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL. Personality as independent predictor of long term mortality in patients with coronary heart disease. *Lancet* 1996;**347**:417–21.
109.Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;**58**:99–110.
110.Krumholz HM, Butler J, Miller J *et al.* Prognostic importance of emotional support for elderly patients hospitalized with heart failure. *Circulation* 1998;**97**:958–64.
111.Murberg TA, Bru E, Svebak S, Tveteras R, Aarsland T. Depressed mood and subjective health symptoms as predictors of mortality in patients with congestive heart failure: a two-years follow-up study. *Int J Psychiatry Med* 1999;**29**: 311–26.
112.Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: adverse effects of type D personality and younger age on 5-year prognosis and quality of life. *Circulation* 2000;**102**:630–5.
113.Herrmann C, Brand-Driehorst S, Buss U, Ruger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. *J Psychosom Res* 2000;**48**: 455–62.
114.Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur Heart J* 2000;**21**:1072–80.
115.Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Effects of depression and anxiety on mortality and quality-of-life 4 months after myocardial infarction. *J Psychosom Res* 2000; **49**:229–38.
116.Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction? *Quarterly J Med* 2000;**93**:739–44.
117.Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000;**160**:1354–60.
118.Baker RA, Andrew MJ, Schrader G, Knight JL. Preoperative depression and mortality in coronary artery bypass surgery: Preliminary findings. *Aust N Z J Surg* 2001;**71**:139–42.
119.Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosom Med* 2001;**63**:221–30.
120.Kubzansky LD, Kawachi I, Spiro A III, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation* 1997;**95**:818–24.
121.Allison TG, Williams DE, Miller TD *et al.* Medical and economic costs of psychologic distress in patients with coronary artery disease. *Mayo Clin Proc* 1995;**70**:734–42.
122.Perski A, Feleke E, Anderson G *et al.* Emotional distress before coronary bypass grafting limits the benefits of surgery. *Am Heart J* 1998;**136**:510–17.
123.Mayou RA, Gill D, Thompson DR *et al.* Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med* 2000;**62**:212–19.
124.Theorell T, Floderus-Myrhed B. "Workload" and risk of myocardial infarction – a prospective psychosocial analysis. *Int J Epidemiol* 1977;**6**:17–21.
125.Lacroix A, Haynes S. Occupational exposure to high demand/ low control work and coronary heart disease incidence in the Framingham cohort. *Am J Epidemiol* 1984;**120**:481.
126.Alfredsson L, Spetz C-L, Theorell T. Type of occupation and near-future hospitalization for myocardial infarction and some other diagnoses. *Int J Epidemiol* 1985;**14**:378–88.
127.Reed DM, Lacroix AZ, Karasek RA, Miller D, MacLean CA. Occupational strain and the incidence of coronary heart disease. *Am J Epidemiol* 1989;**129**:495–502.
128.Netterstrom B, Suadicani P. Self-assessed job satisfaction and ischaemic heart disease mortality: a 10 year follow up of urban bus drivers. *Int J Epidemiol* 1993;**22**:51–6.
129.Suadicani P, Hein HO, Gynetelberg F. Are social inequalities as associated with the risk ischaemic heart disease a result of psychosocial working conditions? *Atherosclerosis* 1993;**101**: 165–75.
130.Alterman T, Shekelle RB, Vernon SW, Burau KD. Decision latitude, psychologic demand, job strain, and coronary heart disease in the Western Electric study. *Am J Epidemiol* 1994; **139**:620–7.
131.Bosma H, Marmot MG, Hemingway H, Nicholson A, Brunner EJ, Stansfeld S. Low job control and risk of coronary heart disease in the Whitehall II (prospective cohort) study. *BMJ* 1997;**314**:558–65.
132.Lynch J, Krause N, Kaplan GA, Tuomilehto J, Salonen JT. Workplace conditions, socioeconomic status, and the risk of mortality and acute myocardial infarction: the Kuopio ischaemic heart disease risk factor study. *Am J Public Health* 1997;**87**:617–22.
133.Steenland K, Johnson J, Nowlin S. A follow up study of job strain and heart disease among males in the NHANES1 population. *Am J Ind Med* 1997;**31**:256–60.
134.Bosma H, Peter R, Siegrist J, Marmot M. Two alternative job stress models and the risk of coronary heart disease. *Am J Public Health* 1998;**88**:68–74.
135.Moore L, Meyer F, Perusse M *et al.* Psychological stress and incidence of ischaemic heart disease. *Int J Epidemiol* 1999; **28**:652–8.
136.Hlatky MA, Lam LC, Lee KL *et al.* Job strain and the prevalence and outcome of coronary artery disease. *Circulation* 1995;**92**:327–33.
137.Orth-Gomer K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. *JAMA* 2000; **284**:3008–14.

138.House JS, Robbins C, Metzner HL. The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community Health Study. *Am J Epidemiol* 1982;**116**:123–40.
139.Berkman LF, Breslow L. *Health and ways of living*. New York: Oxford University Press, 1983.
140.Reed D, McGee D, Yano K, Feinleib M. Social networks and coronary heart disease among Japanese men in Hawaii. *Am J Epidemiol* 1983;**117**:384–96.
141.Kaplan GA, Salonen JT, Cohen RD. Social connections and mortality from all causes and from cardiovascular disease: prospective evidence from Eastern Finland. *Am J Epidemiol* 1988;**128**:370–80.
142.Vogt T, Mullooly J, Ernst D, Pope C, Hollis J. Social networks as predictors of ischemic heart disease, cancer, stroke and hypertension: incidence, survival and mortality. *J Clin Epidemiol* 1992;**45**:659–66.
143.Orth-Gomer K, Rosengren A, Wilhelmsen L. Lack of social support and incidence of coronary heart disease in middle-aged Swedish men. *Psychosom Med* 1993;**55**:37–43.
144.Hedblad B, Ostergren PO, Hanson BS, Janzon L, Johansson BW, Juul-Moller S. Influence of social support on cardiac event rate in men with ischaemic type ST segment depression during ambulatory 24-h long-term ECG recording. The prospective population study "Men born in 1914", Malmo, Sweden. *Eur Heart J* 1992;**13**:433–9.
145.Gorkin L, Schron EB, Brooks MM *et al.* Psychosocial predictors of mortality in the cardiac arrhythmia suppression trial-1 (CAST-1). *Am J Cardiol* 1993;**71**:263–7.
146.Greenwood D, Packham C, Muir K, Madeley R. How do economic status and social support influence survival after initial recovery from acute myocardial infarction? *Soc Sci Med* 1995; **40**:639–47.
147.Farmer IP, Meyer PS, Ramsey DJ *et al.* Higher levels of social support predict greater survival following acute myocardial infarction: the Corpus Christi Heart Project. *Behav Med* 1996;**22**:59–66.
148.Woloshin S, Schwartz LM, Tosteson AN *et al.* Perceived adequacy of tangible social support and health outcomes in patients with coronary artery disease. *J Gen Intern Med* 1997;**12**:613–18.
149.Herlitz J, Wiklund I, Caidahl K *et al.* The feeling of loneliness prior to coronary artery bypass grafting might be a predictor of short- and long-term postoperative mortality. *Eur J Vasc Endovasc Surg* 1998;**16**:120–5.
150.Brummett BH, Barefoot JC, Siegler IC *et al.* Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosom Med* 2001;**63**: 267–72.

18 Emerging approaches in cardiovascular prevention

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Introduction

Reductions in cholesterol and blood pressure, and smoking cessation, have been shown to be effective strategies in the prevention of cardiovascular diseases (CVD).[1] However, these "classic" risk factors, along with known non-modifiable risk factors, such as age, gender, and family history, may not fully explain why certain individuals develop myocardial infarction (MI) and stroke, while others do not.[2]

These observations suggest that factors other than known risk factors for CVD play an important role in the pathogenesis of coronary heart disease (CHD) and stroke and that new preventive therapies aimed at modifying these new risk factors may be additionally useful. In this chapter, we will review a number of emerging risk factors and potential new preventive strategies. In particular, we will review the evidence for:

- The potential role for oxidation of low density lipoprotein (LDL) in atherogenesis and the use of antioxidants in CV prevention.
- The activation of neurohormonal pathways, particularly the renin–angiotensin axis and its modification by angiotensin-converting enzyme (ACE) inhibitors in high-risk groups.
- Hyperhomocysteinemia and its modification by folic acid.
- Inflammation and infection and the potential therapeutic use of anti-inflammatory and anti-infectious agents.

Other chapters in this book deal with dysglycemia, estrogens, and psychosocial factors.

Oxidative stress and use of antioxidants in cardiovascular prevention

Pathophysiology and biologic rationale

Oxidative modification of LDL cholesterol is an important step in the pathogenesis of atherosclerosis.[3,4] Oxidized LDL is potentially more atherogenic than native LDL. It is recognized and rapidly taken up by "scavenger" macrophage receptors, giving rise to foam cells; it is directly cytotoxic for endothelial cells and attracts further macrophages to the subintima; it stimulates vascular smooth muscle proliferation and autoantibody formation; and contributes to increased vascular tone and coagulability. Experimental studies *in vitro* as well as *in vivo* in different animal models of atherosclerosis suggest that antioxidants could decrease or prevent LDL oxidation and inhibit atherosclerosis.[3]

Epidemiology and randomized controlled clinical trials

Epidemiologic studies have generally reported inverse associations between intake of various antioxidants and CHD risk. Most attention thus far has been directed to the study of naturally occurring antioxidants, particularly vitamin E, vitamin C, and beta-carotene, although other carotenoids, flavonoids, selenium, magnesium, and monounsaturated fatty acids are also found in natural food products and may reduce LDL oxidation. The major lipid soluble antioxidant vitamins are vitamin E (alpha-tocopherol), the predominant antioxidant present in plasma membranes, tissues, and LDL cholesterol, and beta-carotene, a precursor of vitamin A. The major water soluble antioxidant vitamin is vitamin C (ascorbic acid), which can regenerate alpha-tocopherol from the tocopheroxyl radical form, thus preserving lipophilic antioxidant within the LDL particles. In addition to foods rich in antioxidant vitamins, antioxidants are available as vitamin supplements, generally at doses much higher than those provided by balanced diets.

A number of epidemiologic studies suggest an inverse association between dietary intake of vegetables and fruits, which are generally rich in antioxidants, and CV risk.[2,5,6] It is unclear, however, which component of these dietary products might be cardioprotective. In addition, a number of cross-sectional geographic correlation studies suggest a strong inverse association between CHD prevalence and the use of diets rich in antioxidants.[7] Large prospective cohort studies have evaluated associations between dietary and/or supplemental antioxidant vitamins and CV risk, and large randomized controlled studies have assessed the role of vitamin supplements in CV prevention.

Vitamin E

Vitamin E supplements, most of which contain 200–800 IU, lead to intake far greater than the Recommended Daily

Allowance (RDA) of 30 IU and well beyond those attainable by diets. Large prospective epidemiological studies such as the US Nurses' Health Study and the US Male Health Professionals' Study suggested that the use of vitamin E *supplements* for two or more years, most commonly at doses of 200–400 IU per day, is associated with a 20–40% lower risk of CHD.[8–10] However, other studies identified vitamin E from *food sources* (but not supplements) to be potentially cardioprotective, although in these studies supplemental vitamin E use was low.[11,12]

In contrast to the epidemiological studies, most randomized clinical trials conducted to date have failed to confirm benefit. A recent randomized trial evaluated the effects of vitamin E on the anatomic progression of carotid atherosclerotic vascular disease. The Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E (SECURE), conducted in 732 middle-aged and elderly patients with vascular disease, found supplementation with natural source vitamin E (RRR-alpha-tocopherol acetate) 400 IU/day to have a neutral effect on the rate of progression of carotid intimal-medial thickness (IMT).[13] Six large randomized placebo-controlled trials of vitamin E supplementation with major CV morbidity and mortality end points have been completed (Table 18.1). These trials have evaluated different populations, comprising both low-risk individuals targeted for primary prevention,[14,15] and high-risk patients with coronary and/or other vascular disease[16–19] and have used different vitamin E preparations and doses. These trials have generally failed to demonstrate a beneficial role for the use of vitamin E supplements both in primary and secondary CV

Table 18.1 Large (>1000 subjects) randomized trials of vitamin E

Trial	Study participants	Follow up (yr)	Daily vitamin E dose	Outcomes	Relative risk reduction (%) (95% CI)
ATBC[14]	29 133 male smokers in Finland	6·1	50 mg	All-cause death	−2[b] (−9–5)
				CV death	2 (−8–11)
PPP[15]	4495 people with risk factor(s) for CHD in Italy	3·6	300 mg	CV death, non-fatal MI and non-fatal stroke	−7 (−56–26)
				All-cause death	−7 (−49–23)
ATBC[16a]	1862 men with previous MI	6·1	50 mg	CHD death and non-fatal MI	3 (−19–20)
				Non-fatal MI	11 (−20–33)
				CHD death	−5 (−37–20)
CHAOS[17]	2002 patients with CHD in the UK	1·4	800 IU/ 400 IU	Non-fatal MI	77 (53–89)
				All-cause death	−29 (−119–24)
				CV death	−10 (−96–39)
GISSI[18]	11 324 patients with recent MI in Italy	3·5	300 mg	All-cause death, non-fatal MI and non-fatal stroke	5 (−5–15)
				CV death, non-fatal MI and non-fatal stroke	2 (10–13)
HOPE[19]	9541 patients with CV disease or diabetes with additional risk factor(s)	4·5	400 IU	CV death, non-fatal MI and non-fatal stroke	−5 (−16–5)
				CV death	−5 (−22–10)
				MI	−2 (−15–10)
				Stroke	−17 (−42–5)

[a] Substudy of study.[14]
[b] Minus sign indicates an increased risk.
Abbreviations: ATBC, Alpha-tocopherol, Beta-carotene Cancer Prevention Study; CHAOS, Cambridge Heart AntiOxidant Study; GISSI, GISSI Prevenzione Trial; HOPE, Heart Outcomes Prevention Evaluation Study; PPP, Primary Prevention Project

prevention and therefore the widespread use of this intervention cannot be endorsed, especially if perceived as a "replacement" for proven, effective preventive lifestyle modifications and pharmacological therapies.

The Secondary Prevention with Antioxidants in Endstage renal disease (SPACE) trial was a randomized placebo-controlled trial of 196 hemodialysis patients with pre-existing CV disease.[20] Patients in the vitamin E arm had a 54% relative risk reduction (95% CI 22–72; $P = 0{\cdot}014$) in the primary study end point, the composite of fatal or non-fatal MI, ischemic stroke, peripheral vascular disease, and unstable angina. This relatively small trial conducted in a very high-risk population requires further confirmation.

Beta-carotene

Large prospective epidemiologic cohort studies suggest an inverse association between beta-carotene intake (derived from nutritional sources and vitamin supplements) and CV risk in men, particularly current or former smokers,[8–12,21] but not in women. Several large, long-term, well-designed randomized trials of beta-carotene in primary prevention have consistently failed to show benefit from beta-carotene, in the prevention of both CVD and cancer (Table 18.2). Furthermore, concern about an increased risk of cancer was present in some investigations. In a subset of patients with previous MI (secondary prevention) enrolled in the ATBC trial there was overall no CV benefit in subjects randomized

Table 18.2 Large randomized trials of beta-carotene

Trial	Study participants	Follow up (yr)	Beta-carotene dose	Outcome	Relative risk reduction (%) (95% CI)
ATBC[14]	29 133 male smokers in Finland	6·1	20 mg/day	All-cause death	−9[b] (−17 to −2)
				CV death	−11 (−23–1)
				Death from cancer	−9 (−23–3)
				New lung cancer	−18 (−36 to −31)
CARET[22]	18 314 male smokers, former smokers and workers exposed to asbestos in the United States	4·0	30 mg/day[a]	All-cause death	−17 (−33–3)
				CV death	−26 (−61–1)
				Death from cancer	−46 (−100 to −7)
				New lung cancer	−28 (−57 to −4)
PHS[23]	22 071 male physicians in the United States	12·0	50 mg/ alternate days	All-cause death	−2 (−11–7)
				CV death	−9 (−27–7)
				Death from cancer	−2 (−18–11)
				New lung cancer	7 (−27–32)
				MI	4 (−9–16)
				Stroke	4 (−11–17)
SCPS[21]	1188 men and 532 women in the United States	8·2	50 mg/day	All-cause death	−3 (−30–17)
				CV death	−16 (−64–18)
				Death from cancer	17 (−29–56)

[a] Patients randomized to beta-carotene also received 25 000 U/day of retinol (vitamin A).
[b] Minus sign indicates an increased risk.
Abbreviations: ATBC, Alpha-tocopherol, Beta-carotene Cancer Prevention Study; CARET, β-Carotene and Retinol Efficacy Trial; PHS, Physicians' Health Study; SCPS, Skin Cancer Prevention Study

to treatment with beta-carotene. A small increase in the risk of fatal CHD was noted in the beta-carotene group.

Vitamin C

The epidemiological studies evaluating the supplemental use of vitamin C are not very persuasive. The National Health and Nutrition Examination Survey (NHANES) prospectively evaluated 11 348 US adults and found a 34% lower standardized mortality ratio (95% CI 18·1–47·1) among subjects who received 50 mg of vitamin C per day by diet or vitamin supplements compared with those who received less vitamin C.[24] The study did, however, not correct for supplemental vitamin E use. Most other prospective data have not clearly identified vitamin C as a significant cardioprotective agent. Overall, the epidemiological data evaluating vitamin C and CVD have significant inconsistencies and a number of large prospective epidemiologic studies, after adjusting for other risk factors and for use of other antioxidant vitamins, failed to identify vitamin C use to be independently associated with lower cardiovascular risk.[10]

There have been no large randomized clinical trials of vitamin C supplementation. Three relatively small randomized trials performed in elderly patients failed to demonstrate beneficial effects of vitamin C supplementation.[25–27]

Clinical trials using combined antioxidant vitamins

It was suggested that combined antioxidant vitamin therapy might be more effective than the use of individual vitamins alone. The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study reported that combined vitamin E and C supplementation caused a significant reduction in carotid IMT progression in men, with no benefit in women.[28] The HDL–Atherosclerosis Treatment Study (HATS), however, found that the addition of antioxidant vitamins (daily administration of 800 IU vitamin E, 1000 mg vitamin C, 25 mg beta-carotene and 100 g selenium) decreased HDL_2-cholesterol levels and tended to diminish the benefits achieved with simvastatin and niacin alone, both on the anatomic progression of coronary lesions and on clinical outcomes.[29] A large primary prevention trial conducted in China reported a marginally significant reduction in total mortality (RR, 9%; 95% CI 0–70) for a combination of daily vitamin E 30 mg, beta-carotene 15 mg, ascorbic acid 120 mg, selenium 50 g, as well as other micronutrients (retinol, zinc, molybdenum, and niacin), with a trend towards reduced CV mortality (RR, 9%; 95% CI −8–24).[30] The generalizability of this study to Western and other populations with very different diets remains uncertain. The Heart Protection Study randomized 20 536 British patients with CVD, diabetes or treated hypertension to simvastatin (40 mg/day) or matching placebo and to antioxidant vitamins – 600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily – or matching placebo using a 2×2 factorial design. Treatment with antioxidant vitamins resulted in a neutral effect on all study outcomes.[31]

Clinical trials using other antioxidants

Probucol is a lipid lowering agent, which reduces low density lipoprotein (LDL) but also lowers high density lipoprotein (HDL) and has been shown to be a potent antioxidant in a number of experimental studies. The Probucol Quantitative Regression Swedish Trial (PQRST) in 274 hypercholesterolemic subjects failed, however, to reveal any benefit in the progression of femoral atherosclerosis.[32] This lack of benefit from probucol may be related to the significant reduction in HDL cholesterol (by 24%) in patients treated with probucol, compared with those in the placebo group. A small study found that probucol reduced the rate of restenosis after balloon angioplasty in small coronary arteries.[33]

Antioxidants: conclusions and recommendations

Antioxidant vitamin supplements do not reduce CVD events. **Grade A**

Renin–angiotensin axis and impact of angiotensin-converting enzyme (ACE) inhibitors

Pathophysiology and biologic rationale

Experimental and human studies suggest that ACE inhibitors may reduce CV risk through both cardioprotective and vasculoprotective effects mediated by blocking both circulating and tissue renin–angiotensin systems, as well as by bradykinin potentiation.[34] ACE inhibitors are antiproliferative, have antimigratory effects on smooth muscle cells, increase nitric oxide bioavailability, restore endothelial-mediated vascular reactivity, are potent antioxidants and have antithrombotic action by decreasing platelet aggregation and enhancing endogenous fibrinolysis.[34] A possible link between the activation of the renin–angiotensin system and CV risk is supported also by some, although not all, epidemiological and genetic studies.[35–38]

Randomized clinical trials

ACE inhibitors are effective agents in the management of hypertension and heart failure. Clinical trials in patients with low left ventricular ejection fraction with or without heart failure had unexpectedly demonstrated significant reductions in the risk of MI in patients receiving long-term ACE inhibitor therapy.[39–41]

More recently, the impact of ACE inhibitor therapy in patients *without hypertension and without heart failure or low left ventricular ejection fraction* has been evaluated. Several mechanistic studies have evaluated the effects of ACE inhibitors on surrogate outcomes. These studies demonstrate a wide range of blood pressure-independent benefits of ACE inhibitor therapy, including: (a) improved endothelial function, resulting in vasodilation in the coronary and brachial circulation,[42] and in enhanced endogenous fibrinolysis;[43] (b) retardation in the anatomic progression of atherosclerosis, shown in some but not all trials;[13] and (c) improvement in myocardial function and structure.[44]

The most persuasive evidence for the beneficial effect of long-term ACE inhibitor therapy in high-risk patients without heart failure and/or low left ventricular ejection fraction and with or without hypertension, has been provided by the Heart Outcomes Prevention Evaluation (HOPE) trial.[45] This trial enrolled 9297 patients aged 55 years or older with coronary artery disease, peripheral arterial disease or prior stroke, or diabetes with additional risk factors. Treatment with the ACE inhibitor ramipril titrated up to 10 mg daily resulted in a highly significant 22% reduction in the composite primary end point of myocardial infarction, stroke or death from cardiovascular causes (Table 18.3; Figure 18.1). In addition, the risk of stroke, myocardial infarction, need for revascularization procedures, heart failure and the development of diabetes were significantly decreased. In the 3577 patients with diabetes, ramipril significantly reduced the risk of the composite primary outcome by 25% (95% CI 12–36; $P = 0{\cdot}0004$), myocardial infarction by 22%, stroke by 33%, CV death by 37%, all-cause death by 24%, revascularizations by 17%, and overt nephropathy by 24%.[46] These effects were attained with only a modest reduction in blood pressure (3 mmHg reduction in systolic and 1·8 mmHg in diastolic blood pressure) in patients already treated with a variety of cardioprotective, blood pressure lowering and antiischemic medications, suggesting that the treatment benefit was largely independent of blood pressure lowering.

Table 18.3 Effect of ramipril on major CV outcomes in the HOPE trial

	Relative risk reduction (%) (95% CI)	*P*
Myocardial infarction, stroke or CV death	22 (14–30)	<0·0001
Myocardial infarction	20 (10–30)	<0·0001
Stroke	32 (16–44)	<0·0001
CV death	26 (13–36)	<0·0001
Revascularization	15 (6–23)	0·002
Heart failure	23 (13–33)	<0·001
New diabetes	34 (15–49)	<0·001

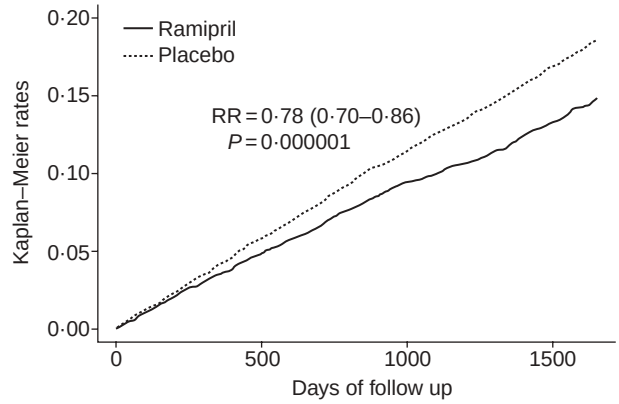

Figure 18.1 Effect of ramipril on the composite primary outcome of myocardial infarction, stroke and death from cardiovascular causes in the HOPE trial. The relative risk of the composite primary outcome in the ramipril group as compared to the placebo group was 0·78 (95% CI 0·70–0·86). (Reproduced with permission from the *New England Journal of Medicine*[45])

The efficacy of a long-term ACE inhibitor-based therapeutic strategy was shown also in the Perindopril pROtection aGainst Recurrent Stroke Study (PROGESS) conducted in 6105 patients with prior stroke or transient ischemic attack. Patients treated with perindopril with or without the addition of indapamide had a 28% reduction in the risk of recurrent stroke and a 26% reduction in the risk of major vascular events.[47]

Ongoing large randomized clinical trials are further evaluating the use of ACE inhibitors in patients with CHD with preserved left ventricular systolic function, the combined use of ACE inhibitors and angiotensin receptor blockers and the use of angiotensin receptor blockers in ACE-intolerant individuals.

ACE inhibitors: conclusions and recommendations

ACE inhibitors are effective in the prevention of major CV events and death in a wide range of patients with vascular disease or diabetes and additional risk factors. In addition, ACE inhibitors are effective in the management of hypertension, heart failure, asymptomatic left ventricular dysfunction and acute myocardial infarction and should be used consistently in these broad categories of patients with vascular disease. **Grade A**

Homocysteine and vascular disease

Pathophysiology and biologic rationale

Homocysteine is a sulfur-containing amino acid produced during catabolism of the essential amino acid methionine. It can be irreversibly degraded by cystathionine-beta-synthase, a process requiring vitamin B_6 as a cofactor. Alternatively,

homocysteine can be remethylated to conserve methionine in a process requiring methionine synthase and methylcobalamin (vitamin B_{12}) as a cofactor and methyl-tetrahydrofolate reductase (MTHFR) as a cosubstrate. This metabolic pathway requires an adequate supply of folate and the enzyme MTHFR. Genetic and acquired abnormalities in the function of these enzymes or deficiencies in folate or vitamin B_6 or B_{12} cofactors can therefore lead to elevated concentrations of intracellular homocysteine, which is then released to the plasma. Very high levels of plasma homocysteine lead to homocystinuria, which is caused by the rare homozygous deficiency of cystathionine-beta-synthase or the even more infrequent homozygous deficiency in MTHFR or defects in cobalamin metabolism. These distinct genetic abnormalities, which share very high levels of plasma homocysteine, have typical clinical manifestations, including severe premature atherosclerotic and thromboembolic disease. Histopathologically, this vascular disease is characterized by vascular endothelial injury, vascular smooth muscle cell proliferation, progressive arterial stenosis, and hemostatic changes consistent with a prothrombotic state. These findings have led McCully to formulate the homocysteine theory of atherosclerosis.[48]

More recently, the modest elevation in plasma homocysteine levels has been evaluated as a potential CV risk factor. Such "modest" elevations in plasma homocysteine can be related to genetic, physiologic, pathologic, and nutritional factors, including MTHFR mutations (for example, thermolabile MTHFR), older age, male gender, postmenopausal status in women, smoking, sedentary lifestyle, dietary factors including increased intake of animal proteins which have a higher methionine content and low intake of folate, vitamins B_6, and B_{12}, renal failure, transplantation, and medications such as corticosteroids and cyclosporin which have been associated with hyperhomocysteinemia.[49]

Potential mechanisms of atherothrombosis associated with elevated homocysteine levels include:

- Endothelial dysfunction related to direct endothelial cell damage and impaired production of nitric oxide.[50]
- Stimulation of smooth muscle cell proliferation.[51]
- Lipid abnormalities, including increased plasma triglycerides and increased susceptibility to oxidation of LDL.[52]
- Increased thrombogenicity mediated by promoting the adherence of platelets and release of platelet-derived growth factors due to homocysteine-induced endothelial damage, activation of factor V, factor Xa, inhibition of protein C activation, inhibition of cell surface expression of thrombomodulin, and decreased tissue plasminogen activator (tPA) activity.[53]

Epidemiology

Several studies have shown associations between the extent of coronary or carotid atherosclerosis and plasma homocysteine levels.[49] A large number of cross-sectional and retrospective observational studies suggest an association between elevated homocysteine levels and CV risk. Boushey *et al* reviewed the major retrospective epidemiologic investigations of homocysteine and CVD up to 1995 and found a linear, independent association between plasma homocysteine concentrations and CV risk;[54] every 5 μmol/l increment in homocysteine was associated with an increased odds ratio for CHD of 1·6 for men (95% CI 1·4–1·7) and 1·8 for women (95% CI 1·3–1·9), of 1·5 for cerebrovascular disease and of 6·8 for peripheral arterial disease.[54] Subsequent retrospective studies have generally confirmed these findings.[49]

Several, but not all, large *prospective* cohort studies (using generally a nested case–control design) also found an independent association between hyperhomocysteinemia and increased CV risk (Table 18.4).

Randomized clinical trials

Homocysteine levels can be easily reduced by supplementation with folic acid and possibly vitamins B_6 and B_{12}, or a combination of these. These simple, inexpensive and likely risk-free interventions are currently evaluated in large randomized clinical trials. To date there are no completed large

Table 18.4 Large prospective cohort studies of homocysteine and CVD

Study[a]	Subject selection (age in years)	Subjects	Follow up (yr)	Major end point(s)	OR (95% CI)
Physicians' Health Study	14 916 men; physicians, USA (40–84)	271 cases 271 controls	5	Fatal/non-fatal MI and CHD death	3·4 (1·3–8·8)[b]
		109 cases 427 controls	5	Ischemic stroke	1·2 (0·7–2·0)[c]
		333 cases 333 controls	7·5	Fatal/non-fatal MI and CHD death	1·7 (0·9–3·3)[h]

Table 18.4 Continued

Study[a]	Subject selection (age in years)	Subjects	Follow up (yr)	Major end point(s)	OR (95% CI)
		149 cases 149 controls	9	New angina, CABG	1·0 (0·4–2·4)[e]
British United Provident Association Study	21 520 men; United Kingdom (35–64)	229 cases 1126 controls	8·7	Fatal CHD	2·9 (2·04–4·1)[f]
British Regional Heart Study	5661 men; United Kingdom (40–59)	107 cases 118 controls	12·8	Fatal and non-fatal stroke	2·8 (1·3–5·9)[g]
Nygard *et al*	587 men and women with angiographic CHD; Belgium (median 62)	64 cases	4·6	CHD death	4·5 (1·22–16·6)[h]
Zutphen study	878 men; The Netherlands (64–84)	162 cases	10	MI Stroke	1·81 (1·07–3·08)[i] 4·61 (1·18–11·89)[i]
Rotterdam study	7983 men and women; The Netherlands (≥55)	224 cases 533 controls	2·7	Stroke/MI	2·53 (1·19–5·35)[c] 2·43 (1·11–5·35)[c]
North Karelia Project	7424 men and women; Finland (40–64)	265 cases 269 controls	9	Fatal/non-fatal MI, stroke	Men: 1·05 (0·56–1·95)[d] Women: 1·22 (0·66–2·78)[d]
Atherosclerosis Risk in Communities (ARIC) study	15 792 men and women; USA (45–64)	232 cases 537 controls	3·3	All CHD events	1·28 (0·5–3·2)[c]
Arneson *et al*	10 963 men and 10 863 women; Norway (12–61)	123 cases 492 controls	3·5	Fatal and non-fatal CHD	1·41 (1·16–1·71)[g]
Multiple Risk Factor Intervention Trial (MRFIT)	12 866 males; USA (35–57)	93 non-fatal MI cases 186 controls 147 CHD death cases 286 controls	11–17	Non-fatal MI, CHD death	0·82 (0·55–1·54)[f]
Jerusalem study[55]	808 men and 980 women; Israel (≥50)	192 deaths 80 CV deaths	9–11	All-cause death CV death	1·70 (1·28–2·25)[i] 1·81 (1·19–2·76)[j]

[a] The studies listed are referenced in the comprehensive review by Eikelboom *et al.*[49]
[b] For ≥95th percentile compared with ≤10th percentile of homocysteine levels.
[c] Highest compared with lowest fifth of total of homocysteine levels.
[d] ≥95th percentile compared with <95th percentile of homocysteine levels.
[e] ≥95th percentile compared with ≤75th percentile of total homocysteine levels.
[f] Highest compared with lowest quartiles of total of homocysteine levels.
[g] Per 4 μmol/l increment in homosysteine level.
[h] Homocysteine levels ≥20 μmol/l versus <9 μmol/l.
[i] Highest compared to lowest third of total homocysteine levels.
[j] Multivariate-adjusted analysis with plasma homocysteine entered as a continuous variable in the model.
Abbreviations: CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty

randomized clinical trials of homocysteine lowering therapies. A number of large randomized clinical trials are ongoing.[49]

Homocysteine: conclusions and recommendations

Although experimental and epidemiologic data are promising, evidence from ongoing randomized controlled trials is critical in clarifying the role of homocysteine and of homocysteine lowering therapies in CVD. In the meantime, it appears prudent to ensure adequate dietary intake of folate and vitamins B_6 and B_{12}. **Grade B**

Inflammation and cardiovascular disease

There is increasing recognition of the involvement of inflammation in human atherosclerosis, although the clinical implications are unclear. Whether inflammation is a fundamental part of the process of atherosclerosis or a secondary phenomenon has yet to be determined. The destabilization of the lipid-rich, "vulnerable" thin-capped arterial plaque may involve activation of peripherally situated macrophages, leading to platelet activation and thrombosis.[56] Chronic atherosclerotic lesions are characterized by inflammatory cells, including lipid laden macrophages and T lymphocytes, and by inflammatory proteins: endothelial expression of adhesion molecules such as Intercellular Adhesion Molecule-1 (ICAM-1) or Vascular Adhesion Molecule-1 (VCAM-1), intralesional localization of C-reactive protein (CRP) or fibrinogen, cytokines such as interleukin-1 or 6, and chemokines such as interleukin-8.[57] Circulating inflammatory molecules provide prognostic information ("risk markers"), although the reproducibility, validity, and tissue-specificity of many assays have been poorly defined. Potentially, measurement of these markers may guide the initiation or withholding of specific therapies and stimulate the development of novel therapies.[58]

C-reactive protein (CRP)

CRP is an acute phase reactant synthesized by the liver on stimulation by interleukin-6. It is a pentameric protein that binds bacterial fragments and oxidized LDL, has a long serum half life, lacks diurnal variability, and has been localized within atheroma.

Elevated serum CRP has been associated with cardiovascular events in primary and secondary prevention cohorts, and in patients presenting with acute coronary syndromes. In a meta-analysis of 14 prospective studies, with 2557 cases (mean age of 58 years and mean follow up of 8 years), CRP concentrations in the highest versus lowest third were associated with an adjusted relative risk of 2·0 (95% CI 1·6–2·5) in primary prevention cohorts, and 1·9 (95% CI 1·5–2·3) in secondary prevention cohorts.[59]

Higher serum CRP concentrations may identify patients more likely to respond to aspirin or statin therapy. Among 543 cases and matched controls in the Physicians', Health Study, aspirin reduced myocardial infarction by 56% among those with the highest quarter of baseline CRP level, versus a 14% reduction in those in the lowest quarter.[60] In the CARE[61] and AFCAPS/Texas CAPS[62] studies, patients with high CRP levels benefitted from statin therapy even in the presence of low to normal LDL cholesterol. Statins lower CRP concentrations,[63] and may have anti-inflammatory properties. The ongoing Pravastatin Inflammation CRP Evaluation (PRINCE) study is testing the effectiveness of statin therapy among patients with high CRP levels.[64] ACE inhibitors may also decrease inflammation. However, CRP levels did not predict response to ramipril in the HOPE study (Smieja *et al.*, 2002, personal communication).

Other inflammatory markers

Two other acute phase reactants, fibrinogen and serum amyloid A (SAA), have also been associated with subsequent CV events. A meta-analysis of 18 prospective studies with 4018 cases found an adjusted relative risk of 1·8 (95% CI 1·6–2·0) for the top versus the bottom third of plasma fibrinogen concentrations.[65] In four studies with 1057 cases, SAA was associated with an RR of 1·6 (95% CI 1·1–2·2) for CV events.[59]

The cytokines interleukin-1, tumor necrosis factor-alpha, and interleukin-6 have been investigated as more "proximal" components of the inflammatory cascade. These are localized within atheroma and are likely key mediators in the induction of acute phase reactants, and in adhesion molecular expression, and have systemic effects including stimulation of acute phase reactant production and altering glucose metabolism. In prospective studies, interleukin-6 was associated with cardiovascular outcomes, but was not independent of CRP.[66]

The adhesion molecules ICAM-1 and VCAM-1, and the selectins E-selectin and P-selectin, play critical roles in endothelial cell adhesion and transmigration of inflammatory cells. ICAM-1 may play an important role within atheroma, but prospective data are limited. In the one prospective study in which the three were compared, VCAM-1 was superior to either ICAM-1 or E-selectin among 1246 patients with angiographically proven CAD, and followed for a mean of 3 years for CV outcomes in the AtheroGene study.[67] The highest quarter of VCAM-1 concentration was associated with an RR of 2·1 (95% CI 1·1–4·0) for fatal CV events.

Inflammation: conclusions and recommendations

The role for measuring inflammatory markers is evolving, with a demonstrated utility of high-sensitivity CRP for risk

stratification. Whether high CRP levels require treatment, and whether other inflammatory risk markers should be measured routinely, is not clear from the available evidence. Whether these inflammatory molecules play a causal role in atheroma formation also remains unknown. The beneficial effects of aspirin and of statins in CV prevention may be mediated in part by their anti-inflammatory actions. **Grade B**

Infection and cardiovascular disease

Human atherosclerotic heart or cerebrovascular disease has been associated with previous exposure to the bacteria *Chlamydia pneumoniae*,[68,69] *Helicobacter pylori*, or *Porphyromonas gingivalis*,[70,71] and with the viruses cytomegalovirus,[72] herpes simplex virus type 1 and 2,[73] enteroviruses,[74] or hepatitis A virus,[73] but prospective studies remain limited for all but the first two infections. Overall, current data have not convincingly demonstrated an important role for infections in human CV disease.

Chlamydia pneumoniae

Chlamydia pneumoniae is a Gram-negative, obligate intracellular pathogen which has been demonstrated within human atherosclerosis.[75] The interpretation of cross-sectional seroepidemiologic data has been difficult due to inter-laboratory differences in antibody measurement and cut off values, varying control groups, emphasis on multiple subgroup analyses, and incomplete ascertainment of potential confounders. A meta-analysis of 15 prospective studies which included 3169 cases, and adjusted for potential confounders including socioeconomic status, found no association between *C. pneumoniae*, IgG antibodies, and subsequent CV events (pooled odds ratio 1·15; 95% CI 0·97–1·36).[76]

Antichlamydial antibiotics have been administered to patients after MI. In two pilot studies, the macrolide antibiotics azithromycin and roxithromycin decreased subsequent CV events.[77,78] These results were not statistically significant on longer follow up in the latter study,[79] nor in a separate larger study.[80] However, two large trials involving 9163 patients found no benefit with azithromycin (Dunne M and Cevek B, 2002. American College of Cardiology 51st Annual Scientific Session).

Helicobacter pylori

Helicobacter pylori, a major cause of peptic ulcers and gastric carcinoma, has been studied in a number of cross-sectional and prospective studies. A meta-analysis of 10 prospective studies, with 2916 cases, found no association between seropositivity and subsequent cardiovascular events, with an adjusted odds ratio of 1·15 (95% CI 0·96–1·37).[81]

Other infection and total pathogen burden

There are more limited data for other infections, such CMV, HSV, or dental infections. These require further study in prospective cohorts, with appropriate adjustment for CV risk factors. A role for influenza can be inferred from observational studies of benefit from influenza vaccination.[82] There has been recent demonstration by two separate groups of investigators of a stepwise association between total pathogen burden and subsequent CV events.[83,84] These investigators used a score including bacterial infections such as *C. pneumoniae* and *H. pylori*, and viral infections such as cytomegalovirus and other viruses in the herpes family. These findings require validation in other study populations, and do not clearly demonstrate whether markers of exposure to infections represent confounding by other CV risk factors, epiphenomena, or a causal association.

Infections: conclusions and recommendations

Meta-analyses of prospective studies of exposure to *C. pneumoniae* and *H. pylori*, as measured by serum antibodies, found no association with human CV disease. The possible association with multiple infections requires further study. Antibiotic treatment is currently not recommended. **Grade A**

Key points

- The antioxidant vitamins E, C, and beta-carotene do not reduce CV events.
- ACE inhibitors reduce the risk of myocardial infarction, stroke and CV death in high-risk patients.
- Homocysteine lowering with folic acid and vitamin B_6 is currently under investigation in large clinical trials. For now, the routine measurement of homocysteine levels in CV risk assessment and the treatment of hyperhomocysteinemia are not widely recommended.
- The role of inflammation in CVD is under investigation. For now, the routine measurement of inflammatory markers such as CRP is not recommended.
- Antibiotics are not recommended in CV prevention. Further trials are awaited.

References

1. Goldman L, Cook EF. The decline in ischemic heart disease mortality rates. An analysis of the comparative effects of medical interventions and changes in lifestyle. *Ann Intern Med* 1984;**101**:825–36.
2. Verschuren WMM, Jacobs DR, Bloemberg BPM *et al.* Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the Seven Countries Study. *JAMA* 1995;**274**:131–6.

3. Steinberg D. Antioxidants in the prevention of human atherosclerosis. Summary of the proceedings of a National Heart, Lung and Blood Institute workshop: September 5–6, 1991, Bethesda, Maryland. *Circulation* 1992;**85**:2338–43.
4. Berliner JA, Navab M, Fogelman AM *et al.* Atherosclerosis: basic mechanisms. Oxidation, inflammation and genetics. *Circulation* 1995;**91**:2488–96.
5. Rimm EB, Ascherio A, Giovannucci E *et al.* Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;**275**:447–51.
6. Hertog MG, Feskens EJ, Holman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet* 1993;**342**: 1007–11.
7. Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. *Am J Clin Nutr* 1991;**53**:326S–34S.
8. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins (E, C and beta-carotene) and cardiovascular disease: a critical summary of epidemiological and clinical trial data. *Ann Intern Med* 1995;**123**:860–72.
9. Stampfer MJ, Hennekens CH, Manson JE *et al.* Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993;**328**:1444–9.
10. Rimm EB, Stampfer MJ, Ascherio A *et al.* Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;**328**:1450–6.
11. Kushi LH, Fulsom AR, Prineas RJ *et al.* Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med* 1996;**334**:1156–62.
12. Knekt P, Reunanen A, Jarvinen R *et al.* Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol* 1994;**139**:1180–90.
13. Lonn EM, Yusuf S, Dzavik V *et al.* Effects of ramipril and vitamin E on atherosclerosis. The Study to Evaluate Carotid Ultrasound changes in patients with Ramipril and vitamin E (SECURE). *Circulation* 2001;**103**:919–25.
14. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;**330**:1029–35.
15. Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;**357**: 89–95.
16. Rapola JM, Virtamo J, Ripatti S *et al.* Randomised trial of α-tocopherol and β-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet* 1977;**349**:1715–20.
17. Stephens NG, Parsons A, Schofield PM *et al.* Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996; **347**:781–6.
18. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Sudio della Sopravvivenze nell-Infarto Miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. *Lancet* 1999;**354**:447–55.
19. The HOPE Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:1150–5.
20. Boaz M, Weinstein T, Matas Z *et al.* Secondary prevention with antioxidants of cardiovascular disease in end-stage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000;**356**:1213–18.
21. Greenberg ER, Baron JA, Karagas MR *et al.* Mortality associated with low plasma concentration of beta-carotene and the effect of oral supplementation. *JAMA* 1996;**275**:699–703.
22. Omenn GS, Goodman GE, Thornquist MD *et al.* Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;**334**:1150–5.
23. Hennekens CH, Burning JE, Manson JE *et al.* Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;**334**:1145–9.
24. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992;**3**:194–202.
25. Wilson TS, Datta SB, Murrell JS, Andrews CT. Relation of vitamin C levels to mortality in a geriatric hospital: a study of the effect of vitamin C administration. *Age Aging* 1973;**2**:163–71.
26. Burr ML, Hurley RJ, Sweetnam PM. Vitamin C supplementation of old people with low blood levels. *Gerontol Clin* 1975: **17**:236–243.
27. Hunt C, Chakkravorty NK, Annan G. The clinical and biochemical effects of vitamin C supplementation in short-stay hospitalized geriatric patients. *Int J Vit Nutr Res* 1984;**54**:65–74.
28. Salonen JT, Nuyyssonen K, Salonen R *et al.* Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized study of the effects of vitamins E and C on 3-year progression of carotid atherosclerosis. *J Intern Med* 2000;**248**:377–86.
29. Brown BG, Shao XQ, Chait A *et al.* Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;**345**:1583–92.
30. Blot WJ, Li JY, Taylor PR *et al.* Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;**85**:1483–92.
31. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:23–33.
32. Walldius G, Erikson U, Olsson AG *et al.* The effect of probucol on femoral atherosclerosis: the Probucol Quantitative Regression Swedish Trial (PQRST). *Am J Cardiol* 1994;**74**: 875–83.
33. Rodes J, Cote G, Lesperance J *et al.* Prevention of restenosis after angioplasty in small coronary arteries with probucol. *Circulation* 1998;**97**:416–20.
34. Lonn EM, Yusuf S, Prabhat J *et al.* Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation* 1994;**90**:2056–69.
35. Alderman MH, Madhavan SH, OOi WL *et al.* Association of the renin–sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med* 1991; **324**: 1098–104.

36.Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med* 1993;**329**:616–19.
37.Cambien F, Poirier O, Lecerf L *et al.* Deletion polymorphism in angiotensin-converting enzyme gene associated with parental history of myocardial infarction. *Nature* 1992;**359**:641–4.
38.Samani NJ, Thompson JR, O'Toole L, Channer K, Woods KL. A meta-analysis of the association of the deletion allele of the angiotensin-converting enzyme gene with myocardial infarction. *Circulation* 1996;**94**:708–12.
39.Yusuf S, Pepine CJ, Garces C *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;**340**:1173–8.
40.Rutherford JD, Pfeffer MA, Moye LA *et al.*, on behalf of the SAVE Investigators. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. *Circulation* 1994;**90**:1731–8.
41.Flather MD, Yusuf S, Køber L *et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;**355**:157–81.
42.Mancini GBJ, Henry GC, Macaya C *et al.* Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) study. *Circulation* 1996;**94**:258–65.
43.Vaughan DE, Rouleau JL, Ridker PM. Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction: HEART Study Investigators. *Circulation* 1997;**96**:422–7.
44.Lonn E, Shaikholeslami R, Yi Q *et al.* Effects of ramipril on left ventricular mass and function in normotensive patients with preserved left ventricular function. A substudy of HOPE. *J Am Coll Cardiol* 2001;**37**(Suppl. A):165A.
45.The Heart Outcomes Prevention Evaluation Study Investigators. Effects of angiotensin-converting enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction, and stroke in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
46.Heart Outcomes Prevention Evaluation (HOPE) Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253–9.
47.PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033–41.
48.McCully KSA, Wilson RB. Homocysteine theory of arteriosclerosis. *Atherosclerosis* 1975;**22**:215–27.
49.Eikelboom JW, Lonn E, Genest J *et al.* Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. *Ann Intern Med* 1999;**131**:363–75.
50.Tawakol A, Omland T, Gerhard M, Wu JT, Creager MA. Hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans. *Circulation* 1997;**95**: 1119–21.
51.Tsai JC, Perella MA, Yoshizumi M *et al.* Promotion of vascular smooth muscle growth by homocysteine: a link to atherosclerosis. *Proc Natl Acad Sci USA* 1994;**91**:6369–73.
52.Frascher G, Karnaukhova E, Muehl A, Hoeger H, Lubec B. Oral administration of homocysteine leads to increased plasma triglycerides and homocysteic acid-additional mechanisms in homocysteine induced endothelial damage? *Life Sci* 1995; **57**:813–17.
53.Mayer EL, Jacobson DW, Robinson K. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol* 1996;**27**:517–27.
54.Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;**274**:1049–57.
55.Kark JD, Selhub J, Adler B, Gofin J *et al.* Nonfasting plasma total homocysteine level and mortality in middle-aged and elderly men and women in Jerusalem. *Ann Intern Med* 1999; **131**:321–30.
56.van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation* 1994;**89**:36–44.
57.Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;**340**:115–26.
58.Libby P, Ridker PM. Novel inflammatory markers of coronary risk: theory versus practice. *Circulation* 1999;**100**:1148–50.
59.Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P *et al.* Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000;**321**:199–204.
60.Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; **336**:973–9.
61.Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S *et al.* Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998;**98**:839–44.
62.Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS *et al.* Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;**344**:1959–65.
63.Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001;**103**:1191–3.
64.Albert MA, Staggers J, Chew P, Ridker PM. The Pravastatin Inflammation CRP Evaluation (PRINCE): rationale and design. *Am Heart J* 2001;**141**:893–8.
65.Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998;**279**:1477–82.
66.Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342**: 836–43.
67.Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L *et al.* Circulating cell adhesion molecules and death in patients with coronary artery disease. *Circulation* 2001; **104**:1336–42.

68. Saikku P, Leinonen M, Mattila K, Ekman MR, Nieminen MS, Makela PH *et al.* Serological evidence of an association of a novel *Chlamydia*, TWAR, with chronic conary heart disease and acute myocardial infarction. *Lancet* 1988;**2**:983–6.
69. Kuo CC, Shor A, Campbell LA, Fukushi H, Patton DL, Grayston JT. Demonstration of *Chlamydia pneumoniae* in atherosclerotic lesions of coronary arteries. *J Infect Dis* 1993;**167**:841–9.
70. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? *Lancet* 1997;**350**:430–6.
71. Deshpande RG, Khan MB, Genco CA. Invasion of aortic and heart endothelial cells by *Porphyromonas gingivalis. Infect Immun* 1998;**66**:5337–43.
72. Nieto FJ, Adam E, Sorlie P, Farzadegan H, Melnick JL, Comstock GW *et al.* Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. *Circulation* 1996;**94**:922–7.
73. Zhu J, Nieto FJ, Horne BD, Anderson JL, Muhlestein JB, Epstein SE. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation* 2001;**103**: 45–51.
74. Roivainen M, Alfthan G, Jousilahti P, Kimpimaki M, Hovi T, Tuomilehto J. Enterovirus infections as a possible risk factor for myocardial infarction. *Circulation* 1998;**98**:2534–7.
75. Grayston JT, Kuo CC, Campbell LA, Wang SP, Jackson LA. *Chlamydia pneumoniae* and cardiovascular disease. *Cardiologia* 1997;**42**:1145–51.
76. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P *et al. Chlamydia pneumoniae* IgG titres and coronary heart disease: prospective study and meta-analysis. *BMJ* 2000;**321**:208–13.
77. Gupta S, Leatham EW, Carrington D, Mendall MA, Kaski JC, Camm AJ. Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. *Circulation* 1997;**96**:404–7.
78. Gurfinkel E, Bozovich G, Daroca A, Beck E, Mautner B. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. ROXIS Study Group. *Lancet* 1997;**350**:404–7.
79. Gurfinkel E, Bozovich G, Beck E, Testa E, Livellara B, Mautner B. Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final report of the ROXIS Study. *Eur Heart J* 1999;**20**:121–7.
80. Muhlestein JB, Anderson JL, Carlquist JF, Salunkhe K, Horne BD, Pearson RR *et al.* Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical results of the ACADEMIC study. *Circulation* 2000;**102**:1755–60.
81. Ridker PM, Danesh J, Youngman L, Collins R, Stampfer MJ, Peto R *et al.* A prospective study of *Helicobacter pylori* seropositivity and the risk for future myocardial infarction among socioeconomically similar US men. *Ann Intern Med* 2001;**135**:184–8.
82. Naghavi M, Barlas Z, Siadaty S *et al.* Association of influenza vaccination and reduced risk of recurrent myocardial infarction. *Circulation* 2000;**102**:3039–45.
83. Rupprecht HJ, Blankenberg S, Bickel C *et al.* Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. *Circulation* 2001; **104**:25–31.
84. Espinola-Klein C, Rupprecht HJ, Blankenberg S *et al.* Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation* 2002;**105**:15–21.

19 Obesity

Arya M Sharma

The worldwide prevalence of obesity is increasing at an alarming rate. Recent estimates indicate that 40–60% of the population in industrialized countries and a substantial proportion of the population in developing countries must now be considered overweight or obese.[1] In the United States, the prevalence of adult obesity (defined as body mass index $>30\,kg/m^2$), based on self-reported weight and height, increased from 12·0% in 1991 to 18·9% in 1999, and it is estimated that this trend is likely to continue over the next decade.[2] In the Third National Health and Nutrition Examination Survey (NHANES III), conducted in two phases from 1988 to 1994, 63% of men and 55% of women had a body mass index of $25\,kg/m^2$ or greater.[3]

In 1998 the American Heart Association reclassified obesity as a major modifiable risk factor for coronary heart disease.[4] This is a step forward from the earlier notion that obesity contributes to heart disease primarily through covariates related to obesity, including hypertension, dyslipidemia, and impaired glucose tolerance or type 2 (non-insulin dependent) diabetes mellitus. Overweight and obesity are now also recognized as important risk factors for stroke, renal dysfunction, gallbladder disease, certain types of cancer, osteoarthritis, sleep apnea and a host of other disorders.[5] Importantly, increased body weight is also an important determinant of impaired quality of life.[6]

Obesity is a complex multifactorial chronic disease that develops from an interaction between genetic and environmental factors. Our understanding of how and why obesity develops is incomplete, but clearly involves the integration of social, behavioral, cultural, physiological, metabolic and genetic factors. Overweight and obesity are especially evident in some minority groups, as well as in those with lower incomes and less education.[1]

Definition of obesity

Definitions of overweight and obesity in adults have varied over time.[7] Ideally, a health-oriented definition of obesity would be based on the amount of excess body fat that determines the presence of weight-responsive health risk in an individual.[8] Body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m^2), is an easily obtained measure that is now widely used, as it has a high correlation with excess body fat or adiposity. However, BMI is not a measure of body fat and does not convey information on regional fat distribution. The latter is important, as it is now well established that central or visceral fat deposition is a major independent determinant of the metabolic and cardiovascular risk associated with an increase in fat mass.[9–11] Recent evidence-based guidelines therefore recommend the use of both BMI and waist circumference in the assessment of overweight or obese patients.[1] Table 19.1 summarizes the current classification of overweight and obesity by BMI, waist circumference and associated disease risk in Caucasians.[1] There are now also data to indicate that in south Asians[12] and other Asian populations,[13] for the same level of BMI or waist circumference health risks may be higher than in Caucasians. Lower cut offs have therefore been recommended for both BMI and waist circumference in adult Asians (Table 19.2).[14] The levels of BMI or waist circumference that can be used to define obesity related risk in other ethnic groups or populations (for example, Pacific Islanders, Native Americans, Australian Aboriginals etc.) remain to be determined.

Although there are benefits to the identification of cut-off points for monitoring overweight and obesity, it is important to realize that (as for other risk factors) health risks associated with increasing weight are part of a continuum, and individuals with BMI $<25\,kg/m^2$ can have substantial weight-associated health problems (for example, impaired glucose tolerance, hypertension), whereas others may have no identifiable health problems at BMIs significantly greater than 25. Individualized assessment of risk status and conditions associated with obesity must therefore form an integral part of patient assessment, before deciding on the potential benefits to be derived from weight management in an individual patient (Figure 19.1).[15]

Key points

- Practitioners should use the BMI to assess and classify overweight and obesity and to estimate relative risk of disease compared with normal weight. **Grade B**
- The waist circumference should be used to assess abdominal fat content. **Grade B**
- For adult patients with a BMI of $25–34·9\,kg/m^2$, sex-specific waist circumference cut offs should be used in conjunction with BMI to identify increased disease risk. **Grade C**
- Body weight alone can be used to follow weight loss and to determine the efficacy of weight loss therapy. **Grade C**

Table 19.1 Classification of overweight and obesity by body mass index (BMI), waist circumference, and associated disease risk in Caucasians[1]

		Disease risk* relative to normal weight and waist circumference	
	BMI, kg/m^2	Men, 102 cm; Women, 88 cm	Men, >102 cm; Women, >88 cm
Underweight	<18·5	–	–
Normal†	18·5–24·9	–	–
Preobese	25·0–29·9	Increased	High
Obesity, class			
I	30·0–34·9	High	Very high
II	35·0–39·9	Very high	Very high
III	40	Extremely high	Extremely high

* Disease risk for type 2 diabetes, hypertension and cardiovascular disease.
– indicates that no risk at these levels of BMI was assigned.
† Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Table 19.2 Proposed classification of weight by BMI in adult Asians[14]

Classification	BMI, kg/m^2	Risk of comorbidities
Underweight	<18·5	Low
Normal range	18·5–22·9	Average
Overweight	23·0	
At risk	23·0–24·9	Increased
Obese I	24·9–25·0	Moderate
Obese II	30·0	Severe

Hypertension

Overweight and obesity have long been recognized as important determinants of elevated blood pressure, in both black and white hypertensive and normotensive individuals.[3,16,17] The same appears true for Asian populations.[18,19] Experimental studies have shown that weight gain consistently elevates blood pressure and weight loss decreases blood pressure independent of changes in sodium intake. Nevertheless, the mechanisms underlying this relationship remain poorly understood. Several mechanisms, including increased sympathetic activity, sodium and volume retention, renal abnormalities, insulin resistance and, more recently, hyperleptinemia, have been implicated in the development of obesity related hypertension.[20,21]

Based on an assessment of 76 RCTs on the effect of weight loss on blood pressure, which included 35 lifestyle trials and 10 on pharmaceutical intervention, the authors of recent *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*[5] concluded that there was strong evidence that weight loss due to lifestyle modifications reduced blood pressure levels, and suggestive evidence that weight loss produced by most weight loss medications in combination with adjuvant lifestyle modifications will be accompanied by reductions in blood pressure. Importantly, substantial reductions in blood pressure, or even normalization, can be achieved with rather modest weight loss of 5–10% of initial weight.[22]

Since the appearance of this report, several newer non-pharmacologic intervention trials have been published[23–26] essentially confirming that lowering body weight lowers blood pressure. Three studies perhaps deserve special mention.

1. The Trials of Hypertension Prevention II (TOHP II),[27] a 36 month randomized trial of weight loss versus usual care in 1191 overweight adults (mean BMI around 31 kg/m^2) with non-medicated diastolic blood pressure of 83–89 mmHg and systolic blood pressure less than 140 mmHg. Although participants who lost at least 4·5 kg at 6 months and maintained this weight reduction for the next 30 months had a relative risk for hypertension of 0·35 (95% CI 0·20–0·59), this group only included 13% of the participants in the weight loss arm. Sadly, over the 36 months body weight returned to −0·2 kg below baseline in the weight loss group and increased by 1·8 kg in controls. This study thus clearly illustrates the limited success of achieving and maintaining weight loss by lifestyle measures even over a relatively short period.
2. The trial of non-pharmacologic interventions in the elderly (TONE),[28] which included 585 obese men and

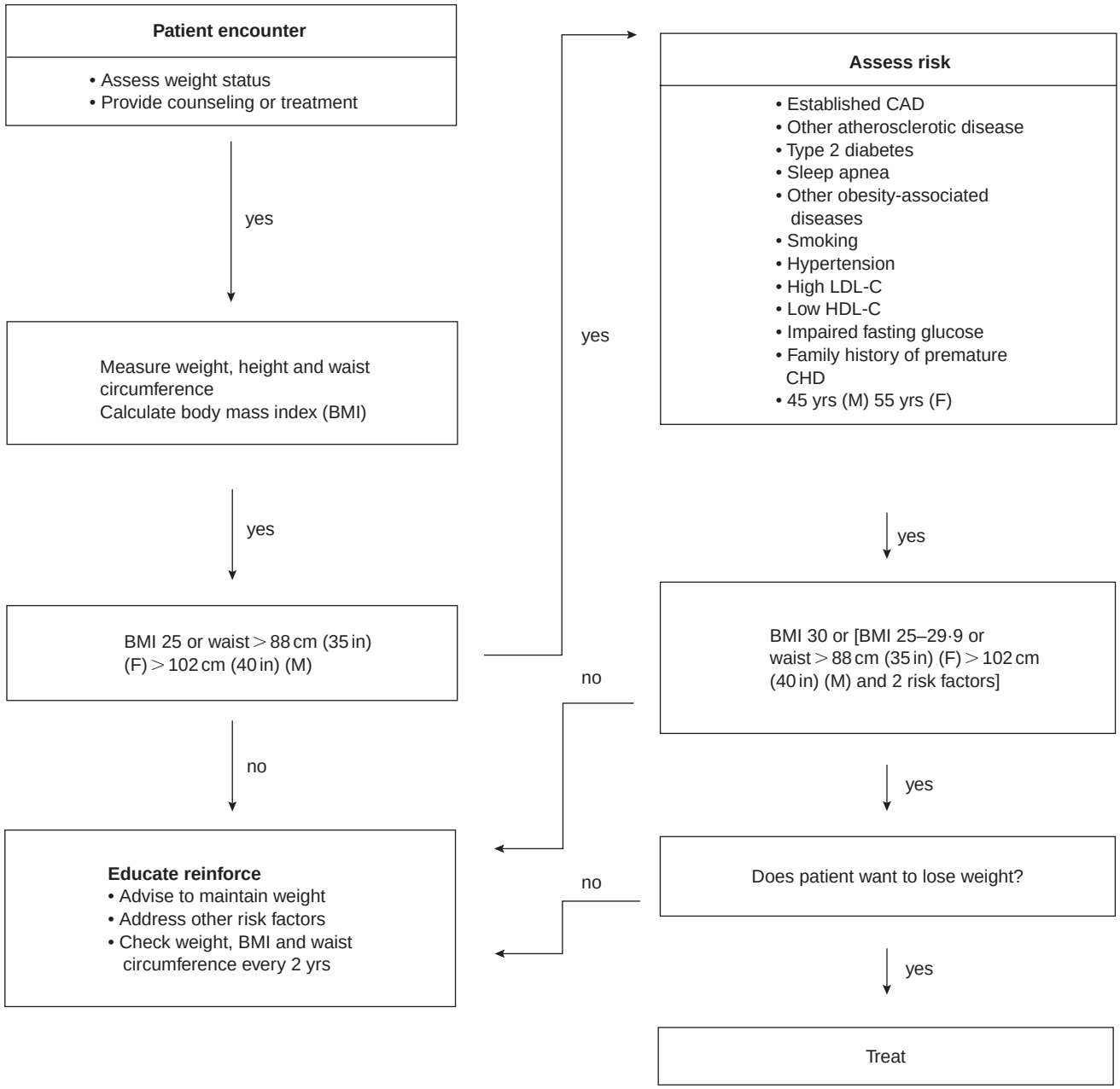

Figure 19.1 Evidence-based algorithm for the treatment of obesity (adapted from the National Institute of Health guidelines)[15]

women aged 60–80 years with systolic blood pressure lower than 145 mmHg and diastolic blood pressure lower than 85 mmHg on antihypertensive monotherapy (withdrawn after 1 month), who were randomized to reduced sodium intake, weight loss, both, or usual care for 29 months. Relative to usual care, hazard ratios for the combined outcome measure (diagnosis of high blood pressure, treatment with antihypertensive medication, or a cardiovascular event during follow up) were 0·60 (95% CI 0·45–0·80; $P < 0·001$) for reduced sodium intake alone, 0·64 (95% CI 0·49–0·85; $P = 0·002$) for weight loss alone, and 0·47 (95% CI 0·35–0·64; $P < 0·001$) for reduced sodium intake and weight loss combined.

3. A study on exercise and weight loss on blood pressure in 133 sedentary overweight men and women with unmedicated high normal BP or stage 1–2 hypertension, randomly assigned to aerobic exercise only; a behavioral weight management program, including exercise; or a waiting list control group.[29] Weight

management was associated with a 7 mmHg systolic and a 5 mmHg diastolic BP reduction, compared to a 4 mmHg systolic and diastolic BP reduction associated with aerobic exercise; the BP for controls did not change. In general, 1 kg weight loss can be expected to result in approximately 1 and 0·5 mmHg reduction in systolic and diastolic blood pressure, respectively (Table 19.3).[30]

Table 19.3 Effect of weight loss on major coronary heart disease risk factors (adapted from[30])

Measure	Units	Mean change/1 kg weight loss
Systolic blood pressure	mmHg	−0·68
Diastolic blood pressure	mmHg	−0·34
Fasting glucose	mg/dl	−3·6
Total cholesterol	mg/dl	−2·28
LDL cholesterol	mg/dl	−0·91
Triglycerides	mg/dl	−1·54
HDL cholesterol	mg/dl	+0·07

New data have also recently emerged for some of the newer pharmacologic weight reducing agents, orlistat and sibutramine. Studies with both compounds have included overweight and obese hypertensive patients. With the lipase inhibitor orlistat the reduction in blood pressure and heart rate for a given weight loss is similar to that expected with weight loss from lifestyle intervention.[31–35] With the centrally active norepinephrine and serotonin reuptake inhibitor sibutramine, weight loss in normotensive and treated hypertensive patients is associated with a modest reduction in blood pressure, that is about half of what might be expected for a given degree of weight loss.[36,37] In some instances (1–5%) patients may experience a clinically significant rise in blood pressure (>10 mmHg). Sibutramine also consistently increases heart rate by 3–5 bpm. Sibutramine therapy should be discontinued if a patient experiences an increase in resting heart rate of >10 bpm, or a rise in systolic or diastolic blood pressure of >10 mmHg at two consecutive visits. **Grade C** Similarly, treatment should be withdrawn in the event of previously well controlled hypertension shifting to a pattern of blood pressure >145/90 mmHg on two consecutive visits, or signs of progressive dyspnea, chest pain or ankle edema. **Grade C**

Which antihypertensive agent is best suited for the obese hypertensive patient? Current hypertension guidelines do not make specific recommendations for the pharmacologic management of obese patients. This may reflect the paucity of "hard data" from prospective intervention studies in obese hypertensives.[38] Indeed, there are currently no studies documenting a reduction in morbidity and mortality, or the superiority of any class of antihypertensive agents in obese hypertensive patients. Few small to moderate-sized studies have specifically addressed the efficacy of antihypertensive agents in obese patients. From these it appears that β blockers are more effective than dihydropiridine calcium-channel blockers,[39] and that hydrochlorothiazide is less effective at lower doses than the angiotensin converting enzyme inhibitor lisinopril.[40] An increased risk of type 2 diabetes[41,42] and weight gain[43] has been noted for β blockers. This may make β blockers less well suited for managing hypertension in the uncomplicated obese hypertensive. In contrast, angiotensin converting enzyme inhibitors[44,45] and AT_1 receptor blockers[46] may reduce the risk of developing type 2 diabetes and may therefore be preferable for use in obese patients.

Key points

- Weight loss by lifestyle modification is recommended to lower blood pressure in overweight and obese patients with high blood pressure. **Grade A**
- Dietary salt reduction (to <5 g/day) is recommended to lower blood pressure in overweight and obese patients with high blood pressure. **Grade A**
- Weight loss with orlistat (120 mg t.i.d) or sibutramine (10–15 mg/day), in combination with lifestyle modification, can lower blood pressure in overweight and obese patients with high blood pressure. **Grade A**
- Patients managed on sibutramine must be regularly monitored for a rise in blood pressure, deterioration in blood pressure control, or a significant increase in heart rate. **Grade C**
- Angiotensin converting enzyme inhibition or angiotensin receptor blockers may be best suited for antihypertensive monotherapy in uncomplicated obese hypertensive patients. **Grade C**
- When other indications (for example, myocardial infarction, congestive heart failure, tachyarrythmias) support the use of β blockers, these can also be used in obese hypertensive patients. **Grade C**

Diabetes

Overweight and obesity have long been recognized as important determinants of elevated blood glucose, and the vast majority of patients with type 2 diabetes are either overweight or obese. Both at a population and at an individual level, the prevalence and incidence of type 2 diabetes is dependent on the degree of obesity. Thus, in the 10 year follow up (1986–1996) of middle-aged women in the Nurses' Health Study and men in the Health Professionals Follow-up Study, the risk of developing diabetes was approximately 20 times as high in those with a BMI of 35 or more as in their same-sex peers with a BMI between 18·5 and 24·9.[47]

Importantly, the rise in risk of developing type 2 diabetes begins at BMI levels as low as 22, suggesting that adults should try to maintain a BMI between 18·5 and 21·9 to minimize their risk of type 2 diabetes and other disease. In addition to BMI, abdominal fat distribution, as indicated by an increased waist to hip ratio, is also an important independent predictor of type 2 diabetes.[48,49] An increased prevalence of obesity has also been recently implicated in the rising prevalence of glucose intolerance in childhood in North America.[50]

Despite the close relationship between obesity and type 2 diabetes, it is important to note that at least 20% of type 2 diabetic patients are not obese, and over 80% of individuals with high BMI and WHR remain non-diabetic. Thus obesity must apparently interact with other inherited or acquired factors that determine insulin resistance and β cell function in order for diabetes to develop.

A large number of studies document the benefits of even moderate (5–10%) weight loss in improving metabolic control in diabetic patients.[30] However, the impact of weight reduction on the long-term incidence of diabetic complications and survival has not been demonstrated. Improvement in metabolic control depends more on the amount of weight loss, rather than on the method by which this is achieved. A 5 kg weight loss should decrease fasting plasma glucose levels in a diabetic individual by 1 mM or 18 mg/dl (Table 19.3).[30] This is of a magnitude similar to that provided by many of the oral hypoglycemic agents. Although pharmacologic or surgical weight loss does not appear to improve glucose control beyond that achieved by lifestyle changes alone, both the degree of loss and the number of individuals achieving and maintaining weight loss are generally higher when lifestyle changes are combined with medication or surgery.[5,15]

Recent evidence from randomized prospective trials indicates that lifestyle modification including modest weight reduction will markedly reduce the incidence of type 2 diabetes in individuals at high risk. Thus in the recent Finnish Diabetes Prevention Study[51] 522 middle-aged overweight subjects (mean BMI 31) with impaired glucose tolerance were randomly assigned to either the control group or the intervention group, where participants received individualized counseling aimed at reducing weight, total fat intake and intake of saturated fat, and increasing their intake of fiber and physical activity. A mean weight loss at the end of 1 year of around 4 kg versus a 1 kg gain in the control group was associated with a 58% reduction in the incidence of diabetes after 4 years. Similarly, in the Diabetes Prevention Project[52] lifestyle intervention aimed at reducing body weight by 7% and at least 150 minutes of physical activity per week over 2·8 years in non-diabetic persons (mean BMI 34), with elevated fasting and postload plasma glucose concentrations, reduced the incidence by 58% compared with placebo; the lifestyle intervention was also significantly more effective than metformin in preventing the development of type 2 diabetes.

In contrast to metformin and acarbose, other antidiabetic medications, including sulphonylureas, thiazolidinediones and insulin, promote weight gain. Weight gain in patients with both type 1 and type 2 diabetes is associated with an increase in blood pressure and deterioration of metabolic control.[53,54] In the UK Prospective Diabetes Study, metformin was more effective than sulphonylureas or insulin in reducing diabetes related end points.[55] Furthermore, metformin is both cost saving and extends life expectancy when used as first-line pharmacologic therapy in overweight type 2 diabetics.[56] Weight gain can be promoted by the use of β blockers,[43] and their use may increase the risk of developing type 2 diabetes.[41,42] In contrast, ACE inhibitors[44,45] and angiotensin receptor blockers[46] have been found to reduce the incidence of diabetes in high-risk individuals.

Pharmacologically induced weight loss with orlistat[57,58] or sibutramine,[59,60] in conjunction with a lifestyle modification program, significantly improves metabolic control and lower HbA1c levels in patients with type 2 diabetes.

Key points

- Adults should maintain a BMI between 18.5 and 21.9 to minimize their risk of developing type 2 diabetes. **Grade C**
- Weight loss is recommended to lower elevated blood glucose levels in overweight and obese individuals with type 2 diabetes. **Grade A**
- Weight loss is recommended to prevent diabetes in overweight and obese individuals at risk for developing type 2 diabetes. **Grade A**
- Metformin is both cost effective and extends life expectancy when used as first-line pharmacologic therapy in overweight patients with type 2 diabetes. **Grade A**
- Use of β blockers is associated with greater weight gain than are ACE inhibitors in patients with type 2 diabetes. **Grade B**
- Use of ACE inhibitors or angiotensin receptor blockers may reduce the risk of developing diabetes in overweight or obese individuals at risk for developing type 2 diabetes. **Grade B**

Dyslipidemia

Lipid abnormalities in overweight and obese individuals are typically characterized by high triglycerides, increased small LDL particles and low HDL cholesterol levels.[61] In the presence of abdominal obesity, high serum triglycerides are commonly associated with a clustering of metabolic risk factors known as the metabolic syndrome (atherogenic lipoprotein phenotype, hypertension, insulin resistance, glucose

intolerance, prothrombotic and proinflammatory states). Thus, in obese patients elevated serum triglycerides are a marker for increased cardiovascular risk. The US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) therefore recognizes the metabolic syndrome as a secondary target of risk reduction therapy, after the primary target – LDL cholesterol.[61]

Numerous studies document the short- and medium-term benefits on blood lipids associated with lifestyle modification, including weight reduction.[62] Current evidence-based guidelines thus recommend weight reduction and increased physical activity as first-line therapies for all lipid and non-lipid risk factors associated with the metabolic syndrome.[61] Weight reduction will enhance LDL lowering and reduce all of the risk factors of the syndrome. Significant reductions in blood triglycerides and increases in HDL cholesterol have been observed in randomized controlled trials of pharmacologically induced weight loss with orlistat[63,64] and sibutramine.[65,66] Possibly because of its mode of action on intestinal lipid absorption,[67] the use of orlistat has been associated with a greater reduction in LDL cholesterol than can be expected by weight reduction alone.[63] Observational studies have shown profound metabolic benefits associated with surgical weight reduction in the morbidly obese.[68,69] However, as for other high-risk groups, the long-term effect of weight reduction on morbidity or mortality in overweight or obese dyslipidemic patients has yet to be demonstrated.

Key point

- Weight loss is recommended to lower elevated levels of total cholesterol, LDL cholesterol and triglycerides and to raise low levels of HDL cholesterol in overweight and obese individuals with dyslipidemia. **Grade A**

Coronary artery disease

Overweight and obesity are now considered major independent risk factors for coronary artery disease;[4] nevertheless, the impact of excess body fat and fat distribution in different populations (men and women, young and elderly, ethnic groups) remains to be fully determined. In a recent review of 11 independent studies, Anderson and Konz[30] estimated an overall RR of 2·71 for women and 2·80 for men for a BMI of 33 *v* 23 kg/m^2, respectively. This increased risk was partly (but not fully) accounted for by other major risk factors for coronary artery disease, including hypertension, lipids and diabetes. This may in part be accounted for by an association between obesity and other non-conventional risk factors for coronary artery disease, including alterations in coagulation and risk for thrombosis or increased inflammatory cytokines.[70–72] A recent study also found a substantially increased risk for angiographically assessed coronary artery disease associated with an increase in waist circumference, that reached an odds ratio of over 12 in patients with familial hypercholesterolemia.[73] Weight gain has also been associated with a significant increase in coronary risk.[30] Thus, a weight gain of 15 kg after age 21 was associated with an increased coronary risk of 83% in women and 46% in men.

Weight reduction has been consistently shown to lower blood pressure, lower plasma glucose and insulin levels, prevent the development of type 2 diabetes, lower plasma triglycerides and raise low levels of HDL cholesterol, and improve other risk factors for coronary artery disease.[5,15] It is therefore very likely that weight reduction will substantially lower coronary risk in obese patients. However, there are currently no hard end-point data from randomized controlled trials of weight loss on morbidity and mortality in patients with coronary artery disease.

In a large prospective study of patients surviving a first myocardial infarction, overweight, grade I and grades II–III obesity were associated with a 1·16, 1·49 and 1·80 relative risk for a recurrent coronary event, respectively.[74] Readily measured markers of diabetes, hypertension and dyslipidemia explained some of the risk conferred by obesity. Other investigators have identified obesity as an independent predictor of hospital mortality in older (but not younger) patients with myocardial infarction.[75] No effect of body weight was found in 1 year mortality in overweight or obese patients. Thus, although obese patients should certainly be targeted for proven preventive therapies following acute myocardial infarction, whether or not weight loss should be included in these treatments remains an important but unresolved question.

Key points

- Weight reduction is recommended to reduce risk factors for coronary artery disease, including hypertension, dyslipidemia and impaired glucose tolerance/type 2 diabetes. **Grade A**
- Weight reduction is recommended in patients with coronary artery disease to reduce morbidity and mortality. **Grade C**

Congestive heart failure

In a recent report from the Framingham cohort, after adjustment for established risk factors, there was an increase in the risk of heart failure of 5% for men and 7% for women for each unit increment in body mass index.[76] Surprisingly, however, a large retrospective observational study suggests that increased BMI may confer a more favorable prognosis in patients with overt heart failure.[77] However, interpretation of these findings is complicated by the fact that lower

BMI may reflect the presence of circulatory compromise, ultimately leading to cardiac cachexia in patients with advanced cardiac function. Nevertheless, based on available data, it currently remains unclear whether weight loss promotion in medically optimized patients with heart failure is a worthwhile therapeutic goal.

Key points

- Increased body weight increases the risk for the development of heart failure. **Grade A**
- Increased body weight may confer a more favorable prognosis in patients with heart failure. **Grade B**
- Weight reduction is currently not recommended for patients with congestive heart failure. **Grade C**

Sleep apnea and obesity hypoventilation syndrome

Obesity is the most common precipitating factor for obstructive sleep apnea and is a requirement for the obesity hypoventilation syndrome, both of which are associated with substantial morbidity and increased mortality.[78] Numerous case reports and non-controlled trials document substantial improvement in sleep apnea and the obesity hypoventilation syndrome, particularly with surgically induced weight loss. In a recent Cochrane review of lifestyle modification for obstructive sleep apnea, the reviewers concluded that there were currently no randomized trial data available for analysis.[79] Thus, there are currently no data regarding the magnitude of weight loss necessary to produce a clinically significant improvement in obesity related obstructive sleep apnea, nor regarding which group of patients is most likely to benefit from this intervention.

Key point

- Surgically induced weight loss can improve the clinical picture of sleep apnea and the obesity hypoventilation syndrome. **Grade B**

Goals for weight loss

The general goals of weight loss and management are to reduce body weight, to maintain lower body weight over the long term, and to prevent further weight gain.[5,15] Weight loss should be recommended for all patients with a BMI ≥30 and for those with a BMI ≥27 with two or more risk factors.[5,15] There is consistent evidence from randomized controlled trials to indicate that overweight and obese patients in well designed programs can achieve and maintain moderate (5–10%) weight loss over time if some form of therapy continues. The initial goal of weight loss therapy should therefore be to reduce body weight by approximately 10% from baseline.

Randomized trials suggest that weight loss at a rate of 0·45–0·90 kg/week commonly occurs for up to 6 months.[5,15] The rate of weight loss in patients with type 2 diabetes may be slower than in non-diabetics.

Key points

- Weight loss should be recommended for all patients with a BMI ≥30 and for those with a BMI ≥27 with two or more risk factors. **Grade B**
- The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. **Grade A**
- Weight loss should be about 0·45–0·90 kg/week for a period of 6 months. **Grade B**

How to achieve weight loss

Successful weight loss requires the combination of multiple interventions and strategies, including diet, physical activity, behavior modification, pharmacotherapy and surgery. Because obesity is a chronic condition, all treatment, including pharmacotherapy, should be initiated with the expectation that it will be long term.[15] An evidence-based algorithm is provided in Figure 19.2.

Lifestyle intervention

With regard to dietary therapy, a review of 48 randomized controlled trials[5] concluded that an average weight loss of 8% can be obtained over 3–12 months with a controlled energy low-calorie diet (LCD) aimed to reduce caloric intake by 500–1000 kcal/day (2092–4184 kJ/day), and that this weight loss effects a decrease in abdominal fat. It also appears that lower-fat diets with energy reduction promote greater weight loss than energy reduction alone. Very low-calorie diets (VLCDs), generally involving the use of protein and dietary supplements, can produce greater initial weight losses that LCDs, but long-term (>1 year) weight loss appears to be only marginally greater.[80] Importantly, unless accompanied by physical activity, weight loss with dietary measures is not associated with an improvement in cardiorespiratory fitness as measured by maximum oxygen consumption.[5,15]

A review of 13 randomized controlled trials provides strong evidence that physical activity alone results in rather modest weight loss but improves cardiorespiratory fitness, may reduce abdominal fat and may help long-term weight maintenance.[5] A review of 15 randomized controlled trials combining dietary measures and physical activity provides strong evidence that

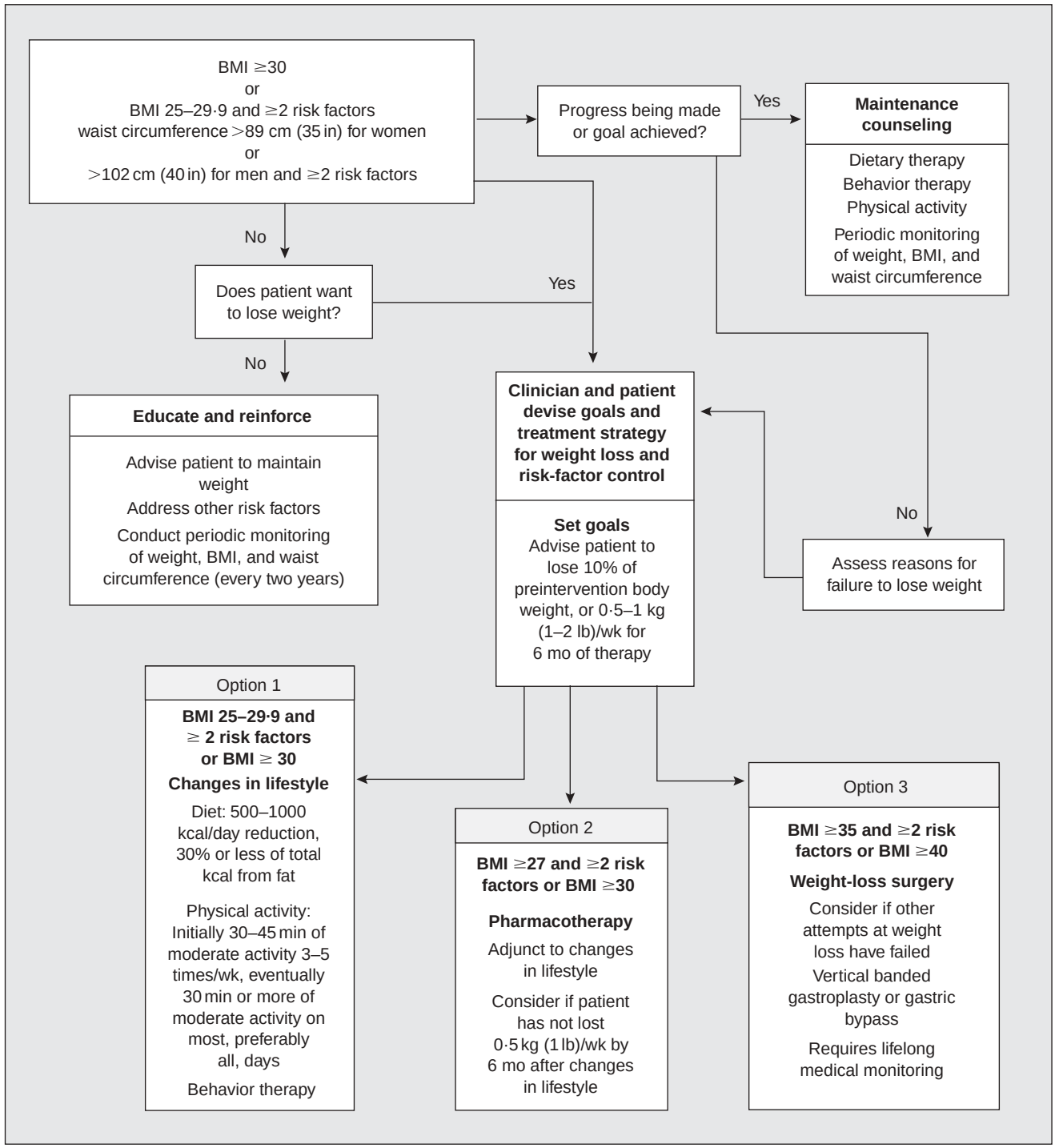

Figure 19.2 Evidence-based algorithm for the treatment of obesity. Adapted from the National Institute of Health guidelines[15]

the combination of these measures results in substantially greater weight loss than either measure alone.[5] There also appears to be additional value in behavioral therapy, although no one behavioral therapy appears to be superior to any other in its effect on weight loss. In general, the greater the intensity of the intervention, the greater the weight loss. No additional long-term benefits of behavioral therapy are found at 3–5 years. Nevertheless, there is evidence to suggest that patient motivation is an important determinant of success in weight loss programs.

Key points

- Weight loss and weight maintenance therapy should use a combination of low-calorie diets (LCDs), increased physical activity and behavioral therapy. **Grade A**
- Low-calorie diets (LCDs) providing a deficit of 500–1000 kcal/day (2092–4184 kJ/day) are a practical way to reduce calories and should be an integral part of any program aimed at achieving a weight loss of 0·45–0·90 kg/wk over 6 months. **Grade A**
- Physical activity should be an integral part of weight loss therapy and weight maintenance, as it contributes modestly to weight loss, **Grade A** increases cardiovascular fitness, **Grade A** modestly decreases abdominal fat, **Grade B** and may help with maintenance of weight loss. **Grade C**
- Initially, moderate levels of physical activity for 30–45 minutes, 3–5 days a week, should be encouraged, with the long-term goal of accumulating at least 30 minutes or more of physical activity on most or all days of the week. **Grade B**
- Behavioral therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance. **Grade B**
- Practitioners need to assess the patient's motivation to begin weight loss therapy, assess their readiness to implement the plan, and take appropriate steps to motivate them for treatment. **Grade C**
- A weight maintenance program should be a priority after the initial 6 months of weight loss therapy. **Grade B**

Pharmacotherapy of obesity

Strong evidence indicates that the use of appropriate weight loss drugs can augment diet, physical activity and behavior therapy in weight loss.[5,15] Orlistat is gastrointestinal lipase inhibitor that reduces enteral fat absorption by around 30%.[81] Sibutramine is a centrally active serotonin and norepinephrine uptake inhibitor that reduces hunger, increases satiety, and which may have a small thermogenic effect.[82] Both compounds have been approved by licensing authorities in most countries for the pharmacologic treatment of obesity and the management of overweight patients with related comorbidities. They can be used as an adjunct to diet and physical activity for patients with a BMI of 30 or greater with no concomitant obesity risk factors or diseases, as well as patients with a BMI of 27 or greater with concomitant obesity related risk factors (hypertension, dyslipidemia, type 2 diabetes), when these patients have failed to reduce and maintain weight loss by lifestyle interventions alone.[5,15] Both have been shown to decrease the rate of weight regain following weight loss induced by combining lifestyle intervention with weight loss medication[66,83,84] or very low-calorie diets.[85] Starting with the lowest dose and discontinuation in non-responders can decrease the likelihood of adverse effects.

Mode of action, efficacy, side effects and contraindications for the use of orlistat and sibutramine are summarized in Table 19.4.

Unlike fenfluramine and dexfenfluramine, sibutramine does not induce serotonin release and has not been implicated in the development of valvular heart disease.[86] Small, dose dependent increases in heart rate and blood pressure have been consistently noted with the use of sibutramine.[87] Furthermore, reductions in blood pressure seen with sibutramine-induced weight loss tend to be less than the reductions seen with weight loss obtained by other treatments. Nevertheless, weight reduction in hypertensive patients is accompanied by a fall in both systolic and diastolic pressure, and several randomized controlled studies have shown that sibutramine can be used in overweight and obese patients with well controlled hypertension.[88] As with other weight loss interventions, sibutramine-induced weight loss is associated with a significant improvement in metabolic parameters.

Because of its lack of systemic effects on the heart and circulation, orlistat has obvious advantages over sibutramine for use in high-risk patients with established coronary artery disease, arrhythmias, stroke or heart failure. Thus, weight loss with orlistat results in a reduction in heart rate and blood pressure corresponding to that expected for a similar degree of weight loss achieved with non-pharmacologic intervention. Furthermore, owing to its mode of action the use of orlistat has been associated with a greater reduction in LDL cholesterol than can be expected by weight reduction alone.[63]

Key points

- Orlistat and sibutramine may be used as part of a weight loss program in patients with a BMI greater than 30, or in patients with a BMI greater than 27 when associated with obesity related comorbid conditions. **Grade B**
- Weight loss drugs should not be used without concomitant lifestyle modification. **Grade B**
- Continual assessment of drug therapy for efficacy and safety is necessary. **Grade C**
- If the drug is efficacious in helping the patient to lose and/or maintain weight loss and there are no serious adverse effects, it can be continued; if not, it should be discontinued. **Grade C**
- Starting with the lowest dose and discontinuation of antiobesity medication in non-responders can decrease the likelihood of adverse effects. **Grade C**

Surgery

There is currently good evidence to support the use of surgical interventions in adults with clinically severe obesity (BMI > 40 or above, or BMI > 35 with obesity related

Table 19.4 Medications approved for the long-term treatment of obesity* (adapted from[15] and [89])

	Orlistat	Sibutramine
Trade names	Xenical	Reductil/Meridia
Mechanism of action	Lipase inhibitor	Mixed norepinephrine and serotonin reuptake inhibitor
Dosage	120 mg 3 times/day with or within 1 h after fat-containing meals, plus a daily multivitamin	5–15 mg/day
Cost (US wholesale price)	$3·56/day	$2·98–3·68/day
Average weight loss when used together with lifestyle modification	4–7%	5–8%
Most frequent side effects	Flatulence with discharge, fecal urgency, fecal incontinence, steatorrhea, oily spotting, increased frequency of defecation, decreased absorption of fat-soluble vitamins	Dry mouth, headache, insomnia, constipation, anorexia, increase in heart rate, increase in blood pressure†
Potential drug interaction	Cyclosporine	SSRIs, MAOIs, centrally active anorexants, sumatriptan, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium, tryptophan
Contraindications	Chronic malabsorption syndromes, cholestasis	Uncontrolled hypertension, severe renal impairment, severe hepatic dysfunction, narrow-angle glycoma, history of substance abuse, coronary artery disease, congestive heart failure, arrhythmias, stroke

*Ephedrine plus caffeine and fluoxetine have also been tested for weight loss but are not approved for use in the treatment of obesity. Mazindol, diethylpropion, phentermine, benphetamine and phendimetrazine are approved only for the short-term use for the treatment of obesity. Herbal preparations are not recommended as part of a weight loss program. These preparations have unpredictable amounts of active ingredients and unpredictable, potentially harmful effects.
† If there is a sustained increase in blood pressure or heart rate, either a reduction in the dose or discontinuation should be considered.

comorbid conditions).[5,15] In these patients, surgery can result in substantial weight loss and a marked improvement in comorbid conditions. Two types of operations have proved effective: those that restict gastric volume (banded gastroplasty) and those that, in addition to limiting food intake, also alter digestion (Roux-en-Y gastric bypass).[15] Patients who have undergone surgery require lifelong medical surveillance.

Key point

- Weight loss surgery is appropriate for carefully selected patients with clinically severe obesity (BMI > 40, or BMI > 35 with comorbid conditions) when less invasive methods have failed and the patient is at high risk for obesity associated morbidity or mortality. **Grade B**

Summary

Obesity is now recognized as an important risk factor for cardiovascular morbidity and mortality. Weight reduction induced by lifestyle, pharmacologic or surgical measures has been shown to substantially improve obesity related comorbidities, perhaps with the exception of congestive heart failure. Weight loss programs should focus on weight maintenance rather than weight loss alone. Randomized controlled outcome studies with hard end points, required to establish weight loss as an effective measure that reduces cardiovascular mortality, are still lacking.

References

1. World Health Organization. Report of a WHO consultation on obesity. *Obesity: preventing and managing the global epidemic*. Geneva: World Health Organization, 1998.
2. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The continuing epidemic of obesity in the United States. *JAMA* 2000;**284**:1650–1·
3. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999;**282**:1523–9.
4. Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. *Circulation* 1998;**97**: 2099–100.
5. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998;**158**:1855–67.
6. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. *Arch Intern Med* 1999;**159**:837–43.
7. Kuczmarski RJ, Flegal KM. Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr* 2000;**72**:1074–81.
8. Hubbard VS. Defining overweight and obesity: what are the issues? *Am J Clin Nutr* 2000;**72**:1067–8.
9. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *BMJ* 1984;**289**:1257–61.
10. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *BMJ* 1984; **288**:1401–4.
11. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998;**351**:853–6.
12. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;**337**: 382–6.
13. Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *Int J Obesity Rel Metab Disord* 1999;**23**:1136–42.
14. Inoue S, Zimmet P. *The Asia-Pacific perspective: redefining obesity and its treatment*. Report coordinated by the International Diabetes Institute, Australia: Health Communications Australia, 2000.
15. *The practical guide: identification, evaluation, and treatment of overweight and obesity in adults*. Bethesda, MD: National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity, 2000 (NIH publication no. 00-4048).
16. Stamler J, Stamler R, Riedlinger WF, Algera G, Roberts RH. Hypertension screening of 1 million Americans. Community Hypertension Evaluation Clinic (CHEC) program, 1973 through 1975. *JAMA* 1976;**235**:2299–306.
17. Kannel WB, Garrison RJ, Dannenberg AL. Secular blood pressure trends in normotensive persons: the Framingham Study. *Am Heart J* 1993;**125**:1154–8.
18. He J, Klag MJ, Whelton PK, Chen JY, Qian MC, He GQ. Body mass and blood pressure in a lean population in southwestern China. *Am J Epidemiol* 1994;**139**:380–9.
19. Reed D, McGee D, Yano K. Biological and social correlates of blood pressure among Japanese men in Hawaii. *Hypertension* 1982;**4**:406–14.
20. Hall JE. Pathophysiology of obesity hypertension. *Curr Hypertens Rep* 2000;**2**:139–47.
21. Mark AL, Correia M, Morgan DA, Shaffer RA, Haynes WG. State-of-the-art-lecture: Obesity-induced hypertension: new concepts from the emerging biology of obesity. *Hypertension* 1999;**33**:537–41.
22. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obesity Res* 2000;**8**:270–8.
23. Kriketos AD, Robertson RM, Sharp TA *et al.* Role of weight loss and polyunsaturated fatty acids in improving metabolic fitness in moderately obese, moderately hypertensive subjects. *J Hypertens* 2001;**19**:1745–54.
24. Saltzman E, Das SK, Lichtenstein AH *et al.* An oat-containing hypocaloric diet reduces systolic blood pressure and improves lipid profile beyond effects of weight loss in men and women. *J Nutr* 2001;**131**:1465–70.
25. Ard JD, Rosati R, Oddone EZ. Culturally-sensitive weight loss program produces significant reduction in weight, blood pressure, and cholesterol in eight weeks. *J Natl Med Assoc* 2000;**92**:515–23.
26. Metz JA, Stern JS, Kris-Etherton P *et al.* A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. *Arch Intern Med* 2000;**160**:2150–8.
27. Stevens VJ, Obarzanek E, Cook NR *et al.* Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001; **134**:1–11.
28. Whelton PK, Appel LJ, Espeland MA *et al.* Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998;**279**:839–46.
29. Blumenthal JA, Sherwood A, Gullette EC *et al.* Exercise and weight loss reduce blood pressure in men and women with

mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. *Arch Intern Med* 2000;**160**: 1947–58.
30. Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on comorbid conditions. *Obesity Res* 2001;**9**(Suppl 4):326S–34S.
31. Sjostrom L, Rissanen A, Andersen T *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicenter Orlistat Study Group. *Lancet* 1998;**352**:167–72.
32. Davidson MH, Hauptman J, DiGirolamo M *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;**281**:235–42.
33. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000;**9**:160–7.
34. Rossner S, Sjostrom L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obesity Res* 2000; **8**:49–61.
35. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicenter study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obesity Rel Metab Disord* 2000; **24**:306–13.
36. Hazenberg BP. Randomized, double-blind, placebo-controlled, multicenter study of sibutramine in obese hypertensive patients. *Cardiology* 2000;**94**:152–8.
37. McMahon FG, Fujioka K, Singh BN *et al.* Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 2000;**160**:2185–91.
38. Sharma AM, Pischon T, Engeli S, Scholze J. Choice of drug treatment for obesity-related hypertension: where is the evidence? *J Hypertens* 2001;**19**:667–74.
39. Schmieder RE, Gatzka C, Schachinger H, Schobel H, Ruddel H. Obesity as a determinant for response to antihypertensive treatment. *BMJ* 1993;**307**:537–40.
40. Reisin E, Weir MR, Falkner B, Hutchinson HG, Anzalone DA, Tuck ML. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trial. Treatment in Obese Patients With Hypertension (TROPHY) Study Group. *Hypertension* 1997;**30**:140–5.
41. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK, Wilhelmsen L. Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Goteborg, Sweden. *J Hum Hypertens* 1994; **8**:257–63.
42. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000;**342**:905–12.
43. Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension* 2001;**37**:250–4.
44. Hansson L, Lindholm LH, Niskanen L *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;**353**:611–16.
45. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
46. Dahlöf B, Devereux RB, Kjeldsen SE *et al.* for the LIFE study group. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**:995–1003.
47. Field AE, Coakley EH, Must A *et al.* Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;**161**:1581–6.
48. Ohlson LO, Larsson B, Svardsudd K *et al.* The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985;**34**:1055–8.
49. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994;**17**:961–9.
50. Sinha R, Fisch G, Teague B *et al.* Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;**346**:802–10.
51. Tuomilehto J, Lindstrom J, Eriksson JG *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;**344**: 1343–50.
52. Knowler WC, Barrett-Connor E, Fowler SE *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393–403.
53. The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. *Diabetes Care* 1988;**11**:567–73.
54. Kanoun F, Ben Amor Z, Zouari B, Ben Khalifa F. Insulin therapy may increase blood pressure levels in type 2 diabetes mellitus. *Diabetes Metab* 2001;**27**:695–700.
55. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854–65.
56. Clarke P, Gray A, Adler A *et al.* Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type II diabetes (UKPDS No. 51). *Diabetologia* 2001;**44**:298–304.
57. Hollander PA, Elbein SC, Hirsch IB *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* 1998;**21**: 1288–94.
58. Heymsfield SB, Segal KR, Hauptman J *et al.* Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000;**160**: 1321–6.
59. Finer N, Bloom SR, Frost GS, Banks LM, Griffiths J. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomised, double-blind,

placebo-controlled study. *Diabetes Obesity Metab* 2000;**2**: 105–12.
60. Fujioka K, Seaton TB, Rowe E *et al.* Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obesity Metab* 2000;**2**:175–87.
61. National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Executive summary. Bethesda, MD: National Heart, Lung, and Blood Institute, 2001 (NIH publication No. 01-3670).
62. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;**56**:320–8.
63. Muls E, Kolanowski J, Scheen A, Van Gaal L. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicenter study. *Int J Obesity Rel Metab Disord* 2001;**25**:1713–21.
64. Reaven G, Segal K, Hauptman J, Boldrin M, Lucas C. Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X. *Am J Cardiol* 2001;**87**:827–31.
65. Dujovne CA, Zavoral JH, Rowe E, Mendel CM. Effects of sibutramine on body weight and serum lipids: a double-blind, randomized, placebo-controlled study in 322 overweight and obese patients with dyslipidemia. *Am Heart J* 2001;**142**: 489–97.
66. James WP, Astrup A, Finer N *et al.* Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;**356**:2119–25.
67. Mittendorfer B, Ostlund RE Jr, Patterson BW, Klein S. Orlistat inhibits dietary cholesterol absorption. *Obesity Res* 2001;**9**: 599–604.
68. Luyckx FH, Scheen AJ, Desaive C, Dewe W, Gielen JE, Lefebvre PJ. Effects of gastroplasty on body weight and related biological abnormalities in morbid obesity. *Diabetes Metab* 1998;**24**:355–61.
69. Busetto L, Pisent C, Rinaldi D *et al.* Variation in lipid levels in morbidly obese patients operated with the LAP-BAND adjustable gastric banding system: effects of different levels of weight loss. *Obesity Surg* 2000;**10**:569–77.
70. Yudkin JS. Abnormalities of coagulation and fibrinolysis in insulin resistance. Evidence for a common antecedent? *Diabetes Care* 1999;**22**(Suppl 3):C25–30.
71. Fujii S, Goto D, Zaman T *et al.* Diminished fibrinolysis and thrombosis: clinical implications for accelerated atherosclerosis. *J Atheroscler Thromb* 1998;**5**:76–81.
72. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999;**19**:972–8.
73. Gaudet D, Vohl MC, Perron P *et al.* Relationships of abdominal obesity and hyperinsulinemia to angiographically assessed coronary artery disease in men with known mutations in the LDL receptor gene. *Circulation* 1998;**97**:871–7.
74. Rea TD, Heckbert SR, Kaplan RC *et al.* Body mass index and the risk of recurrent coronary events following acute myocardial infarction. *Am J Cardiol* 2001;**88**:467–72.
75. Hoit BD, Gilpin EA, Maisel AA, Henning H, Carlisle J, Ross J Jr. Influence of obesity on morbidity and mortality after acute myocardial infarction. *Am Heart J* 1987;**114**:1334–41.
76. Kenchaiah S, Evans JC, Levy D *et al.* Obesity and the Risk of Heart Failure. *N Engl J Med* 2002;**347**:305–13.
77. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001; **38**:789–95.
78. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci* 2001;**321**:249–79.
79. Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea. Cochrane Database Syst Rev. 2001:CD002875.
80. Saris WH. Very-low-calorie diets and sustained weight loss. *Obesity Res* 2001;**9**(Suppl 4):295S–301S.
81. Guerciolini R. Mode of action of orlistat. *Int J Obesity Rel Metab Disord* 1997;**21**(Suppl 3):S12–23.
82. Stock MJ. Sibutramine: a review of the pharmacology of a novel anti-obesity agent. *Int J Obesity Rel Metab Disord* 1997;**21**(Suppl 1):S25–9.
83. Hill JO, Hauptman J, Anderson JW *et al.* Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* 1999;**69**:1108–16.
84. Rossner S, Sjostrom L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obesity Res* 2000; **8**:49–61.
85. Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med* 1999; **106**: 179–84.
86. Bach DS, Rissanen AM, Mendel CM *et al.* Absence of cardiac valve dysfunction in obese patients treated with sibutramine. *Obesity Res* 1999;**7**:363–9.
87. Bray GA, Blackburn GL, Ferguson JM *et al.* Sibutramine produces dose-related weight loss. *Obesity Res* 1999;**7**:189–98.
88. Sharma AM. Sibutramine in overweight/obese hypertensive patients. *Int J Obesity Rel Metab Disord* 2001;**25** (Suppl 4): S20–3.
89. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002; **346**:591–602.

20 Postmenopausal hormone therapy and cardiovascular disease

Jacques E Rossouw

Gender and cardiovascular disease

In the United States the number of women who die annually from cardiovascular disease is higher than men. The cardiovascular disease burden is particularly high in older women. In women aged 55 and older, major cardiovascular diseases (ICD 390–448·9) accounted for 473 569 deaths in 1997 compared to 402 310 deaths in older men.[1] Major cardiovascular diseases accounted for 44% of all deaths in older women and 40% of all deaths in older men. The number of deaths from coronary heart disease (CHD) was only slightly higher in older women (229 628) than in men (223 246), but the number of deaths from stroke was considerably higher in women (88 768 compared to 55 149 respectively). There were 4607 deaths from pulmonary embolism in older women compared to 3465 in men. As exemplified by these absolute numbers of deaths, cardiovascular disease now represents a larger health problem in older women than in older men.

CHD in particular occurs at a later age in women than in men, and this is one reason why early trials (including estrogen trials) attempting to prevent "premature" CHD focused on middle-aged men. On average, death from CHD occurs about 10 years later in women (Figure 20.1) than in men. The incidence rate of CHD mortality rises after the age of 65, and rises particularly steeply after 75 years when the great majority of CHD events occur. Though their incidence rates remain lower at any age than in men, the fact that older women with CHD outnumber men explains why the absolute number of CHD deaths is higher in women. Deaths from strokes and pulmonary embolism also rise markedly with age. Since CHD and strokes are the major contributors to overall cardiovascular disease rates, the effects of estrogen on these conditions will dominate the overall cardiovascular outcome.

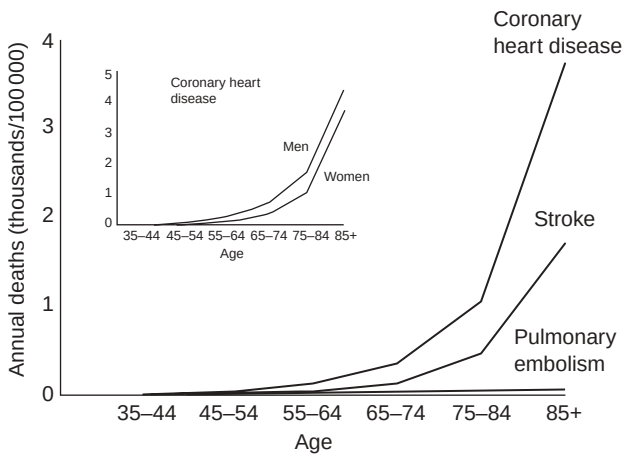

Figure 20.1 Annual mortality rates by 10 year age groups for CHD, stroke, and pulmonary embolism in US women, 1997.[1] Inset: Comparison of coronary heart disease mortality rates by age for men and women.

The sex differential in the age of onset of CHD is also one of the reasons why estrogen is of interest as a potential preventive treatment for CHD. Lipid levels in children of both sexes are similar until puberty, when high density lipoprotein (HDL) cholesterol levels fall by about 10 mg/dl in boys only, while low density lipoprotein (LDL) cholesterol levels decrease by about 5 mg/dl in girls.[2] These changes may be attributable to rising androgen and estrogen levels in boys and girls respectively. The sex differential for HDL cholesterol persists through adult life, but is less marked in older persons. LDL cholesterol levels rise during adulthood, and in older women LDL cholesterol levels eventually catch up with those in men. Estrogen levels in women gradually decline, starting some years before the menopause, during which time LDL cholesterol levels rise and HDL cholesterol levels decrease.[3] These lipid changes may underlie the lower CHD risk in premenopausal women, and the gradual increase in postmenopausal women. However, the menopause does not represent a sharp demarcation in risk; some longitudinal studies have not shown changes in risk factors over the menopause, and the rise in coronary rates may simply reflect the effects of aging itself, as suggested when the data for coronary deaths are plotted on a semi-logarithmic scale (Figure 20.2).[1,4] Nonetheless, premature menopause due to oophorectomy is associated with a higher CHD risk, and oophorectomy followed by estrogen therapy is not associated with increased risk for CHD.[5] When exogenous estrogen is administered via the oral route to postmenopausal women, LDL cholesterol levels decrease, HDL cholesterol levels increase, triglyceride levels increase, and lipoprotein (a) levels decrease.[6–10] However, exogenous oral estrogen has multiple non-lipid effects. Some changes in coagulation factors are potentially favorable (for example,

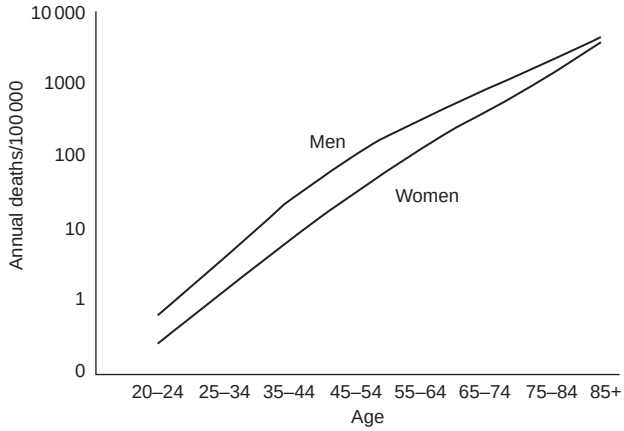

Figure 20.2 Annual mortality rates for CHD by age for US men and women on a semi-logarithmic scale

a decrease in fibrinogen level[7–9]) while others are potentially unfavorable (for example, an increase in factor VII[8,9]), and the net effect of estrogen on coagulation is uncertain. Similarly, some effects on markers of inflammation are potentially unfavorable (for example, increases in C-reactive protein) and others favorable (for example, decreases in vascular endothelial adhesion molecules).[11,12] Other potential influences of estrogen on vascular biology include direct effects on the vessel wall, which improve blood flow,[13,14] and antioxidant properties that may slow the early stages of atherosclerosis.[15] It should be noted that many, but not all, of the biologic effects of estrogen are counteracted by the progestins, which are now routinely prescribed in combination with estrogen in women with intact uterus.[7–9]

Thus, there is a plethora of potential mechanisms by which estrogen may reduce the risk of CHD.[16] Unfortunately, the existence of mechanisms does not necessarily translate into clinical benefit. A treatment that has a favorable effect on an intermediate mechanism may decrease the incidence of target clinical events, or may turn out to have no effect, or may actually increase the event rates. The treatment may also have unanticipated adverse effects on other clinical events.[17] For example, a number of early lipid lowering drugs, such as thyroxin and estrogen, were abandoned after it was found that, although these drugs decrease cholesterol levels, they also increase the cardiovascular morbidity and mortality in men.[18]

Box 20.1

- Cardiovascular disease is a major health problem in older women.
- Coronary heart disease occurs at a later age in women than in men.
- The later onset of coronary disease may be due to gender-specific hormone-induced changes in blood lipid levels.
- Increased rates of coronary heart disease after the menopause may be due to declining estrogens or may be due to aging.

Coronary heart disease

Throughout this chapter, the term postmenopausal hormone therapy (sometimes shortened to hormone therapy) is used to describe the use of estrogen or estrogen plus a progestin in postmenopausal women. The term hormone replacement therapy is not used, because this term implies a judgment that postmenopausal women suffer from a hormone "deficiency" that needs treatment.

More than 30 observational studies have suggested that women who are taking estrogen appear to have a lower risk of heart disease, and several have shown similar apparent risk reductions for estrogen when it is used in combination with progestin.[19–23] Only a few key studies will be reviewed in detail, since they illustrate sufficiently the findings from observational studies, and their limitations. "Primary prevention" studies are those in which women with prevalent coronary artery disease (CAD) were removed from the cohort, while "secondary prevention" studies followed only those women with a history or other evidence of CAD at baseline. The growing body of evidence from clinical trials with surrogate outcomes and clinical trials, with "hard" clinical outcomes for secondary prevention, will be reviewed in detail. Thus far, these secondary prevention trials have failed to confirm the cardiovascular benefit predicted from observational studies, and in fact the trials suggest that there is likely to be harm in the first few months to years after initiation of hormone therapy. Substantive data from primary prevention trials have yet to be published.

Primary prevention

Observational studies

With the exception of the initial report from Framingham on this issue, all the observational studies of healthy postmenopausal women comparing hormone users with non-users described an association of hormone use (particularly current hormone use) with lower risk for CHD.[19–24] However, as reviewed elsewhere, the consistency of these results may be due to powerful systematic biases in observational studies, which may lead to an overestimation of benefit and an underestimation of harm associated with hormone use.[25,26]

The Nurses' Health Study is representative of the observational studies, and the women in this study comprise one of the largest and best studied cohorts in the USA.[21] The 1976 baseline examination included 121 700 nurses aged 30–55 years of whom 21 726 were postmenopausal. With the passage of time a progressively larger proportion entered the menopause and these women contributed data to a series of papers on the associations between menopause, hormone therapy, and cardiovascular disease. Data on

hormone use and health status were updated biennially by questionnaire. The most recent analysis included 70 533 women with up to 20 years average follow up for a total experience of 808 825 person-years during which time the study accrued 1258 major coronary events (non-fatal myocardial infarction or coronary death).[21] There were 662 major coronary events during the 358 125 person-years of never users, 337 events during the 185 497 person-years of past users, and 259 events during the 265 203 person-years of current users of postmenopausal hormone therapy. Conjugated equine estrogen (CEE) accounted for about two thirds of the estrogen used. Proportional hazards models were used to calculate relative risks for incidence of clinical outcomes, using women who had never used hormones as the reference group. Multivariate adjustments were made for age, body mass index, history of diabetes, hypertension, high cholesterol level, cigarette smoking, and parental history of premature heart disease.

The adjusted relative risk of major coronary disease in current users compared to never users was 0·61 (95% CI 0·52–0·71), and in past users it was 0·82 (95% CI 0·72–0·94). Current users of CEE alone had a relative risk of 0·55 (95% CI 0·45–0·68), and current users of CEE with medroxyprogesterone acetate (MPA) had a relative risk of 0·55 (95% CI 0·49–0·85). Duration of hormone use appeared to have little influence; however the relative risk appeared to be lowest in current users for less than 1 year (0·41, 95% CI 0·21–0·77) (Figure 20.3). The reduced risk for CHD was observed at all estrogen doses, but appeared to be more marked at the doses of 0·3 mg conjugated equine estrogen (0·58, 95% CI 0·37–0·92) and 0·625 mg (0·54, 95% CI 0·44–0·67) than at the dose of 1·25 mg or higher (0·70, 95% CI 0·51–0·97) (Figure 20.3).

An earlier publication from the Nurses' Health Study noted that the rates of coronary revascularization did not differ between current users and non-users.[27] Since it differs from the findings for fatal and non-fatal myocardial infarction, this observation argues against an immediate beneficial effect of estrogen on the vessel wall. Most patients undergo revascularization for symptoms and, if estrogens had a direct effect, symptoms would have been less likely in users. The data as regards to revascularization have implications for the interpretation of the data for CHD events: if estrogen confers no immediate benefit, the finding of lower CHD rates in current users may be due to the compliance bias known to operate in subjects who are regularly taking medications, or to selection bias as to who goes onto estrogen and who is removed from therapy.

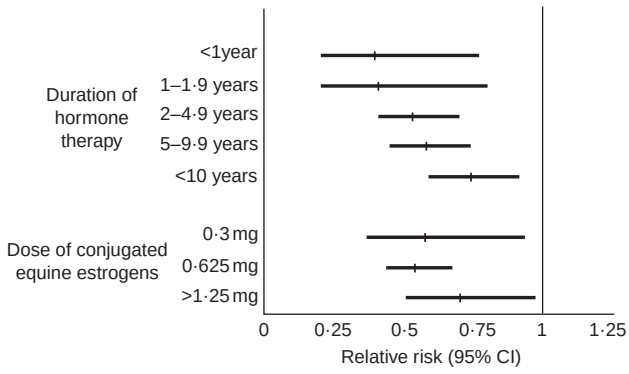

Figure 20.3 Relative risks and 95% confidence intervals for CHD by duration and dose of current hormone use in the Nurses' Health Study[21]

Data on risk for CHD in healthy women soon after initiation of estrogen therapy are sparse and inconsistent, although most studies suggest reduced initial risk in estrogen users. As noted above, the Nurses' Health Study observed the lowest relative risk during the first year of use.[21] Several other studies found little or no association of hormone use with risk in the first year or two after initiating therapy,[28–30] while two suggested some early increase in risk.[31,32] By contrast (see below) the data for secondary prevention are much more consistent in suggesting cardiovascular harm after initiation of therapy.

Clinical trials

A pooled analysis of 23 randomized controlled trials, which were done for the study of non-cardiovascular short-term effects of hormone therapy but which recorded numbers of clinical events, found twelve cardiovascular (arterial) events in the hormone groups and five in the control groups.[33] Though not statistically significant, the results were in the opposite direction to that predicted by the observational studies.

Large clinical trials of estrogen in healthy women with sufficient statistical power to provide a definitive answer to the question of benefit for cardiovascular disease are underway (Table 20.1). The first of these forms part of the Women's Health Initiative (WHI) in the USA. The WHI enrolled 27 347 women aged 50–79 in the trials of menopausal hormone therapy during 1993–1998 and will be completed in 2005 after 8·4 years average follow up.[34] The study comprises two randomized controlled clinical trials: the 16 608 women with an intact uterus randomized to CEE 0·625 mg/day plus MPA 2·5 mg/day or placebo, and the 10 739 women with a hysterectomy randomized to CEE 0·625 mg/day or placebo. No results have yet been published, but in 2000 the trial participants were advised that during the first 2 years after randomization small excesses in numbers of heart attacks, strokes, and blood clots in the lungs were observed in the active treatment groups.[35] In 2001 a follow up communication to participants stated that small absolute excesses of these conditions persisted beyond the first 2 years, but that the trials will continue because the overall risk and benefit remained uncertain.[35]

Table 20.1 Randomized controlled clinical trials for primary or secondary prevention of coronary heart disease or stroke in postmenopausal women

Trial	Population	Number	Age range	Active treatment	Primary end points	Findings
WHI (Women's Health Initiative)[34,35]	Primary prevention	27 347	50–79	CEE 0·625 mg plus MPA 2·5 mg/day, or CEE 0·625 mg/day	Non-fatal MI or CHD death	Small excess of heart attacks and strokes in first few years after randomization, planned stop in 2005
WISDOM (Women's International Study of long Duration Oestrogen after the Menopause)[36]	Primary prevention	Target 22 000 in UK, 34 000 with international collaboration	50–69	CEE 0·625 mg plus MPA 2·5 mg/day, or CEE 0·625 mg/day	Non-fatal MI, CHD death, non-fatal or fatal stroke	Results expected approx. 2010
RUTH (Raloxifene Use for The Heart)[55]	High risk primary and secondary prevention	10 101	>55	Raloxifene 60 mg/day	(1) Non-fatal MI, CHD death, or hospitalized ACS (2) Breast cancer	Results expected approx. 2005
HERS (Heart and Estrogen/progestin Replacement Study)[45]	Secondary prevention	2763	55–80	CEE 0·625 mg plus MPA 2·5 mg/day	Non-fatal MI or CHD death	No overall effect on risk for CHD; excess CHD in first year
WEST (Women's Estrogen for Stroke Trial)[53]	Secondary prevention of stroke	664	46–91	Estradiol 1 mg/day	Stroke	No overall effect on risk for stroke; excess stroke in first 6 months
PHASE (Papworth HRT and Survival Enquiry)[52]	Secondary prevention	255	?	Transdermal estradiol with or without cyclic norethisterone	Non-fatal MI, death, or hospitalized ACS	Non-significant excess of events in active treatment group, trial stopped after average 2·5 years follow up because of futility and possibility of harm
ESPRIT (oEStrogen in the Prevention of Re-infarction study)[54]	Secondary prevention	1017	50–69	Estradiol valerate 2 mg/day	Non-fatal MI or CHD death	Results expected in 2002

Abbreviations: ACS, acute coronary syndromes; CEE, conjugated equine estrogens; CHD, coronary heart disease; MI, myocardial infarction; MPA, medroxyprogesterone acetate

A second large trial being conducted in the United Kingdom and New Zealand, known as the Women's Intervention Study of long-Duration Oestrogen after the Menopause (WISDOM), is enrolling women aged 50–64 and randomizing women with a uterus to CEE 0·625 mg/day plus MPA 2·5 mg/day or placebo, and women who have had a hysterectomy to CEE 0·625 mg/day, CEE 0·635 mg/day plus MPA 2·5 mg/day, or placebo.[36] Up to 34 000 women will be enrolled. The primary analysis will compare CEE plus MPA to placebo, and the secondary analysis will compare CEE plus MPA to CEE alone. The primary outcome of interest is combined CHD and stroke.

Box 20.2

- The effect of postmenopausal hormone therapy on risk for CHD in healthy women remains unknown.
- Observational studies suggest potential benefit for CHD in long-term hormone users, but these studies can be biased towards benefit.
- Pooled data from short-term clinical trials suggest possible cardiovascular harm.
- One major clinical trial in healthy women has informed participants of a small excess of CHD in the hormone groups during the first few years of the study, but has not published the results.

Secondary prevention

Observational studies

Observational studies in women undergoing angioplasty or coronary artery bypass grafting (CABG) have found that use of postmenopausal hormone therapy was associated with lower rates of cardiovascular events and improved survival.[37–40] A retrospective analysis of postmenopausal women undergoing angioplasty found that 12% of patients taking hormones had cardiovascular events over 7 years of follow up, compared to 35% of non-users.[37] A second similar study found that inhospital and 2 year mortality after angioplasty was lower in hormone users.[38] In women undergoing CABG, one study found that hormone use was associated with a 62% survival benefit; however, this was not confirmed in a subsequent study.[39,40] Several observational studies have compared the experience of women currently on hormone therapy and who suffer a myocardial infarction with those who were not on hormone therapy at the time of the myocardial infarction.[41–44] These studies have consistently found better outcomes for women who were currently on hormone therapy at the time of the event.

The largest study of inhospital mortality was performed prospectively in 114 724 women aged over 55 who were entered into the National Registry of Myocardial Infarction-3.[41] At the time of hospitalization, 6·4% of women reported current use of hormone therapy. There were significant differences between hormone users and non-users. Hormone users were younger, more likely to be white, less likely to have a history of diabetes, heart failure, prior myocardial infarction, and prior stroke compared to non-users, but were more likely to have high blood cholesterol and family history of CAD, or to smoke. Hormone users were also more likely to receive aggressive inhospital care including angiography, angioplasty, bypass grafting, reperfusion therapy, aspirin, heparin, β blockers, and nitrates (Table 20.2). Complication rates were similar in users and non-users; however, after adjustment for the potential confounders, hormone use was associated with a reduced odds of inhospital mortality (0·65, 95% CI 0·59–0·72). The association was strongest in the youngest group of women (age 55–64 years). The authors acknowledge that some or all of this apparent survival benefit could be due to one or more sources of bias – for example, residual differences between users and non-users or the healthier profile that decreased mortality may also have increased the likelihood of taking hormone therapy; or the hormone users may have received care at hospitals with greater experience of myocardial infarction care; or hormone users may have been better at compliance with treatment and may thus have an improved survival. The many differences in patient characteristics and inhospital treatment observed between hormone users and non-users illustrate the difficulties of interpretation of observational studies.

Three observational studies have suggested that recent initiation of hormones after the index myocardial infarction

Table 20.2 Observational study of inhospital treatment of postmenopausal women with myocardial infarction and adverse events by prior usage of hormone therapy[41]

	Hormone replacement therapy	
	Users ($n = 7353$) (%)	Non-users ($n = 107\,371$) (%)
Antiplatelet agent	87	79
Heparin	74	64
β blocker	56	47
ACE inhibitor	25	26
Nitrate	55	46
Initial reperfusion	29	19
Coronary angiography	65	42
Revascularization procedure	37	23
Heart failure	19	28
Recurrent ischemia	14	10
Recurrent myocardial infarction	2	2
Stroke	2	2
Death	7	16

is associated with an increased risk for recurrent events in the short term; two of these studies provided data suggesting a possible decreased risk in later years among the survivors (Table 20.3).[42–44] This pattern of increased risk in the first year with apparently reduced risk in later years is similar to that observed in several randomized controlled clinical trials, notably the Heart and Estrogen/progestin Replacement Study (HERS).[45] It should be noted that these analyses of risk by recency of hormone use were performed after publication of the HERS results; therefore the possibility of publication bias cannot be excluded.

Clinical trials with surrogate outcomes

The primary outcome of the Estrogen Replacement and Atherosclerosis (ERA) trial was change in the angiographic minimal diameter of coronary artery lesions.[46] Women ($n = 309$) with angiographically defined CAD were randomized to one of three groups: CEE 0·625 mg, CEE 0·625 mg plus MPA 2.5 mg, or placebo. At the end of the trial, compliance ranged from 74% in the estrogen-only group to 84–86% in the other groups. Over the mean treatment duration of 3·2 years, all three groups showed a decrease in minimal coronary artery diameter and there were no differences between the groups. In other words, treatment with estrogen with or without MPA failed to arrest the progression of existing coronary artery lesions, even though the estrogen and estrogen plus MPA treatments lowered LDL cholesterol by 9·4 and 16·5%, and raised HDL cholesterol levels by 18·8 and 14·2%, respectively. Several additional clinical trials with angiographic outcomes are underway.

Clinical trials

A randomized controlled clinical trial in 293 postmenopausal women with unstable angina, aged 43–93, failed to demonstrate benefit with estrogen or estrogen plus progestin for reduction in number of ischemic episodes.[47] The premise of the trial was that endothelial dysfunction with subsequent impairment of coronary blood flow has an important pathophysiologic role in acute coronary syndromes, and that reversal of the endothelial dysfunction by estrogen would improve the clinical outcome. Participants received one of three study treatments within 24 hours of the onset of symptoms: an infusion of 1·25 mg of CEE followed by oral CEE 1·25 mg/day for 21 days, or an infusion of CEE followed by oral CEE plus MPA 2·5 mg/day, or an infusion of placebo followed by oral placebo. The trial was

Table 20.3 Risk of recurrent coronary events in relation to recent initiation of hormone therapy in observational studies of women with prior coronary heart disease

Author	Type of study	Risk for recurrent coronary events by interval since starting hormone therapy[a]		Comment
		Short-term	Long-term	
Grodstein[42]	Cohort of 2489 female nurses with prior myocardial infarction or documented atherosclerosis	1·25 (0·78–2·00%) for use <1 year[b]	0·38 (0·22–0·66%) for use >2 years	$P = 0·002$ for trend, main analysis; replicates HERS and includes women who commenced hormones before initial event
		2·10 (0·88–5·10%) for use <1 year[b]	0·50 (0·32–0·77%) for use >2 years	$P = 0·02$ for trend, alternative analysis; short-term use largely reflects women who commenced hormones after initial event
Heckbert[43]	Cohort of 981 women hospitalized for acute myocardial infarction	2·16 (0·94–4·95%) for use 0–60 days[b]	0·76 (0·42–1·36%) for use >1 year	$P = 0·05$ for trend
Alexander[44]	Cohort of 1857 postmenopausal women enrolled in trial of coumadin and aspirin within 3–21 days of acute myocardial infarction	1·44 (1·05–1·99%) over median of 15 months[c]	No data	Increased risk for composite primary outcome exclusively due to unstable angina; no increase in risk among prior/current users

[a] Current hormone users compared to never users.
[b] Acute myocardial infarction or coronary death.
[c] Death/acute myocardial infarction/unstable angina.

stopped short of its planned enrollment of 351 when the Data and Safety Board determined that there was no difference between treatment groups. During the first 48 hours the mean number of ischemic episodes per patient recorded by ambulatory ECG monitoring was 0·74, 0·86, and 0·74 in the estrogen, estrogen plus progestin, and placebo groups respectively, and symptomatic ischemia occurred in 39%, 52%, and 42%. Inhospital incidence of refractory ischemia, death, myocardial infarction, and revascularization procedures were similar in the three groups (Table 20.4). The groups did not differ at 21 days for ischemia, or at 6 months for clinical events. The authors cite several possible reasons for the failure of the estrogen therapy to improve ischemia: lack of functional estrogen receptors in advanced lesions or with age, countervailing adverse effects of estrogen on thrombosis or inflammation, and the fact that participants almost uniformly received standard anti-ischemia therapy (including heparin, aspirin, β blockers, and nitroglycerin). The numbers of ischemic episodes were also lower than anticipated in the power calculations. From this study it would appear that acute estrogen therapy is not a useful addition to the standard therapy for acute coronary syndromes.

HERS is a landmark study, as it represents the first substantive test of the hypothesis that hormone therapy prevents coronary events in women with existing disease (Table 20.1).[45] The 2763 postmenopausal women aged 44–79 who enrolled all had established CAD and had not had a hysterectomy. They were randomized to CEE 0·625 mg/day plus MPA 2·5 mg/day or to placebo. The hormones induced the expected lipid changes, reducing LDL cholesterol by 11%, raising HDL cholesterol by 10%, and raising triglycerides by 8% compared to placebo. Over the average study duration of 4·1 years there was no net benefit for the principal outcome of CHD (non-fatal myocardial infarction plus coronary death) with 172 cases in the placebo group and 176 cases in the active treatment group.

However, in the first year of HERS there was a nominally significant ($P < 0{\cdot}05$) 52% excess of coronary events in the treatment group compared to the placebo group (Figure 20.4). In the second year there was no difference in event rates and thereafter there was a trend towards a reduction in the active treatment group, mainly due to a reduction in non-fatal myocardial infarction. The trend for coronary heart disease risk over time was significant ($P = 0{\cdot}009$). However, it should be noted that the significance of the trend depended on the adverse direction of events in the first year, and that events after the first year were recorded in survivors of the first year (that is, after the first year the arms were no longer balanced). There was no benefit for any other cardiovascular outcome, including angina or revascularization procedures. Other important findings were a significant increase in venous thromboembolism and a marginally significant increase in gallbladder disease (84 in hormone

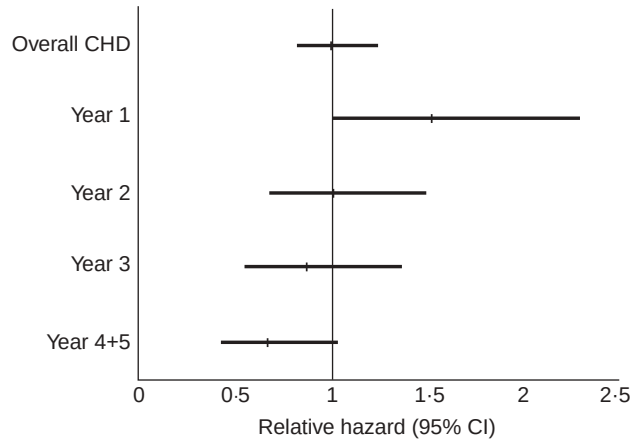

Figure 20.4 Relative hazard and 95% confidence intervals for CHD in HERS over the entire trial duration and by year since randomization[45]

Table 20.4 Inhospital treatment and clinical outcomes of postmenopausal women with unstable angina randomized to hormone therapy or placebo[47]

	Conjugated equine estrogen 1·25 mg ($n = 100$) (%)	Conjugated equine estrogen 1·25 mg plus MPA 2·5 mg ($n = 94$) (%)	Placebo ($n = 99$) (%)
Antiplatelet agent	92	93	98
Heparin	79	85	77
β blocker	75	77	80
Nitrate	74	72	77
Refractory ischemia	16	20	15
Revascularization procedure	36	35	34
Myocardial infarction	3	3	5
Death	5	5	3

Abbreviation: MPA, medroxyprogesterone acetate

group and 62 in the placebo group, $P = 0{\cdot}05$). There was no reduction in fractures (130 compared to 138).

Thus, HERS provided some results for hormone therapy that were expected (increased risk for venous thromboembolism and gallbladder disease) and some that were unexpected (no overall reduction in CHD, and no reduction in fractures). The trend over time for coronary disease was also unexpected, and in fact the investigators anticipated that the immediate effects of estrogen – for example, on fibrinolysis and vascular reactivity – might have led to early benefit, sustained in later years by beneficial changes in plasma lipid concentrations. The observed early adverse effect needs to be explained: possibilities include that hormone therapy induces inflammatory changes in unstable plaques, or that a procoagulant effect predominates early on. There is no doubt that menopausal hormone therapy is procoagulant, as shown by the excess of venous thromboembolism. The findings may be explained by the existence of a subset of women who are particularly susceptible to one or more of the adverse metabolic or local tissue changes induced by hormone therapy, and that the remaining women who did not have an early event reap the later benefit of lipid lowering. Alternatively, there may be no real benefit, and the apparent later benefit may simply reflect a survivor effect in that women most susceptible to an adverse effect of the treatment have been removed from the cohort. A post-hoc analysis of HERS data indicated that women with higher lipoprotein (a) levels were less likely to have an initial adverse outcome, and were more likely to benefit in later years, presumably because some of the adverse effects of the hormones were counteracted by a reduction in high lipoprotein (a) levels.[10]

One possible explanation for the HERS findings is that MPA negated any possible benefit from estrogen, for example by blocking the direct vascular effects of estrogen and blunting the rise in HDL cholesterol induced by estrogen. (However, it is noted that HDL cholesterol levels in fact increased by 10%.) Another explanation might be that many participants were receiving medications that would lower risk for recurrent coronary events (for example, aspirin, β blockers, lipid lowering medications, and to a lesser extent angiotensin-converting enzyme [ACE] inhibitors), thus masking any potential for benefit from estrogen. This seems unlikely, but even if true the trial still demonstrates that hormone therapy is not a useful adjunct to established secondary prevention treatments. Other possible explanations offered are that the women in HERS were too old and their arteries too diseased to benefit from hormone therapy, or that the type and dose of hormones was not optimal.[48–50] These explanations ignore the fact that the observational studies suggesting benefit and which prompted the need for HERS were conducted in populations similar to that studied in HERS, and the hormones were the same as those tested in HERS.

Though unexpected and controversial, the pattern of early harm observed in HERS has found support in two other secondary prevention trials for coronary disease and one for stroke (and as noted above, in the WHI primary prevention trial, a pooled analysis of short-term studies, and in several observational studies).[35,42–44,51–53] Stimulated by the HERS findings, a re-analysis of data from an earlier trial of CEE 2·5 mg/day in men with existing heart disease revealed a pattern of no overall benefit but with increased risk for CHD in the first 4 months after randomization (relative hazard 1·58, 95% CI 1·04–2·40) similar to that found in HERS for the same period (2·29, 95% CI 0·94–5·56).[51] A trial of transdermal estradiol (with cyclic norethisterone for women with a uterus) was stopped after an average of 2·5 years follow up for reasons of futility and possible harm (Table 20.1).[52] At the time of stopping this trial, 255 women with angiographically defined CAD had been enrolled and only 61% of women were still on estrogen. Though clearly underpowered, with short follow up, and reported only in abstract form, the results were nonetheless consistent with HERS in that there was a 23% ($P = 0{\cdot}3$) excess of unstable angina, myocardial infarction, and death. Finally, the Women's Estrogen for Stroke Trial (WEST) in women with a recent stroke found that oral estradiol did not prevent recurrent strokes overall, and compared to placebo there was a higher risk for fatal strokes, and a higher risk for all strokes in the first 6 months.[53] The combined data from these clinical trials leave little room for doubt that, at least in women with existing arterial disease (coronary or cerebrovascular), estrogen use for up to 4 years is unlikely to result in benefit, and in the first few months to a year is associated with an increased risk for arterial complications.

One other trial testing estradiol valerate versus placebo in 1017 women with CHD is due to report results soon.[54] A secondary analysis of safety data from a trial of raloxifene (a selective estrogen receptor modulator) in 7705 women with osteoporosis showed no benefit for cardiovascular outcomes over 4 years of treatment, but suggested a risk reduction of 40% (95% CI 5–62) in a subset of 1035 women with increased cardiovascular risk at baseline.[55] A randomized controlled clinical trial of raloxifene (a selective estrogen receptor modulator) versus placebo is underway in several countries in order to test whether raloxifene reduces the risk for CHD and breast cancer in women with existing heart disease or who are at high risk for heart disease.[56] This trial has enrolled 10 101 women and the study is planned to end after 1670 participants have experienced a coronary event (expected in 2005).

Box 20.3

- Postmenopausal hormone therapy does not benefit women with existing heart disease, and initiation of hormone therapy after a coronary event may increase risk in the short term.
- Observational studies of women with heart disease suggest reduced risk for coronary disease in long-term hormone users.

Box 20.3 continued

- Several observational studies suggest increased risk for recurrent coronary disease during the first year in women who initiate hormone therapy after a coronary event.
- In a randomized controlled trial, conjugated equine estrogens and conjugated equine estrogens with MPA failed to slow progression of coronary disease on angiography.
- Acute postmenopausal hormone therapy did not reduce the rate of recurrent ischemia in women with unstable angina.
- Two randomized controlled trials with clinical outcomes failed to show benefit for postmenopausal hormones, and provide evidence for an increased initial risk.
- The apparent reduction in risk after the first 2 years observed in one of these trials is subject to a variety of interpretations, including real long-term benefit or a survivor effect only.

Abbreviation: MPA, medroxyprogesterone acetate

Cerebrovascular disease

Primary prevention

Because stroke may be fatal, and often leaves the survivors cognitively and functionally impaired, primary prevention is of the greatest importance.

Observational studies

As reviewed elsewhere, the data for stroke are less consistent than those for CHD.[57] Five case–control studies of risk for incidence of all stroke or ischemic stroke reported essentially null results, and six of 16 internally controlled cohort studies reported a significant reduction in risk while two reported significantly increased risk among hormone users. Data on stroke subtypes are scanty and variable. Among current users in five cohort studies, three studies found essentially no effect on ischemic stroke while one each found an increased risk and the other a decreased risk. Similarly, the data on duration and type of hormone therapy (estrogen alone or combined with progestin) are variable. Data for thromboembolic, intracerebral hemorrhage, and subarachnoid hemorrhage stroke subtypes are very scanty.

A meta-analysis of stroke studies suggested that, in aggregate, estrogen users had the same risk for all incident strokes as non-users; however, this meta-analysis antedated the most recent data from the large Nurses' Health Study.[19] Examination of the 20 year follow up data from the Nurses' Health Study is not entirely reassuring.[27] The relative risk for all strokes (767 strokes during 808 825 person-years) in current hormone users compared to never users was 1·13 (95% CI 0·94–1·35), but for ischemic strokes (432 cases) the relative risk was somewhat higher (1·26, 95% CI 1·00–1·61). Furthermore, for all strokes and for ischemic strokes there was a significant increase in relative risk at the usual dose of 0·625 mg, with a further increase at the higher dose of 1·25 mg or greater (Figure 20.5). For example, at the most commonly used dose of 0·625 mg/day the relative risk for all stroke was 1·35 (95% CI 1·08–1·68) and for ischemic stroke it was 1·44 (95% CI 1·07–1·93). The association of stroke with hormone use was stronger in women who used estrogen combined with progestin (1·45, 95% CI 1·10–1·92) than in women who used estrogen alone (1·18, 95% CI 0·95–1·46). There was no excess of strokes in past users. Unlike in CHD, duration of hormone therapy did not appear to influence the risk for stroke (Figure 20.5).

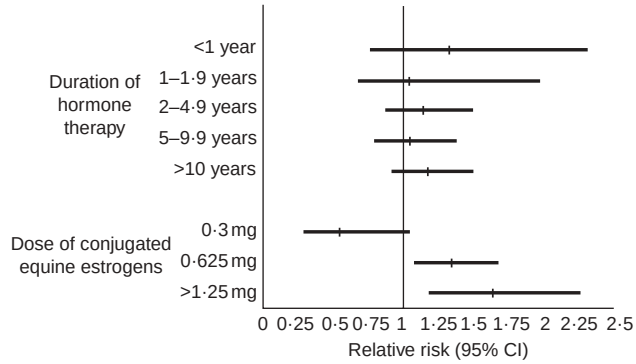

Figure 20.5 Relative risks and 95% confidence intervals for stroke by duration and dose of current hormone use in the Nurses' Health Study[21]

Data for fatal stroke are somewhat more consistent across studies in suggesting an association with reduced risk in current users. Of nine internally controlled cohort studies, there was a significantly reduced risk in three, and with one exception the point estimates for the remaining six studies were below unity.[56]

Clinical trials with surrogate outcomes

A randomized placebo-controlled trial of oral estradiol in 202 (199 with evaluable outcomes) healthy postmenopausal women aged 46–80 years found that the rate of progression of carotid intima media thickness (IMT) over 2 years was lower in those taking unopposed estradiol than in those on placebo ($P = 0·046$).[58] Adherence to study medications was very good (95% in estradiol group and 92% in placebo group). Per protocol, 122 participants received lipid lowering medications (primarily statins) because their LDL cholesterol values exceeded 160 mg/dl. The numbers were similar in the estradiol and placebo groups. The participants in the estradiol group who received lipid lowering medications lowered their LDL cholesterol levels by 20%, compared to 15·1% change in the placebo group ($P = 0·02$), and both estradiol and placebo groups experienced some regression of intima media thickness. In the 77 participants who did not receive lipid-lowering therapy, estradiol lowered LDL cholesterol by 10·5% compared to 1·1% in the placebo

group ($P = 0{\cdot}001$), and in this subgroup the estradiol group but not the placebo group showed regression ($P = 0{\cdot}002$ for difference). The authors conclude that reduction in the progression of subclinical carotid atherosclerosis was seen in women who did not take lipid lowering medication but not in those who took these medications. From these results, it would appear that estrogens would not augment the known benefits of statins for inhibiting atherosclerosis.

Clinical trials

WHI is the only clinical trial of healthy women that has provided any indication of the effect of hormone therapy on strokes. As noted above, study participants have been informed of a small absolute increase in the number of strokes in the hormone groups compared to the placebo groups during the first few years of the trial.[35] Stroke is also a predefined outcome of interest in the WISDOM trial.[36]

Box 20.4

- The effect of postmenopausal hormone therapy on stroke in healthy women remains unknown.
- Observational studies provide mixed results for strokes, but several suggest no effect on stroke incidence but some reduction in stroke mortality.
- The Nurses' Health Study suggested an increased risk for ischemic stroke, and an increased risk for all strokes at higher doses of estrogen or if estrogen was combined with progestin.
- One randomized trial of estradiol showed less increase in carotid intima media thickness in the subset of women who did not receive statin therapy.
- One major clinical trial in healthy women has informed participants of a small excess of strokes in the hormone groups during the first few years of the study, but has not published the results.

Secondary prevention

Clinical trials with surrogate outcomes

A randomized trial of oral estradiol 1 mg with standard dose progestin (gestodene 0·025 mg 12 days every month), or estradiol with low-dose progestin (gestodene 0·025 mg 12 days every third month), or placebo for 4 years in 321 women aged 40–70 at high risk for cardiovascular disease (that is, carotid IMT >1 mm) failed to show any benefit for reducing the rate of progression of subclinical atherosclerosis in the carotid arteries.[59] Exclusion of the small number of subjects (14%) who received lipid lowering therapy did not alter these results. LDL cholesterol decreased by 13% in the active treatment groups and fibrinogen by 20%. Adherence was good with only 12–20% of participants discontinuing study medications; compliance was 98% in the remaining participants. Reasons for the difference in outcome of this study with the study of Hodis *et al*[58] are not known. It is possible that the addition of a progestin to the estradiol may have negated the effects of estradiol, but the fact that the results in the standard and low-dose gestodene groups did not differ argues against that possibility. Though this study is regarded as secondary prevention, the distinction is somewhat artificial and is based on the entry level of carotid IMT.

Clinical trials

Where HERS examined the effect of hormone therapy on recurrent coronary disease, WEST is its counterpart for recurrent stroke.[53] There are important parallels between the two trials, and also a few differences. WEST randomized 664 women aged 46–91 who had suffered a transient ischemic attack or stroke in the previous 90 days to receive oral estradiol 1 mg or placebo and followed them for an average of 2·8 years. By the end of the trial 34% had stopped estradiol and 24% had stopped placebo. Compared to placebo, estradiol had no effect on the primary outcome of combined non-fatal stroke and all-cause mortality, or on non-fatal stroke or death individually (Table 20.5). However, estradiol increased the risk for fatal stroke (relative risk 2·9, 95% CI 0·9–9·0) and the non-fatal strokes in the estradiol group were associated with more functional and neurologic deficits. A post-hoc analysis of strokes by time since randomization indicated that during the first 6 months, there were three fatal strokes and eighteen non-fatal strokes in the estradiol group, compared to one fatal and eight non-fatal strokes in the placebo group (relative risk for any stroke 2·3, 95% CI 1·1–5·0). There were no differences in the rates of transient ischemic attacks or myocardial infarction.

Table 20.5 Selected outcomes according to treatment assignment in the WEST[53]

Outcome	Estradiol group ($n = 337$)	Placebo group ($n = 327$)	Relative hazard (95% CI)
Death or non-fatal stroke	99	98	1·1 (0·8–1·4)
Death	48	41	1·2 (0·8–1·8)
fatal stroke	12	4	2·9 (0·9–9·0)
CHD	11	13	0·8 (0·4–1·9)
Non-fatal stroke	51	52	1·0 (0·7–1·4)
Non-fatal myocardial infarction	14	12	1·2 (0·5–2·5)

HERS has published a more complete analysis of the stroke data, which indicated that there was no significant effect of hormone therapy on any category of stroke (fatal, non-fatal, ischemic, hemorrhagic, any stroke, transient ischemic attack).[60] However, the point estimate was above

unity for each category except transient ischemic attack (0·90, 95% CI 0·57–1·42), and the highest relative risk was for fatal stroke (1·61, 95% CI 0·73–3·55). The trend towards an excess of more severe strokes in the hormone group is similar to that observed in WEST.

Box 20.5

- Postmenopausal hormone therapy has no effect on the overall risk for strokes in women with existing cerebrovascular disease or with existing CHD.
- Observational studies suggest no effect of postmenopausal hormone therapy on stroke incidence but a possibly reduced risk for fatal strokes.
- Estradiol failed to reduce progression of carotid intima media thickness in a randomized controlled trial.
- A randomized controlled trial of estradiol in women who had recently suffered a stroke failed to show benefit for recurrent strokes, but strokes in the active treatment group tended to be more severe and there was increased risk for strokes in the first 4 months after randomization.
- A secondary prevention trial of women with CAD did not show benefit for strokes, and fatal strokes were non-significantly higher in the active treatment group.

Venous thromboembolism

Observational studies

Early observational studies did not suggest an increased risk for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in postmenopausal hormone users; however, as reviewed elsewhere, several more recent studies have found a two- to fourfold increased risk in hormone users.[61] The studies are consistent in showing an increased relative risk for current but not past use of hormones. Recent onset of current use conferred higher risk than long duration of use, consistent with an immediate effect on coagulation factors. Some but not all studies reported a dose-response relationship. Estrogen alone, as well as estrogen with progestin, appeared to be associated with higher risk. Though transdermal estradiol causes less perturbation of coagulation proteins than oral estrogen, one study suggested that the risk for venous thromboembolism was present for this formulation also.

Clinical trials

Venous thromboembolism is usually recorded as an adverse effect in clinical trials of hormone therapy. A pooled analysis of short-term trials found five thromboembolic events in the hormone groups and one in the control groups.[33] HERS found a significant, almost threefold increase in the risk for venous thromboembolism (34 in the hormone group and 13 in the placebo group, relative hazard 2·7, 95% CI 1·4–5·0, $P = 0·003$).[62] The trend towards higher excess risk in the first few years was not significant, and some excess persisted over the duration of the study. These findings on an adverse event from a clinical trial are very similar to those from the observational studies. In exploratory analyses, other risk factors for venous thromboembolism included older age at menopause, lower extremity fractures, cancer, being within 90 days of inpatient surgery, or non-surgical hospitalization. After non-fatal MI the risk was increased for 90 days. Use of statins or aspirin appeared to decrease risk; it should be noted, however, that these were non-randomized comparisons and that the large number of comparisons performed may have led to chance findings. The WEST study investigators stated that there were no differences in venous thromboembolism between treatment groups.[53] As noted above, healthy women in the WHI have been informed of an excess risk during the first few years of the study.[35] Some trials with intermediate or surrogate outcomes (for example, the Postmenopausal Estrogen-Progestin Interventions and ERA) have also noted small numbers of venous events, with more events in the active treatment groups than the placebo groups, although numbers were too small for statistical testing.[7,46]

One randomized controlled trial, initiated before it was known that estrogen increases risk for venous thromboembolism, strongly suggested that hormone therapy increases the risk for recurrent events.[63] Women with prior venous thromboembolism ($n = 140$) received either oral estradiol 2 mg and norethisterone acetate 1 mg or placebo for 2 years. Though predefined stopping boundaries had not been crossed, the trial was stopped prematurely because of the emergence of data from observational studies and clinical trials, and the clustering of end points (recurrent venous thromboembolism) in one treatment group. There were eight events in the active treatment group (10·7%) and one in the placebo group (2·3%) indicating a 4·6-fold increase in the hormone group. All of the recurrent events in the active treatment group occurred during the 9 months, while the single event in the placebo group occurred at 14 months. Five of the eight cases with recurrent events in the hormone group also had familial thrombophilia (three with factor V Leiden, two with anticardiolipin antibodies).

Box 20.6

- Postmenopausal hormone therapy increases the risk for venous thromboembolism two- to fourfold.
- The risk is increased more markedly in the first few months to years after initiation, but persists for up to 4 years.
- Several observational studies have shown an association of hormone therapy with risk for venous thromboembolism.
- A pooled analysis of short-term clinical trials suggested an increased risk for venous thromboembolism, but numbers were small.
- One major clinical trial in healthy women has informed participants of a small excess of venous thromboembolism in the hormone groups during the first few years of the study, but has not published the results.

contd

- A large trial for the secondary prevention of coronary heart disease showed an increased risk for venous thromboembolism.
- A randomized trial in women with prior venous thromboembolism strongly suggested that hormone therapy increases the risk for recurrent events, particularly in women with familial thrombophilia.

Treatment recommendations

Based on current evidence, postmenopausal hormone therapy is not recommended for prevention or treatment of CHD or stroke.[64] For primary prevention, the American Heart Association (AHA) states that firm recommendations should await the results of ongoing randomized clinical trials, and that there are currently insufficient data to suggest that hormone therapy should be initiated for the sole purpose of primary prevention of cardiovascular disease.[64] The AHA makes a stronger statement that hormone therapy should not be initiated for the secondary prevention of cardiovascular disease; however women on hormone therapy for several years do not necessarily have to stop since they have presumably passed through the period of initial increased risk. Women with a prior history of venous thromboembolism should be counseled against using hormone therapy.[62]

Because the trials have failed to show benefit for secondary prevention, and there are no published trial data for primary prevention, in both instances decisions about hormone therapy should be based on established non-cardiovascular risks and benefits.[64] The major proven benefits of estrogen are relief of the symptoms accompanying the menopause, urogenital atrophy, and prevention of osteoporosis. Known risks include endometrial cancer, venous thromboembolism, pancreatitis (in women with high blood triglycerides), and gallbladder disease. At the average age of menopause, the risk for cardiovascular and non-cardiovascular disease conditions is low, and therefore, the short-term use of estrogens to manage the menopause is not at issue.[65]

However, long-term use (5 years or more) of hormone therapy is more problematic, given the possible increase in breast cancer associated with prolonged use.[65] Calculations show that in older women and with prolonged use, the potential risks for breast cancer, stroke, and venous thromboembolism, may outweigh the potential benefit for reduction in fractures if the treatment does not reduce risk for CHD.[66] Since CHD and stroke are by far the most common causes of disease and death in older women, the clinical trial data on the long-term effects of hormone therapy on cardiovascular disease will provide the key information on whether long-term estrogen should be prescribed for any indication in older women. If these trials show that long-term use confers cardiovascular benefit (and if methods are found to screen out women at high initial risk for cardiovascular complications), then hormone therapy may in future play a more prominent role as a viable prevention strategy.

However, until these clinical trial data are known, it may be wise to consider alternatives to hormone therapy even for proven indications such as prevention of osteoporosis.[65] For osteoporosis prevention, exercise, diet, calcium, and vitamin D may be recommended, and for treatment the bisphosphonates and raloxifene have been shown to prevent fractures. Lifestyle measures and medical management of risk factors such as high blood cholesterol and high blood pressure will prevent many cases of CHD and stroke, and for secondary prevention of CHD aspirin, statins, β blockers, and ACE inhibitors have all been found to be effective.[64] The AHA statement acknowledges that the current recommendations are based mainly on data from trials using standard doses of conjugated equine estrogens and medroxyprogesterone, and that evidence is insufficient for different preparations, routes of delivery, and doses that may have a more favorable or more adverse effect on cardiovascular outcomes.

Box 20·7

- Postmenopausal hormone therapy is not recommended for primary prevention of CHD, because the observational studies may have overestimated benefit, and there are no substantial clinical trial data. **Grade B**
- If there is no benefit from reductions in CHD, the potential harm from breast cancer, endometrial cancer, venous thromboembolism, gallbladder disease, and pancreatitis may exceed the benefit from reduced fracture risk. **Grade B**
- Postmenopausal hormone therapy is not recommended for secondary prevention because trials have not shown benefit for CHD or stroke, and observational studies and trials suggest cardiovascular harm in the first few months to 1 year after initiation. **Grade A**
- Until and unless the currently ongoing clinical trials provide evidence to the contrary, the focus of CHD prevention efforts should be on proven effective and safe measures. **Grade A**
- Reasons for early coronary harm need to be identified with a view towards screening out a subset of women at high risk.
- Clinical trials of different hormone regimens (dose, formulation, route of administration) are needed.
- Women with prior venous thromboembolism should be counseled against using hormones. **Grade A**

Addendum

On July 9, 2002, the National Heart, Lung, and Blood Institute announced that the WHI trial[67] of estrogen plus progestin versus placebo in 16 608 healthy women with an intact uterus had been stopped early, after an average of

5·2 years of follow up rather than the planned 8·5 years. The reasons for stopping were that an increased risk for breast cancer started emerging at 4 years, which by 5 years had crossed the prespecified monitoring boundary. In addition, there was evidence of overall harm. At the time of stopping, the hazard ratios (HR) for the major adverse effects were: breast cancer 1·26 (95% CI 1·00–1·59), CHD 1·29 (95% CI 1·02–1·63), stroke 1·41 (95% CI 1·07–1·85), and pulmonary embolism 2·13 (95% CI 1·39–3·25). There were benefits for colorectal cancer, HR 0·63 (95% CI 0·43–0·93), and for hip fracture, HR 0·66 (95% CI 0·45–0·98), while endometrial cancer and all-cause mortality were not affected. The investigators conclude that the risk-benefit profile found in this trial is not consistent with the requirements for a viable prevention treatment, and in particular that this regimen should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents for osteoporosis. WHI has answered the question of whether combined estrogen plus progestin, given by mouth for several years, prevents cardiovascular disease: it does not, and it does in fact increase the risk. However, as stated by the investigators, the use for a few years (less than 4 years) to treat the symptoms of menopause may be reasonable, since the benefits may outweigh the small absolute risk of cardiovascular disease in younger women. Of importance, the WHI trial of estrogen only in women who have had a hysterectomy is continuing, because the overall balance of benefits and risks remains uncertain.

Disclaimer

The views expressed in this chapter are those of the author and do not necessarily reflect the views or policy of the National Heart, Lung, and Blood Institute, or of the Steering Committee of the Women's Health Initiative. The conclusions are based on a review of the published literature and public documents, and not on any confidential or unpublished information to which the author might have access.

References

1. http://wonder.cdc.gov/
2. National Heart, Lung, and Blood Institute. *The Lipid Research Clinics Population Studies Data Book: Volume I – The Prevalence Study*. Bethesda: US Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Pub. No. 80-1527, July 1980.
3. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med* 1989;**321**:641–6.
4. Do KA, Green A, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Longitudinal study of risk factors for coronary heart disease across the menopausal transition. *Am J Epidemiol* 2000;**151**:584–93.
5. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987;**316**:1105–10.
6. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991;**325**:1196–204.
7. Writing Group. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;**273**;199–208.
8. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. *Obstet Gynecol* 1994;**84**:987–95.
9. Medical Research Council's General Practice Research Framework. Randomized comparison of estrogen versus estrogen plus progestogen hormone replacement therapy in women with a hysterectomy. *BMJ* 1996;**312**:473–8.
10. Shlipak MG, Simon JA, Vittinghoff E *et al.* Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heartdisease events after menopause. *JAMA* 2000;**283**: 1845–52.
11. Cushman M, Legault C, Barrett-Connor E *et al.* Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999;**100**:717–22.
12. Herrington DM, Brosnihan KB, Pusser BE *et al.* Differential effects of E and droloxifene on C-reactive protein and other markers of inflammation in healthy postmenopausal women. *J Clin Endocrinol Metab* 2001;**86**:4216–22.
13. Leiberman EH, Gerhard MD, Uehata A *et al.* Estrogen improves endothelium-dependent, flow-mediated vasodilatation in post-menopausal women. *Ann Intern Med* 1994;**121**: 936–41.
14. Rosano GMC, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of estrogen on exercise-induced myocardial ischemia in women with coronary artery disease. *Lancet* 1993;**342**:133–6.
15. Bhavnani BR, Cecutti A, Gerulath A, Woolever AC, Berco M. Comparison of the antioxidant effects of equine estrogens, red wine components, vitamin E, and probucol on low-density lipoprotein oxidation in postmenopausal women. *Menopause* 2001;**8**:408–19.
16. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;**340**: 1801–11.
17. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996;**125**: 605–13.
18. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CF. Cholesterol reduction yields clinical benefit: a new look at old data. *Circulation* 1995;**91**:2274–82.
19. Grady D, Rubin SM, Petitti DB *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;**117**:1016–37.
20. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Ann Rev Public Health* 1998;**19**:55–72.

21. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;**133**:933–41.
22. Falkeborn M, Persson I, Adami HO *et al.* The risk of acute myocardial infarction after estrogen and estrogen-progestogen replacement. *Brit J Obstet Gynecol* 1992;**99**:821–8.
23. Psaty BM, Heckbert SR, Atkins D *et al.* The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med* 1994;**154**:1333–9.
24. Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham study. *N Engl J Med* 1985; **313**:1038–43.
25. Rossouw JE. Debate: the potential role of estrogen in the prevention of heart disease in women after menopause. *Curr Control Trials Cardiovasc Med* 2000;**1**:135–8.
26. Sotelo MM, Johnson SR. The effects of hormone replacement therapy on coronary heart disease. *Endocrinol Metab Clin North Am* 1997;**26**:313–28.
27. Grodstein F, Stampfer MJ, Manson JE *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;**335**:453–61.
28. Criqui MH, Suarez L, Barrett-Connor E, McPhillips J, Wingard DL, Garland C. Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. *Am J Epidemiol* 1988;**128**:606–14.
29. Hernandez Avila M, Walker AM, Jick H. Use of replacement estrogens and the risk of myocardial infarction. *Epidemiology* 1990;**1**:128–33.
30. Sidney S, Petitti DB, Quesenberry CP Jr. Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997;**127**:501–8.
31. Rosenberg L, Slone D, Shapiro S, Kaufman D, Stolley PD, Miettinen OS. Noncontraceptive estrogens and myocardial infarction in young women. *JAMA* 1980;**244**:339–42.
32. Heckbert SR, Weiss NS, Koepsell TD *et al.* Duration of estrogen replacement therapy in relation to the risk of incident myocardial infarction in postmenopausal women. *Arch Intern Med* 1997;**157**:1330–6.
33. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;**315**:149–53.
34. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;**19**:61–109.
35. http://www.nhlbi.nih.gov/whi/hrt.htm
36. Vickers MR, Meade TW, Wilkes HC. Hormone replacement therapy and cardiovascular disease: the case for a randomized controlled trial. *Ciba Found Symp* 1995;**191**:150–60.
37. O'Keefe JH Jr, Kim SC, Hall RR, Cochran VC, Lawhorn SL, McCallister BD. Estrogen replacement therapy after coronary angioplasty in women. *J Am Coll Cardiol* 1997;**29**:1–5.
38. Abu-Halawa SA, Thompson K, Kirkeeide RL *et al.* Estrogen replacement therapy and outcome of coronary balloon angioplasty in postmenopausal women. *Am J Cardiol* 1998;**82**: 409–13.
39. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol* 1997;**79**:847–50.
40. Shackelford DP, Daniels S, Hoffman MK, Chitwood R. Estrogen therapy in women undergoing coronary artery bypass grafting: effect on surgical complications. *Obstet Gynecol* 2000;**95**: 732–5.
41. Shlipak MG, Angeja BG, Go AS, Frederick PD, Canto JG, Grady D. Hormone therapy and in-hospital survival after myocardial infarction in postmenopausal women. *Circulation* 2001; **104**:2300–4.
42. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study: a prospective, observational study. *Ann Intern Med* 2001;**135**:1–8.
43. Alexander KP, Newby LK, Hellkamp AS *et al.* Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. *J Am Coll Cardiol* 2001;**38**:1–7.
44. Heckbert SR, Kaplan RC, Weiss NS *et al.* Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy. *Arch Intern Med* 2001;**161**: 1709–13.
45. Hulley S, Grady D, Bush T *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.
46. Herrington DM, Reboussin DM, Brosnihan KB *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;**343**:522–9.
47. Schulman SP, Thiemann DR, Ouyang P *et al.* Effects of acute hormone therapy on recurrent ischemia in postmenopausal women with unstable angina. *J Am Coll Cardiol* 2002;**39**: 231–7.
48. Mendelsohn ME, Karas RH. The time has come to stop letting the HERS tale wag the dogma. *Circulation* 2001;**104**: 2256–9.
49. Rosano GM, Fini M. Postmenopausal women and cardiovascular risk: impact of hormone replacement therapy. *Cardiol Rev* 2002;**10**:51–60.
50. Rosano GM, Simon T, Mercuro G *et al.* Hormone replacement therapy: where we stand in Europe. *Eur Heart J* 2001; **22**:439–41.
51. Wenger NK, Knatterud GL, Canner PL. Early risks of hormone therapy in patients with coronary heart disease. *JAMA* 2000;**284**:41–3.
52. Clarke S, Kelleher J, Lloyd-Jones H, Sharples L, Slack M, Schofield PM. Transdermal hormone replacement therapy for the secondary prevention of coronary artery disease in postmenopausal women (abstract). *Eur Heart J* 2000; **21**:212.
53. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;**345**:1243–9.
54. Khan MA, Heagerty AM, Kitchener H, McNamee R, Cherry NM, Hannaford P. Oestrogen and women's heart disease: ESPRIT-UK. *Q J Med* 2000;**93**:699–702.
55. Barrett-Connor E, Grady D, Sashegyi A *et al.* MORE Investigators. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. *JAMA* 2002;**287**:847–57.

56.Mosca L. Rationale and overview of the Raloxifene Use for the Heart (RUTH) trial. *Ann N Y Acad Sci* 2001;**949**:181–5.
57.Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? *Maturitas* 2001;**38**:243–61.
58.Hodis HN, Mack WJ, Lobo RA *et al.* Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;**135**:939–53.
59.Angerer P, Stork S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. *Arterioscler Thromb Vasc Biol* 2001;**21**:262–8.
60.Simon JA, Hsia J, Cauley JA *et al.* Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001;**103**:638–42.
61.Castellsague J, Perez Gutthann S, Garcia Rodriguez LA. Recent epidemiological studies of the association between hormone replacement therapy and venous thromboembolism. A review. *Drug Saf* 1998;**18**:117–23.
62.Grady D, Wenger NK, Herrington D *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000;**132**:689–96.
63.Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy – results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000;**84**:961–7.
64.Mosca L, Collins P, Herrington DM *et al.* Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;**104**:499–503.
65.Manson JE, Martin KA. Postmenopausal hormone-replacement therapy. *N Engl J Med* 2002;**345**:34–40.
66.Rossouw JE. What we still need to know about hormone replacement therapy. *Infertility Reprod Clin North Am* 1999;**10**:189–209.
67.Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2002; **288**:321–33.

21 Ethnicity and cardiovascular disease

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Introduction

The major risk factors for cardiovascular disease (CVD), which include elevated blood pressure, elevated cholesterol, cigarette smoking, and diabetes, have been derived from epidemiologic studies conducted primarily in white populations.[1] Globally, non-white populations constitute the majority of the world's population, although the most influential risk factors for CVD in these populations remain unconfirmed. Ethnicity-related research provides important epidemiologic information that documents the rates of known risk factors for a disease, identifies new risk factors, provides us with clues regarding similarities and differences in disease causation, and allows us to define high-risk populations for specific diseases.[2] Further, knowledge of variations in response to preventive strategies, medical therapies, and healthcare utilization patterns can lead to specific prevention strategies that are appropriately tailored to culturally diverse groups. Therefore, studies that explore reasons for the differences in CVD rates among ethnic populations are of major public health importance.

General issues

Defining ethnic groups

The concept of race was based on the belief that members of a race were homogeneous with respect to biological inheritance.[3] However, over the past 20 years, as our ability to unravel the genetic code has increased, there is little evidence to support the contention that the historical "racial" divisions represent differences in genetic make-up.[3,4]

Ethnicity on the other hand is used to describe a group of people whose lifestyles are characterized by distinctive social and cultural traditions which are maintained within the group and passed on from generation to generation. Therefore ethnicity has both sociocultural and biological components.[5] Given that variations in disease rates between populations may be explained by socioeconomic, sociocultural, biologic, and genetic factors, classification by ethnic origin rather than race is desirable.[6]

Interpretation of studies in ethnic populations

The methodologic limitations of studies of ethnic populations must be recognized.[7] Mortality statistics often provide the first clues of differences in CVD rates between ethnic groups. Most developed countries have methods to collect reliable mortality statistics, although this system is not as well developed among poor nations.[8] In developing countries, where mortality statistics are not available, conclusions about disease rates are usually based upon data from sample registration systems, community surveys, and hospital admissions.

Worldwide patterns of disease

Globally, 58·8% of the total global morality is attributable to non-communicable diseases such as cardiovascular disease (CVD), cancer, and diabetes.[9] CVD accounted for approximately 30·9% of all deaths in 1998, as well as 10·3% of the total disease-related burden.[10] Approximately 78% of global CVD mortality, and 86% of the global CVD morbidity is experienced in the low and middle income countries.[9–11]

In most developed countries CVD rates are declining due to primary prevention of CVD risk factors, and improved secondary prevention strategies.[12] However, in developing countries an epidemiologic transition from acute infectious diseases to a rise in the major non-communicable diseases is occurring. Reasons for this include increasing life expectancy associated with a decline in childhood and adult deaths from infections, and an increase in the prevalence of CVD risk factors associated with industrialization and urbanization.[13]

Population differences in the CVD mortality rates are influenced by geographical and environmental differences. Ethnic variations in disease rates are closely tied to geographical patterns of disease.[14] Often the first clue that ethnic variations in disease burden exist comes from observations made between countries. These geographical differences have provided many of the initial hypotheses of the association between lifestyle factors and CVD. One of the first epidemiologic studies to highlight the variation in coronary heart disease (CHD) rates between countries was the Seven Countries Study.[15] In this major longitudinal cohort study, 16 cohorts of men aged 49–59 years were examined and followed for CHD mortality and total mortality. Large differences in CHD mortality between countries were observed, with low CHD rates in Japan and the Mediterranean countries, and high CHD rates in Finland and the USA. These differences were in large part explained

Table 21.1 Inter-country CVD mortality rates, 1996–99

Country	CHD mortality rates (men)	CBVD mortality rates (men)	CHD mortality rates (women)	CBVD mortality rates (women)
Russian Federation (1998)	639	361	230	229
Finland (1998)	288	72	81	40
USA (1999)	230	41	95	33
Argentina (1996)	140	116	39	63
China, rural (1999)	64	243	41	152
China, urban (1999)	106	217	71	147
France (1998)	85	41	21	22
Japan (1997)	57	79	20	41

*Rates for ages 35–74 per 100 000, adjusted to the European Standard population.
Source: Bothing (MONICA Project)[16]

by differences in diet, serum cholesterol, and blood pressure. More recent data from WHO MONICA (MONItoring of trends and determinants in CArdiovascular disease), a CVD surveillance project which includes 117 reporting units in 40 centers from 26 countries,[16] indicate a greater than 14-fold difference in CHD mortality among men, and more than 11-fold differences in CHD mortality for women exists between countries (Table 21.1). These inter-country observations have raised questions as to whether these differences are due to differences in ethnic group susceptibility to CVD, differences in environmental factors, or both.

Migrant groups

Observational studies reveal that when members of a given ethnic group change to a new environment (migration) their physical response to a given set of environmental factors differs from those who remain in their native lands. This suggests that environmental influences are very powerful factors in CVD causation. Conversely, despite different environments, similarities in disease rates within an ethnic group suggest a predominant genetic propensity towards or protection from CVD. Comparing the mortality rates of long-settled migrants to the disease rates in their country of origin helps to establish the relative contribution of genetic and environmental influences to differences in mortality rates. The Ni-Ho-San Study of Japanese migrants to Hawaii and San Francisco revealed that changes in disease rates in this population likely reflected changing environmental influences.[17] The age adjusted CHD mortality rate rose as the Japanese moved from Japan, to Hawaii, and to California. More than half of the increase in CHD was attributable to different levels of conventional risk factors, as the US cohort had a higher fat diet and higher mean serum cholesterol compared to the Hawaii or Japan cohorts.[17] This suggests that the low rates of CHD mortality in Japan may be attained in Japanese migrants by maintaining their risk factors at levels similar to those in Japan. This, however, can only be achieved if the Japanese maintain their traditional lifestyle, most notably their dietary and physical activity patterns.

Specific ethnic groups

The following sections review the CVD profile of seven major ethnic groups. Based on the best available data, we will document their disease burden and changes in disease rates over time, and review common/influential CVD risk factors. We then suggest special ethnic group specific preventive strategies which need to be developed or reinforced.

European origin (including North Americans)

People of European origin include those who originate from Northern Europe such as the Nordic countries and Germany, Western Europe including the United Kingdom and France, Southern Europe including Spain and Italy, and Eastern Europe which includes the Slavic countries.

Disease burden

Differences in the Age Standardized Mortality Rates (ASMR) vary widely between European populations. Data from the WHO indicate that wide variations in disease rates exist between the Eastern European countries and Southern European countries such as Italy and France.[18] In 1998, the ASMR for CHD among males in the Russian Federation was 639 per 100 000 compared to 85 per 100 000 among males in France.[18] The cerebrovascular disease (CBVD) ASMR was 361 per 100 000 among males in the Russian Federation compared to 41[18] per 100 000 in France.[18] Although in all countries the CVD mortality rates are much lower among

Table 21.2 CVD mortality rates in selected Eastern European countries

Country	CHD mortality rates (men) 1996/98	CBVD mortality rates (men) 1996/98	CHD mortality rates (women) 1996/98	CBVD mortality rates (women) 1996/98
Bulgaria	216/222	183/189	126/131	140/144
Czech Republic	240/207	122/112	129/106	92/91
Estonia	392/385	166/150	208/203	120/117
Kyrgyzstan	328/326	225/207	196/190	172/164
Latvia	394/382	204/190	178/195	152/151
Romania	247/232	212/202	155/149	172/161
Ukraine	454/453	187/172	279/277	141/133

Source: WHO[18] and Thorvaldsen *et al* (MONICA Project)[19]

women, these impressive between-country differences persist. Over the past 30 years most European countries have experienced declines in the CVD mortality rates. The Eastern European countries (for example, Ukraine, the Russian Federation, Hungary, and the Czech Republic) continue to have among the highest rates of CHD and CBVD in the world, with a few showing a decline (Poland) and several showing an increase (Ukraine) (Table 21.2).[18,19]

Common risk factors

Throughout European populations the high rates of CVD are mainly attributable to the classical CVD risk factors, namely diets high in saturated fats, elevated serum cholesterol, elevated blood pressure, diabetes, and smoking. The epidemic of CVD in the Eastern European countries is in part related to high levels of smoking in the face of diets high in saturated fat, along with excessive alcohol consumption and social disparity.[14,20] Research to explain why the Italian and French populations remain relatively "protected" from CHD has yielded numerous hypotheses. It is likely that dietary differences primarily account for the differences in disease rates. It is believed that the high consumption of monounsaturated fats such as olive oil and antioxidants are responsible for the low rates of CHD in Italy. In France, despite having similar saturated fat consumption, serum cholesterol, blood pressure, and smoking, the CHD mortality rate remains very low.[21] This immunity to CHD has been attributed to high consumption of ethanol (wine), which is usually ingested with meals and may offer cardioprotection by increasing HDL cholesterol levels, or inhibiting postprandial hyperlipidemia and platelet aggregation.[22] Others believe the lower rate of CHD mortality may simply be due to a time lag between increases in consumption of animal fat and elevations in serum cholesterol concentrations (which have occurred only recently) and the expected increase in CHD mortality.[23] The total mortality rate in France is no different from other Western countries, which suggests an increase in alcohol-related non-CHD deaths such as cirrhosis occurs.[22]

Influential risk factors

CHD, like other epidemics, relates closely to social conditions and its prevalence appears to be strongly related to the social and cultural conditions of society more so than its genetic make-up. This is evidenced by the rapid decline in the rates of CHD in parallel to economic changes in the United States and Japan, and the increase in CHD rates in the Eastern European countries. These changes have occurred too quickly for changes in gene frequencies to have occurred.[14] Therefore, rather than explaining differences in CHD rates between populations largely on genetic differences, rapid changes in CHD rates can occur and are usually explained by changes in diet (including alcohol consumption), smoking or economic factors.

Special approaches to prevention

It is clear that major lifestyle changes, and vigilant treatment of risk factors, result in declines in CVD rates. In Finland, an impressive 60% reduction in CHD mortality and stroke was observed between 1972 to 1994, and it is estimated that approximately 75% of this decline in CHD mortality can be explained by a substantial lowering of serum cholesterol by 13% (0·88 mmol/l) in men and by 18% (1·19 mmol/l) in women, diastolic blood pressure by 9% (6·6 mmHg) in men and 13% (12·2 mmHg) in women, and a significant reduction in smoking rates (30% in men).[24]

Furthermore in the USA a 34% decline in CHD mortality occurred between 1980 and 1990. One quarter of this decline is attributable to primary prevention efforts, and 29% is explained by secondary prevention efforts such as reduction in serum cholesterol, diastolic blood pressure,

and smoking. Furthermore, 43% of this decline is attributed to improved medical and surgical management in patients with established coronary disease.[25] More recently in Poland, during the 1990s, a rapid decrease (about 25%) in CHD deaths in early middle age was observed. This decline in CHD rates is attributed in large part to marked dietary changes such as the reduction in consumption of animal fats.[26] Therefore efforts at reducing the consumption of animal fat, diastolic blood pressure, and decreasing tobacco consumption can lead to large reductions in CHD deaths. By contrast, a marked increase in death rates from CVD, accidents, violence, and infectious diseases has been observed in Russia over a relatively short time period, and is thought to be due to socioeconomic upheaval.[27] The rapidity with which CV diseases rise (as in Russia) or fall (as in Poland) indicates that societal factors can have a substantial and rapid impact on disease rates.

Japanese

Disease burden

Mortality rates from CVD are much lower in Japan than Western countries[18] (see Figure 21.1) Initial data from the Seven Countries study confirmed that the Japanese experience relatively lower rates of CVD compared to Western populations.[15] In Japan, the pattern of CVD differs from Western populations as they tend to experience relatively higher proportions of CBVD (ASMR: M 79, F 41/100 000) and less CHD (ASMR: M 57, F 21/100 000).

Temporal trends

In parallel with a rise in economic prosperity, the CHD rates in Japan have declined more markedly than those of Western countries. For CHD the ASMR has decreased from 47/100 000 in 1995 to 42/100 000 in 1997 among males, and from to 25 to 21/100 000 during the same time period among females.[18] Given the low rate of CHD in Japan, the life expectancy in Japan is among the highest in the world.[28] The mortality from CBVD has also declined substantially in men and women in Japan since 1950.[14] Between 1995 and 1997, ASMR decreased for both men from 82/100 000 in 1995 to 79/100 000, and in women from 54 to 41 during the same time period. Dietary changes such as reduction in salt consumption and increased pharmacologic treatment of hypertension in a socially stable environment are probably responsible for the declines in CHD and CBVD.[14,28]

Common risk factors

A review of CVD risk factors in the Japanese population reveals that hypertension is the most significant determinant of CVD, more so than cholesterol and cigarette smoking.[28] Low serum cholesterol related to a diet low in saturated fat and cholesterol is probably responsible in part for the low rates of CHD mortality observed in the Japanese. Despite the fact that two thirds of Japanese men smoke, CHD rates remain unexpectedly low. However, the prevalence of type 2 (non-insulin dependent) diabetes in Japanese males and females is higher than the rates in most Western countries. In the Hisayama cohort study the prevalence of type 2 diabetes was 13% in males, and 9% in females and the relative risk of type 2 diabetes for CVD was 3·0 (95% CI 1·8–5·2).[29] Furthermore, the prevalence of type 2 diabetes appears to be increasing among young children, with a 1·5-fold increase observed over the past two decades among children younger than 18 year of age.[30] This increase has been associated with the increasing prevalence of obesity. Therefore, type 2 diabetes appears to be an emerging and important risk factor for both stroke and CHD in the general Japanese population.[29,31]

Influential risk factors

Over the past 30 years blood pressure levels have declined in Japan due to increased diagnosis and treatment of hypertension.[32] However, during this period a two- to threefold increase in glucose intolerance and type 2 diabetes, as well as obesity, and more recently hypercholesterolemia (the mean cholesterol is only 10% lower than in the USA in 1989) has occurred.[28,31] The increase in diabetes, obesity, and serum cholesterol is most likely due to "Westernization" of Japanese lifestyle. It is possible that as cholesterol levels and glucose levels rise the impact of high cigarette smoking may result in increased CVD rates in the future.

Special approaches to prevention/treatment

With increasing adoption of urban lifestyles in Japan,[32] the rates of CHD risk factors are approaching those of Americans. Ecological studies between Japan and the USA demonstrate this difference in CHD rates may be explained by differences in diet and serum cholesterol. However, recent studies have documented that the average serum cholesterol concentration among Japanese has increased from 1980 to 1989. The age adjusted total serum cholesterol levels increased from 4·84 to 5·22 mmol/l in men and from 4·91 to 5·24 mmol/l among women, and this combined with the substantial use of tobacco among Japanese males (59%) suggests that Japan may soon experience a significant increase in CHD rates.[28] Therefore, maintenance of a low fat diet, prevention of obesity (through decreased energy intake and regular physical activity), and avoidance of cigarette smoking should prevent the development of elevated cholesterol, type 2 diabetes, and ultimately CVD.

Chinese

Disease burden

Although the overall mortality from CVD is less in China than in Western countries, CVD is the most common cause of death in mainland China and Taiwan. When compared to Western populations, Chinese experience higher stroke rates, and relatively lower rates of CHD, a pattern similar to that observed in Japan. In 1999 in urban China, the ASMR for CHD in men aged 35–74 was 106/100 000 and women 71/100 000.[18] These rates are fivefold lower than the highest rates observed in the MONICA project from Western and Eastern Block countries.[18] In 1999, the ASMR for CBVD in men aged 35–74 was 217 and 147 per 100 000 in Chinese women.[18] Recent data from the Sino-MONICA study in China reveal that by international standards, the incidence of CHD in Chinese is low. The highest incidence was 108·7/100 000 (1987 to 1989) for men 35–64 years of age whereas by international standards the incidence of cerebrovascular disease is high. The highest incidence of stroke was 553·3/100 000 (1987 to 1989) for men 35–64 years. There were significant geographic variations in both CVD incidence and mortality rate, with higher rates in the north and lower rates in the south. Comparison with five stroke registries from the West suggests that intracerebral hemorrhage occurs between two and three times more frequently in the Chinese than in Caucasians.[33] Only 6–12% of strokes in whites are reported as intracerebral hemorrhages compared to 25–30% of hemorrhagic strokes in Chinese.[19]

Temporal trends

Death rates from the major adult CVD (particularly CHD) have been increasing in China in recent decades.[34] Mortality attributable to CVD increased from 86/100 000 (12% of total death) in 1957 to 214/100 000 (36%) in a recent analysis of urban Chinese.[34] Although most Western countries report a decline in CVD mortality, the decline in stroke deaths in China has not been as striking. A recent study in Shanghai from 1984 to 1991 reported no changes in the stroke incidence, yet a decline in the case fatality rate from stroke in both rural and urban China.[33] In China, CVD mortality increased as a proportion of total deaths from 12·8% in 1957 to 35·8% in 1990.[35] This rise is attributable to the rapid pace of urbanization, with the associated lifestyle changes. Data from the Sino-MONICA project, which is a 7 year study monitoring trends and determinants of cardiovascular disease (CVD) in geographically defined populations in different parts of China, indicate that between 1987 to 1993 increasing trends were found in CVD rates in some populations, whereas decreasing trends were found in others.[36]

Common risk factors

A case–control study from Hong Kong of acute myocardial infarction (AMI) sufferers provides evidence that conventional CVD risk factors are important among people of Chinese origin.[37] The odds ratio for AMI associated with cigarette smoking was 4·3, 3·3 for hypertension, and 2·4 for diabetes. Although the mean serum cholesterol among Chinese would be considered low by Western standards, a prospective observational study of approximately 9000 Chinese in urban Shanghai demonstrated that serum cholesterol was directly related (continuous relationship) to CHD mortality even at these low levels.[38] Cigarette smoking is highly prevalent among Chinese males, as over 60% of men smoke and there is evidence that these rates are increasing.[39,40] Positive associations between body mass index (BMI) and CV risk factors have also been reported for a very lean rural Chinese population (mean BMI approximately 20).[41] While the problem of underweight and undernutrition still exists in rural China, the prevalence of overweight is increasing in both urban and rural areas, with larger increases observed among urban residents.[42] Further, in a recent prospective cohort study conducted among 37 655 urban Chinese, systolic blood pressure was a significant determinant of stroke, as the risk of stroke increased by 25% for every 10 mmHg rise in systolic blood pressure.[43]

Influential risk factors

Although the rates of cigarette smoking are high, elevated blood pressure appears to be the most influential risk factor for CVD in this group. However, with increasing urbanization (increasing BMI), and the subsequent increase in serum cholesterol, these factors may lead to increased rates of CHD.

Geographic variations

Trends in morbidity and mortality from CVD within China indicate that the mortality rate attributable to CVD is higher in North China (Beijing) than in South China (Guangzhou)[44] (Table 21.3). Comparison of urban and rural areas in China indicate that CHD rates increase by twofold in urban areas compared to rural areas, although the stroke rates are higher among rural Chinese compared to urban dwellers, especially among men[44] (see Table 21.1). The prevalence of hypertension, mean serum cholesterol, and mean BMI were all lower in the South compared to the North and in rural compared to urban areas (see Table 21.3). However, the greatest differences in the prevalence of cigarette smoking exist between men and women (74% *v* 20%), and it does not share the same geographic distribution as do the other major CVD risk factors.

Table 21.3 North (Beijing)–South (Guangzhou) and urban–rural comparisons of CVD risk factors in China

Factor	Urban Beijing	Rural Beijing	Urban Guangzhou	Rural Guangzhou
Hypertension (men) (%)	29·6	25·5	9·4	7·6
Hypertension (women) (%)	25·1	17·9	12·4	4·0
Cholesterol (men) (mmol/l)	4·78	4·42	4·71	4·11
Cholesterol (women) (mmol/l)	4·83	4·34	4·83	4·0
HDL (men) (mmol/l)	1·37	1·39	1·29	1·26
HDL (women) (mmol/l)	1·52	1·47	1·37	1·24
Smoking – current (men) (%)	71·0	78·0	73·0	77·0
Smoking – current (women) (%)	23·0	31·0	3·0	7·0
BMI (men)	23·0	22·0	21·0	20·0
BMI (women)	24·0	23·0	22·0	20·0

Source: PRC–US Cardiovascular and Cardiopulmonary Epidemiology Research Group[44]

Migrant patterns

Data from Chinese migrants to Singapore and Mauritius provide evidence that the effects of exposure to urban environments lead to adverse risk factor profiles for CVD.[45,46] Another survey of three populations undergoing three different grades of transition in mainland China and Taiwan confirmed that adverse risk factor profile (based on blood pressure, BMI, lipid levels, HbA1c and dietary patterns) was associated with increased level of urbanization.[47] In a comparative study of Chinese migrants to Mauritius the prevalence of CHD revealed by ECG was six times greater (24% *v* 4%) than in Beijing, China. Also, the prevalence of diabetes and the mean serum cholesterol was higher in Mauritius Chinese (5·5 mmol), than in Beijing Chinese (4·4 mmol/l), whereas the prevalence of hypertension and smoking was greater in Beijing.[45] Therefore, although the prevalence of hypertension and smoking may decline with migration, the rates of obesity, late onset diabetes, elevated serum cholesterol, and CHD appear to increase. A comparison of rural Chinese in China to urban Chinese subjects living in Hong Kong and Australia, found that despite a slightly better risk factor profile among the urban Chinese (based on HDL cholesterol and lower blood pressure), carotid atherosclerosis was lower among the rural subjects (0·50 + 0·10 mmHg) than among urban subjects (0·56 + 0·12 mmHg).[48] Among Chinese migrants to Canada, Chinese exhibit markedly lower rates of CHD compared with other groups, and have low and similar rates of CBVD compared with Canadians of South Asians and European origin.[49] Given that Canada has the second lowest rate of strokes in the world, these data indicate that marked declines in stroke rates can occur among Chinese without a concomitant increase in CHD. The low rates of risk factors among Chinese in Canada are accompanied by relatively lower prevalence of the conventional CV risk factors, atherosclerosis, and CHD.[50] These data also suggest that if risk factors levels rise among Chinese to levels that are similar to Europeans, the rates of CHD may become similar.

Special approaches to prevention

Economic modernization in China is resulting in an increased prevalence of conventional CVD risk factors over time in urban populations.[30,42,51] This offers a major challenge for prevention efforts among urban Chinese both in China and abroad, as the Chinese who have traditionally had a very low prevalence of CHD will likely not remain protected from developing CHD with their changes in lifestyle. Important prevention strategies in this group include smoking cessation/prevention, maintenance of a traditional Chinese diet (high consumption of vegetables, high fish intake, and low saturated fat intake) to prevent increases in BMI, diabetes, serum cholesterol, and blood pressure.

South Asians

South Asians include people who originate from India, Sri Lanka, Bangladesh, and Pakistan.

Disease burden

Studies of South Asian migrants demonstrate that this group suffers a higher mortality from CHD when compared to other ethnic groups (Table 21.4).

Within India

There are relatively few mortality studies from India as there is no uniform completion of death certificates, and no centralized death registry for CVD.[52] However, the WHO and the World Bank data indicate that mortality attributable to

Table 21.4 Standardized mortality ratios (SMR) (per 100 000) for CHD in South Asians worldwide

Study (first author)	Country	Reference group	Age (yr)	Age SMR[a]
Wyndham[128] 1968–77	South Africa	Whites	15–64	300
Steinberg[129] 1968–85	South Africa	Whites	35–74	502
Baligadoo[130]	Mauritius	Europeans	40–45	260
Toumilehto[131] 1971–80	Fiji	Melanese	40–60+	350
Beckles[132] 1977–84	Trinidad	Blacks	35–69	260
Hughes[133] 1980–84	Singapore	Chinese	30–69	380
Hughes[133] 1980–84	Singapore	Malays	30–69	190
Adelstein[134] 1970–72	UK	Whites	20+	115
McKeigue[135] 1979–83	UK	Whites	20–64	160
Balarajan[55] 1979–83	UK	Whites	20–69	M:136, F:146
Sheth[56] 1979–83	Canada	Whites	35–74	M:122, F:139
Sheth[56] 1979–83	Canada	Chinese	35–74	M:329, F:344
Sheth[56] 1989–93	Canada	Whites	35–74	M:95, F:131
Sheth[56] 1989–93	Canada	Chinese	35–74	M:275, F:369

[a] Standardized mortality to reference indigenous population of 100.

CVD has increased in parallel with the expanding population in India, and now accounts for a large proportion of disability adjusted life years (DALY). Of all deaths in 1990, approximately 25% were attributable to CVD, which is greater than the 10% due to diarrheal diseases, the 13% due to respiratory infections, and the 8% due to tuberculosis.[11]

South Asian migrants

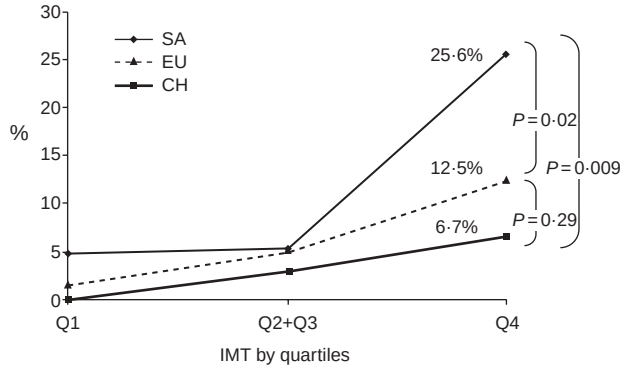
Studies of South Asian migrants to countries such as the United Kingdom, South Africa, Singapore, and North America provide evidence that South Asians suffer between 1·5 and 4·0 times higher CHD mortality compared to other ethnic groups (see Table 21.4).[53]

Temporal trends

In India the CHD rate is expected to rise in parallel with the increase in life expectancy due to an increase in per capita income, and a decline in infant mortality. The average life expectancy has increased from 47 years in 1960 to 58 in 1990. This trend is expected to continue, with life expectancy at birth reaching 72 years by 2030 leading to large increases in CVD prevalence.[54] Although the CHD mortality rate of South Asians compared to other populations remains high, a decline in CHD rates has been observed in most South Asian migrants over the past ten years, although this decline has been less than that observed in the general population in most countries except Canada.[55,56]

Common risk factors

South Asians, despite having increased rates of CHD, do not typically display an excess of conventional cardiovascular risk factors such as smoking, hypertension, or elevated cholesterol.[50,57,58] However, over the past several decades, the prevalence of these conventional risk factors – for example, hypertension – has been increasing, especially in urban areas.[59] These factors remain strong determinants of CHD in South Asians. Data from a case–control study in Bangalore, India[60] in which 200 cases of AMI were compared to 200 age and sex matched controls, revealed[60] an increasing relative risk of MI as the number of conventional risk factors increased. The odds ratio for smoking was 3·6, 2·6 for diabetes, and 2·7 for hypertension. In this study serum cholesterol did not seem to differ between cases and controls and the levels were similar to Western values. Cross-sectional studies of CHD risk factors in South Asians living in North America have identified that this group suffers a high prevalence of diabetes, impaired glucose tolerance, central obesity, elevated LDL cholesterol,[53] elevated triglycerides, and low HDL cholesterol.[58,61] The prevalence of impaired glucose tolerance and type 2 diabetes is four to five times higher in South Asian migrants than in Europeans by the age of 55 (20% *v* 4%).[57,58] The prevalence of diabetes in South Asians in the UK was 10–19%, 21% in Trinidad, 25% in Fiji, 22% in South Africa, 25% in Singapore, 20% in Mauritius, and 10% in Canada.[50,58] In rural India it is 3%, and between 11% and 30% in urban India, which is similar to the rates reported among Indians living abroad.[62] There is preliminary evidence that South Asians have elevated levels of Lp(a) – a lipoprotein which is genetically mediated and associated with increased atherosclerosis and thrombogeneis.[63,64] Recent studies have confirmed that South Asians also have higher levels of homocysteine, fibrinogen, and plasminogen activator inhibitor (PAI-1),[50] all of which could increase the risk for thrombosis. Although the



	Q1	Q2+Q3	Q4	*P* for trend
South Asians (SA)	5/104 (4·8%)	8/149 (5·4%)	22/86 (25·6%)	0·0001
Europeans (EU)	1/63 (1·6%)	8/155 (5·2%)	13/104 (12·5%)	0·004
Chinese (CH)	0/102 (0%)	5/169 (3·0%)	3/45 (6·7%)	0·016

Figure 21.1 Overall *P* value >0·0001, comparing slopes of atherosclerosis *v* CVD between SA, CH and EU. For a particular level of atherosclerosis, the rates of clinical events vary between the three ethnic groups. *P* for trend is within each ethnic group. IMT, intimal medial thickness.

Table 21.5 Urban–rural comparisons of CVD risk factors in India

Factor	Delhi urban	Haryana rural
Diabetes mellitus (men) (%)	10·9	2·9
Diabetes mellitus (women) (%)	11·2	2·6
Hypertension (men) (%)	25·5	14·0
Hypertension (women) (%)	29·0	10·8
Cholesterol (men) (mmol/l)	4·96	4·4
Cholesterol (women) (mmol/l)	5·01	4·28
HDL (men) (mmol/l)	1·01	1·02
HDL (women) (mmol/l)	1·12	1·08
Smoking – current (men) (%)	28·7	54·7
Smoking – current (women) (%)	2·6	25·3
BMI (men)	23·6	19·9
BMI (women)	25·1	20·3
W/H ratio (men)	0·99	0·95
W/H ratio (women)	0·83	0·83

Source: Adapted from Reddy *et al*[70]

degree of subclinical atherosclerosis is related to clinical events, it appears that South Asians have a higher propensity for clinical events compared with Europeans or Chinese, even after adjusting for all known risk factors and the degree of atherosclerosis (Figure 21.1). This suggests that South Asians may have an increased rate of plaque rupture due to differences in plaque composition, and or an increased propensity to develop thrombosis in response to plaque rupture which leads to an increased number of clinical events.

Influential risk factors

Glucose intolerance, abdominal obesity, and its associated dyslipidemia appear to be dominant factors associated with the development of CHD in South Asians. This cluster of factors is also associated with impaired fibrinolysis, increased C-reactive protein, and enhanced thrombogenesis. Increasingly, data support the idea that elevations of glucose in the non-diabetic range which is prevalent among South Asians is associated with the development of atherosclerosis among South Asians.[65,66]

Geographic variations

During the last half of the twentieth century, the urban population of India doubled from 17% to 34% of the total population.[67] Epidemiologic data support a striking urban–rural difference in the prevalence of CHD and CHD risk factors in South Asians living in India and abroad.[68] Data from India demonstrate at least a twofold excess of CHD in urban compared to rural environments. A recent overview of prevalence surveys in India reported a ninefold increase of CHD in urban centers, compared with a twofold increase in rural population over two decades of study.[69] Although these studies used somewhat different methods of sampling and varying definitions for CHD, collectively, they suggest that this is likely a real increase in CHD; however, the magnitude of the increase remains uncertain. Data from a study by Reddy *et al.* conducted in 1989–94 in which a population-based sample from urban Delhi was compared to a similar sample from rural Haryana revealed the CHD prevalence was 10/1000 in Delhi compared to 2/1000 in rural Haryana.[70] Associated with this increase in CHD rates in urban areas is an increase in the prevalence of lipid and glucose abnormalities. An increased prevalence of IGT, and type 2 diabetes, lower HDL cholesterol and higher triglycerides, increased abdominal obesity BMI, and hypertension is observed in the urban areas compared to the rural[71] (Table 21.5). By contrast, the rates of tobacco smoking are higher within rural environments among both men and women.

Migration patterns

An urban–rural difference in CHD prevalence and risk factors is observed within India and abroad. A recent study which compared the risk profiles of urban South Asians living in the UK with their siblings living in India revealed that the UK cohort had a higher BMI (27 *v* 23), systolic BP (144 mmHg *v* 137 mmHg), total cholesterol (6·35 *v* 5·0 mmol/l), a lower HDL cholesterol (1·14 *v* 1·27 mmol/l), and higher fasting glucose (5·4 *v* 4·6 mmol/l) compared to

Table 21.6 Comparison of South Asians from India and migrants in the United Kingdom

	Indian subcontinent	Sibling migrants UK	Significance
Mean age (yr)	45·0	46·0	NS
Serum glucose (men) (mmol/l)	4·5	5·7	0·001
Serum glucose (women) (mmol/l)	4·7	5·1	0·05
Serum cholesterol (men) (mmol/l)	4·9	6·5	0·001
Serum cholesterol (women) (mmol/l)	5·1	6·2	0·001
HDL cholesterol (men) (mmol/l)	1·21	1·12	NS
HDL cholesterol (women) (mmol/l)	1·34	1·16	0·05
Serum Lp(a) (men) (mg/dl)	17·4	18·8	NS
Serum Lp(a) (women) (mg/dl)	18·9	20·4	NS
Systolic/diastolic blood pressure (men) (mmHg)	132/87	146/93	0·001/NS
Systolic/diastolic blood pressure (women) (mmHg)	142/88	143/86	NS/NS
BMI (men)	22·9	26·8	0·001
BMI (women)	22·7	27·4	0·001

Source: Bhatnagar *et al*[72]

their siblings. Lp(a), which is genetically determined, was similarly high in both groups (Table 21.6).[72] Therefore, adverse changes in CVD risk factors and disease rates are observed when South Asians adopt an urban lifestyle, whether they live in India or abroad (see Table 21.5).

Prevention strategies

Changes in the risk factor profiles of South Asians are attributable to lifestyle changes associated with urbanization such as decreased physical activity and increased energy consumption which leads to obesity, abdominal obesity, and its harmful sequelae. Clearly strategies to prevent the development of obesity are required to decrease the number of South Asians who suffer from glucose intolerance, its associated dyslipidemia, and ultimately CHD.

Arabs

The term Arab refers to Semitic people who originate from the Middle East. Included in this region are the countries of Egypt, Saudi Arabia, Jordan, Iran, Iraq, and the United Arab Emirates.

Disease burden

CVD is the leading cause of death among Arabs living in the Middle East.[11] This is primarily caused by the rapid socioeconomic development, urbanization, and improved survival over the past several decades. The Global Burden of Disease report estimates that the acute myocardial infarction (AMI) rate among men and women was 139/100 000 and 124/100 000 respectively in 2000, which is an increase of 12% among men and 5% among women since 1990.[11]

Temporal trends

While national incidence and mortality data are not readily available for many Arab counties, one indication of the increase in CVD is the rise in hospital admission for CVD over time. In Egypt the proportion of hospital admissions due to CVD has increased in Egypt from 12% of deaths in 1970 to close to 40% in 1990.[73] In Saudi Arabia, CHD represented the leading cause of admissions in 1995.[74,75] In Oman during 1985–87 CHD and CBVD accounted for 30% of hospital deaths in the age group 15 years and above.[76]

Common risk factors

Overweight (defined as BMI in the range of 25–30) and obesity (BMI $>$ 30) are highly prevalent in the Arabian Peninsula, and over half of all adults aged 40–69 years are either overweight or obese.[77] Obesity rates vary from 16% to 25% among men and from 17% to 43% among women. Adverse lifestyles associated with socioeconomic development and urbanization, such as diminished physical activity (with the availability of domestic help, private cars, popularity of television etc.) and altered dietary patterns (increased fat and energy intakes) influence the prevalence of obesity.[77] The prevalence of leisure time physical activity from a nationally representative sample in Bahrain was low among all age and sex groups, though higher among men (30–49 years: 19·9%) than among women (30–49 years: 9·9%).[78] The high rates of overweight and obesity in this region are associated with the increasing prevalence of type 2 diabetes observed in this region. In 1995, prevalence of diabetes in Middle Eastern was approximately 6·3% (18·3 million people), and the prevalence of diabetes is expected to increase to 8·2% (53·5 million people) by the year 2025.[79] Rapid

urbanization, increasing obesity, abdominal obesity, and sedentary lifestyles are key factors underlying this increase of type 2 diabetes. In 1995, there were approximately twice the number of diabetics in urban compared to rural areas of the Middle East. By 2025, this ratio will increase dramatically, and there will be approximately 3·5 times the number of diabetics in urban compared to rural areas.[79] The high prevalence of obesity and sedentary lifestyles may also be associated with high levels of hypertension in this region. National surveys have demonstrated high prevalence of hypertension in Oman (27%),[80] Egypt (26%),[81] and the United Arab Emirates (37%).[82] In the United Arab Emirates, 26% of hypertensive subjects were aware that they had high blood pressure, 41% were being treated for the disease, and only 19% were under control.[82] This high prevalence, coupled with low awareness and poor control, suggest the need for additional focus on prevention. The prevalence of hypercholesterolemia in Saudi Arabia is also associated with age level of obesity and glucose tolerance.[83] Results of a National Survey conducted in Saudi Arabia, indicated that the prevalence of total cholesterol levels >5·2–6·2 mmol/l was 9% for males and 11% among females respectively, while prevalence of total cholesterol >6·2 mmol/l was 7% for males and 8% among females.[84] These levels are lower than observed elsewhere, however they reflect a young population (60% of the Saudi population is <30 years old), therefore the prevalence of hyperlipidemia is likely to increase as the population ages. Smoking is typically more common among men than women for cultural reasons, and the prevalence varies markedly between countries within the region. In Saudi Arabia, the prevalence of smoking is 12% among men, compared to only 1% among women.[83] However, the increasing use of the "water pipe" has resulted in increased smoking among women. In Bahrain, approximately 46% of men and 30% of women reported smoking. Furthermore, women more often reported exposure to passive smoke (44%) compared to men (29%).[78]

Influential risk factors

In comparison with European populations with similar degrees of obesity and glucose tolerance, Arabs experience more hyperglycemia associated with insulin resistance. This suggests that Arab people may have an increased genetic susceptibility to abdominal obesity (for example, the "thrifty gene"), which is expressed as glucose intolerance and excess abdominal fat in the face of an environment of abundant energy intake and relatively little physical activity.[85] Profound changes associated with urbanization which have occurred in Arab countries during the past 30 years are associated with the emergence of both obesity and diabetes, and this trend is expected to continue.

Special approaches to prevention

Increased susceptibility to insulin resistance among Arabs suggests that control of obesity and primary prevention and control of type 2 diabetes are critical. Attention to lifestyle practices that promote obesity, such as sedentary lifestyles and increased energy intake, should be a focus. Cultural beliefs about overweight and obesity for both men and women must be understood in order to develop effective prevention strategies. These directions have already been established in many countries of the Arabian Peninsula, and more recently in collaboration with the World Health Organization.

Hispanics

The term Hispanic includes Cuban Americans, Mexican Americans, and Puerto Rican Americans. There are approximately 35·3 million Mexican Americans living in the USA, and they comprise approximately 12·5% of the US population.[86,87] The majority of information on CVD in Hispanics has been derived from studies in Mexican Americans.

Disease burden

CVD is the leading cause of death among Hispanic males (28%) and females (34%).[87] Although death certificate registries report that the age adjusted mortality rates for major CVD among Mexican Americans (28·8 and 26·6 per 100 000 men and women respectively) are lower than those of African Americans (40·5 and 39·6 respectively) and whites (30·0 and 23·8 respectively) in the USA,[88] the Corpus Christi Heart Project (CCHP), Texas reported a greater incidence of MI in Mexican Americans compared to non-Hispanic whites over a 4 year period.[89] This population-based surveillance project conducted between 1988 and 1992 reported that age adjusted incidence ratios comparing Mexican Americans to non-Hispanic whites were 1·52 (95% CI 1·28–1·80) and 1·25 (95% CI 1·10–1·42) among women and men respectively.[89] Although cross-sectional studies reveal a similar or lower prevalence of MI among Mexican Americans than non-Hispanic whites, the CCHP has reported a greater case-fatality rate following MI among Mexican Americans than non-Hispanic whites. Therefore a lower CHD prevalence in Mexican Americans does not necessarily reflect a lower incidence of CHD.

Under the age of 60 years Hispanics have a significantly elevated CBVD death rate compared to non-Hispanics whites (M 32 *v* 19, F 23 *v* 18 per 100 000 respectively). However in older age categories the CBVD rate in Hispanics is substantially lower than whites (M 589 *v* 765, F 535 *v* 847 per 100 000).[18] Therefore, overall the CBVD death rate over 45 years of age in Hispanics is lower when compared to whites (M 115 *v* 147 per 100 000 and F 110 *v* 209 per 100 000).[18]

Temporal trends

Although declines in CHD and CBVD mortality have occurred in Mexican Americans over the past 20 years, this decline has been less than that which has occurred among non-Hispanic whites.[18,90,91]

Common risk factors

Mexican Americans suffer a high prevalence of conventional CVD risk factors such as smoking (42·5% in men and 23·8% in women), hypertension (17% men and 14% women), low HDL cholesterol (<0·90 mmol/l: 15·2% men and 5% women), elevated cholesterol (total cholesterol >6·2 mmol/l: 16·5% men and 16·5% women), diabetes (24%), physical inactivity (39%), and obesity (BMI >85th percentile, 30% men and 39% women).[92] The San Antonio Heart Study reported that Mexican Americans had 2·5 times the prevalence of NIDDM compared to the non-Hispanic whites as diagnosed by the oral glucose tolerance test.[92] They also observed that a socioeconomic gradient within the Hispanic population existed, with diabetes being more prevalent in the lower socioeconomic groups.[93] Furthermore, Mexican Americans have higher blood concentrations of triglycerides and lower HDL cholesterol levels compared to non-Hispanic whites.[91]

Influential risk factors

Glucose intolerance appears to be the most influential risk factor for CHD among Mexican Americans.[87] The greater mortality observed among Mexican Americans following MI in comparison to non-Hispanic whites is attributed in large part to the increased prevalence of diabetes.[94] Furthermore, glucose intolerance also defines which Mexican Americans are more likely to suffer CHD events within their own population, as diabetic Mexican Americans are four times more likely to suffer an MI compared to their non-diabetic counterparts.[95]

Geographic variations

This population suffers a high prevalence of glucose metabolic derangements upon the adoption of an urban lifestyle.

Special approaches to prevention/treatment

Due to the discrepant data concerning the CHD mortality rates of Mexican Americans, despite their adverse risk factor profile, many researchers believe they remain "protected" from CHD.[95] Clearly, the burden of CHD among Mexican Americans is considerable, and risk factor modification of conventional CHD risk factors must be initiated. Furthermore, primary prevention strategies such as prevention of obesity through environmental changes, and increased physical activity will reduce the rate of glucose intolerance in this group. Promotion of these strategies is important given that Mexican Americans are less likely to receive treatment for diabetes, hypercholesterolemia, and hypertension compared to non-Hispanic whites.[88,89] Therefore, it is critical that culturally sensitive strategies to bring about both primary and secondary prevention in this growing group of Americans be developed.

Aboriginal populations

Disease burden

Although mortality rates for CVD among aboriginal populations appear to be lower than whites, CHD is the leading cause of death in North American Indian and Alaskan Native males and females.[18] Although research in this ethnic group is limited, the Strong Heart Study,[96] which was initiated in 1988, studied 4549 American Natives aged 45–74 years from 13 tribes in the Southern US. The prevalence estimates of definite MI in those aged 45–74 years was 2·8% in men without diabetes, and 5·3% in men with diabetes, 0·4% in women without diabetes, and 1·4% in women with diabetes. Data from US cohort studies indicate that Native Americans may have a lower prevalence of MI than whites (7·9%), African Americans (6·1%), and Hispanics (5·6%).[96] However, data from Canada indicate that Aboriginal people suffer higher rates of CHD compared to the general population.[97,98]

There is little published information concerning the epidemiology of CBVD in native populations. In the USA the CBVD mortality rate under the age of 65 years is similar in Native Americans and white Americans, and substantially lower than rates in African Americans.[99] Over the age of 65, the CBVD rate in Native Americans is substantially lower than whites. The age adjusted mortality rate for CBVD in Native American men in 1988–98 was approximately 80 per 100 000 compared to 120 per 100 000 in white American men, and 60 per 100 000 compared to 100 per 100 000 in Native women compared to white American women.[18] In Canada, CVD is the leading cause of death among Aboriginal peoples.[100,101] Although the CHD mortality rates among Aboriginal and Canadian males are similar, the CHD mortality among Aboriginal women is 61% higher compared with Canadian women. In addition, the stroke mortality rate is 44% and 93% higher among Aboriginal men and women respectively, compared with the general Canadian population.[101] However, all of the above data are based on studies conducted more than 10 years ago. More recent data from a prevalence study in Canada indicates a 2·5-fold higher rate of CVD among Aboriginal peoples compared with Canadians of European origin.[98]

Temporal trends

As more Aboriginal people give up their traditional lifestyles and adopt "urban" lifestyles, the prevalence of CVD and its risk factors will likely increase.

Common risk factors

The common CHD risk factors among Aboriginal people include obesity, abdominal obesity, diabetes, elevated blood pressure, low HDL cholesterol, and tobacco use. The prevalence of cigarette smoking is generally high and increasing among Aboriginal people; the prevalence varies greatly between reserves.[98,102] The prevalence of diabetes in the Strong Heart Study was an astounding 48% in the 45–64 year age group compared to approximately 5·5% in the US general population, and the prevalence of obesity was between 26% and 41%, with an average BMI of 31 and waist–hip ratio of 0·96 in men.[103] Interestingly, the prevalence of hypertension and elevated serum cholesterol among Aboriginal people appears to be lower when compared to the general US population. In Canada, however, the prevalence of hypertension requiring drug treatment, and elevated cholesterol requiring medication, was significantly increased among Aboriginal people compared to a similar sample of non-Aboriginal people.[98] In addition, the prevalence of low HDL cholesterol is greater in this group, as approximately 25% of Aboriginal people have HDL cholesterol values less than 0·90 mmol/l.[98] In a recently completed Canadian study, Aboriginal people had a higher prevalence of CVD, atherosclerosis, glucose abnormalities, obesity, abdominal obesity, and tobacco use compared to European-origin Canadians.[98] Furthermore, a high proportion of Aboriginal people in North America live in poverty.[98] This is important to note as a strong inverse relationship exists between low income and an increased prevalence of CVD risk factors and CVD (Figure 21.2).[104]

Influential risk factors

Clearly obesity, diabetes, and tobacco use among Aboriginal people are the most influential risk factors for future CHD. Aboriginal people who are diabetic are two to four times more likely to suffer CVD than non-diabetic people.[102,103] In the Strong Heart Study other important risk factors for CHD included hypertension, obesity, and low HDL cholesterol.[103]

Geographic variations

Studies in aboriginal populations in North America have revealed important regional and inter-tribal differences in the prevalence of CVD risk factors (diabetes and cigarette smoking) and disease rates.[96–98] Most of the current data on Aboriginal CVD rates and risk factors have come from studies of Native people living on reserves. There is relatively little information regarding these profiles among city-dwelling Aboriginal people.

Special approaches to prevention/treatment

Control of obesity using environmental strategies to promote increased physical activity and lower energy consumption is

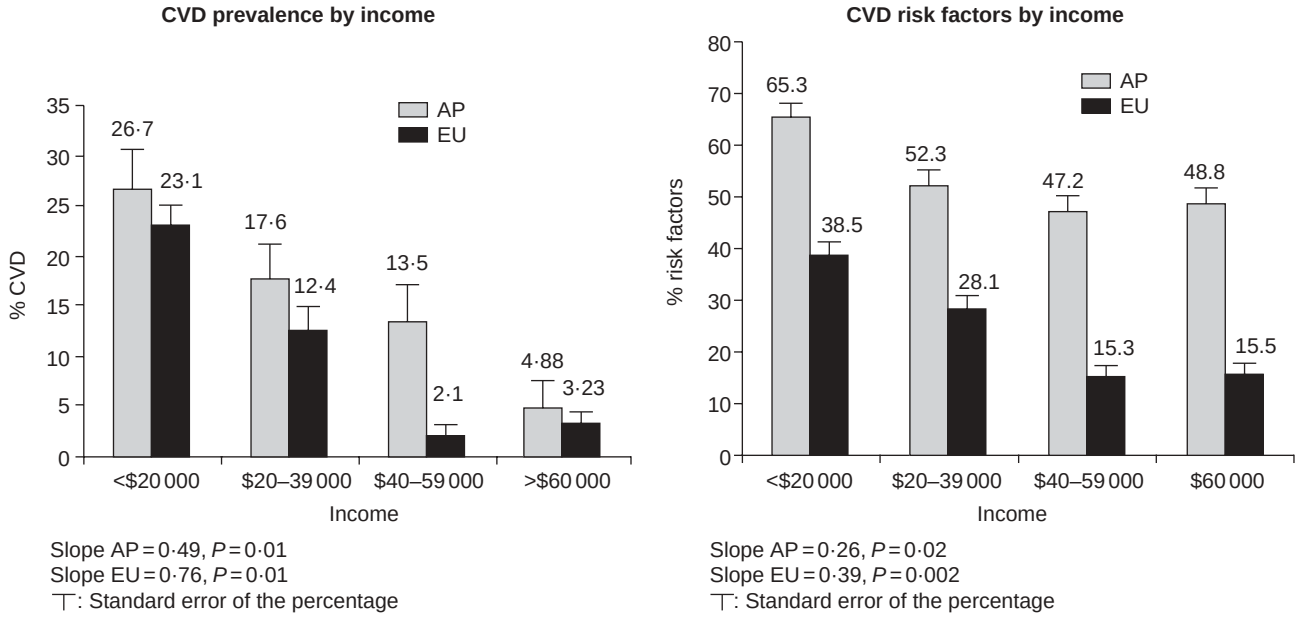


Figure 21.2 Relationship between low income and prevalence of CVD and number of CVD risk factors

required by Aboriginal people who have adopted a predominantly Western lifestyle. While tobacco has a cultural role in the lives of some Aboriginal people, increased tobacco taxes and other disincentives are required to prevent smoking initiation and promote smoking cessation on reserves. Despite community prevention strategies, the imbalance in socioeconomic circumstances between Aboriginal people and non-Aboriginal peoples must be addressed, as socioeconomic disparity is clearly associated with adverse lifestyle practices, psychosocial stress, and CVD prevalence.

Blacks of African origin

Disease burden

CVD mortality data from countries in Sub-Saharan Africa (SSA) are limited, as only 1·1% of all deaths are registered with a central agency.[10] Data from other sources such as sample registries and small scale population studies in 1990 indicate that the prevalence of acute MI in males and females of all ages was 4·5 million DALY, and that the CHD mortality was 41/100 000.[105] These rates are considerably lower than those of whites and South Asians who live in Africa, as well as rates of most Western countries, which are on average five times higher. Even so, in SSA, the proportional mortality rate from CHD accounts for 26% of all deaths, and in the 60–70 year age group it is responsible for over 80% of all deaths.[10,105] Furthermore, the case-fatality rate of CHD is higher in SSA compared to Western countries, meaning that once an individual develops CHD in SSA, the probability of death in SSA is higher than in Western countries. This probably reflects the limited access to acute and chronic treatment strategies.

Risk factors

The prevalence of most conventional risk factors for CHD is lower among blacks compared to other groups within Africa, and the world, with the exception of hypertension and smoking among urban blacks.[106–110] Data from the WHO Inter-Health Program, a substudy of the MONICA project, assessed the risk factor profile of men and women aged 35–64 years from Tanzania.[107] The prevalence of smoking was 37% among men, and 4% among women, the mean BMI was 21 in men, and 22 in women, the mean BP was 126/79 mmHg among men compared to 125/79 mmHg in women, the mean serum cholesterol was 4·1 mmol/l in men, and 4·3 mmol/l in women. When compared to the risk factor profile of other developing and developed countries, Tanzania's was more favorable, with the exception of smoking among men. Furthermore, the prevalence of multiple risk factors for CHD was low, as 65% of the population had no identifiable risk factors, 30% had a single risk factor, and only 5% had at least two risk factors, compared to 50%, 40%, and 10% in the USA.[107]

Geographic variations

In most urban and virtually all rural regions of SSA the prevalence of traditional CVD risk factors among blacks is low. However, with urbanization, an increase in conventional cardiovascular risk factors and CVD rates is expected.[111] An example of this is found in South Africa, as the rapid migration of blacks to urban centers has led to increased poverty, obesity, hypertension, LDL cholesterol, and a decrease in HDL cholesterol.[112–115]

Special approaches to disease prevention

Although CHD rates among people of African origin remains relatively low, the data are limited, and given the increased migration of blacks to urban centers, and a subsequent rise in the number of conventional CHD risk factors, the rates of CHD and CBVD are expected to rise. Primordial prevention strategies such as reducing the availability of saturated fats, and increasing the availability of monounsaturated fats, control of cigarette smoking by increasing the price of cigarettes, controlling the amount of salt consumption, and promoting regular physical activity are required on a community level, especially among urban populations. Key primary and secondary prevention strategies among blacks include control of hypertension, and tough antismoking campaigns.

West Indies

Disease burden

In Trinidad, data from 1989 reveal that the age adjusted incidence of CHD in people of African origin was 6·8/1000 person years at risk among men, and 5·4/1000 person years at risk among women. The rate in men approximated that of males of European decent (6·8 *v* 6·5/1000), whereas the rates among women were higher in blacks (5·4 *v* 2·9/1000). The rates in both sexes and groups were substantially lower than males (16 per 1000) and females (13/1000) of South Asian origin.[116]

Risk factors

The most prevalent and influential risk factor among West Indian blacks is hypertension. In Trinidad the prevalence of hypertension among African blacks was 33%, diabetes 8·1%, and smoking 39%.[116] Furthermore, the mean HDL and LDL cholesterol in men was 1·03 and 4·04 mmol/l, and in women 1·30 and 4·11 mmol/l. The most important predictors of CHD in this cohort were hypertension, high LDL cholesterol, low HDL cholesterol, and diabetes mellitus.

African Americans

African Americans comprise the largest non-white population in the USA and represent approximately 13% of the population.

Disease burden

CVD is the leading cause of death among African Americans, and the incidence of both CHD and CBVD is higher in African Americans compared to white Americans. The CHD mortality rate in African American males is 2·4% higher than in white males (138·1 *v* 134·8 per 100 000), and 33% higher in African American women compared to white American women (85 *v* 64 per 100 000).[18] Moreover, sudden cardiac death (defined by ICD codes 410-414) are more common among African American men (137/100 000) compared to white American men (122/100 000) aged 35–74 years, and women (67 *v* 41/100 000) respectively.[117] The CBVD mortality rate is 98% higher in African American males compared to white males (52 per 100 000 *v* 26 per 100 000) and 77% higher in African American females compared to white females (40 per 100 000 *v* 22 per 100 000).[18]

Temporal trends

Although there has been a decline in mortality rates from CVD in both African Americans and white Americans over the past 30 years, these declines have been less marked in African Americans.[18]

Common risk factors

Compared to whites, African Americans develop high blood pressure at an earlier age, and it is more severe.[18] The reason for black–white differences in hypertension prevalence likely involves a complex interaction between environmental response to diet, and stress, and a potential genetic/physiologic difference such as differences in sodium/potassium excretion, perhaps linked to their origins in Africa. Serum cholesterol levels are not higher among African Americans than white Americans, as 47% of African American men have cholesterol values over 5·2 mmol/l, compared to 54% of white males, and 51% of women have levels greater than 5·2 mmol/l, compared to 53% of white females.[18] On average, African Americans have higher HDL cholesterol levels compared to whites, a difference which is more marked among women. The prevalence of cigarette smoking is greater among African American males (33% *v* 27%) than in white men, whereas fewer African American females smoke compared to white American women.[18] Obesity is an emerging problem among African Americans especially in women, as approximately 50% of African American women are reported to be overweight, compared to 33% of white American women.[18] Closely linked to the prevalence of obesity is a low prevalence of self-reported regular physical activity. Approximately 65% of African Americans lead a sedentary lifestyle compared to about 56% of whites.[18] Furthermore, the prevalence of diabetes in African Americans is higher than in whites, as demonstrated by NHANES II conducted from 1976 to 1980 in which African Americans aged 20–74 years showed a prevalence of type 2 diabetes of 9·9% compared to 6% in white Americans.[18] Furthermore, the rate of type 2 diabetes is increasing faster among African Americans than among whites, especially in women, as it is closely tied to the development of obesity.[18] Although elevated levels of Lp(a) are found more often in African Americans than whites, whether or not elevated Lp(a) levels are related to an increased CHD risk among African Americans is unclear.[118] However, even after consideration of "biomedical" differences in conventional risk factor prevalence such as hypertension, smoking, and obesity, other factors are likely to play a role in slower decline in CVD rates which has been observed among blacks. Differences in socioeconomic status between African American and whites translate into decreased access to medical therapies and hospital services and results in the performance of fewer diagnostic tests and lower rates of coronary revascularization procedures.[119,120]

Influential risk factors

Black and white differences in CVD mortality appear to be largely due to differences in hypertension prevalence. However, late onset diabetes is an increasing problem among African Americans due to the increase in obesity. Even so, at least 30% of the excess CHD mortality between blacks and whites can be accounted for by differences in socioeconomic status, and these socioeconomic differentials lead to less access to healthcare services and acceptance of preventive strategies.[120]

Geographical variations

Early investigators noted high stroke mortality rates among black Americans in the Southeastern coastal states. By late 1980s, this "stroke belt" had dissipated in the Southeastern coastal areas and shifted to the Midwest regions of the Mississippi and Ohio river valleys.[121] CHD mortality has shown a similar westward shift to the so called coronary valley. The increased CVD mortality among blacks has been mainly confined to the Southern states (Mississippi river valley). Although changes in regional profile of risk factors, local environment, and migration pattern may have played a role, recent economic shifts in these areas may be the principal reason for changes in disease rates.[122] Whereas Southeastern coastal areas have undergone considerable economic development, the more westwardly regions have

not kept pace.[124] In Mississippi, one of the most economically and educationally disadvantaged US states, CVD mortality has risen among African Americans over the past two decades while among whites there has been a decline.[123] Similar patterns are also observed in the Northeastern states and the Midwest.[124,125]

Special approaches to prevention/treatment

The rates of CHD among blacks in Africa are relatively low compared to the rates in most Western countries. With urbanization, however, both within Africa and among migrant Africans to the West Indies and the USA, the rates of CVD are comparable to or higher than the rates of most Western countries. As in other populations, conventional CVD risk factors remain important, but the dominant CVD risk factor among people of African origin is hypertension. Special efforts at detection, prevention, and treatment of hypertension, both through lifestyle changes and appropriate pharmacologic therapy, are necessary. In the USA, the socioeconomic disparity of this population results in enhanced disease burden. This black–white differential in disease rates, risk factors, and access to medical treatments necessitates that specific prevention strategies be initiated in this group. Such strategies include primary prevention programs to prevent unhealthy lifestyle behaviors such as poor dietary practices and cigarette smoking. As these risk factors are closely tied to low SES, other factors besides "biomedical" ones must be targeted. Health care providers must ensure equal access to healthcare services especially among the lower socioeconomic status black population. However, in order to overcome the larger differential in socioeconomic status between African Americans and whites, overall changes in social policy are required at the national level.

Studies of multiple ethnic groups

Studies of diverse ethnic populations who reside in a single country and hence are exposed to a similar environment indicate that the pattern of CHD mortality between these groups initially resembles that of their home country. However, through the process of acculturation, prolonged exposure to new environmental factors results in similarities in CVD risk factors and trends within multiethnic populations. A study of multiple ethnic groups in the US revealed that CVD mortality rates were highest among African Americans, followed by whites, and Hispanics.[126] By contrast Japanese, Chinese, Koreans and Filipinos had much lower CHD mortality rates. Another study conducted in

Table 21.7 Summary of disease rates by ethnic group in North America[a]

USA[b]	White Caucasian	Japanese	Black African	Hispanic	Aboriginal
CHD mortality per 100 000 in North America	M 230 F 95	M 81 F 38	M 222 F 120	M 112 F 52	124
CBVD mortality per 100 000 in North America	M 41 F 33	M 25 F 33	M 102 F 83	M 31 F 25	40
CVD prevalence (aged 35–75 yr)	7·5%	3%	8%	4%	4%
CHD incidence per 1000 (65–74 yr)	M 26 F 8	M 11	M 16 F 13	M 14 F 14	M 7 F 12
CBVD incidence per 1000 (65–74 yr)	M 14 F 6	M 8	M 12 F 16	M 8 F 3	M 15 F 8

Canada	White Caucasian	Chinese	South Asians	Aboriginal
CHD mortality per 100 000[c]	M 320 F 110	M 107 F 40	M 320 F 144	M 320 F 176[d]
CBVD mortality per 100 000[c]	M 49 F 35	M 46 F 42	M 47 F 39	M 71 F 67
CVD prevalence (aged 35–75 yr)[e]	5·4%	2·4%	10·7%	17%

[a] Note that disease rates will vary by study. This table provides a useful but approximate comparison between ethnic groups.
[b] From the American Heart Association. *2002 Heart and stroke statistical update*. Dalls TX: American Heart Association, 2001.
[c] Age (35–74 yr) standardized death rates per 100 000.
[d] Estimated from Mao *et al*, 1992.
[e] From the Study of Health Assessment and Risk in Ethnic Groups.

California between 1985 and 1990 compared CHD and CBVD death rates in six ethnic groups. Once again, African American men and women in all age groups were found to have the highest CVD death rates. Hispanics, Chinese, and Japanese had much lower CVD rates, although the CBVD deaths were proportionally a more important cause of death among the Chinese and Japanese. Furthermore, a study that compared the rates of hospitalization for CHD among Asian Americans compared to Americans in Northern California revealed that the risk of hospitalization for CHD was the lowest among the Chinese Americans (0·6), and the highest among the South Asians (3·7, $P < 0{\cdot}001$).[126] Recent data from the United Kingdom (UK) reveals that although the CHD mortality rates were approximately 43% higher among South Asian men and women compared to the general UK population (ASMR men 282/100 000, women 89/100 000), among South Asians a decline of 26% in men and 18% in women in the CHD rates occurred.[127] This is in keeping with a decline in CHD mortality in the UK as a whole over the past decade. In Canada, an analysis of the Canadian national mortality database of South Asians, Chinese and Canadians of European origin (EU), demonstrated that the ASMR per 100 000 for CHD in South Asians (M 320, F 144) was similar compared to those of EU origin (M 320, F 110), yet was much higher than Chinese (M 107, F 40). Furthermore, a significant decline in CHD death rates between 1979–83 and 1989–93 was observed in all groups, with the greatest declines being apparent among South Asian men and women compared to EU and Chinese respectively (M 22%, 13%, and 5·4%, F 6%, 4%, and 2%)[49] (Table 21.7). Furthermore, in Canada the inverse relationship between mortality and socioeconomic status is observed in European Canadians, but not in South Asians and Chinese. This raises the issue of whether this relationship is acquired within societies and therefore is potentially preventable/modifiable.

Conclusions

CVD accounts for the largest percentage of deaths worldwide. To date, recognition and modification of the major CVD risk factors have led to declines in CVD rates in most Western countries, although these declines have lagged behind in most non-white populations. Socioeconomic development, urbanization, and increasing life expectancy have led to a progressive rise in the CVD rates in developing countries such as India and China.

It is clear that elevated serum cholesterol, elevated blood pressure, cigarette smoking, and glucose intolerance are the major risk factors for CHD and CBVD in most populations. However, the prevalence of these factors and the strength of association of these factors to CVD vary between ethnic groups. Furthermore, other risk or protective factors (levels of endogenous fibrinolysis, dietary factors such as flavonoids and antioxidants) probably exist. Identification of these factors is important so that new approaches to prevention of CVD in these populations may be developed. Research into ethnic populations who suffer adverse glucose and lipid changes upon urbanization (that is, Hispanics, Aboriginal, and South Asians) should be a priority, as a greater proportion of these groups are adopting urban lifestyles which are associated with observed increases in CVD rates. Furthermore, in developed countries, research into reasons for social disparity and its impact on the distribution of CVD risk factors among ethnic groups must be continued so that specific interventions may be developed to reduce the adoption of unhealthy lifestyle behaviors, and barriers to healthcare services may be reduced. Ultimately all of this information will lead to special strategies for prevention which may be tailored to ethnic populations, and generate important areas for future study.

References

1. Lenfant C. Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases (news). *Circulation* 1994;**90**:2609–17.
2. Anand SS. Using ethnicity as a classification variable in health research: perpetuating the myth of biological determinism, serving socio-political agendas, or making valuable contributions to medical sciences? *Ethnicity Health* 1999;**4**:241–4.
3. Littlefield A, Lieberman L, Reynolds L. Redefining race: the potential demise of a concept in physical anthropology. *Curr Anthropol* 1982;**23**:641–55.
4. Jackson FL. Race and ethnicity as biological constructs. *Ethnicity Dis* 1992;**2**:120–5.
5. Crews DE, Bindon JR. Ethnicity as a taxonomic tool in biomedical and biosocial research. *Ethnicity Dis.* 1998;**1**:42–9.
6. Cooper R. A note on the biologic concept of race and its application in epidemiologic research. *Am Heart J* 1984;**108**:715–22.
7. Chaturvedi N, McKeigue PM. Methods for epidemiological surveys of ethnic minority groups (Review). *J Epidemiol Comm Health* 1994;**48**:107–11.
8. Lopez AD. Assessing the burden of mortality from cardiovascular diseases. *World Health Stat Q* 1993;**46**:91–6.
9. The World Health Report 1999. *Making a difference*. Geneva: World Health Organization, 1999.
10. Murray CJL, Lopez AD, eds. *The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020*. Cambridge MA: Harvard University Press, 1996.
11. The World Heart Federation's White Book. Chockalingam A, Balaguer-Vintro I, eds. *Impending global pandemic of cardiovascular diseases: challenges and opportunities for the prevention and control of cardiovascular diseases in developing countries and economies in transition*. Barcelona: Prous Science.
12. McGovern PG, Jacobs DR Jr, Shahar E *et al.* Trends in acute coronary heart disease mortality, morbidity, and medical care

from 1985 through 1997: the Minnesota heart survey. *Circulation* 2001; **104**:19–24.
13. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases Part 1: General considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001;**104**:2746–53.
14. Marmot M. Coronary heart disease: rise and fall of a modern epidemic. In: Marmot M, Elliot P, eds. *Coronary heart disease epidemiology*. Oxford: Oxford University Press, 1995.
15. Menotti A, Keys A, Kromhout D *et al.* Inter-cohort differ-ences in coronary heart disease mortality in the 25-year follow-up of the seven countries study. *Eur J Epidemiol* 1993; **9**:527–36.
16. Bothing S. WHO MONICA Project: objectives and design. *Int J Epidemiol* 1989;**18**:S29–37.
17. Benfante R. Studies of cardiovascular disease and cause-specific mortality trends in Japanese-American men living in Hawaii and risk factor comparisons with other Japanese populations in the Pacific region: a review. *Hum Biol* 1992; **64**:791–805.
18. World Health Organization web page 2002. wwww.who,int/whosis2000
19. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization monitoring trends and determinants in cardiovascular disease (published erratum appears in *Stroke* 1995;**26**:1504). *Stroke* 1995;**26**:361–7.
20. Bobak M, Marmot M. Alcohol and mortality in Russia: is it different than elsewhere? *Ann Epidemiol* 1999;**9**:335–8.
21. Artaud-Wild SM, Connor SL, Sexton G, Connor WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. A paradox. *Circulation* 1993; **88**:2771–9.
22. Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994;**344**:1719–23.
23. Law MR, Wald N. Why heart disease mortality is low in France: the time-lag explanation. *BMJ* 1999;**318**: 1471–80.
24. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ* 1994;**309**: 23–7.
25. Hunink MG, Goldman L, Tosteson A *et al.* The recent decline in mortality from coronary heart disease, 1980–1990. *JAMA* 1997;**277**:535–42.
26. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991. *BMJ* 1998;**316**:1047–51.
27. Leon D, Chenet L, Shkolnikov VM *et al.* Huge variation in Russian mortality rates 1984–1994; artifact, alcohol, or what? *Lancet* 1997;**350**:383–8.
28. Kitamura A, Iso H, Iida M *et al.* Trends in the incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994. *Am J Med* 2002;**112**:104–9.
29. Fujishima M, Kiyohara Y, Kato I *et al.* Diabetes and cardiovascular disease in a prospective population survey in Japan. *Diabetes* 1996;**45**:S14–16 (Abstract).
30. Cockram CS. The epidemiology of diabetes mellitus in the Asia–Pacific Region. *HKMJ* 2000;**6**:43–52.
31. Ohmura T, Ueda K, Kiyohara Y *et al.* Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayma study. *Diabetologia* 1993;**36**:1198–263.
32. Shimako M. The influence of changing lifestyles on health education and chronic disease prevention in Japan. In: Shetty P, Gopalan C, eds. *Diet, nutrition and chronic disease, an Asian perspective*. London: Smith-Gordon, 1998.
33. Hong Y, Bots ML, Pan X, Hofman A, Grobbee DE, Chen H. Stroke incidence and mortality in rural and urban Shanghai from 1984 through 1991. Findings from a community-based registry. *Stroke* 1994;**25**:1165–9.
34. Woo KS, Donnan SP. Epidemiology of coronary arterial disease in the Chinese (Review). *Int J Cardiol* 1989;**24**:83–93.
35. Khor GL. Cardiovascular epidemiology in the Asia–Pacific region. *Asia Pac J Clin Nutr* 2001;**10**:76–80.
36. Wu Z, Yao C, Zhao D, Sino-MONICA Project. A collaborative study on trends and determinants in cardiovascular diseases in China, Part I: morbidity and mortality monitoring. *Circulation* 2001;**103**:462–8.
37. Donnan SP, Ho SC, Woo J *et al.* Risk factors for acute myocardial infarction in a southern Chinese population. *Ann Epidemiol* 1994;**4**:46–58.
38. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991; **303**:276–82.
39. Tao SC, Huang ZD, Wu XG *et al.* CHD and its risk factors in the People's Republic of China. *Int J Epidemiol* 1989; **18**:S159–63.
40. Yang G, Fan L, Tan J *et al.* Smoking in China: findings of the 1996 National Prevalence Survey. *JAMA* 1999;**282**:1247–53.
41. Hu FB, Wang B, Chen C *et al.* Body mass index and cardiovascular risk factors in a rural Chinese population. *Am J Epidemiol* 2000;**151**:88–97.
42. Popkin BM, Paeratakul S, Ge K, Fengying Z. Body weight patterns among the Chinese: results from the 1989 and 1991 China Health and Nutrition Surveys. *Am J Publ Health* 1995; **85**:690–4.
43. Fang XH, Longstreth WT Jr, Li SC *et al.* Longitudinal study of blood pressure and stroke in over 37 000 People in China. *Cerebrovasc Dis* 2001;**11**:225–9.
44. People's Republic of China–United States Cardiovascular and Cardiopulmonary Epidemiology Research Group. An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the People's Republic of China. *Circulation* 1992;**85**:1083–96.
45. Li N, Tuomilehto J, Dowse G *et al.* Electrocardiographic abnormalities and associated factors in Chinese living in Beijing and in Mauritius. The Mauritius Non-Communicable Disease Study Group. *BMJ* 1992;**304**:1596–601.
46. Hughes K, Yeo PP, Lun KC *et al.* Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. *J Epidemiol Commun Health* 1990;**44**: 29–35.
47. Gao M, Ikeda K, Hattori H, Miura A, Nara Y, Yamori Y. Cardiovascular risk factors emerging in Chinese populations undergoing urbanization. *Hypertens Res* 1999;**22**:209–15.

48.Woo KS, Chook P, Raitakari OT, McQuillan B, Feng JZ, Celermajer DS. Westernization of Chinese adults and increased subclinical atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;**19**:2487–93.
49.Sheth T, Nair C, Nargundkar M, Anand S, Yusuf S. Cardiovascular and cancer mortality among Canadians of European, South Asian and Chinese origin from 1979 to 1993: an analysis of 1.2 million deaths. *Can Med Assoc J* 1999; **161**:132–8.
50.Anand S, Yusuf S, Vuksan D *et al.*, for the SHARE Investigators. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000;**356**:279–84.
51.Chonghua Y, Zhaosu W, Yingkai W. The changing pattern of cardiovascular diseases in China. *World Health Stat Q* 1993;**46**:113–18.
52.Reddy KS. Cardiovascular diseases in India. *World Health Stat Q* 1993;**46**:101–7.
53.Enas EA, Yusuf S, Mehta J. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol* 1992;**70**:945–9.
54.Lowy AGJ, Woods KL, Botha JL. The effects of demographic shift on coronary heart disease mortality in a large migrant population at high risk. *J Publ Health Med* 1991;**13**:276–80.
55.Balarajan R. Ethnic differences in mortality from ischemic heart disease and cerbrovascular disease in England and Wales. *BMJ* 1991;**302**:560–4.
56.Sheth T, Chagani K, Nargundkar M, Anand S, Nair C, Yusuf S. Ethnic differences in cause-specific mortality: South Asians, Chinese, Whites in Canada. *Eur Heart J* 1996;**17**:234 (Abstract).
57.McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation* 1993;**87**:152–61.
58.McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991; **337**: 382–6.
59.Gupta R. Meta-analysis of prevalence of hypertension in India. *Ind Heart J* 1997;**49**:450.
60.Pais P, Pogue J, Gerstein H *et al.* Risk factors for acute myocardial infarction in Indians: a case–control study. *Lancet* 1996;**348**:358–63.
61.Joseph A, Kutty VR, Soman CR. High risk for coronary heart disease in Thiruvananthapuram City: a study of serum lipids and other risk factors. *Ind Heart J* 2000;**52**:29–35.
62.Ramachandran A, Dharmaraj D, Snehalatha C, Viswanathan M. Prevalence of glucose intolerance in Asian Indians. *Diabetes Care* 1992;**15**:1348–55.
63.Anand S, Enas E, Pogue J *et al.* ELevated lipoprtoein (a), low HDL cholesterol and elevated glucose in South Asians compared to North American Whites. *Eur Heart J* 1996; **17**:398.
64.Gambhir JK, Harsimrut K, Gambhir DS, Prabhu KM. Lipoprotein (a) as an independent risk factor for coronary artery disease in patients below 40 years of age. *Ind Heart J* 2000;**52**:411–15.
65.Gerstein HC, Yusuf S. Dysglycaemia and risk of cardiovascular disease. *Lancet* 1996;**347**:949–50.
66.Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of MI: a case control study. *J Am Coll Cardiol* 1999;**33**:612–19.
67.Gopalan C. Demographic and developmental transition in India: its impact on nutrition-related chronic diseases. In: Shetty P, Gopalan C, eds. *Diet, nutrition and chronic disease: an Asian perspective*. London: Smith-Gordon, 1998.
68.Reddy S. Coronary heart disease in different racial groups. In: Yusuf S, Wilhelmsen L, eds. *Advanced issues in prevention and treatment of atherosclerosis*. Surrey: Euromed Communications, 1995.
69.Gupta R, Gupta VP. Meta-analysis of coronary heart disease prevalence in India. *Ind Heart J* 1996;**48**:241–5.
70.ICMR cross-sectional study of CHD risk factors in urban and rural India. 1997 – a report: Personal communication, Dr S Reddy.
71.Kutty VR, Soman CR, Joseph A, Pisharody R, Vijayakumar K. Type 2 diabetes in southern Kerala: variation in prevalence among geographic divisions within a region. *Natl Med J India* 2000;**13**:287–92.
72.Bhatnagar D, Anand IS, Durrington PN *et al.* Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. *Lancet* 1995;**345**:405–9.
73.Central Agency for Public Mobilization and Statistics (CAMPAS). *Annual health report for the year 1990*. Cairo: CAMPAS, 1990.
74.Al Balla SR, Bamgboye EA, Sekait M, Balla M. Causes of morbidity in the elderly population of Saudi Arabia. *J Trop Med Hyg* 1993;**96**:157–62.
75.Al Balla SR, Bamgboye EA, Al Sekait M, Al Rasheed R. Pattern of adult admission into medical wards of King Khalid University Hospital, Riyad (1985–1990). *Saudi Med* 1993;**13**:8–13.
76.*Annual statistical report*, 1985, 1986, and 1987. Ministry of Heath, Oman.
77.Al Mahroos F, Al Roomi K. Overweight and obesity in the Arabian Peninsula: an overview. *J R Soc Health* 1999;**119**: 251–3.
78.Musaiger AO, al-Roomi KA. Prevalence of risk factors for cardiovascular diseases among men and women in an Arab Gulf Community. *Nutr Health* 1997;**11**:149–57.
79.King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025. Prevalence, numerical estimates, and projections. *Diabetes Care* 1998;**21**:1414–31.
80.Hasab AA, Jaffer A, Hallaj Z. Blood pressure patterns among the Omani population. *East Medit Health J* 1999;**5**:46–54.
81.Ibrahim MM, Rizk H, Appel LJ. Hypertension prevalence, awareness, treatment and control in Egypt. Results from the Egyptian National Hypertension Project (NHP). NHP investigative team. *Hypertension* 1995;**26**:886–90.
82.Yassin IM, Sherif ZB, Nizar F *et al.* Hypertension in UAE citizens – preliminary results of a prospective study. *Saudi J Kidney Dis Transplant* 1999;**10**:376–81.
83.Al Nuaim AR. High prevalence of metabolic risk factors for cardiovascular diseases among Saudi population, aged 30–64 years. *Int J Cardiol* 1997;**62**:227–35.
84.Al-Nuaim AR, Al-Rubeaan K, Al-Mazrou Y, Al-Attas O, Al-Daghari N. Prevalence of hypercholesterolemia in Saudi Arabia, epidemiological study. *Int J Cardiol* 1996;**54**: 41–9.

85.Neel JV. The "thrifty genotype" in 1998. *Nutr Rev* 1999; **57**:S2–9.
86.US Bureau of Census. *Census*. Washington, DC: US Bureau of the Census, 2000.
87.Becker T, Wiggins C, Key C, Samet J. Ischemic heart disease mortality in Hispanic American Indians and non-Hispanic whites in New Mexico, 1958–1982. *Circulation* 1988; **78**:302–9 (Abstract).
88.Goff D, Nichaman M, Chan W *et al.* Greater incidence of hospitalized myocardial infarction among Mexican-Americans than Non-Hispanic Whites: the Corpus Christi Heart Project, 1988–1992. *Circulation* 1997;**95**:1433–40.
89.Gillum RF. Epidemiology of stroke in Hispanic Americans. *Stroke* 1995;**26**:1707–12.
90.Stern M, Gaskill S. Secular decline in death rates due to ischemic heart disease in Mexican Americans and non-Hispanic Whites, Texas 1970–1980. *Circulation* 1987;**76**: 1245–50 (Abstract).
91.Pappas G, Gergen PJ, Carroll M. Hypertension prevalence and the status of awareness, treatment, and control in the Hispanic Health and Nutrition Examination Survey, 1982–84. *Am J Publ Health* 1990;**80**:1431–6.
92.Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992;**41**:715–22.
93.Wei M, Valdez RA, Mitchell BD, Haffner SM, Stern MP, Hazuda HP. Migration status, socioeconomic status, and mortality rates in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. *Ann Epidemiol* 1996;**6**:307–13.
94.Goff DC, Ramsey D, Labarthe DR, Nichaman MZ. Acute myocardial infarction and coronary heart disease mortality among Mexican Americans and non-Hispanic whites in Texas, 1980 through 1989. *Ethnicity Dis* 1993;**3**:64–9 (Abstract).
95.Goff DC Jr, Ramsey DJ, Labarthe DR, Nichaman MZ. Greater case-fatality after myocardial infarction among Mexican Americans and women than among non-Hispanic whites and men. The Corpus Christi Heart Project. *Am J Epidemiol* 1994;**139**:474–83.
96.Howard BV, Lee ET, Cowan LD *et al.* Coronary heart disease prevalence and its relation to risk factors in American Indians. The Strong Heart Study. *Am J Epidemiol* 1995;**142**: 254–68.
97.Shah BR, Hux JE, Zinman B. Inreasing rates of ischemic heart disease in the native population of Ontario, Canada. *Arch Intern Med* 2000;**160**:1862–6.
98.Anand S, Yusuf S, Jacobs R *et al.,* for the SHARE-AP Investigators. Risk factors, atherosclerosis, and cardiovascular disease among Aboriginal people in Canada: the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP). *Lancet* 2001;**358**:1147–53.
99.Gillum RF. The epidemiology of stroke in Native Americans. *Stroke* 1995;**26**:514–21.
100.Royal Commission on Aboriginal People. Report of the Royal Commission on Aboriginal People, Volume 3. *Gathering strength*. 1996. Canberra: Office of the Government Printer.
101.Mao Y, Moloughney B, Semenciw R, Morrison H. Indian reserve and registered Indian mortality in Canada. *Can J Publ Health* 1992;**83**:350–3.
102.Howard BV, Lee ET, Fabsitz RR *et al.* Diabetes and coronary heart disease in American Indians: the Strong Heart Study. *Diabetes* 1996;**45**(Suppl. 3):S6–13.
103.Welty TK, Lee ET, Yeh J *et al.* Cardiovascular disease risk factors among American Indians: the Strong Heart Study. *Am J Epidemiol* 1995;**42**:269–87.
104.Kaplan GA, Lynch JW. Socioeconomic considerations in the primordial prevention of cardiovascular disease (Review). *Prev Med* 1999;**29**(Pt 2):S30–5.
105.Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997;**349**:1498–504.
106.Berrios X, Koponen T, Huiguang T *et al.* Distribution and prevalence of major risk factors of noncommunicable diseases in selected countries: the WHO Inter-Health Programme. *Bull WHO* 1997;**75**:99–108.
107.Seedat YK. Ethnicity, hypertension, coronary heat disease, and renal diseases in South Africa. *Ethnicity Health* 1996; **1**:349–57.
108.Seftel HC, Asvat MS, Joffe BI *et al.* Selected risk factors for coronary heart disease in male scholars from the major South African population groups. *S Afr Med J* 1993;**83**:891–7.
109.Steyn K, Fourie J, Bradshaw D. The impact of chronic diseases of lifestyle and their major risk factors on mortality in south Africa. *S Afr Med J* 1992;**82**:227–31.
110.Akinkugbe OO. World epidemiology of hypertension in blacks. *J Clin Hypertens* 1987;**3**(Suppl 3):15–85.
111.Fourie J, Steyn K, eds. *Chronic diseases of lifestyle in South Africa*. MRC Technical Report, Cape Town, 1995.
112.Steyn K, Fourie J, Lombard C *et al.* Hypertension in the black community of the Cape Peninsula, South Africa. *E Afr Med J* 1996;**73**:758–63.
113.Levitt NS, Katzenellenbogen JM, Bradshww D, Hoffman MN, Bonnici F. The prevalence and identification of risk factors for NIDDM in urban Africans in Cape Town, South Africa. *Diabetes Care* 1993;**16**:601–7.
114.Omar MAK, Seedat MA, Motala AA, Dyer RB, Becker P. The prevalence of diabetes mellitus and impaired glucose tolerance in a group of urban south African blacks. *S Afr Med J* 1993;**83**:641–3.
115.Steyn K, Kazenellenbogen JM, Lombard CJ, Bourne LT. Urbanization and the risk for chronic diseases of lifestyle in the black population of the cape Peninisula. *S Afr J Cardiovasc Risk* 1997;**4**:135–42.
116.Miller GJ, Beckles GL, Maude GH *et al.* Ethnicity and other characteristics predictive of coronary heart disease in a developing community: principal results of the St James Survey, Trinidad. *Int J Epidemiol* 1989;**18**:808–17.
117.Gillum RF. Sudden coronary death in the United States, 1980–1985. *Circulation* 1989;**79**:756–65.
118.Moliterno DJ, Jokinen EV, Miserez AR *et al.* No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African-Americans. *Arterioscler Thromb Vasc Biol* 1995;**15**:850–5.
119.Geronimus AT, Bound J, Waidmann TA, Hillemeier MM, Burns PB. Excess mortality among blacks and whites in the United States. *N Engl J Med* 1996;**335**:1552–8.
120.Fang J, Madhavan S, Alderman MH. The association between birthplace and mortality from cardiovascular causes among

black and white residents of New York City. *N Engl J Med* 1996;**335**:1545–51.
121. Casper ML, Wing S, Anda RF *et al.* The shifting stroke belt and the geographic pattern of stroke mortality in the US 1962 to 1998. *Stroke* 1995;**26**:755–60.
122. Casper M, Wing S, Strogatz D. Variation in the magnitude of black–white difference in stroke mortality by community occupational structure. *Epidemiol Commun Health* 1991;**45**: 302–6.
123. Jones DW, Sempos CT, Thom TJ *et al.* Rising levels of cardiovascular mortality in Mississippi, 1979–1995. *Am J Med Sci* 2000;**319**:131–13.
124. Geronimus AT, Bound J, Waidmann TA *et al.* Is there is an excess mortality among blacks and whites in the United States? *N Engl J Med* 1996:**336**:1552–8.
125. Frerichs RR, Chapman JM, Maes EF. Mortality due to all causes and to cardiovascular diseases among seven race-ethnic populations in Los Angeles County, 1980. *Int J Epidemiol* 1984;**13**:291–8.
126. Klatsky AL, Tekawa I, Armstrong MA, Sidney S. The risk of hospitalization for ischemic heart disease among Asian Americans in northern California. *Am J Publ Health* 1994;**84**: 1672–5.
127. Balarajan R. Ethnicity and variations in mortality from coronary heart disease. *Health Trends* 1996;**28**:45–51.
128. Wyndham CH. Trends with time of cardiovascular mortality rates in the populations of the RSA for the period 1968–1977. *S Afr Med J* 1982;**61**:987–93.
129. Steinberg WJ, Balfe DL, Kustner HG. Decline in the ischemic heart disease mortality rates of South Africans, 1968–1985. *S Afr Med J* 1988;**74**:547–50.
130. Baligadoo S, Manraj M, Krishnamoorthy R, Jankee S, Ramasawmy R. Genetic contribution to the height mortality from coronary disease in Indian Diaspora: case study of Mauritius. *Eur Heart J* 1994;**15**:162 (Abstract).
131. Tuomilehto J, Ram P, Eseroma R, Taylor R, Zimmet P. Cardiovascular diseases and diabetes mellitus in Fiji: analysis of mortality, morbidity and risk factors. *Bull WHO* 1984; **62**:133–43.
132. Beckles GL, Miller GJ, Kirkwood BR *et al.* High total and cardiovascular disease mortality in adults of Indian descent in Trinidad, unexplained by major coronary risk factors. *Lancet* 1986;**1**:1298–301.
133. Hughes K, Lun KC, Yeo PP. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. I. Differences in mortality. *J Epidemiol Commun Health* 1990;**44**:24–8.
134. Adelstein AD, Marmot MG, Bulusu L. Migrant studies in Britain. *Br Med Bull* 1984;**40**:315–19.
135. McKeigue PM, Marmot MG. Mortality from coronary heart disease in Asian communities in London. *BMJ* 1988;**297**:903.

22 The fetal origins of coronary heart disease

David JP Barker

Hitherto the search for the causes of coronary heart disease (CHD), and the way to prevent it, has been guided by a "destructive" model. The principal causes to be identified are thought to act in adult life and to accelerate destructive processes, for example the formation of atheroma, rise in blood pressure, and loss of glucose tolerance. This model, however, has had limited success. Obesity, cigarette smoking, and psychosocial stress have been implicated, and evidence on dietary fat has accumulated to the point where a public health policy of reduced intake is prudent, if not proven. The effects of modifying adult lifestyle, when formally tested in randomized trials have, however, been disappointingly small.[1] The model has proved incapable of answering important questions. For example, in Western countries the steep increase in the disease has been associated with rising prosperity, so why do the poorest people, and those living in the poorest parts of these countries, have the highest rates?[2]

One explanation for our failure to understand and prevent rising epidemics of CHD is that people are heterogeneous in their responses to environmental influences. Smoking, for example, is harmful to some people but not others. Some statisticians argue that we therefore need much larger studies to overcome this, while geneticists argue that the heterogeneity results from genes as yet unknown. There is, however, another way forward which is to examine the biologic basis of the differences between individuals. The recent discovery that people who develop CHD grew differently to other people during fetal life, infancy, and childhood encourages this view,[3] and has led to a new "developmental" model for the disease.[4,5]

Growth and CHD

Figure 22.1 shows the growth of 357 boys who in later life were either admitted to hospital with CHD or died from it.[3] They belong to a cohort of 4630 men who were born in Helsinki, and their growth is expressed as Z-scores. The Z-score for the cohort is set at zero, and a boy maintaining a steady position as large or small in relation to other boys would follow a horizontal path on the figure. Boys who later developed CHD, however, were small at birth, remained small in infancy but had accelerated gain in weight and body mass index (BMI) thereafter. In contrast, their heights remained below average. Table 22.1 shows hazard ratios for CHD according to size at birth. The hazard ratios fall with increasing birthweight and, more strongly, with increasing ponderal index (birthweight/length^3), a measure of thinness at birth. These trends were found in babies born at term or prematurely and therefore reflect slow intrauterine growth. Table 22.2 shows that the hazard ratios also fell with increasing weight, height, and BMI at age 1 year. Small size at this age predicts CHD independently of size at birth. In a simultaneous analysis with birthweight the hazard ratio associated with each unit decrease in Z-score for weight between birth and 1 year is 1·21 (95% CI 1·08–1·36, $P = 0·001$).

Figure 22.1 Growth of 357 boys who later developed CHD in a cohort of 4630 boys born in Helsinki.[3] BMI, body mass index; CHD, coronary heart disease.

The association between CHD and small size at birth has been shown in studies in Europe, North America, and India.[6–10] The association with poor weight gain in infancy was first shown in Hertfordshire,[6] and confirmed in Helsinki:[3] the strength of the association being similar in the two studies. The association with rapid childhood weight gain was first shown in a study of an older cohort of men

Table 22.1 Hazard ratios for CHD according to body size at birth[3]

	Hazard ratio (95% CI)	Cases (*n*)/ Men (*n*)
Birthweight (kg)		
≤2500	3·63 (2·02–6·51)	24/160
up to 3000	1·83 (1·09–3·07)	45/599
up to 3500	1·99 (1·26–3·15)	144/1775
up to 4000	2·08 (1·31–3·31)	123/1558
>4000	1·00	21/538
P for trend	0.006	
Ponderal index (kg/m^3)		
≤25	1·66 (1·11–2·48)	104/1093
up to 27	1·44 (0·97–2·13)	135/1643
up to 29	1·18 (0·78–1·78)	84/1260
>29	1·00	31/578
P for trend	0·0006	

Abbreviation: CHD, coronary heart disease

Table 22.2 Hazard ratios for CHD according to body size at one year[3]

	Hazard ratio (95% CI)	Cases (*n*)/ Men (*n*)
Weight (kg)		
up to 9	1·82 (1·25–2·64)	96/781
up to 10	1·17 (0·80–1·71)	85/1126
up to 11	1·12 (0·77–1·64)	89/1243
up to 12	0·94 (0·62–1·44)	49/852
>12	1·00	38/619
P for trend	<0·0001	
Height (cm)		
up to 73	1·55 (1·11–2·18)	79/636
up to 75	0·90 (0·63–1·27)	68/962
up to 77	0·94 (0·68–1·31)	87/1210
up to 79	0·83 (0·58–1·18)	64/1011
>79	1·00	59/802
P for trend	0·007	
Body mass index (kg/m^2)		
≤16	1·83 (1·28–2·60)	72/654
up to 17	1·61 (1·15–2·25)	89/936
up to 18	1·29 (0·91–1·81)	83/1136
up to 19	1·12 (0·77–1·62)	59/941
>19	1·00	54/954
P for trend	0·0004	

Abbreviation: CHD, coronary heart disease

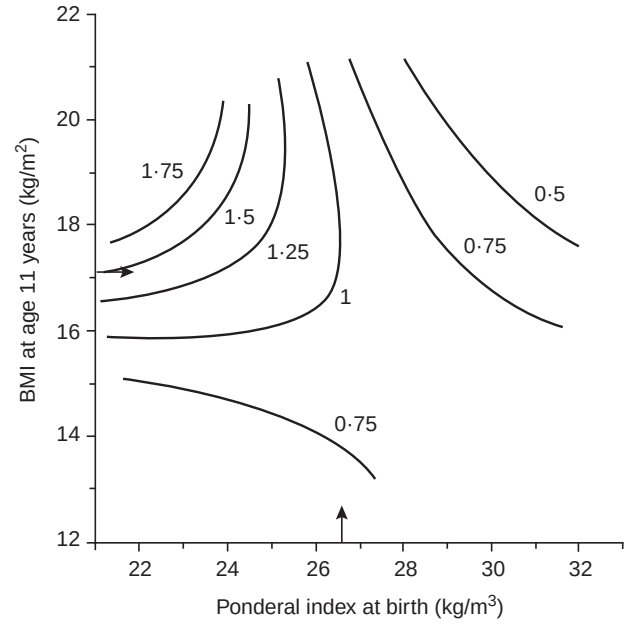


Figure 22.2 Hazard ratios for CHD (coronary heart disease) according to ponderal index at birth and BMI (body mass index) at 11 years. Arrows indicate average values: lines join points with the same hazard ratios.[3]

born in Helsinki,[11] while the association with low rates of height growth is consistent with the known association between the disease and short adult stature in men.[12]

Figure 22.2, based on the same data used in Figure 22.1, shows the combined effects of ponderal index at birth and BMI in childhood in the Helsinki cohort.[3] The figure uses BMI at age 11 years, but BMI at ages around this gives similar results. The lines on the figure join points with the same hazard ratios. For example, the line for the highest ratio, 1·75, is associated with low ponderal index at birth but above average BMI in childhood. Boys who had a low ponderal index at birth increased their risk of CHD if they attained even average BMI in childhood. In contrast, among boys with a high ponderal index, no increased risk was associated with a high childhood BMI. The interaction between ponderal index at birth and BMI in childhood is strongly statistically significant ($P < 0{\cdot}001$). Findings among girls are similar, and again the risk of CHD is determined more by the tempo of weight gain than the body size attained.[13]

Table 22.3 is taken from the total Helsinki cohort which comprises 15 846 men and women of whom 13 517 had their BMI recorded at 11 years of age.[3,11,13] It is based on 1235 patients who were admitted to hospital or died from CHD, and 480 patients who died from the disease. It shows hazard ratios according to birthweight and quarters of BMI at age 11 years. The risk of disease falls with increasing birthweight and rises with increasing BMI. The pattern is similar in the two sexes. The hazard ratios for admissions and deaths are 0·80 (95% CI 0·72–0·90) for each kilogram

Table 22.3 Hazard ratios (95% CI) for CHD according to birthweight and BMI at 11 years: 13 517 men and women born 1924 to 1944

Birthweight (kg)	BMI at 11 years (kg/m^2)			
	up to 15·7	up to 16·6	up to 17·6	>17·6
Hospital admissions and deaths (1235 cases)				
up to 3·0	1·4 (0·8–2·4)	1·6 (0·9–2·8)	1·8 (1·0–3·2)	2·1 (1·1–3·8)
up to 3·5	1·3 (0·7–2·2)	1·5 (0·9–2·7)	1·5 (0·8–2·6)	1·6 (0·9–2·9)
up to 4·0	1·3 (0·7–2·3)	1·4 (0·8–2·4)	1·3 (0·8–2·4)	1·4 (0·8–2·6)
>4·0	1·0	1·2 (0·6–2·3)	1·1 (0·6–2·1)	1·0 (0·5–1·8)
Deaths (480 cases)				
up to 3·0	1·4 (0·5–4·0)	1·8 (0·6–5·1)	2·1 (0·7–6·2)	3·0 (1·0–8·6)
up to 3·5	1·4 (0·5–3·9)	1·9 (0·7–5·2)	2·2 (0·8–6·1)	2·7 (1·0–7·6)
up to 4·0	1·9 (0·7–5·3)	1·8 (0·7–5·2)	1·7 (0·6–4·8)	1·6 (0·6–4·5)
>4·0	1·0	1·4 (0·4–4·6)	1·6 (0·5–4·7)	1·3 (0·4–4·0)

Abbreviations: BMI, body mass index; CHD, coronary heart disease

increase in birthweight and 1·06 (95% CI 1·03–1·10) for each kg/m^2 increase in BMI at age 11 years. The hazard ratios for deaths alone are 0·83 (95% CI 0·69–0·99) and 1·10 (95% CI 1·04–1·16).

Growth and hypertension and type 2 diabetes

There is now a substantial body of evidence showing that people who were small at birth remain biologically different to people who were larger. The differences include an increased susceptibility to hypertension and type 2 diabetes, two disorders closely linked to CHD.[14–17] Table 22.4 is based on 698 patients being treated for type 2 diabetes and 2997 patients being treated for hypertension. It again shows odds ratios according to birthweight and quarters of BMI at age 11 years. The two disorders are associated with the same general pattern of growth as CHD. The risks for each disease fall with increasing birthweight and rise with increasing BMI. The odds ratio for type 2 diabetes is 0·67 (95% CI 0·58–0·79) for each kilogram increase in birthweight and

Table 22.4 Odds ratios (95% CI) for hypertension and type 2 diabetes according to birthweight and BMI at 11 years: 13 517 men and women born 1924 to 1944[3,11,13]

Birthweight (kg)	BMI at 11 years (kg/m^2)			
	up to 15·7	up to 16·6	up to 17·6	>17·6
Men and women (n)				
up to 3·0	991	719	581	560
up to 3·5	1394	1422	1264	1246
up to 4·0	827	984	1122	1110
>4·0	167	254	413	463
Type 2 diabetes (698 cases)				
up to 3·0	1·3 (0·6–2·8)	1·3 (0·6–2·8)	1·5 (0·7–3·4)	2·5 (1·2–5·5)
up to 3·5	1·0 (0·5–2·1)	1·0 (0·5–2·1)	1·5 (0·7–3·2)	1·7 (0·8–3·5)
up to 4·0	1·0 (0·5–2·2)	0·9 (0·4–1·9)	0·9 (0·4–2·0)	1·7 (0·8–3·6)
>4·0	1·0	1·1 (0·4–2·7)	0·7 (0·3–1·7)	1·2 (0·5–2·7)
Hypertension (2997 cases)				
up to 3·0	2·0 (1·3–3·2)	1·9 (1·2–3·1)	1·9 (1·2–3·0)	2·3 (1·5–3·8)
up to 3·5	1·7 (1·1–2·6)	1·9 (1·2–2·9)	1·9 (1·2–3·0)	2·2 (1·4–3·4)
up to 4·0	1·7 (1·0–2·6)	1·7 (1·1–2·6)	1·5 (1·0–2·4)	1·9 (1·2–2·9)
>4·0	1·0	1·9 (1·1–3·1)	1·0 (0·6–1·7)	1.7 (1.1–2.8)

Abbreviation: BMI, body mass index

1·18 (95% CI 1·13–1·23) for each kg/m^2 increase in BMI at age 11 years. The corresponding figures for hypertension are 0·77 (95% CI 0·71–0·84) and 1·07 (95% CI 1·04–1·09). Similarly to CHD the risk of disease is determined not only by the absolute value of BMI in childhood but also by the combination of body size at birth and during childhood.[15,17] It is the tempo of growth as well as the attained body size that determine risk.

Associations between low birthweight and hypertension and type 2 diabetes have been found in other studies.[14–17] There is also a substantial literature showing that birthweight is associated with differences in blood pressure and insulin secretion within the normal range.[14,18,19] These differences are found in children and adults but they tend to be small. For example, a 1 kg difference in birthweight is associated with around 1–2 mmHg difference in systolic pressure.[19] This contrasts with the large effects on hypertension. A possible explanation for this is that, following an intrauterine lesion, regulatory mechanisms may maintain homeostasis for many years until further damage, owing to age, obesity, or other influences, initiates a self-perpetuating cycle of progressive functional loss.[20] Brenner has proposed such a model for the development of hypertension following reduced nephron numbers at birth, a known correlate of low birth weight.[20]

Biologic mechanisms

The association between altered growth and CHD has led to the suggestion that the disease may originate in two phenomena associated with development – "developmental, or phenotypic plasticity" and "compensatory growth". Phenotypic plasticity is the phenomenon whereby one genotype gives rise to a range of different physiologic or morphologic states in response to different environmental conditions during development.[21,22] Such gene–environment interactions are ubiquitous in development. Their existence is demonstrated by the numerous experiments showing that minor alterations to the diets of pregnant animals, which may not even change their offspring's body size at birth, can produce lasting changes in their physiology and metabolism – including altered blood pressure and glucose/insulin and lipid metabolism.[23,24] The evolutionary benefit of phenotypic plasticity is that, in a changing environment, it enables the production of phenotypes that are better matched to their environment than would be possible if one genotype produced the same phenotype in all environments.[22] When undernutrition during development is followed by improved nutrition many animals stage accelerated or "compensatory" growth in weight or length. This restores the animal's body size but may have long-term costs which include reduced life span.[25]

There are several possible mechanisms by which reduced fetal and infant growth followed by accelerated weight gain in childhood may lead to CHD. Babies who are thin at birth lack muscle, a deficiency that will persist as the critical period for muscle growth is around 30 weeks *in utero*, and there is little cell replication after birth.[26] If they develop a high BMI in childhood, they may have a disproportionately high fat mass. This may be associated with the development of insulin resistance, as children and adults who had low birthweight but are currently heavy are insulin resistant.[18,27,28]

Small babies have reduced numbers of nephrons.[20,29] It has been suggested that this leads to hyperperfusion of each nephron and resulting glomerular sclerosis, further nephron death, and a cycle of increasing blood pressure and nephron death. This may be exacerbated if accelerated growth increases the degree of hyperperfusion. This framework fits with the hypothesis that essential hypertension is a disorder of growth with two separate mechanisms, a growth-promoting process in childhood and a self-perpetuating mechanism in adult life.[30]

People who were small at birth also have different vascular structure. One aspect of this is that they have reduced elastin in their larger arteries as a consequence, it is thought, of the hemodynamic changes that accompany growth retardation *in utero*.[31] Elastin is laid down *in utero* and during infancy and thereafter turns over slowly. Reduced elastin leads to less compliant, "stiffer" arteries and to a raised pulse pressure. The gradual loss of elastin, and its replacement with collagen that accompanies aging, tends to amplify the increase in pulse pressure.[31]

The existence of such self-perpetuating cycles, initiated *in utero*, but triggered by aging, obesity, or other influences in later life, would explain the small effects of birth size on blood pressure in the normal population, but its large effects on blood pressure in people with hypertension. Studies in South Carolina showed that hypertensive patients with low birthweight more often require second-line therapy, with calcium-channel blocking agents or ACE inhibitors, as opposed to first-line therapy with diuretics or β blocking agents.[32] The suggestion that among hypertensive patients those with the lowest birthweights have the highest blood pressures has been confirmed in the Helsinki cohort (unpublished).

Findings in Hertfordshire suggest that one of the mechanisms linking poor weight gain in infancy with CHD is altered liver function, reflected in raised serum concentrations of total and low density lipoprotein cholesterol, and raised plasma fibrinogen concentrations.[33,34] Unlike organs such as the kidney, the liver remains "plastic" during its development until the age of around 5 years. Its function may be permanently changed by influences that affect its early growth.[35–37] Support for an important role for liver development in the early pathogenesis of CHD comes from findings in Sheffield.[38] Among men and women, reduced abdominal circumference at birth a measure that reflects reduced liver size, gave stronger predictions of later serum

cholesterol and plasma fibrinogen than any other measure of body size at birth.

Responses to adult living standards

Observations on animals show that the environment during development permanently changes not only the body's structure and function but also its responses to environmental influences encountered in later life.[21] Men who had low birthweight are more vulnerable to developing CHD and type 2 diabetes if they become overweight.[8,17] Table 22.5 shows the effect of low income in adult life on CHD occurrence among men in Helsinki.[39] As expected, men who had a low taxable income had higher rates of the disease.[2,40,41] There is no known explanation for this and it is a major component of the social inequalities in health in Western countries. The effect of low income, however, is confined to men who had slow fetal growth and were thin at birth, defined by a ponderal index less than 26 kg/m^3. Men who were not thin at birth were resilient to the effects of low income on CHD, so that there was a statistically significant interaction between the effects of fetal growth and adult income.

Table 22.5 Hazard ratios (95% CI) for CHD according to ponderal index (kg/m^3) at birth and taxable income in adult life

Household income 1000 marks (pounds sterling) per year	Ponderal index ≤26.0 (n = 1475)	Ponderal index >26.0 (n = 2154)
>140 (15 700)	1·00	1·19 (0·65–2·19)
111–140 (15 700)	1·54 (0·83–2·87)	1·42 (0·78–2·57)
96–110 (12 400)	1·07 (0·51–2·22)	1·66 (0·90–3·07)
76–95 (10 700)	2·07 (1·13–3·79)	1·44 (0·79–2·62)
≤75 (8400)	2·58 (1·45–4·60)	1·37 (0·75–2·51)
P for trend	<0·001	0·75

P for interaction between the effects of ponderal index at birth and income = 0·005.
Abbreviation: CHD, coronary heart disease

One explanation of these findings emphasizes the psychosocial consequences of a low position in the social hierarchy, as indicated by low income and social class, and suggests that perceptions of low social status and lack of success lead to changes in neuroendocrine pathways and hence to disease.[42] The findings in Helsinki seem consistent with this. People who are small at birth are known to have persisting alterations in responses to stress, including raised serum cortisol concentrations.[43] Rapid childhood weight gain could exacerbate these effects.

Strength of effects

The associations between slow fetal, infant, and childhood growth and later CHD are strong and graded. Men and women in the Helsinki cohort who had birthweights above 4 kg and whose body mass index at 11 years was in the lowest quarter, had around half the risk of CHD, type 2 diabetes, and hypertension when compared with people who had birthweights below 3 kg but whose BMI was in the highest quarter (Tables 22.3 and 22.4). Boys who at birth had a ponderal index above 26 kg/m^3 and who at 1 year of age were above the cohort average for BMI (17·7 kg/m^2) and height (76·2 cm) were at half the risk of developing CHD before the age of 65 years.[3] Such findings confirm the strong effects of early growth on later disease.

Statements such as, "Low birthweight explains only a small proportion of diabetes",[44] are not merely statistically incorrect but misrepresent biology in two ways. First, birthweight is an inadequate description of those phenotypic characteristics of a baby that determine its long-term health.[5] One commentator has pointed out that, "Birthweight and ponderal index (as well as body mass index) are crude measures of how fetal nutrition has affected body composition, so the true size of the effect of fetal growth on later disease is hard to measure."[45] Furthermore, the wartime famine in the Netherlands produced lifelong insulin resistance in babies who were *in utero* at the time with little alteration in birthweight.[46]

The second point has been described already. The effect of a high body mass in childhood is conditioned by size at birth (Figure 22.2). The effect of poor living standards in adult life is conditioned by size at birth (Table 22.5). The effects of any single influence cannot therefore be quantified as "small proportion" or "large proportion" of disease. It depends on the path of development that preceded it. The pathogenesis of CHD or type 2 diabetes cannot be understood within a model in which risks associated with adverse influences at different stages of life add to each other.[47] Rather the consequences of adverse influences depend on events at earlier critical stages of development.[3] This embodies the concept of developmental "switches" triggered by the environment.[21] The effects of any particular birthweight on disease will depend not only on the subsequent path of development but also on the path of growth that led to that birthweight. The same weight can be attained by many different paths of fetal growth and each is likely to be accompanied by different gene–environment interactions, though this remains to be demonstrated.[48]

Mothers and babies today

Given the body of evidence showing that CHD, and the related disorders stroke, hypertension, and type 2 diabetes, originate through undernutrition and other adverse

influences *in utero*, followed by accelerated weight gain thereafter, protecting the nutrition and health of young women and their babies must be part of any effective strategy for preventing these diseases. The so-called "fetal origins" hypothesis resulted from studies of the geographical association between CHD and poor living standards in England and Wales, and the realization that a poor intrauterine environment played a major role in this association.[49] Areas of the country with high coronary mortality are characterized historically by poor maternal nutrition and health, reflected in high maternal and neonatal mortality.[50]

As yet we do not know the impact of maternal nutrition on fetal development.[51] The relatively disappointing effects of dietary interventions in pregnancy on birthweight in humans have led to the erroneous view that fetal nutrition is little affected by maternal nutrition.[48] It is becoming clear, however, that the concept of maternal nutrition must be extended beyond the mother's diet in pregnancy to include her body composition and metabolism both during pregnancy and at the time of conception.[51–55] Moreover, birthweight is an inadequate summary measure of fetal experience, and we need a more sophisticated view of optimal fetal development, which takes account of the long-term sequelae of fetal responses to undernutrition. If we are to protect babies, we must also protect girls in childhood and adolescence. Body composition is established by childhood growth, and obesity and eating habits are entrained during childhood and adolescence.

CHD epidemics

As Westernization improves the nutrition of undernourished populations, fetal nutrition improves more slowly than nutrition during childhood or adult life, because the fetus is linked to its mother by a long and precarious supply line that is partly established during the mother's fetal life. It may require more than one generation of improved nutrition before fetal growth responds, whereas child growth responds in one generation. During this phase of economic development, children who were small at birth undergo accelerated, compensatory growth. This is the path of growth that leads to CHD and, it seems, may generate the epidemics of the disease (Figure 22.1). As a consequence of phenotypic plasticity and the costs of compensatory growth, people who follow this path are permanently biologically different and at increased risk of CHD. They are also more vulnerable to the effects of poor living standards (Table 22.5), obesity, and other adverse influences in adult life.

Conclusion

This chapter outlines a new "developmental" model for the origins of CHD and the related disorders type 2 diabetes, hypertension, and stroke. The finding that people who develop these disorders have altered growth *in utero*, during infancy, and childhood provides a new starting point for research. This research, now being carried out in many countries, has two goals: preventing disease in the next generation and treating disease in the present one. The immediate prospect for prevention is through protecting infant growth and preventing accelerated weight gain in children made vulnerable to later disease by small size at birth and during infancy. Ultimately we need to optimize maternal diet and body composition before and during pregnancy. Despite current levels of nutrition in Western countries the nutrition of many fetuses and infants remains suboptimal, because the nutrients available are unbalanced or because their delivery is constrained by the long and vulnerable fetal supply line.[5,48] We need to know more about fetal responses to undernutrition; what they are; what genes underlie them; what induces them; how they leave a lasting mark upon the body; and how this gives rise to CHD.

References

1. Ebrahim S, Davey Smith G. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *BMJ* 1997;**314**:1666–74.
2. Acheson D. *Independent inquiry into inequalities in health*. London: HM Stationery Office, 1998.
3. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Early growth and coronary heart disease in later life: longitudinal study. *BMJ* 2001;**322**:949–53.
4. Barker DJP. Fetal origins of coronary heart disease. *BMJ* 1995;**311**:171–4.
5. Barker DJP. *Mothers, babies and health in later life, 2nd ed*. Edinburgh: Churchill Livingstone, 1998.
6. Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;**2**:577–80.
7. Leon D, Lithell HO, Vagero D *et al.* Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ* 1998;**317**:241–5.
8. Frankel S, Elwood P, Sweetnam P, Yarnell J, Davey Smith G. Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet* 1996;**348**:1478–80.
9. Rich-Edwards JW, Stampfer MJ, Manson JE *et al.* Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;**315**:396–400.
10. Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP. Fetal growth and coronary heart disease in South India. *Lancet* 1996;**348**:1269–73.
11. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJP. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 1999;**318**:427–31.
12. Marmot MG, Shipley MJ, Rose G. Inequalities in death – specific explanations of a general pattern? *Lancet* 1984;**i**: 1003–6.

13.Forsen T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJP. Growth *in utero* and during childhood among women who develop coronary heart disease: longitudinal study. *BMJ* 1999;**319**:1403–7.
14.Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;**303**:1019–22.
15.Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Fetal and childhood growth and hypertension in adult life. *Hypertension* 2000;**36**:790–4.
16.Curhan GC, Chertow GM, Willett WC *et al.* Birth weight and adult hypertension and obesity in women. *Circulation* 1996;**94**:1310–15.
17.Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 2000;**133**: 176–82.
18.Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 1996;**312**:406–10.
19.Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* 2000;**18**:815–31.
20.Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 1994;**23**:171–5.
21.Bateson P, Martin P. *Design for a life: how behaviour develops*. London: Jonathan Cape, 1999.
22.West-Eberhard MJ. Phenotypic plasticity and the origins of diversity. *Ann Rev Ecol Systematics* 1989;**20**:249–78.
23.Kwong WY, Wild A, Roberts P, Willis AC, Fleming TP. Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. *Development* 2000; **127**: 4195–202.
24.Desai M, Hales CN. Role of fetal and infant growth in programming metabolism in later life. *Biol Rev Camb Philos Soc* 1997;**72**:329–48.
25.Metcalfe NB, Monaghan P. Compensation for a bad start: grow now, pay later? *Trends Ecol Evol* 2001;**16**:254–60.
26.Widdowson EM, Crabb DE, Milner RDG. Cellular development of some human organs before birth. *Arch Dis Child* 1972;**47**:652–5.
27.Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;**36**:62–7.
28.Bavdekar A, Chittaranjan S, Fall CHD *et al.* Insulin resistance syndrome in 8-year-old Indian children. Small at birth, big at 8 years, or both? *Diabetes* 1999;**48**:2422–9.
29.Merlet-benichou C, Leroy B, Gilbert T, Lelievre-Pegorier M. Retard de croissance intra-uterin et deficit en nephrons (Intrauterine growth retardation and inborn nephron deficit). *Med/Sci* 1993;**9**:777–80.
30.Lever AF, Harrap SB. Essential hypertension: a disorder of growth with origins in childhood? *J Hypertens* 1992;**10**: 101–20.
31.Martyn CN, Greenwald SE. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet* 1997;**350**:953–5.
32.Lackland DT, Egan BM, Syddall HE, Barker DJP. Associations between birthweight and antihypertensive medication in black and white Americans. *Hypertension* 2002;**39**: 179–83.
33.Fall CHD, Barker DJP, Osmond C, Winter PD, Clark PMS, Hales CN. Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *BMJ* 1992;**304**:801–5.
34.Barker DJP, Meade TW, Fall CHD, Lee A, Osmond C, Phipps K, Stirling Y. Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *BMJ* 1992; **304**:148–52.
35.Gebhardt R. Metabolic zonation of the liver: regulation and implications for liver function. *Pharmacol Ther* 1992;**53**: 275–354.
36.Desai M, Crowther NJ, Ozanne SE, Lucas A, Hales CN. Adult glucose and lipid metabolism may be programmed during fetal life. *Biochem Soc Trans* 1995;**23**:331–5.
37.Kind KL, Clifton PM, Katsman AI, Tsiounis M, Robinson JS, Owens JA. Restricted fetal growth and the response to dietary cholesterol in the guinea pig. *Am J Physiol* 1999;**277**: R1675–82.
38.Barker DJP, Martyn CN, Osmond C, Hales CN, Fall CHD. Growth *in utero* and serum cholesterol concentrations in adult life. *BMJ* 1993;**307**:1524–7.
39.Barker DJP, Forsen T, Uutela A, Osmond C, Eriksson JG. Size at birth and resilience to the effects of poor living conditions in adult life: longitudinal study. *BMJ* 2001;**323**:1273–6.
40.Marmot M, McDowell ME. Mortality decline and widening social inequalities. *Lancet* 1986;**2**:274–6.
41.Macintyre K, Stewart S, Chalmers J *et al.* Relation between socio-economic deprivation and death from a first myocardial infarction in Scotland: population based analysis. *BMJ* 2001; **322**:1152–3.
42.Marmot M, Wilkinson RG. Psychosocial and material pathways in the relation between income and health: a response to Lynch *et al. BMJ* 2001;**322**:1233–6.
43.Phillips DIW, Walker BR, Reynolds RM *et al.* Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension* 2000;**35**:1301–6.
44.Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;**414**: 782–7.
45.Robinson R. The fetal origins of adult disease. *BMJ* 2001;**322**: 375–6.
46.Ravelli ACJ, van der Meulen JHP, Michels RPJ *et al.* Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998;**351**:173–7.
47.Kuh D, Ben-Shlomo Y. *A life-course approach to chronic disease epidemiology*. Oxford: Oxford University Press, 1997.
48.Harding JE. The nutritional basis of the fetal origins of adult disease. *Int J Epidemiol* 2001;**30**:15–23.
49.Barker DJP, Osmond C. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. *Lancet* 1986;**1**:1077–81.

50. Barker DJP, Osmond C. Death rates from stroke in England and Wales predicted from past maternal mortality. *BMJ* 1987; **295**:83–6.
51. Godfrey KM, Barker DJP. Fetal programming and adult health. *Public Health Nutr* 2001;**4**(2B):611–24.
52. Mi J, Law CM, Zhang KL, Osmond C, Stein CE, Barker DJP. Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. *Ann Intern Med* 2000;**132**:253–60.
53. Campbell DM, Hall MH, Barker DJP, Cross J, Shiell AW, Godfrey KM. Diet in pregnancy and the offspring's blood pressure 40 years later. *Br J Obstet Gynaecol* 1996;**103**: 273–80.
54. Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJP. High-meat, low-carbohydrate diet in pregnancy: relation to adult blood pressure in the offspring. *Hypertension* 2001;**38**:1282–8.
55. Forsen T, Eriksson JG, Tuomilehto J, Teramo K, Osmond C, Barker DJP. Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. *BMJ* 1997;**315**:837–40.

23 Molecular genetics of cardiovascular disorders

AJ Marian, Robert Roberts

The sequencing of the human genome is likely to be a landmark study of millennium proportions. The implications for cardiology of knowing the sequence of the human genome are many, among which the most obvious is identifying the gene responsible for familial disorders. Abnormalities of the heart and blood vessels are the most common of human birth defects, occurring in about 1% of live births.[1,2] Genetic diagnosis and management are expected to be routinely incorporated into the practice of cardiology by the end of this decade.[3] Knowing the etiology and understanding the pathogenesis of genetic disorders is most likely to improve the diagnosis, prevention and treatment of those disorders, and in addition often provides fundamental insights into acquired disorders that simulate the phenotype. A good example is that of familial hypercholesterolemia, in which there is a defective receptor for cellular uptake of cholesterol.[4] This confirmed that cholesterol was a major factor in coronary artery disease and subsequently led to unraveling of the synthesis, transport and degradation of cholesterol. The standard treatment today for coronary artery disease, both familial and acquired, is the use of statins to lower the cholesterol. The identification of a gene responsible for disease and its associated network should provide new targets for which specific therapy can be developed to treat the acquired form of the disease. It must be emphasized that practically all genetic disorders have an environmental component, and the resulting phenotype is usually due to an interaction between the gene (genotype) and the environment (phenotype).[5] An obvious example of the importance of environmental factors is that of familial hypertrophic cardiomyopathy. This is a single gene disorder that is transmitted in an autosomal dominant fashion, giving rise to a phenotype of left ventricular hypertrophy.[6] The same genetic defect is present in the same abundance in the right ventricle, yet the disease is seldom manifested in the right ventricle. This would imply that the high pressure of the left ventricle is an important stimulus in the pathogenesis of the phenotype of hypertrophy. Genetic disorders are considered in three categories, namely, chromosomal abnormalities, single gene disorders and polygenic disorders. Chromosomal abnormalities are usually detected by the pediatric cardiologist while the infant is still very young. Examples of adult forms of chromosomal abnormality would be Turner's syndrome. In this discussion, emphasis will be on single gene disorders because we do not yet have much information on polygenic disorders; however, the future promise will be with polygenic disorders.

Mutations responsible for single gene disorders

Inherited diseases caused by an abnormality in a single gene are inherited in a predictable pattern termed mendelian transmission. Each individual has two copies of the gene, one from each parent, referred to as alleles. The odds of inheriting the mother's allele rather than the father's are by chance alone, that is, 50%. Genes are units of heredity that are passed on and transmitted independently to the next generation. The two genes, separated on different chromosomes, assort themselves independently through the process of crossover between chromosomes. The greater the distance between two loci, the more likely they are to be separated during genetic transmission. The same disease may be due to multiple mutations in the same gene (allele heterogeneity), or to a single or multiple mutation(s) in two or more genes (locus heterogeneity). It is important to bear in mind, however, that within any one family the gene and the mutations responsible for the disease are the same, and that only rarely would two genes be transmitted for the same disease. Mutations involving only a single nucleotide are known as point mutations and are responsible for 70% or more of all adult single gene disorders (Table 23.1). A point mutation may be due to substitution of one nucleotide for another (missense mutation); or it may change the amino acid to a stop signal which will truncate the protein (truncated mutant); or it may eliminate a stop signal so that the protein is elongated (elongated mutant). Nucleotides may be deleted or added, which will result in a different reading from left to right, and the gene may be read entirely differently, resulting in a non-functioning product (nonsense).

Patterns of inheritance of single gene disorders

Autosomal dominant disorders are so named because the disease occurs despite a mutation in only one of the alleles.

Table 23.1 Cardiac diseases with an identified genetic locus or gene Grade A1a

Cardiomyopathies	Chromosomal locus
Hypertrophic cardiomyopathy	1q3, 3p, 7q3, 11q11, 12q, 14q, 15q2, 19p3
Dilated cardiomyopathy without conduction defects	1q32, 6q1, 9q12, 10q24, 15q1, 2q31
Dilated cardiomyopathy with conduction defects	1q1, 3p22, 6q23
Arrhythmogenic right ventricular dysplasia	1q12, 2q32, 14q12, 14q23, 3p23
Mitochondrial cardiomyopathies	
	Mitochondrial DNA
Cardiac septal defects	
Holt–Oram syndrome	12q2
Di George syndrome	22q
Noonan syndrome	12q
Aortic diseases	
Aneurysms	11q23–24
Supravalvular aortic disease	9q
Marfan's syndrome	15q
Conduction disorder	
Familial heart block	19q13, 1q32
Ventricular arrhythmias	
Long QT Syndrome	3p21, 4q24, 7q35, 11p15, 21q22
Brugada syndrome	3p21
Idiopathic VT	3p21
Atrial arrhythmias	
WPW	7q3
Atrial fibrillation	9q

Males and females are equally affected, with about 50% of the offspring being expected to have the defective gene (Figure 23.1). The following features are characteristic of autosomal dominant inheritance: each affected individual has at least one affected parent; 50% of the offspring will have the defective gene; normal children of an affected individual bear only normal offspring; males and females are equally affected; both sexes are equally likely to transmit the abnormal allele to male and female offspring, and male to male transmission occurs; vertical transmission through successive generations occurs; and it is typical for autosomal dominant disorders to have a delayed age of onset and variable clinical expression. Autosomal dominant is the main form of inheritance in adult cardiovascular disorders, and examples would be familial hypertrophic cardiomyopathy (HCM) and long QT syndrome. Autosomal recessive inheritance, in contrast, requires both alleles to be defective and so both parents must have the defective gene. The following are characteristics: parents are clinically normal heterozygotes; alternate generations are affected, with no vertical transmission; both sexes are affected with equal frequency; and each offspring of heterozygous carriers has a 25% chance of being affected, a 50% chance of being an unaffected carrier and a 25% chance of inheriting only normal alleles. Examples of autosomal recessive disorders affecting the heart include Jervell and Lang-Nielson long QT syndrome and Pompe's disease.

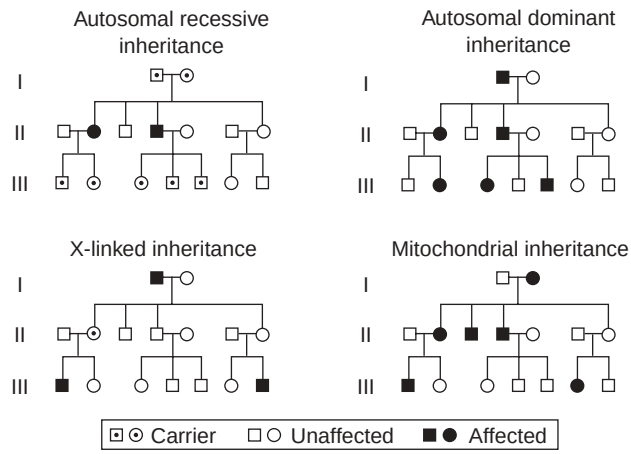


Figure 23.1 Mendelian patterns of inheritance

X-linked inherited disorders are caused by genes located on the X chromosome. Because a female has two X chromosomes, she may carry either one mutant allele or two mutant alleles; the trait may therefore display dominant or recessive expression. Because males have only a single X chromosome they are likely to display the full syndrome

whenever they inherit the abnormal gene from their mother. Hence, the terms X-linked dominant and X-linked recessive apply only to the expression of the gene in females. As males must pass on their Y chromosome to all male offspring, they cannot pass on mutant X alleles to their sons; therefore, no male to male transmission of X-linked disorders can occur. All females receiving a mutant X chromosome are thus carriers, and those who become affected clinically are usually homozygous for the defective gene. The characteristic features of X-linked inheritance are as follows: (1) no male to male transmission; (2) all daughters of affected males are carriers; (3) sons of carrier females have a 50% risk of being affected and daughters have a 50% chance of being carriers; (4) affected homozygous females occur only when an affected male and a carrier female have children; and (5) the pedigree pattern in X-linked recessive traits tends to be oblique because of the occurrence of the trait in the sons of normal carrier sisters of affected males. Examples of X-linked disorders of the heart include X-linked cardiomyopathy, Barth's syndrome and muscular dystrophy.

Another uncommon inheritance pattern is that of mitochondrial abnormalities. Mitochondria have their own genome of about 37 genes contained in 16K of DNA in a single circular chromosome. Most of the disorders involve oxidative phosphorylation and are usually evident very early in life. Phenotypes due to mitochondrial DNA mutations are transmitted by maternal inheritance only, as the ovum has mitochondria but the sperm does not. The characteristic features of mitochondrial disease inheritance include: equal frequency and severity of disease for each sex; transmission through females only, with offspring of affected males being unaffected; all offspring of affected females may be affected; extreme variability of expression of disease within a family; phenotypes may be age dependent; and organ mosaicism is common. An example of mitochondrial inherited cardiac disease is the cardiomyopathy of Kearns–Sayre syndrome.

Polygenic inheritance of cardiac disease

Many important cardiac disorders are due not to a single gene but rather to several genes, which increases susceptibility to the disease; examples are hypertension and coronary artery disease. There is ample evidence from dizygotic and monozygotic twins, as well as endemic populations, to indicate that such diseases have a significant genetic predisposition,[7] owing to the inheritance of multiple genes. However, each gene may contribute less than 5% susceptibility to the phenotype, and thus most computer models for mapping and detecting genes require a much more dominant effect, such as in single gene disorders. There is a lack of mathematical models for detecting a 5% influence on a disease. It is highly likely that 20 or 30 genes contribute to the susceptibility of diseases such as atherosclerosis or hypertension. The small effect of any one gene requires a sample size of several thousand. The sequencing of the human genome in itself will accelerate finding the susceptible genes, but the recent hope for polygenic diseases is with the new chromosomal markers referred to as single nucleotide polymorphisms (SNP). The new markers (SNP) distributed throughout the human genome are present about every 1000 base pairs (bp), as opposed to conventional markers at every 10 million bp.[8] Thus, as the markers are so close they can detect even a 5% effect. This is still a formidable task, in that one must genotype for several hundred thousand markers, but the sample size can be less. Automation is now available for high throughput of SNP. It is hoped that some of the SNP represent mutations that alter susceptibility to polygenic diseases. The SNP will at the very least serve as signposts to map genes responsible for susceptibility to disease. The combination of technology for high-throughput genotyping of thousands of markers, together with high-throughput sequencing, may enable one to map and identify genes responsible for polygenic disorders. Several genes have been identified to add susceptibility to disorders such as hypertrophy and coronary artery disease, but primarily from association through case studies, which remain suspect until there is a proven causative relationship. Examples would be the DD allele of angiotensin-converting enzyme, which predisposes to hypertrophy and sudden death,[9] and alleles of fibrinogen that predispose to thrombosis.[10]

Family history and inherited cardiovascular disorders

Diseases that segregate in a particular family are identified from the family history. Obtaining a careful family history has not been a priority for the cardiologist and so represents an area not hitherto emphasized. Recognizing the importance of family history in single gene disorders, and also in family cluster disorders such as atherosclerosis and hypertension, must be at the fore-front of the history and physical examination. Certain ethnic groups may direct specific testing, such as for hemoglobinopathies in populations from the Mediterranean, or sickle cell disease in African Americans. The first individual to be recognized as having the disease is usually referred to as the proband. Once a proband is recognized, information should be collected on all first, second and third degree relatives. The information should include also medical problems, pregnancies, and information on deceased relatives. Frequently, it is important to pursue miscarriages, birth defects and other problems that might appear to be unrelated. A pedigree should be constructed to determine the pattern of inheritance, analogous to those shown in Figure 23.1.

Genetic counseling

Once it has been established that there is a familial disease it is important to provide information appropriate to the level of education of the individual or parents. Every attempt must be made to explain the disease, so that important issues are understood by the individual. An attempt must be made to outline the diagnosis, prognosis if known, and mode of transmission, together with a discussion of the psychological and social issues. It is also important in young couples to emphasize the mode of transmission and their chances of passing on the disease, as well as the availability of prenatal diagnosis if appropriate. The information must be provided in a non-judgmental and unbiased manner. The family must be able to make a decision with respect to their religious, social and cultural background. It is sometimes frustrating for the counselor but personal bias must be avoided. Sometimes the issues are extremely sensitive and the options must be presented with concern and compassion while still remaining non-directional.

Single gene cardiovascular disorders

Several cardiovascular disorders have been shown to have a familial basis. These diseases cover a wide spectrum, from structural defects such as familial atrial septal defects to functional defects such as long QT syndrome (Table 23.1). For most of these diseases the chromosomal location (locus) has been mapped but the gene has not yet been identified. However, diseases such as the cardiomyopathies, particularly hypertrophic cardiomyopathy, have undergone major investigations, with elucidation of the pathogenesis. Animal models of human familial HCM have been developed and therapies have been evaluated. There is considerable progress in the identification of genes responsible for ventricular arrhythmias, particularly the long QT and Brugada syndromes. It is still premature to manage these disorders based on their genetic etiology. This is partly because genetic screening is not available and the populations studied have not yet been adequately characterized to provide generalized approaches to treatment. A few of these disorders will be discussed to indicate progress in improving diagnosis, prevention and treatment. It also indicates the trends for the future, when most of these genes will be identified and data be available on the pathogenesis and prognosis as they relate to the specific molecular defects.

Long QT syndrome

Several mutations have been identified in the sodium or potassium channel genes responsible for long QT syndrome, which predisposes to ventricular arrhythmias and sudden death. The inherited form of long QT syndrome is caused by discrete mutations in genes that encode ion channels. Several mutations have been identified in the sodium channel gene *SCN5A*.[11–13] The long QT associated mutations in *SCN5A* are associated with increased sodium flux and prolong depolarization. The mechanism believed to be responsible for the arrhythmias is an imbalance between the inward and outward currents during the plateau of the action potential. Most of the mutations in the sodium channel appear to be gain of function. The pattern of inheritance is most frequently autosomal dominant, although a rare recessive form has also been identified.

Several mutations have also been noted in potassium channels, which reduce potassium flux through a loss of function.[12,14] These mutations appear to have a dominant negative effect. Rarely, the QT syndrome is inherited in an autosomal recessive manner and may be associated with deafness, such as in the Jervell and Lang-Nielsen syndrome. This led to the recognition that the inward potassium current is necessary for endolymph production in the inner ear.[15] There is extensive phenotypic variability among these various genes and mutations, and within the same family, in keeping with other genes, there are many modifiers yet to be recognized to properly interpret genotype/phenotype correlations.

Another form of cardiac channelopathy is idiopathic ventricular fibrillation. The electrocardiogram may be normal, although some individuals have an associated electrocardiographic abnormality that includes ST segment elevation V1–3 together with right bundle branch block, referred to as Brugada syndrome.[16–18] Mutations responsible for this disease have been linked to *SCN5A* with dominant inheritance. There is at present no proven mechanism for the ventricular arrhythmias; however, it is believed to be due to inhomogeneity between the epicardium and the endocardium during repolarization, which leads to reentry.

Genetic studies have led to improved treatment for some of these disorders. Patients with long QT syndrome due to mutations in *SCN5A* can be treated by sodium channel blockers such as mexelitine. These drugs block the mutant sodium channel's current and have been shown to be selective and effective. No specific treatment for long QT syndrome due to potassium channels has yet been identified, except for oral potassium supplementation and automatic indwelling defibrillators. It is expected that many more of these channelopathies will be identified, and it is reasonable to assume that most of the channels responsible for atrial and ventricular currents will be discovered through mutations. A locus for familial atrial fibrillation has been mapped to 10q32 but the gene has yet to be identified.[19] A gene responsible for an uncommon form of Wolff–Parkinson–White (WPW) syndrome was identified and shown to be *AMPK*.[20,21] Several mutations in *AMPK* have since been identified[22–24] as inducing WPW, which is associated with hypertrophic cardiomyopathy, conduction disorders and a high incidence of atrial fibrillation. It appears that *AMPK* induces abnormalities in glycogen which leads to all three phenotypes.

Familial hypertrophic cardiomyopathy

Clinical and pathological features of HCM

HCM is an autosomal dominant disease defined by cardiac hypertrophy in the absence of an increased external load (unexplained hypertrophy). Patients exhibit protean clinical manifestations, ranging from minimal or no symptoms to severe heart failure and sudden cardiac death (SCD). The clinical manifestations often do not develop until the third or fourth decades of life and the majority of patients are asymptomatic or mildly symptomatic. HCM is a relatively benign disease with an estimated annual mortality rate of <0·7% in the adult population.[25] However, SCD is often the first and tragic manifestation of HCM in the young.[26] HCM is the most common cause of SCD in young competitive athletes, accounting for approximately one third of all SCD cases.[26] The main pathological features of HCM include myocyte hypertrophy and disarray, interstitial fibrosis and, to a lesser extent, thickening of the media of intramural coronary arteries. Whereas hypertrophy and fibrosis are the common responses of the heart to all forms of injury, myocyte disarray is considered the pathological hallmark of HCM.[27] Cardiac hypertrophy and interstitial fibrosis are the major determinants of mortality and morbidity in HCM.[28–32] In those with mild or no cardiac hypertrophy, myocyte disarray is a major predictor of SCD.[33]

Molecular genetics

HCM is a genetic disease with an autosomal dominant mode of inheritance. A family history is present in approximately two thirds of all index cases (familial HCM) and the remainder are sporadic. Sporadic cases are also caused by genetic mutations, albeit *de novo*, and affected individuals transmit the mutation and disease to their offspring in the same patterns as familial cases. HCM usually is due to mutations in at least 10 contractile sarcomeric proteins (Table 23.2). Over 100 mutations in 10 genes have been identified.

Genotype/phenotype correlations

Genotype/phenotype correlation studies suggest that causal mutations affect the magnitude of cardiac hypertrophy and the risk of SCD (Figure 23.2). Mutations in β-MyHC are generally associated with an early onset and more extensive hypertrophy and a higher incidence of SCD.[34–36] In contrast, mutations in MyBP-C are associated with a low penetrance, relatively mild hypertrophy, late onset of clinical manifestations and a low incidence of SCD.[34–38] Mutations in cTnT are usually associated with a mild degree of hypertrophy but a high incidence of SCD and more extensive disarray.[33,39,40] Mutations in α tropomyosin are generally associated with a benign phenotype and mild left ventricular hypertrophy. However, a phenotype of mild hypertrophy and a high incidence of SCD also has been described.[41] Mutations in essential and regulatory myosin light chains have been associated with midcavity obstruction in HCM and skeletal myopathy in some,[42] but not in others.[43] Mutations in titin[44] and α actin[45–47] have been observed in a small number of families.

The results of genotype/phenotype correlation studies are subject to a large number of confounding factors, such as the small size of the families; the small number of families with identical mutations owing to the low frequency of each mutation; variability in the phenotypic expression in affected individuals within the same family or among families with identical mutations; the influence of modifier genes;[48] the influence of non-genetic factors; and, rarely, homozygosity for causal mutations and compound

Table 23.2 Causal genes for HCM: genes coding for sarcomeric proteins Grade A1a

Gene	Symbol	Locus	Frequency %	Mutations
β-Myosin heavy chain	*MYH7*	14q12	~35	>70, predominantly missense mutations
Myosin binding protein-C	*MYBPC3*	11p11·2	~20	>40, predominantly splice junction and insertion/deletion mutations
Cardiac troponin T	*TNNT2*	1q32	~20	>15, mostly missense
α-Tropomyosin	*TPM1*	15q22·1	~5	>5 missense mutations
Cardiac troponin I	*TNNI3*	19p13·2	~5	3 missense and 1 deletion mutations
Essential myosin light chain	*MYL3*	3p21·3	<5	2 missense mutations
Regulatory myosin light chain	*MYL2*	12q23-24·3	<5	7 missense and 1 truncation mutations
Cardiac α-actin	*ACTC*	15q11	<5	2 missense mutations
Titin	*TTN*	2q24·1	<5	1 missense mutation
α-Myosin heavy chain	*MYH6*	14q1	Rare	1 missense and 1 rearrangement mutation
Cardiac troponin C	*TNNC1*	3p21·3-3p14·3	Rare	1 missense mutation in a patient with HCM

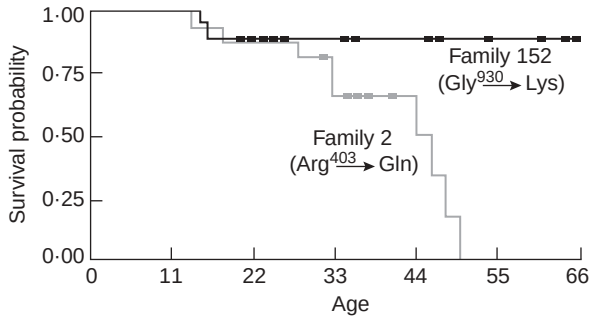


Figure 23.2 Stratification of risk according to mutation. Shown here are two different mutations in the β-MHC gene. The mutation in Family 152 is associated with essentially normal life span, whereas Family 2 has a mean life span of about 28 years. This emphasizes the potential prognostic significance of individual mutations.

mutations.[49–51] Correlations between the small number of patients studied suggest prognostic stratification by the mutations, but caution must be exercised until larger studies are performed[52] (Figure 23.2).

Pathogenesis of HCM

The initial defects induced by the mutant sarcomeric proteins are diverse. They comprise impaired actomyosin interaction and cardiac myocyte contractile performance, altered Ca^{2+} sensitivity, reduced ATPase activity, sarcomere dysgenesis, altered subcellular localization and altered stoichiometry of the sarcomeric protein.[53] However, despite the diversity of the initial defects, the final phenotype is hypertrophy, fibrosis and disarray. We have proposed that a common link between the initial defect and the final phenotype is impaired cardiac myocyte contractile function,[54] which increases myocyte stress and leads to the activation of stress-responsive intracellular signaling kinases and trophic factors. Release of trophic factors activates the transcription machinery, leading to cardiac hypertrophy, interstitial fibrosis and other histological and clinical phenotypes of HCM.[54] Accordingly, myocyte hypertrophy and disarray, interstitial fibrosis and thickening of the media of intramural coronary arteries are considered "secondary" phenotypes and thus potentially reversible. In addition, the severity of the phenotype is affected by factors other than the causal genes, that is, the environmental factors and the modifier genes. In support of this hypothesis, we have shown that stress-responsive signaling kinases ERK1 and 2 are activated in the heart of transgenic animal models of HCM, and that cardiac hypertrophy and interstitial fibrosis could be reversed or attenuated by pharmacologic interventions discussed later.

Dilated cardiomyopathy (DCM)

Genetics of dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary disease of the myocardium, diagnosed by a decreased left ventricular ejection fraction (<0·45) and an increased left ventricular cavity size (end diastolic diameter $>2{\cdot}7\,cm/m^2$). Clinical features of DCM are those of heart failure, including syncope, cardiac arrhythmias and SCD. The etiology of DCM is diverse and a family history is present in approximately half of all index cases.[55–57] In such cases DCM is therefore considered a familial disease. The remainder have no family history and thus DCM is considered sporadic. A significant number of patients with DCM and their affected relatives are asymptomatic and are mistakenly considered normal, unless subjected to clinical and genetic investigation.[55] Familial DCM is commonly inherited as an autosomal dominant disease[55] which clinically manifests during the third and fourth decades of life. An X-linked and an autosomal recessive pattern of inheritance also occur, which often manifest early and often during the second decade of life. The mode of transmission is matrilineal when DCM occurs because of mutations in the mitochondrial DNA. DCM also occurs in conjunction with the triplet repeat syndromes and follows their pattern of inheritance.

DCM is an extremely heterogeneous disease (Table 23.3). Despite the diversity of the causal genes and mutations, the vast majority of them encode for proteins that are either components of the myocardial cytoskeleton or support it. Therefore, DCM is considered a disease of cytoskeletal proteins. Given the diversity of causal genes and mutations, it is not surprising that each causal gene accounts for a very small fraction of familial DCM and that none predominates. Collectively, the mapped genes account for approximately half of all familial DCM cases, and in a significant number of families although the chromosomal loci have been mapped, the causal genes remain unidentified. The gene encoding cardiac α actin (*ACTC*) was the first causal gene identified for familial DCM, with an autosomal dominant mode of inheritance.[58] The authors proposed that defects in the cytoskeletal proteins could, by impairing the transmission of contractile force, cause DCM.[58] Recently, mutations in two additional components of the sarcomere, namely the β myosin heavy chain and cardiac troponin T, were found in patients with DCM.[59] As discussed earlier, mutations in *ACTC*, *MYH7* and *TNNT2* are also known to cause HCM. Thus, these findings suggest that the topography of the mutations within the sarcomeric proteins plays a significant role in determining the ensuing clinical phenotype. Mutations in cytoskeletal proteins δ sarcoglycan,[60] metavinculin and dystrophin[61] are also known to cause DCM. Mutations in α sarcoglycan (adhalin) cause an autosomal recessive form of DCM that occurs in conjunction with limb–girdle muscular dystrophy. An intriguing causal gene for familial DCM is the

Table 23.3 Genetic causes of dilated cardiomyopathy Grade A1a

Gene	Symbol	Locus	Frequency	Phenotypes
Cardiac α-actin	*ACTC*	15q11-14	Low	DCM or HCM, based on topography of the mutation and probably genetic background
β-Myosin heavy chain	*MYH7*	14q11-13	Low	DCM or HCM, based on topography of the mutation and probably genetic background
Cardiac troponin T	*TNNT2*	1q32	Low	DCM or HCM, based on topography of the mutation and probably genetic background
δ-Sarcoglycan	*SGCD*	5q33-34	Low	DCM
Dystrophin	*DMD*	Xp21	Low	X-linked DCM
Lamin A/C	*LMNA*	1p21.2	Low	DCM and conduction defect Emery–Driefus muscular dystrophy, lipodystrophy (Dunnigan variety)
Taffazin (G4.5)	*TAZ*	Xq28	Low	DCM, ventricular non-compaction, skeletal myopathy, mitochondrial abnormalities
Desmin	*DES*	2q35	Low	Desmin-related myopathies
αB-Crystallin	*CRYAB*	11q35	Low	Desmin-related myopathy
Desmoplakin	*DSP*	6p23-25	Low	Recessive DCM
?	?	1q32	?	
?	?	2q14-22	?	DCM + conduction defect
?	?	2q31	?	
?	?	3p22-25	?	DCM + conduction defect
?	?	6q23-24	?	DCM + hearing loss
?	?	9q13-22	?	DCM + conduction defect + adult-onset limb–girdle dystrophy
?	?	10q21-23	?	DCM + MVP

lamin A/C gene,[62–64] which encodes a nuclear envelope protein. The observed phenotype resulting from mutations in the rod domain of lamin A/C is progressive conduction disease, atrial arrhythmias, heart failure and SCD. Finally, mutations in the intermediary filament desmin and its associated protein α/B crystallin have been identified in patients with DCM.[65–67] Often such mutations lead to a phenotype of cardiac and skeletal myopathy referred to as desmin-related myopathy.[66] Collectively, these findings suggest that mutations affecting the integrity of the cytoskeleton can cause DCM. Systematic genotype/phenotype studies are not yet available.

Pathogenesis of DCM

Mutations in cardiac α actin, β myosin heavy chain, cardiac troponin T and other cytoskeletal proteins impart a dominant-negative effect on transmission of the contractile force to the extracellular matrix proteins.[58] Mutations in the dystrophin gene lead to a decreased expression level of dystrophin, a major cytoskeletal protein in skeletal and cardiac muscles. Decreased expression of dystrophin impairs efficient mechanical coupling and myocyte shortening. In X-linked DCM, the severity of the clinical phenotype correlates inversely with the expression level of dystrophin. The pathogenesis of DCM resulting from mutations in desmin and α/B crystallin involves the deposition of desmin, and α/B crystallin aggregates in the myocardium. The molecular pathogenesis of DCM caused by mutations in lamin A/C or emerin remains largely unknown. It is likely that lamin A/C is also involved in maintaining the integrity of the cytoskeleton. The pathogenesis of cardiomyopathies in patients with the triplet repeats syndrome is also unclear. Expansion of the CTG (CUG in mRNA) repeats in the 3′ untranslated region of the myotonin protein kinase gene could lead to unstable mRNA and decreased expression of the protein. It is also possible that proteins that bind to CUG repeats may be necessary for proper transcription, splicing, translation and nuclear transport of mRNAs of cardiac genes.

Arrhythmogenic right ventricular dysplasia (ARVD)

ARVD is the primary abnormality of the myocardium, characterized by a progressive loss of myocytes, fatty infiltration and replacement fibrosis, which occur predominantly in the right ventricle.[68] ARVD, also named arrhythmogenic right ventricular cardiomyopathy, often manifests as ventricular arrhythmias originating from the right ventricle. A characteristic electrocardiographic pattern is the presence of ε wave,

and less characteristic findings are depolarization/repolarization abnormalities in the right precordial leads. The age of onset of the disease is variable but commonly ARVD manifests with minor arrhythmias during adolescence, progressing to serious ventricular arrhythmias during the third and fourth decade of life leading to SCD. In Italy, ARVD is a relatively common cause of SCD in the young.[69] Gradual fibrofatty infiltration of the myocardium leads to regional and global right ventricular dysfunction and, less frequently, left ventricle failure. In advanced stages both ventricles are involved and heart failure is the predominant manifestation.

Several loci for ARVD have been mapped, including loci on 14q23-q24 (ARVD1),[70] 1q42-q43 (ARVD2),[71] 14q12-q22 (ARVD3),[72] 2q32-q32·3 (ARVD4),[73] 3p23 (ARVD5)[74] and 10p14-p12 (ARVD6).[75] The causal gene for the ARVD2 locus on chromosome 1q42-q43 has been identified as the cardiac ryanodine receptor gene (*RYR2*).[76] Mutations in *RYR2* have been identified in four independent families with ARVD.[76] It is also likely that catecholaminergic (stress-induced) ventricular tachycardia, although it classically occurs in a structurally normal heart, is a phenotypic variant of ARVD, as mutations in *RYR2* have been identified in such patients.[77] Naxos disease, so named because it was first reported from the island of Naxos in Greece, is an autosomal recessive disorder characterized by ARVD, palmoplantar keratoderma and other ectodermal features, such as woolly hair.[78] Recently, a 2 bp deletion mutation in the plakoglobin gene, located on 17q21, was identified in patients with Naxos disease.[78]

Genetics of hypertension

Hypertension is among the top three or four most common diseases worldwide. It is an independent risk factor for cardiac morbidity and mortality and a major stimulus for cardiac hypertrophy, which itself significantly increases susceptibility for sudden cardiac death. Hypertension, as indicated previously, is primarily a polygenic disease. It is expected that there are several genes that increase susceptibility to developing hypertension. These genes interact with the environment, and the onset of hypertension is usually age dependent, with 20–30% of the population being hypertensive in their elderly years. Identification of the susceptibility genes remains an elusive goal and is likely to occupy most of the present decade. A recent study emphasizes the importance of identifying the genes responsible for hypertension. Geller and his associates[79] recently identified a family with early onset of hypertension. The disease segregates as a dominant mendelian disorder. A mutation was identified in the mineralocorticoid receptor. The patient had severe hypertension, decreased plasma renin activity, decreased serum aldosterone, and no other underlying cause for hypertension. The mutation was a missense in which leucine was substituted for serine at codon 810, and is in the domain of the receptor that binds to the hormone. Normally, 21-hydroxyl group steroids are necessary to activate this receptor. In contrast, the receptor with the mutation seems to activate itself and does not require 21-hydroxyl stimulation. The potent antagonist spironolactone, which normally would block mineralocorticoid activity in normal individuals, acts as an agonist in individuals with this mutation, causing hypertension and further activating mineralcorticoid activity. This is quite a drastic and unexpected change for the mutation not only to have a positive effect, but to change the receptor to respond to hormones and drugs in a manner opposite to normal. Another important observation was in pregnancy, in which about 6% of individuals develop hypertension and may proceed to pre-eclampsia. It was noted that progesterone, which normally does not activate the mineralcorticoid receptor, does so in individuals with the mutation. This has significant implications in pregnancy, as progesterone levels are normally increased 100-fold and thus women with this mutation would be expected to develop hypertension. Furthermore, treatment with spironolactone would increase the hypertension and may precipitate pre-eclampsia. Two of the carriers in this family had undergone pregnancies all complicated by hypertension. It is also of note that while pregnant, these women had a decreased serum potassium and aldosterone levels, in keeping with the expected abnormal response induced by the mutation. Although this is not one of the polygenic causes of hypertension, it emphasizes the pathogenetic mechanism involved and has clearly improved the treatment of this condition, which is particularly important in pregnancy. It is hoped that other mendelian disorders causing hypertension will be identified, as although they form a very small percentage of the etiology of hypertension compared to polygenic forms, they could have significant implications for prevention and treatment.[79]

Coronary artery disease

Although atherosclerosis is a polygenic disease, certain susceptible genes have been ascertained through association studies in populations enriched for coronary artery disease. The results of these studies are still regarded as preliminary until causation is proved. Nevertheless, these susceptibility genes have shed light on the pathogenesis and are likely to be incorporated into future genetic profiles for risk stratification and treatment. There are obviously several components to coronary artery disease, namely, lipids and coagulation factors. The list of potential candidate genes for coronary atherosclerosis is extensive (Table 23.4). Two examples, *ABCA1* and *CYBA*, are discussed briefly. Plasma levels of high density lipoprotein C (HDL-C) and its apolipoprotein A1 are under tight control of genetic factors, which are largely

Table 23.4 Selected candidate genes for coronary atherosclerosis and myocardial infarction Grade B3

Gene	Locus	Polymorphism	Allele	Function
Vascular homeostasis				
ACE	17q23	I/D	D	↑ ACE
AGT	1q42	M235T	T	↑ AGT
AT1	3q22	C1166A	AA	Unknown
ENOS	7q35-36	A/b	a	Unknown
		Gln298Asp	Asp	?
Hemostatic factors				
β-Fibrinogen	4q2	G-453A	A	↑ Fibrinogen
PAI-1	7q21·3-22	4G/5G	4G	↑ PAI-1
GpIIb/IIIa	17q21·32	PI A1/A2 (T/C)PIA2	?	
Factor V	1q25-25	Arg506Gln	Gln	Resistance to APC
Factor VII	13q34	Arg353Gln	Arg	↓ VII
Thrombomodulin	20p1	GG-9/-10AT	AT	?
Lipids and associated factors				
Paraxoxonase	7q21-22	A/B (Gln92Arg)	B (Arg)	↑ activity
LPL	8p22	Asn291Ser	Ser	↓ HDL, ↑ TG
		Asp9Asn	Asn	↓ HDL, ↑ TG
		Gly188Glu	Glu	↓ HDL, ↑ TG
Hepatic lipase	15	Various mutations		↓ HDL
LDLr	19p13·3	Various mutations		↑ LDL
ApoE, (& C1, CII)	19q13·2	E2/E3/E4	E4	↑ LDL, ↑ VLDL
ApoAI-CIII-AIV	11q23	Various mutations	–	↓ HDL, ↑ TG
ApoB100	2p24	Various mutations		↑ LDL, ↑ VLDL
Apo(a)	6q26	KIV repeats		↑ Lp(a)
CETP	16q22	Few mutations		↓ HDL
LCAT	16q22	Few mutations		↓ HDL
Metabolic factors				
MTHFR	1p36·3	C677T	T	↑ Homocysteine
CBS	21q22·3	Various mutations	–	↑ Homocysteine

Abbreviations: ACE, angiotensin-1 converting enzyme; AGT, angiotensinogen; AT1, angiotensin II receptor 1; CBS, cystathionine β synthase; CETP, cholesteryl ester transfer protein; eNOS, endothelial nitric oxide synthase; GpIIb-IIIa, glycoprotein IIb-IIIa; HDL, high density cholesterol; LCAT, lecithin cholesteryl acyltransferase; LDLr, low density lipoprotein receptor; LPL, lipoprotein lipase; MTHFR, methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor-1; VLDL, very low density cholesterol

unknown. Mutations in the adenosine triphosphate (ATP) binding cassette transporter (*ABCA1*) gene in patients with Tangier disease[80] have very low plasma levels of HDL-C and apoA1 and an increased risk of coronary atherosclerosis. This suggests a major role for the ABCA1 protein in regulating plasma HDL-C and apoA1 levels and thus the risk of atherosclerosis. This notion is further supported by a recent observation of increased frequency of coronary artery disease in members of families with Tangier or familial hypoalphalipoproteinemia who are heterozygous for mutations in the *ABCA1* gene.[81]

Recent studies have implicated variants of *ABCA1* in susceptibility to coronary atherosclerosis in the general population.[81,82] We recently reported that a single nucleotide polymorphism (SNP) located in the promoter region of *ABCA1* was associated with increasing severity and progression of coronary atherosclerosis.[82] Subjects with the TT variant, which is associated with reduced promoter activity, had more severe coronary atherosclerosis than those with the CC genotype, and those with the CT genotype had an in-between risk.

A second example is the *CYBA* gene, which is involved in maintaining the delicate balance between oxidation and reduction (redox) in the vessel wall. *CYBA* codes for $p22^{phox}$ protein, which is a component of the plasma membrane-associated enzyme NADPH oxidase. NADPH oxidase is the most important source of superoxide anion, the precursor to a variety of potent oxidants, in intact vessel walls. $p22^{phox}$ in conjunction with gp91 forms a membrane-bound

heterodimeric protein referred to as flavocytochrome b_{558}. The latter is considered the redox center of the NADPH oxidase. The $p22^{phox}$ protein is essential for the assembly and activation of the NADPH oxidase and plays a major role in NADPH-dependent O_2^- production in the vessel wall.

CYBA is located on chromosome 16q24 and has several allelic variants, including a 242C/T transition that results in replacement of histidine by tyrosine at amino acid position 72 (H72Y), a potential heme binding site. We determined the association for the 242C/T variant with severity and progression of coronary atherosclerosis and response to treatment with a statin in a well characterized cohort of Lipoprotein Coronary Atherosclerosis Study (LCAS) patients.[83] We showed that in the placebo group, subjects with the mutation had three to fivefold greater loss in mean minimum lumen diameter (MLD) and lesion-specific MLD than those without. Progression was also more and regression less common in those with the mutation. These results suggest that variants of $p22^{phox}$ are involved in the progression of coronary atherosclerosis.

Genetics and future therapy

Once the gene responsible for a disease is identified, it is usually possible through genetic animal models to determine the function as well as the pathogenesis of the disease. Genetic animal models of human FHCM have been developed in both mice and rabbits.[84–86] In mice, expression of Arg 403, known to cause human FHCM, exhibited myocyte and myofibrillar disarray, impaired cardiac function and extensive fibrosis. However, there is very little hypertrophy. Expression of this same mutation Arg 403 in rabbits was associated with a phenotype that is virtually identical to that observed in human FHCM.[86] This may be because the rabbit has βMHC as the predominant myosin in the heart, just as is found in human myocardium, whereas the mouse heart has αMHC. In the transgenic rabbit there is myocyte disarray, impaired systolic and diastolic function, extensive interstitial fibrosis, and extensive septal and posterior wall hypertrophy. There is also a significant incidence of sudden death. Utilizing these two models, the pathogenesis of FHCM has been considerably elucidated. It does appear that impaired contractility due to the inherited defect in βMHC leads to impaired contractility,[54] which in turn is associated with disarray and upregulation of several growth factors that stimulate fibroblast proliferation, with increased matrix formation, myocyte hypertrophy and further disarray.[54] It has been shown that in human FHCM several growth factors are upregulated,[54] and the pathology is that of fibrosis and hypertrophy. As the fibrosis and hypertrophy are secondary phenotypes, it would imply that, with appropriate therapy, there could be attenuation, prevention or even regression of these phenotypes.

A single blinded placebo controlled study[87] was performed in the animal mouse model with 12 transgenic mice receiving placebo, 12 receiving losartan, and 12 controls. This study showed that, despite a fully developed phenotype of disarray and fibrosis, there was essentially a reversal of the phenotype to normal after about 6 weeks of therapy. The fibrosis in the treated group was similar to that in controls, along with improved cardiac function. Transforming growth factor β (TGFβ), which is known to be a stimulus of fibroblastic activity and collagen deposition, also returned to control levels. It is thus likely that TGFβ is a major mediator of fibrosis in the mouse. In the rabbit model, a similar single blinded placebo controlled study[88] was performed with simvastatin. After 12 weeks of therapy this model showed a 37% reduction in hypertrophy and fibrosis and a significant improvement in ventricular function. The mechanism whereby simvastatin induces regression of hypertrophy and fibrosis is most likely via the inhibition of isoprenylation of signaling proteins. This process is necessary to induce growth of the cardiac myocytes and/or fibroblasts. These studies are very exciting and provide compelling evidence for an appropriate clinical study in patients. We are even more excited about these results because both drugs are known to be safe, as they have been taken by millions of patients for other reasons. These animal models provide the potential to identify other targets for the development of new therapies, but clearly losartan and simvastatin can be evaluated in the near future. Studies are now under way in animals to determine whether it is possible to prevent the development of hypertrophy and fibrosis in the transgenic rabbit expressing βMYC. It is of note that one seldom sees FHCM in humans prior to puberty, and thus there is at least a 10–12 year window in those positive for the mutation in which one could, with appropriate therapy, prevent or modulate the rate of development of the phenotype of fibrosis and hypertrophy. There is also of course the possibility that one could inhibit the fibrosis separately, which would lead to more specific therapy for the treatment of the disease in humans. It is an example of how one can work from the bedside to the bench in identifying the gene, and then back to the bedside having developed therapies in animal models that can be evaluated in clinical trials.

A diagnostic test for preclinical FHCM derived from genetic animal models

We are very excited about a novel diagnostic means for the preclinical diagnosis of FHCM. In the transgenic rabbit model of human FHCM induced by expression of the Arg 403 mutation, tissue Doppler velocities of the myocardium were assessed. It was observed that rabbits positive for the mutation, and despite having no hypertrophy, exhibited impaired tissue Doppler velocities. These animals developed hypertrophy and the full phenotype, but not until several months

later.[89] Tissue Doppler velocities were evaluated in patients with FHCM, those positive for a mutation but without any clinical features, and controls:[90] 11 patients positive for mutations without hypertrophy or any other clinical phenotype exhibited decreased myocardial tissue velocity. We compared their findings with controls and patients with a clinical phenotype of FHCM. Tissue Doppler imaging had a sensitivity of 85% and specificity of 90% in individuals without other clinical findings. These findings have been confirmed by other investigators (personal communication) and hopefully will be used to initiate therapy for prevention, and possibly for screening of athletes. The combination of effective therapy in animal models and a non-invasive test for preclinical diagnosis in patients offers great promise for the future.

Key points

- In single gene disorders the phenotype is predominately due to the effect of a single gene. Other genes (modifier genes), together with environmental factors, interact to give the observed differences in the phenotype.
- Polygenetic disorders often have no predominant gene, but rather multiple genes interacting with the environment to give the phenotype.
- Single gene disorders exhibit mendelian patterns of inheritance and the genes can be mapped and identified utilizing two and three generation families.
- Familial hypertrophic cardiomyopathy is caused by more than 10 genes involving more than 150 mutations.
- Familial dilated cardiomyopathy: although several have been mapped only a few have been identified.
- Long QT syndrome and Brugada syndrome are present in either the sodium or the potassium channels.
- Wolff–Parkinson–White syndrome has so far been shown to be due to mutations in *AMPK* gene.
- A gene responsible for atrial fibrillation has been mapped to chromosome 10q32 but the gene has not yet been identified.
- Genetic animal models of human familial FHCM treated with losartan or simvastatin have had a reversal of the phenotype, including fibrosis and hypertrophy.
- Tissue Doppler echocardiography has been shown to diagnose FHCM in humans and in animal models prior to the development of cardiac hypertrophy and other features on the phenotype.

References

1. Hoffman JIE. Incidence of congenital heart disease: II. Prenatal incidence. *Pediatr Cardiol* 1995;**16**:155–65.
2. Berko BA, Swift M. X-linked dilated cardiomyopathy. *N Engl J Med* 1987;**316**:1186–91.
3. Roberts R. A perspective: the new millennium dawns on a new paradigm for cardiology – molecular genetics. *J Am Coll Cardiol* 2000;**36**:661–7.
4. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;**232**:34–47.
5. Roberts R, Towbin J. Principles and techniques of molecular biology. In: Roberts R, ed. *Molecular Basis of Cardiology*. Oxford: Blackwell Scientific Publications, 1993.
6. Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2001;**33**:655–70.
7. Risch N. Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *J Genet Hum* 1990;**46**:229–41.
8. Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science* 1996;**273**:1516–17.
9. Marian AJ, Yu QT, Workman R, Greve G, Roberts R. Angiotensin converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. *Lancet* 1993;**342**:1085–6.
10. Yu QT, Safavi F, Roberts R, Marian AJ. A variant of β fibrinogen is a genetic risk factor for coronary artery disease and myocardial infarction. *J Invest Med* 1996;**44**:154–9.
11. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. *Cell* 2001;**104**:569–80.
12. Wang Q, Shen J, Splawski I *et al.* SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;**80**:805–11.
13. Dumaine R, Wang Q, Keating MT *et al.* Multiple mechanisms of Na^+ channel–linked long-QT syndrome. *Circ Res* 1996; **78**:916–24.
14. Hoppe UC, Marban E, Johns DC. Distinct gene-specific mechanisms of arrhythmia revealed by cardiac gene transfer of two long QT disease gene, HERG and KCNE1. *Proc Natl Acad Sci USA* 2001;**98**:5335–40.
15. Kimura A, Harada H, Park J-E *et al.* Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. *Nature (Genet)* 1997;**16**:379–82.
16. Chen Q, Kirsch GE, Zhang D *et al.* Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;**392**:293–6.
17. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol* 2001; **12**:268–72.
18. Brugada R, Roberts R. Brugada syndrome: Why are there multiple questions to a simple answer? *Circulation* 2001; **104**:3017–19.
19. Brugada R, Tapscott T, Czernuszewicz GZ *et al.* Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;**336**:905–11.
20. Gollob MH, Green MS, Tang A *et al.* Identification of a gene responsible for familial Wolff–Parkinson–White syndrome. *N Engl J Med* 2001;**344**:1823–64.
21. Gollob MH, Roberts R. AMP activated protein kinase and familial Wolff–Parkinson–White syndrome: new perspectives on heart development and arrhythmogenesis. *Eur Heart J* (in press).
22. Gollob MH, Seger JJ, Gollob TN *et al.* Novel PRKAG2 mutation in the genetic syndrome of ventricular preexcitation and conduction defects with childhood onset and absence of cardiac hypertrophy. *Circulation* 2001;**104**:3030–3.
23. Arad M, Benson DW, Perez-Atayde A *et al.* Constitutively active AMP kinase mutations cause glycogen storage disease mimicking. *J Clin Invest* 2002;**109**:357–62.

24.Blair E, Redwood CS, Ashrafian H *et al.* Mutations in the gamma(2) subunit of AMP-activated protein kinase cause hypertrophic cardiomyopathy: evidence for the central role of energy comp disease pathogenesis. *Hum Mol Genet* 2001; **10**:1215–20.

25.Cannan CR, Reeder GS, Bailey KR, Melton LJ III, Gersh BJ. Natural history of hypertrophic cardiomyopathy. A population-based study, 1976 through 1990. *Circulation* 1995; **92**:2488–95.

26.Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA* 1996; **276**:199–204.

27.Maron BJ, Anan TJ, Roberts WC. Quantitative analysis of the distribution of cardiac muscle cell disorganization in the left ventricular wall of patients with hypertrophic cardiomyopathy. *Circulation* 1981;**63**:882–94.

28.Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. *J Am Coll Cardiol* 2000;**35**:36–44.

29.Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnititude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000; **342**:1778–85.

30.Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy; histopathological features of sudden death in cardiac troponin T disease. *Circulation* 2001;**104**:1380–4.

31.Rouslin W. The mitochondrial adenosine 5′-triphosphatase in slow and fast heart rate hearts. *Am J Physiol* 1987;**252**: H622–7.

32.Mimbs JW, Roberts R. Coronary heart disease and rheumatic fever. In: Freitag JJ, Miller LW, eds. *Manual of Medical Therapeutics*. Boston: Little, Brown and Company, 1980.

33.Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. *Am J Cardiol* 2001;**88**:275–9.

34.Nimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W. Mutations in the gene for cardiac myosin-binding protein C and late onset familial hypertrophic cardiomyopathy. *N Engl J Med* 1998;**338**:1248–57.

35.Charron P, Dubourg O, Desnos M *et al.* Genotype–phenotype correlations in familial hypertrophic cardiomyopathy. A comparison between mutations in the cardiac protein-C and the beta-myosin heavy chain genes. *Eur Heart J* 1998;**19**:139–45.

36.Fulton M, Julian DG, Oliver MF. Sudden death and myocardial infarction. *Circulation* 1969;**40**:182–91.

37.Erdmann J, Raible J, Maki-Abadi J *et al.* Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2001;**38**:322–30.

38.Cohn JN, Franciosa JA, Francis GS *et al.* Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. *N Engl J Med* 1982;**306**:1129–35.

39.Watkins H, McKenna WJ, Thierfelder L *et al.* Mutations in the genes for cardiac troponin T and α-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;**332**:1058–64.

40.Hackel DB, Reimer KA, Ideker RE *et al.* and the MILIS Study Group. Comparison of enzymatic and anatomic estimates of myocardial infarct size in man. *Circulation* 1984;**70**:824–35.

41.Karibe A, Tobacman LS, Strand J *et al.* Hypertrophic cardiomyopathy caused by a novel a-tropomyosin mutation (V95A) is associated with mild cardiac phenotype, abnormal calcium binding to troponin and myosin cycling, and a poor prognosis. *Circulation* 2001;**103**:65–71.

42.Poetter K, Jiang H, Hassenzadeh S *et al.* Mutations in either the essential or regulatory light chains of myosin are associated with a rare myopathy in human heart and skeletal muscle. *Nature Genet* 1996;**13**:63–9.

43.Flavigny J, Richard P, Isnard R *et al.* Identification of two novel mutations in the ventricular regulatory myosin light chain gene (MYL2) associated with familial and classical forms of hypertrophic cardiomyopathy. *J Mol Med* 1998; **76**:208–14.

44.Satoh M, Takahashi M, Sakamoto T, Hiroe M, Marumo F, Kimura A. A structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. *Biochem Biophys Res Commun* 1999;**262**:411–17.

45.Mogensen J, Klausen IC, Pedersen AK *et al.* α-Cardiac actin is a novel disease gene in familial hypertrophic cardiomyopathy. *J Clin Invest* 1999;**103**:R39–R42.

46.Olson TM, Doan TP, Kishimoto NY, Whitby FG, Ackerman MJ, Fananapazir L. Inherited and de novo mutations in the cardiac actin gene causing hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 1999;**32**:1687–94.

47.Roberts R, Sobel BE. Creatine kinase isoenzymes in the assessment of heart disease. *Am Heart J* 1978;**95**:521–8.

48.Marian AJ. Modifier genes for hypertrophic cardiomyopathy. *Curr Opin Cardiol* 2002;**17**:242–52.

49.Ho CY, Lever HM, DeSanctis R, Farver CF, Seidman JG, Seidman CE. Homozygous mutation in cardiac troponin T: implications for hypertrophic cardiomyopathy. *Circulation* 2000;**102**:1950–5.

50.Jeschke B, Uhl K, Weist B *et al.* A high risk phenotype of hypertrophic cardiomyopathy associated with a compound genotype of two mutated beta-myosin heavy chain genes. *Hum Genet* 1998;**102**:299–304.

51.American Heart Association. *Heart Facts* 1983. Dallas: American Heart Association, 1982.

52.Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2001;**33**: 655–70.

53.Marian AJ, Salek L, Lutucuta S. Molecular genetics and pathogenesis of hypertrophic cardiomypathy. *Minerva Med* 2001; **92**:435–51.

54.Marian AJ. Pathogenesis of diverse clinical and pathological phenotypes in hypertrophic cardiomyopathy. *Lancet* 2000; **355**:58–60.

55.Mestroni L, Rocco C, Gregori D *et al.* Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. *J Am Coll Cardiol* 1999;**34**:181–90.

56.Kasper EK, Agema WRP, Hutchins GM, Deckers JW, Hare JM, Baughman KL. The causes of dilated cardiomyopathy: a clinicopathological review of 673 consecutive patients. *J Am Coll Cardiol* 1994;**23**:586–90.

57.Puleo PR, Guadagno PA, Roberts R *et al.* Early diagnosis of acute myocardial infarction based on assay for subforms of creatine kinase-MB. *Circulation* 1990;**82**:759–64.

58.Olson TM, Michels VV, Thibodeau SN, Tai Y-S, Keating MT. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. *Science* 1998;**280**:750–2.

59.Kamisago M, Sharma SD, DePalma SR *et al.* Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. *N Engl J Med* 2000;**343**:1688–96.
60.Tsubata S, Bowles KR, Vatta M *et al.* Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. *J Clin Invest* 2000;**106**:655–62.
61.Arbustini E, Diegoli M, Morbini P *et al.* Prevalence and characteristics of dystrophin defects in adult male patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2000;**35**:1760–8.
62.Fatkin D, MacRae C, Sasaki T *et al.* Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–24.
63.Bonne G, Di Barletta MR, Varnous S *et al.* Mutations in the gene encoding lamin A/C cause autosomal dominant Emery–Dreifuss muscular dystrophy. *Nature Genet* 1999;**21**:285–8.
64.Roberts R. Editorial: The two out of three criteria for the diagnosis of infarction – is it passe? *Chest* 1984;**86**:511–13.
65.Li D, Tapscott T, Gonzalez O *et al.* Desmin mutation responsible for idiopathic dilated cardiomyopathy. *Circulation* 1999; **100**:461–4.
66.Perng MD, Muchowski PJ, Van Den IJ *et al.* The cardiomyopathy and lens cataract mutation in alphaB-crystallin alters its protein structure. *J Biol Chem* 1999;**274**:33235–43.
67.Hamer A, Vohra J, Hunt D, Sloman G. Prediction of sudden death by electrophysiologic studies in high risk patients surviving acute myocardial infarction. *Am J Cardiol* 1982; **50**:223–9.
68.Corrado D, Fontaine G, Marcus FI *et al.* Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. *Circulation* 2000;**101**:E101–6.
69.Corrado D, Basso C, Thiene G *et al.* Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *Am Coll Cardiol* 1997;**30**:1512–20.
70.Rampazzo A, Nava A, Buja G *et al.* The gene for arrhythmogenic right ventricular cardiomyopathy maps to chromosome 14q23-q24. *Hum Mol Genet* 1994;**3**:959–62.
71.Rampazzo A, Nava A, Erne P *et al.* A new locus for arrhythmogenic right ventricular cardiomyopathy (ARVD2) maps to chromosome 1q42-q43. *Hum Mol Genet* 1995;**4**:2151–4.
72.Severini GM, Krajinovic M, Pnamonti B *et al.* A new locus for arrhythmogenic right ventricular dysplasia on the long arm of chromosome 14. *Genomics* 1996;**31**:193–200.
73.Rampazzo A, Nava A, Miorin M *et al.* ARVD4, a new locus for arrhythmogenic right ventricular cardiomyopathy, maps to chromosome 2 long arm. *Genomics* 1997;**45**:259–63.
74.Ahmad F, Li D, Karibe A *et al.* Localization of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. *Circulation* 1998;**98**:2791–5.
75.Li D, Ahmad F, Gardner MJ *et al.* The locus of a novel gene responsible for arrhythmogenic right ventricular dysplasia characterized by early onset and high penetrance maps to chromosome 10p12-p14. *Am J Hum Genet* 2000;**66**:148–56.
76.Tiso N, Stephan DA, Nava A *et al.* Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). *Hum Mol Genet* 2001;**10**:189–94.
77.Priori SG, Napolitano C, Tiso N *et al.* Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;**103**: 196–200.
78.McKoy G, Protonotarios N, Crosby A *et al.* Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and wooly hair (Naxos disease). *Lancet* 2000;**355**:2119–24.
79.Geller DS, Farhi A, Pinkerton CA. Activating mineralcorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* 2000;**289**:119–223.
80.Rust S, Rosier M, Funke H *et al.* Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nature Genet* 1999;**22**:352.
81.Clee SM, Kastelein JJ, Van Dam M *et al.* Age and residual cholesterol efflux affect HDL cholesterol levels and coronary artery disease in ABCA1 heterozygotes. *J Clin Invest* 2000; **106**:1263–70.
82.Lutucuta S, Ballantyne CM, Elghannam H, Gotto AM, Marian AJ. Novel polymorphisms in promoter region of ATP binding cassette transporter gene and plasma lipids, severity, progression, and regression of coronary atherosclerosis and response to therapy. *Circ Res* 2001;**88**:969–73.
83.Cahilly C, Ballantyne CM, Lim DS, Gotto A, Marian AJ. A variant of p22(phox), involved in generation of reactive oxygen species in the vessel wall, is associated with progression of coronary atherosclerosis. *Circ Res* 2000;**86**:391–5.
84.Seidman CE. Hypertrophic cardiomyopathy: from man to mouse. *J Clin Invest* 2000;**106**:S9–S13.
85.Oberst L, Zhao G, Park J-T *et al.* Expression of a human hypertrophic cardiomyopathy mutation in transgenic mice impairs left ventricular systolic function, detected by 178Ta radionuclide angiography, which precedes histological changes. *J Am Coll Cardiol* 1999;**33**:3A.
86.Marian AJ, Wu Y, Lim D-S *et al.* A transgenic rabbit model for human hypertrophic cardiomyopathy. *J Clin Invest* 1999; **104**:1683–92.
87.Lim DS, Lutucuta S, Bachireddy P *et al.* Angiotensin II blockade reverses myocardial fibrosis in a transgenic mouse model of human hypertrophic cardiomyopathy. *Circulation* 2001; **103**: 789–91.
88.Patel R, Nagueh SF, Tsybouleva N *et al.* Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation* 2001;**104**:r27–r34.
89.Nagueh SF, Kopelen H, Lim DS, Zoghbi WA, Quinones MA, Roberts R. Tissue Doppler imaging consistently detects myocardial contraction and relaxation abnormalities, irrespective of cardiac hypertrophy, in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation* 2000;**102**:1346–50.
90.Nagueh SF, Bachinski LL, Meyer D *et al.* Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation* 2001;**104**:128–30.

24 Cost effectiveness of prevention of cardiovascular disease

Daniel B Mark

Introduction

Medical care for cardiovascular disease is expensive. In the US, the total annual direct cost of caring for coronary heart disease, stroke, hypertension and heart failure patients is estimated to be $130 billion, with another $18·6 billion lost owing to the effects of these diseases on employment and productivity.[1] Although Canada, western Europe and many other industrialized countries spend less on medical care than the US, their incidence and prevalence of cardiovascular diseases are similar and their spending on this segment of the medical population as a proportion of all medical spending is comparable to that of the US. Because cardiovascular diseases are chronic, therapies are largely palliative rather than curative. Patients may live 20 or 30 years with these disorders, during which time they can experience numerous cardiovascular complications, often necessitating expensive hospitalizations and interventions.

In this context, it is easy to see why preventive medical care is appealing. By pre-empting the first manifestation of disease, the entire set of downstream consequences (with their attendant morbidity and cost) is also prevented. Because it is rarely (if ever) possible to know precisely which at-risk subject will develop clinically manifest disease, however, preventive therapies must be given to many in order to protect a few. Consequently, the number needed to treat to prevent one new case of cardiovascular disease is often quite large. Also, as preventive therapies must generally be used indefinitely, the associated lifetime treatment costs are often substantial. For this reason, the economic attractiveness (assessed as the cost per additional unit of medical benefit produced) of preventive therapies has been controversial.[2]

In an earlier chapter, Hlatky reviewed the basic principles of cost-effectiveness analysis (see Chapter 6). As he pointed out, cost effectiveness is a type of economic analysis that relates the extra benefits of a new strategy or therapy to the extra costs required to produce those benefits. Most commonly, such cost-effectiveness ratios are expressed as dollars (or other currency) required to add an extra life year (or a quality-adjusted life year) with the new therapy. In this context, an economically attractive ("cost effective") therapy is one that yields an extra life year for ≤$50 000, whereas an economically unattractive ("not cost effective") therapy is one that requires ≥$100 000 for every extra life year produced. (These benchmarks should not be interpreted dogmatically.[3]) For reasons reviewed in detail by Hlatky, the incremental effectiveness of a new therapy often has a much greater impact on its cost-effectiveness ratio than its incremental cost. Consequently, therapies where the number needed to treat to produce one extra unit of benefit (for example, one extra survivor, one extra coronary artery disease (CAD) free subject) is large may not be economically attractive at even a modest price per subject treated, whereas therapies that are very effective or which are applied to high-risk populations may be economically attractive at a substantially greater cost per subject.

Preventive therapies are now typically divided into those used in disease-free subjects to prevent the initial manifestation of disease (that is primary prevention) and those used to prevent complications or disease progression in patients with established disease (that is secondary prevention). In this chapter we will review what is known about the economics of both types of prevention for atherosclerotic coronary artery disease.

Cholesterol lowering

Primary prevention Grade A

Many observational studies (reviewed in Chapter 12) have established a strong dose–response relationship between cholesterol level and risk of coronary artery disease (CAD). These data suggest that therapies that reduce cholesterol the most should prevent the greatest number of coronary events. Trials evaluating the first generation of lipid-lowering agents (for example, Helsinki [gemfibrozil], LRC-CPPT [cholestyramine], and WHO [clofibrate]) yielded modest reductions in cholesterol (~10%) and produced equivocal clinical results. Given the limited clinical effectiveness of these agents, cost-effectiveness analyses indicated that cholesterol reduction using them in primary prevention was economically unattractive, although therapy targeted at high-risk subjects with multiple risk factors had a more favorable economic profile.[4] With HMG-CoA reductase inhibitors (statins), total and LDL

cholesterol reductions of 20–30% or more can be achieved, with a resulting decrease in all-cause mortality of 21%.[5] As a consequence, the cost effectiveness of preventive therapy with these agents appears more favorable.

There are two major primary prevention trials with statin therapy that have published economic data: the West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). WOSCOPS randomized 4159 men between the ages of 45 and 65 without overt coronary disease who had LDL cholesterol levels ≥155 mg/dl to either pravastatin (40 mg/day) or placebo.[6] During the mean follow up of 4·9 years, pravastatin reduced the total cholesterol by 20% and decreased all-cause mortality by 22% ($P = 0{\cdot}051$) (Table 24.1).

To evaluate the economic profile of statin therapy in primary prevention, Caro and colleagues[7] used the WOSCOPS database along with long-term survival of Scottish subjects (matched to the WOSCOPS subjects on age, gender and cardiac event profile) obtained from the Scottish Record Linkage system. This allowed the creation of a full survival curve for each treatment arm (empirical data for 5 years, Scottish survival data after 5 years based on subject event profile). Cost data were derived from Scottish 1996 medical prices and are cited below in their US dollar equivalents. Caro and colleagues estimated that to prevent one extra subject progressing from an asymptomatic state to clinical disease (indicated in the WOSCOPS database by death, MI, stroke, revascularization or angina) 31·4 men would need to be started on statin therapy.[8] Pravastatin therapy (the average daily dose in the trial was 40 mg) was assigned a cost of $934 per year. The investigators estimated a drug treatment cost (over 5 years) of $3735 per subject, with a cost offset of $85 per subject owing to adverse events prevented by treatment, leaving a net undiscounted 5 year incremental cost per subject of $3650 ($3196 discounted at 6%). On the medical benefit side, the investigators projected an average (undiscounted) increase in life expectancy per subject of 0·25 years (approximately 0·10 years discounted). The resulting base case cost-effectiveness ratio indicated that statin therapy as primary prevention in the WOSCOPS population added an additional life year at a cost of approximately $29 132. Using the benchmarks cited earlier, this would be an economically attractive therapy (that is <$50 000 per life year added).

The AFCAPS/TexCAPS trial randomized 6605 subjects free of clinically evident CAD who had average total cholesterol and LDL cholesterol levels to lovastatin or placebo.[9] Over a mean follow up of 5·2 years, lovastatin reduced the incidence of a first major acute coronary event by 37% ($P < 0{\cdot}001$) (Table 24.1). In an analysis of the cost consequences in this trial, lovastatin cost $4654 per patient over the duration of the trial and saved $524 owing to reduced cardiac events and procedures.[10] These savings came from a 19% reduction in coronary bypass graft surgery (CABG), a 37% reduction in percutaneous transluminal coronary angioplasty (PTCA), and a 26% reduction in cardiovascular hospital days. A cost-effectiveness analysis of AFCAPS/TexCAPS is not planned. The availability of generic lovastatin in the near future will probably substantially reduce the net cost of this therapy.

A third important analysis in this area was performed using the Coronary Heart Disease (CHD) Policy Model, a computer simulation model that estimates the annual incidence of coronary disease in subjects aged 35–84 based on their risk factor profile.[11] The effectiveness of diet and statin therapy was estimated from analysis of pooled clinical trials. The model estimated that for men with an LDL cholesterol ≥160 mg/dl primary prevention with statin therapy relative to a Step I diet had a cost-effectiveness ratio between $130 000 and $260 000 per QALY added.[12] Further classifying risk by considering HDL cholesterol, smoking status and blood pressure led to the identification of subgroups with cost-effectiveness ratios as low as $54 000 per QALY (male aged 35–49 years with all three additional risk factors) or as high as $420 000. Most of the subgroups had

Table 24.1 5 Year clinical outcomes and costs of lipid lowering in major randomized trials

Study	Reductions per 1000 patients			Cost per patient ($)		
	Deaths	MI	Revasc	Tx	Offset	Net
1° Prevention						
WOSCOPS	5	19	8	3700	100	3600
AFCAPS	4	26	31	4654	524	4130
2° Prevention						
4S	32	47	59	4650	3900	780
CARE	11	18	47	5550	1660	3890

Adapted from Mark DB, Hlatky MA. Clinical cardiology: new frontiers medical economics and the assessment of value in cardiovascular medicine. *Circulation* 2002;**106**:516–20.

ratios above $100 000. For women, cost effectiveness (CE) ratios for primary prevention with statin therapy were even higher, with the most favorable being $61 000 per QALY and the least favorable subgroup having a ratio of $1·4 million per QALY.

There are several possible reasons why the WOSCOPS analysis and the CHD Policy Model analysis reached different conclusions about the economic attractiveness of statin therapy as primary prevention. The most important is probably the different amount of incremental life expectancy attributed to statin therapy by the two models. In particular, the 0·25 year incremental life expectancy per patient estimated in the WOSCOPS analysis may overstate the benefit of a therapy that saves one life per 1000 per year of therapy.

Primary prevention with statins is most economically attractive in high-risk subjects. Thus, a recent model-based analysis estimated that primary prevention with statin therapy was economically attractive in both diabetic men (CE ratio <$10 000 per year of life saved) and women (CE ratio <$40 000 per year of life saved).[13]

Secondary prevention Grade A

The National Cholesterol Education Program May 2001 update identifies an LDL level of <100 mg/dl as optimal in patients with established CAD.[14] Several major clinical trials have demonstrated significant clinical benefit for statin therapy as secondary prevention. The Scandinavian Simvastatin Survival Study (4S) was a double-blind placebo-controlled trial of adjusted-dose simvastatin in 4444 men and women between the ages of 35 and 60 with a history of angina or prior MI and total cholesterol levels between 210 and 310 mg/dl despite dietary interventions.[15] Median follow up was 5·4 years. The majority of patients received 20 mg/day of simvastatin, but more than one third required 40 mg/day. Simvastatin reduced total cholesterol by 25% and LDL-C by 35%, and it decreased all-cause mortality by 30% ($P = 0·003$) (Table 24.1).

Pedersen and colleagues[16] evaluated the incremental cost of simvastatin therapy in the 4S trial. During the 5·4 years of trial follow up, simvastatin therapy reduced hospitalizations for acute cardiovascular disease by 26% ($P < 0·0001$) and total hospital days by 5138 ($P < 0·0001$). The beneficial effect of simvastatin on hospitalization first became evident after 10 months of therapy, became statistically significant after 22 months, and appeared to increase over time. The use of antianginal and other cardiovascular drugs was not altered by statin therapy. Using US DRG-based reimbursement rates as cost weights, Pedersen and coworkers estimated that simvastatin therapy would save an average of $3872 per patient, owing to reduced need for hospitalization. The cost of the drug itself over the 5 year trial period averaged $4400 (discounted) per patient. Added to this were the cost of laboratory monitoring of the statin therapy (three to four lipid and transaminase measurements in the first year, and annually thereafter), which amounted to $250 (discounted) per patient. Thus, the net cost of the statin arm in the 4S trial over a mean of 1915 days of follow up was $778 per patient, which equates to approximately $148 per patient per year.[16]

Johanesson and colleagues[17] constructed a modified Markov model to estimate the cost effectiveness of using statin therapy for 5 years as secondary prevention for subgroups defined by age, sex and cholesterol level. The increased life expectancy produced by statin therapy was estimated from the 4S trial data. For a 59 year old male with a pretreatment cholesterol level of 261 mg/dl, life expectancy was prolonged by 0·28 years; for a 59 year old woman the corresponding figure was 0·16 years. Cost figures were derived from four Swedish hospitals and converted to US dollars. For the prototypical 59 year old man cited above, treatment costs averaged $2242 with a cost offset of $718 owing to reduced morbidity, leaving a net incremental cost of $1524 per patient. The cost per year of life added with statin therapy for this patient was $5400.[17] For the corresponding 59 year old woman, the net incremental cost was $1685 and the cost per life year added with statin therapy was $10 500. The cost effectiveness of 5 years of simvastatin ranged from $3800 per life year added for a 70 year old man with a cholesterol of 309 mg/dl, to $27 400 for a 35 year old woman with a cholesterol of 213 mg/dl. Extensive sensitivity analyses showed that statin therapy as secondary prevention was economically attractive under a wide range of assumptions. A recent model-based analysis estimated that statin therapy for secondary prevention was economically attractive in the diabetic subpopulation in the US, with CE ratios from $7000 to $15 000 for diabetic men and $24 000 to $40 000 for diabetic women.[13]

Differences between cardiovascular care in Sweden and North America raise the question of how generalizable an economic analysis of the 4S trial is. For example, Swedish use of coronary revascularization procedures was far lower than in the US and many European countries. In the 4S trial, the 5 year rate of revascularization was 17·2% in the placebo arm, and 81% of those procedures were coronary bypass surgeries. With the higher procedure rates in the US, even a modest relative reduction in the need for revascularization could generate greater cost savings than were seen in 4S. In addition, important benefits of therapy may be seen in patients who have undergone revascularization. For example, in the Post Coronary Artery Bypass Graft Trial, aggressive lipid lowering with lovastatin to an LDL-cholesterol <100 mg/dl reduced the need for repeat revascularization over a 4 year follow up by 29% relative to moderate lipid lowering therapy.[18]

The CARE (Cholesterol and Recurrent Events) trial randomized 4159 postmyocardial infarction (MI) patients with an average total cholesterol of 209 mg/dl to either pravastatin

40 mg/day or placebo.[19] After 5 years of follow up, death and non-fatal MI were reduced by 24% ($P = 0{\cdot}003$) (Table 24.1).

A cost-effectiveness analysis based on the CARE trial results has recently been published.[20] Based on the mean pravastatin dose in the active therapy arm, the cost of pravastatin therapy in the trial was $925 per year ($5 550 for the 6 years of the trial). Use of other cardiac medications was similar in the two arms (about $1250 per year). Over the 6 year follow up, the pravastatin arm saved about $1700 in hospital costs relative to placebo. Extrapolated to a lifetime perspective, the average cost of the pravastatin strategy discounted at 3% per year was $53 177, whereas that for the placebo arm was $42 223 for an incremental cost of $10 954. Extrapolating the observed (non-significant) mortality difference in CARE yielded a discounted quality-adjusted life expectancy of 13·62 QALYs for the pravastatin arm and 13·27 QALYs for placebo, for an incremental benefit of 0·35 QALYs. The resulting cost-effectiveness ratio was $31 000 per QALY saved with pravastatin therapy. Results were similar in men and women. For patients 60 and older the CE ratio was $9100 per QALY, and a similar result was obtained in patients with pretreatment LDL-cholesterol >150 mg/dl. On the other hand, for patients with an LDL-cholesterol <125 mg/dl, this analysis estimated that pravastatin therapy would be both more costly and less effective than placebo. These results show that statin therapy is economically attractive when applied to the majority of CARE participants, namely post-MI patients with an "average" cholesterol level.

What remains unsettled is the value of treating previously untreated patients with LDL-cholesterol values <125 mg/dl. Also unsettled is the value of very aggressive lipid lowering in secondary prevention populations to LDL-cholesterol levels substantially below 100 mg/dl. Ongoing clinical trials should provide additional guidance in these areas over the next 5 years.

Cessation of smoking Grade A

Cigarette smoking has many adverse health effects, including a significant risk of coronary disease. Given the addictive nature of smoking, most smoking cessation programs have limited success (~6% more patients stop smoking in 12 months than do controls).[21] As reviewed in previous chapters, observational data suggest that those who succeed in quitting experience a sharp decline in the high cardiovascular risk associated with smoking in the first 6 months, and their risk reaches the level of non-smokers after 1–2 years. This decrease in cardiovascular risk from smoking cessation has been estimated to increase life expectancy for each quitter by between 2 and 5 years.[22] Furthermore, each smoker who quits is associated with an average reduction in CAD-related medical costs of about $900 over the ensuing 8 years.[23]

In a primary prevention study, Cummings and colleagues[24] created a model to examine the cost effectiveness of physician counseling (versus no counseling) on smoking cessation. In their model, the authors assumed that physician counseling led to a 2·7% decrease in smoking at 1 year, with a subsequent 10% relapse rate. They assumed that the cost of this brief advice would be $12. These data yielded CE ratios from about $1000 to $1400 per year of life saved for men, and from about $1700 to $3000 per year of life saved for women. Sensitivity analysis of a worst case scenario (cost increased to $45, cessation rate decreased to 1%, 50% relapse after the first year) still indicated that brief physician advice to quit smoking was economically attractive. Although physician counseling is only very modestly effective, it remains an important prevention strategy because it is so inexpensive.

A similar analysis was performed by Oster and coworkers comparing nicotine gum as an adjunct to physician advice versus physician advice alone.[25] Based on randomized clinical trials, the authors assumed that nicotine gum for 4 months resulted in a cessation rate of 6·1% versus 4·5% for physician counseling. The cost of 4 months of nicotine gum was $161 (1984 figures). The CE ratios for this form of smoking cessation intervention ranged from about $6000 to $9000 per life year added for men, and about $9500 to $13 000 for women.

In the arena of secondary prevention, Krumholz and colleagues evaluated the effect of a nurse counseling smoking cessation program for post-MI patients.[26] Data from a previously published randomized trial was used in a decision model to define the 1 year quit rate and postcessation mortality.[27] The model assumed an incremental life expectancy of 1·7 years per quitter. The estimated cost of the program was $100 per patient. With an incremental smoking cessation rate of 26%, the program's cost-effectiveness ratio was highly favorable at $265 per life year added. Sensitivity analyses showed that the cost-effectiveness ratio remained attractive at below $10 000 per life year added if only 1% of smokers quit (instead of 26%), or if quitters gained only 0·1 year of life expectancy (instead of 1·7 years).

For those who are able to stop smoking, observational data suggest significant gains in life expectancy. When these favorable estimates are combined with the relatively modest cost of smoking cessation interventions, these programs appear very economically attractive.

Treatment of hypertension Grade A

Hypertension is an ideal disease for preventive therapy. It is a highly prevalent disorder, with more than 60 million Americans (one in four adults) estimated to have the disease.[1] If untreated, hypertension leads to significant morbidity and mortality, with coronary disease, heart failure and

strokes being the main cardiovascular complications. Finally, numerous interventions capable of lowering the blood pressure are available, including a wide spectrum of antihypertensive pharmacologic agents.

Using data from the Framingham study, Stason and Weinstein evaluated the cost effectiveness of treatment of hypertension as primary prevention by modeling stepped care, from screening for hypertension to drug compliance.[28] When stratified by initial blood pressure, age, gender and race, most subgroups had cost-effectiveness ratios of less than $50 000 per quality-adjusted life year. Not surprisingly, the cost effectiveness was more favorable for those with higher initial blood pressures. Other determinants of cost effectiveness were gender, age and compliance.

Because hypertension usually requires lifetime therapy, and as most antihypertensive agents are equally efficacious at reducing blood pressure, an important determinant of the economic profile of this form of prevention is the cost of the antihypertensive regimen. Edelson[29] evaluated the cost effectiveness of five specific monotherapies in persons without coronary disease aged 35 to 64. The study involved simulation of 20 years of therapy (1990–2010) based on the Coronary Heart Disease Policy Model. Effectiveness data was based on a meta-analysis of 153 studies in the literature. A key assumption was that if different agents produce the same reduction in diastolic blood pressure, then the clinical benefit would be the same. Of the five agents studied, propranolol and hydrochlorothiazide had the most favorable cost-effectiveness ratios, at $10 900 per year of life saved and $16 400 per year of life saved, respectively (expressed in 1987 dollars). Captopril had a higher cost and a lower estimated reduction in diastolic blood pressure, yielding a cost-effectiveness ratio of $72 100 per life year saved. A limitation of the study was that estimates of 20 year outcomes were based on trials often lasting only several months. More recently, Littenberg and colleagues[30] modeled the cost effectiveness of treating mild hypertension (diastolic pressure from 90 to 105) and also found that the cost-effectiveness ratio was more attractive when the least costly antihypertensive agent was used.

Even though the various antihypertensive agents are all capable of lowering blood pressure, evidence for a mortality benefit is strongest for diuretics and β blockers.[31] In an overview of four trials, ACE inhibitors were found to reduce stroke (by 30%) and coronary heart disease (by 20%).[32] In placebo-controlled trials, calcium channel blockers reduced stroke (by 39%) and major cardiovascular events (by 28%). Some continue to argue that long-acting calcium-channel blockers are inferior to other antihypertensives based on the available trial data, but this point remains contentious.[33]

Although no recent economic models have evaluated treatment of hypertension in the elderly, an overview of the available randomized trial data showed that two to four times as many younger subjects needed to be treated for 5 years to equal the benefits of therapy in preventing morbid and fatal events in the older population.[34] Thus, the economic profile of treatment in the elderly would be expected to be correspondingly favorable.

No large randomized clinical trials have evaluated hypertension control as secondary prevention, and no cost-effectiveness models addressing this issue have been published.

Exercise as therapy

Many epidemiologic data support the idea that regular exercise is associated with less coronary heart disease and improved longevity (see Chapter 16). The improved outcomes are attributed, at least in part, to improvements in blood pressure, weight and cholesterol levels. Analysis of the economic benefits of regular exercise in the primary prevention of cardiovascular disease has been limited to model simulations of clinical outcomes based on epidemiologic data. In 1000 hypothetical 35 year old males, a 2000 kcal/week jogging program (~20 miles) was assumed to reduce CHD risk by 50% compared with no exercise.[35] Direct costs attributed to the program included exercise equipment and a portion of an annual physician visit ($100 per year). The model also used a sliding scale of indirect costs due to lost productivity for time spent in jogging, based on how much the individual disliked exercise ($9·00 per hour for subjects who disliked exercise, $4·50 per hour for neutral subjects, and $0 for subjects who enjoyed exercise). The cost-effectiveness ratio using direct costs was $1395 per quality-adjusted life year added; with the indirect costs, the ratio increased to $11 313 for regular exercise versus no exercise. The model assumed that compliance was 100% even for those who disliked exercise.

A second analysis of this issue used the Cardiovascular Disease Life Expectancy Model to forecast the long-term benefits of exercise training.[36] This model is based on the risk factor and outcome data from the Lipid Research Clinics Program Prevalence and Follow-Up Studies. This model was applied to the average risk profiles of a population-based cohort of Canadian men and women with and without cardiovascular disease to estimate life expectancy. The effectiveness of exercise was projected based on its reported effects on blood lipids (a 4% decrease in LDL, a 5% increase in HDL) and blood pressure (6 mmHg decrease in systolic pressure). Costs were based on Canadian sources and converted to 1996 US dollars. Two exercise programs were considered: a supervised exercise class at $605 for the first year and $367/year after year 1, and an unsupervised walking program at $311 for the first year and $73/year after that. Adherence was estimated at 50% for the first year, dropping to 30% for all subsequent years. The unsupervised exercise program had an estimated cost per year of life saved of $12 000, for both primary and secondary prevention.

The supervised exercise program was also economically attractive, with cost-effectiveness ratios of $20 000 per year of life saved for secondary prevention in men, and between $20 000 and $40 000 per year of life saved for secondary prevention in women and for primary prevention in men. With greater adherence than was assumed, the economic attractiveness of both exercise programs improves.

Most studies of exercise as secondary prevention in coronary disease involve structured programs of cardiac rehabilitation in post-MI patients. Because of limited sample size, no single randomized trial has definitely shown that cardiac rehabilitation reduces cardiac events. Two meta-analyses pooled data from the available trials and estimated a 20–25% reduction in death and non-fatal MI with cardiac rehabilitation in post-MI patients.[37,38] In 1993, Oldridge[39] published an economic evaluation of an 8 week cardiac rehabilitation program in post-MI patients with mild to moderate depression and/or anxiety. There were no differences in mortality or non-fatal MI, but quality of life, as measured by the time trade-off method, did improve, leading to 0·052 quality-adjusted life years gained during the 1 year of follow up. The corresponding cost-effectiveness ratio in this analysis was around $10 000 per quality-adjusted life year added. A second, more recent analysis of formal cardiac rehabilitation after acute MI estimated a cost-effectiveness ratio of $4950 per year of life saved (1995 dollars).[40]

The value of these analyses on the cost effectiveness of exercise is heavily dependent on the credibility of the assumptions about the amount of benefit to be derived. In this respect, the absence of large-scale mortality trials represents a weakness in the evidence that economic models cannot rectify.

Pharmacologic secondary prevention Grade A

For those with coronary disease, aspirin therapy leads to a substantial reduction in death and non-fatal MI, and its costs and long-term side effects are minimal.[41] Even though there are no formal cost-effectiveness analyses of aspirin therapy, its efficacy and low price make aspirin a "best buy" of secondary prevention therapy.

For post-MI patients, several trials have shown that β blockers prevent death and cardiac events. Goldman and coworkers performed a cost-effectiveness analysis of β blocker therapy after an acute MI in men.[42] The model assumed a mortality reduction of 25% per year for the first 3 years of therapy, and 7% per year for years 4–6, with gradual attenuation over the subsequent 9 year period, based on an overview of the available literature. After 6 years of therapy, the model assumed that β blockers were discontinued. The average cost of propranolol therapy used in this study was $208 per patient per year (1987 rates). The cost-effectiveness ratios ranged from $2300 per life year added in high-risk patients, to $13 600 per life year saved for low-risk patients. The β-blocker trials upon which this model was based were all completed in the prethrombolytic era and the cost effectiveness of this form of secondary prevention has not been re-examined in patients undergoing reperfusion therapy. Furthermore, recent analyses of the Beta Blocker in Heart Attack Trial (BHAT) showed that MI patients who survived the first year with low- to moderate-risk courses (the typical profile of a postreperfusion therapy patient) did not evidence any long-term benefit from β blockers.[43]

A more recent analysis using the CHD Policy Model examined the epidemiologic impact and cost effectiveness of increasing β blocker use in acute MI survivors from current levels (estimated to be 44% in 2000) to target levels (estimated to be 92%).[44] Treatment was projected to continue over 20 years. The additional costs of this full-use β-blocker strategy were estimated at $570 million for the USA. However, with a cost offset from decreased CAD-related events, the net cost was estimated at $158 million. The incremental cost per QALY added with full use β blocker therapy was $4500. A strategy of phasing in higher β blocker use by concentrating on achieving target use levels in all first-MI survivors over the next 20 years was estimated to save 72 000 lives and be cost saving (a dominant strategy). Thus, improving evidence-based use of β blockers in CAD offers major health gains at a very attractive cost, and may even be cost saving.

Angiotensin-converting enzyme (ACE) inhibitor efficacy in secondary prevention was demonstrated in the SAVE (Survival and Ventricular Enlargement) trial, a double-blinded placebo-controlled trial of captopril in 2231 acute MI survivors with an ejection fraction (EF) ≤40%. SAVE showed a 19% reduction in mortality during the average follow up of 3·5 years. Based on the SAVE results, Tsevat and colleagues[45] created a decision model to determine the cost effectiveness of ACE inhibitors in 50–80 year old acute MI survivors with an ejection fraction (EF) of ≤40%. Assuming that the survival benefits of captopril extended beyond 4 years, the cost-effectiveness ratios averaged $10 400 per QALY or less (1991 dollars), depending on age. The use of 6 weeks of lisinopril therapy in acute MI patients was recently reported to be economically attractive ($2080 [1993 US dollars] per extra 6-week death avoided), based on the GISSI-3 trial data.[46]

Between 1993 and 1995, the Heart Outcomes Prevention Evaluation (HOPE) Study randomized 9297 patients aged 55 or greater who had either manifest vascular disease (CAD, stroke, peripheral vascular disease) or diabetes plus one other risk factor to ramipril or placebo.[47] Over a mean follow up of 4·5 years, the ramipril group experienced a 22% reduction in the composite of cardiovascular death, MI or stroke ($P = 0{\cdot}005$). All-cause mortality was reduced 16% ($P = 0{\cdot}005$) and non-fatal MI was reduced 20% ($P < 0{\cdot}001$). In addition, ramipril decreased the need for revascularization by 15% ($P = 0{\cdot}002$). Lamy and colleagues recently

examined the economic implications of ramipril therapy in HOPE.[48] Medicare reimbursements were used to estimate hospital costs and the Medicare Fee Schedule provided physician costs. The retail cost of 10 mg per day of ramipril therapy in the US is approximately $440 per year. Over the follow up of the HOPE Study the cost of the ramipril was $1480 per patient. Use of ramipril had no significant effect on use of other cardiac medicines. However, hospitalization costs were reduced by $614, and revascularization costs (coronary, carotid, peripheral) were reduced by $750. Although this economic analysis was retrospective and therefore could not include all costs of interest, use of the Medicare cost weights was conservative. Similar results were obtained when the analysis was done using Canadian cost weights. Thus, over the duration of the study follow up, ramipril appeared to pay for itself by reducing complications and related need for hospital-based care. This study did not attempt to project results out to a lifetime perspective. Based on the HOPE economic analysis, therefore, ramipril used in HOPE-eligible patients is a dominant therapy (better clinical outcomes, equivalent costs).

Preventive strategies ripe for cost-effectiveness analysis

Multiple risk factor interventions Grade B

The studies reviewed thus far have focused on the cost effectiveness of single risk factor interventions independent of other risk factors. In clinical practice patients have multiple risk factors that require multiple concurrent interventions. The Stanford Coronary Risk Intervention Program (SCRIP) evaluated the effect of multifactor risk modification on the progression of angiographic CAD in 300 patients.[49] The intervention program consisted of exercise, dietary modifications, weight loss, lipid lowering pharmacotherapy and smoking cessation. After 4 years, patients in the intervention arm had on average a 20% increase in exercise capacity, a 4% decrease in weight, and a 22% reduction in LDL cholesterol compared with those receiving usual care. Angiographically, those in the risk intervention arm had significant attenuation of coronary disease progression. In addition, there was a decrease in the composite end point of death, non-fatal MI, PTCA and CABG ($P = 0{\cdot}05$). Based on these results and the reduction in cardiac hospitalizations, Superko and coworkers estimated the net cost of the program at $630 per patient per year.[50]

Diabetes Grade A

Diabetes leads to many long-term complications, including retinopathy, neuropathy, nephropathy and atherosclerosis. However, only recently has control of glucose level been demonstrated to reduce these complications. The DCCT (Diabetes Control and Complications Trial) randomized 1441 insulin-dependent diabetic patients to intensive insulin therapy versus conventional therapy, with a mean follow up of 6·5 years.[51] The intensive therapy arm showed significant reductions in retinopathy, neuropathy and nephropathy. However, as there were few cardiovascular events in this primary prevention study the lower rate of cardiovascular events in the intensive therapy arm was not significant ($P = 0{\cdot}08$). A Monte Carlo simulation model based on the reduction of renal, neurological and retinal complications estimated that the cost effectiveness of lifetime intensive insulin therapy compared with conventional therapy was $28 661 per life year added.[52]

Conclusions

Based on the available cost-effectiveness data, the following preventive strategies are considered economically attractive: secondary prevention with statins in hyperlipidemia; smoking cessation programs for both primary and secondary prevention; treatment of hypertension for primary prevention, especially with β blockers and thiazide diuretics; secondary prevention with ACE inhibitors in high-risk vascular disease patients (meeting eligibility for the HOPE Trial); primary prevention with a regular exercise program; secondary prevention with cardiac rehabilitation; and for post-MI patients, the use of β blockers and ACE inhibitors. Even though no formal cost-effectiveness analysis has been carried out for aspirin (in secondary prevention), given its low cost and substantial clinical benefits it should be considered in the "best buy" category. The cost effectiveness of clopidogrel added to aspirin for secondary prevention is currently under study. The cost effectiveness of primary prevention with statins in hyperlipidemia remains unsettled. We await more clinical effectiveness data prior to consideration of cost-effectiveness analysis for achieving euglycemia in diabetics for both primary and secondary prevention. Finally, it is important to bear in mind that as therapeutic options and their associated cost change, cost effectiveness will need to be reassessed.

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References

1. American Heart Association. *Heart and Stroke Statistical Update 2000*. Dallas: AHA, 2001.
2. Krumholz HM, Weintraub WS, Bradford WD *et al*. The cost of prevention: can we afford it? Can we afford not to do it? *J Am Coll Cardiol* 2002; (in press).

3. Mason J, Drummond M, Torrance G. Some guidelines on the use of cost effectiveness league tables. *BMJ* 1993;**306**:570–2.
4. Goldman L, Gordon DJ, Rifkind BM *et al.* Cost and health implications of cholesterol lowering. *Circulation* 1992;**85**:1960–8.
5. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;**282**:2340–6.
6. Shepherd J, Cobbe SM, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;**333**:1301–7.
7. Caro J, Klittich W, McGuire A *et al.* International economic analysis of primary prevention of cardiovascular disease with pravastatin in WOSCOPS. West of Scotland Coronary Prevention Study. *Eur Heart J* 1999;**20**:263–8.
8. Caro J, Klittich W, McGuire A *et al.* The West of Scotland Coronary Prevention Study: weighing the costs and benefits of primary prevention with pravastatin. *BMJ* 1997;**315**:1577–84.
9. Downs JR, Clearfield M, Weis S *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;**279**:1615–22.
10. Gotto AM, Boccuzzi SJ, Cook JR *et al.* Effect of lovastatin on cardiovascular resource utilization and costs in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS Research Group. *Am J Cardiol* 2000;**86**:1176–81.
11. Weinstein MC, Coxson PG, Williams LW *et al.* Forecasting coronary heart disease incidence, mortality, and cost: the coronary heart disease policy model. *Am J Public Health* 1987;**77**:1417–26.
12. Prosser LA, Stinnett AA, Goldman PA *et al.* Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;**132**:769–79.
13. Grover SA, Coupal L, Zowall H *et al.* Cost-effectiveness of treating hyperlipidemia in the presence of diabetes: who should be treated? *Circulation* 2000;**102**:722–7.
14. National Cholesterol Education Program (Adult Treatment Panel III). Detection, evaluation, and treatment of high blood cholesterol in adults. (NIH Publication No. 01-3670). NIH, 2001.
15. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
16. Pedersen TR, Kjekshus J, Berg K *et al.* Cholesterol lowering and the use of healthcare resources: results of the Scandinavian Simvastatin Survival Group. *Circulation* 1996;**93**:1796–802.
17. Johannesson M, Jonsson B, Kjekshus J *et al.* Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *N Engl J Med* 1997; **336**: 332–6.
18. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous vein coronary artery bypass grafts. *N Engl J Med* 1997;**336**:153–62.
19. Sacks FM, Pfeffer MA, Moye LA *et al.* Cholesterol and recurrent events (CARE). *N Engl J Med* 1996;**335**:1001–9.
20. Tsevat J, Kuntz KM, Orav EJ *et al.* Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;**141**:727–34.
21. Ockene JK. Smoking intervention: a behavioral, educational, and pharmacologic perspective. In: Ockene IS, Ockene JK, eds. *Prevention of Coronary Heart Disease*. Boston: Little, Brown & Company, 1992.
22. Tsevat J, Weinstein MC, Williams LW *et al.* Expected gains in life expectancy from various coronary heart disease risk factor modifications. *Circulation* 1991;**83**:1194–201.
23. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. *Circulation* 1997;**96**:1089–96.
24. Cummings SR, Rubin SM, Oster G. The cost-effectiveness of counseling smokers to quit. *JAMA* 1989;**261**:75–9.
25. Oster G, Huse DM, Delea TE *et al.* Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. *JAMA* 1986;**256**:1315–18.
26. Krumholz HM, Cohen BJ, Tsevat J *et al.* Cost-effectiveness of a smoking cessation program after myocardial infarction. *J Am Coll Cardiol* 1993;**22**:1697–702.
27. Taylor CB, Houston-Miller N, Killen JD *et al.* Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. *Ann Intern Med* 1990;**113**:118–23.
28. Weinstein MC, Stason WB. Hypertension: a policy perspective. Cambridge: Harvard University Press, 1976.
29. Edelson JT, Weinstein MC, Tosteson AN *et al.* Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. *JAMA* 1990;**263**:407–13.
30. Littenberg B. A practice guideline revisited: screening for hypertension. *Ann Intern Med* 1995;**122**:937–9.
31. Psaty BM, Smith NL, Siscovick DS *et al.* Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 1997;**277**:739–45.
32. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;**356**:1955–64.
33. Pahor M, Psaty BM, Alderman MH *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000;**356**:1949–54.
34. Mulrow CD, Cornell JA, Herrera CR *et al.* Hypertension in the elderly: implications and generalizability of randomized trials. *JAMA* 1994;**272**:1932–8.
35. Hatziandreu EI, Koplan JP, Weinstein MC, *et al.* A cost-effectiveness analysis of exercise as a health promotion activity. *Am J Public Health* 1988;**78**:1417–21.
36. Lowensteyn I, Coupal L, Zowall H *et al.* The cost-effectiveness of exercise training for the primary and secondary prevention of cardiovascular disease. *J Cardiopulm Rehab* 2000;**20**: 147–55.
37. Oldridge NB, Guyatt GH, Fischer ME *et al.* Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA* 1988;**260**:945–50.
38. O'Connor GT, Buring JE, Yusuf S *et al.* An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;**80**:234–44.

39. Oldridge N, Furlong W, Feeny D *et al.* Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. *Am J Cardiol* 1993;**72**:154–61.
40. Ades PA, Pashkow FJ, Nestor JR. Cost-effectiveness of cardiac rehabilitation after myocardial infarction. *J Cardiopulm Rehab* 1997;**17**:222–31.
41. Antiplatelet Trialist's Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81–106.
42. Goldman L, Sia STB, Cook EF *et al.* Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. *N Engl J Med* 1988;**319**:152–7.
43. Viscoli CM, Horwitz RI, Singer BH. Beta-blockers after myocardial infarction: influence of first-year clinical course on long-term effectiveness. *Ann Intern Med* 1993;**118**:99–105.
44. Phillips KA, Shlipak MG, Coxson P *et al.* Health and economic benefits of increased beta-blocker use following myocardial infarction. *JAMA* 2000;**284**:2748–54.
45. Tsevat J, Duke D, Goldman L *et al.* Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol* 1995;**26**:914–19.
46. Franzosi MG, Maggioni AP, Santoro E *et al.* Cost-effectiveness analysis of early lisinopril use in patients with acute myocardial infarction. Results from GISSI-3 trial. *Pharmacoeconomics* 1998;**13**:337–46.
47. Yusuf S, Sleight P, Pogue J *et al.* Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
48. Lamy A, Gafni A, Pogue J *et al.* Cost-effectiveness of ramipril in high risk patients: analysis of the HOPE Study. *Can J Cardiol* 2000;**16**(Suppl F):233F.
49. Haskell WL, Alderman EL, Fair JM *et al.* Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: the Stanford Coronary Risk Intervention Project (SCRIP). *Circulation* 1994;**89**:975–90.
50. Superko HR. Sophisticated primary and secondary atherosclerosis prevention is cost effective. *Can J Cardiol* 1995;**11**:35–40.
51. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
52. The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *JAMA* 1996;**276**:1409–15.

25 Diet and cardiovascular disease

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Introduction

The rapid escalation of the global epidemic of cardiovascular diseases (CVD), projected for the first quarter of the twenty-first century, requires a comprehensive public health response that can reduce risk at both population and individual levels.[1] Diet, as regularly consumed, and the nutrients supplied by it are major determinants which initiate and influence the course of atherothrombotic vascular disease. Identification of increased or decreased risk associated with dietary patterns or specific nutrients, in a methodologically rigorous manner, should lay the scientific foundation for general dietary recommendations to populations as well as specific nutritional interventions in individuals at a high risk of CVD.

Methodological issues in the study of causal associations

Issues related to study design

Studies investigating the influence of diet on CVD or cardiovascular risk factors have employed a wide variety of study designs: ecological studies within and across populations, cross-sectional surveys, case–control studies (*de novo* or nested), cohort studies, community-based demonstration projects, randomized clinical trials, and before-after type of metabolic studies. These differ widely in terms of their ability to (a) identify, avoid, and adjust for confounding; (b) establish a temporal relationship of cause preceding the effect; (c) minimize bias; (d) provide a wide range of exposure; (e) ascertain composite end points, including fatal outcomes; (f) evaluate population attributable risk; and (g) yield generalizable results.

These issues related to study design become relevant when interpreting the results of reported studies on diet and CVD and assessing their public health implications. Frequently, conclusions from studies employing weak designs are negated by the results emerging from methodologically stronger studies. Public policy and clinical practice must both be judiciously guided by credible evidence provided by scientifically stronger studies and not be misled by controversial results emerging from feeble study designs.

Clinical trials, if well designed, provide the best framework for studying associations, as free from the effects of bias and confounding as possible. However, they often evaluate interventions that are relatively short term and introduced late in the natural history of disease and may not replicate the effects of long-term dietary exposures. Genetics now offer a possible alternative to clinical trials through "mendelian randomization". This approach takes into account that genotypic differences in the metabolism of food ingredients may cause lifelong differences in exposure to food components and their metabolites or to purported risk factors. It may be a powerful way to establish causality without the need for prolonged follow up.[2,3]

A related issue is the use of experimental animals. Although these are often referred to as "animal models" their validity in predicting outcomes in humans is unclear. Lipid metabolism especially is species-specific, as exemplified by the lack of efficacy of cholesterol lowering statin drugs in many animal species, including monkeys.[4] Experiments in animals are therefore best reserved for elucidating mechanisms, and cannot be used to argue that a particular food will have a particular effect on cardiovascular disease in humans.

Issues involving outcome variables

These principally relate to a choice between disease end points and intermediate variables and the types of variables, which are selected for study within each category. Ideally, disease-related end points are preferable since they clearly demonstrate the benefits or risks of dietary exposures. In an exposure such as diet, effects may extend beyond cardiovascular outcomes. The need to evaluate impact of diet on total mortality and major co-morbidities, therefore, becomes an imperative. It must also be recognized that dietary exposures which influence thrombotic pathways may have different effects on the risk of hemorrhagic stroke and thrombotic stroke, often in opposite directions. The need to differentiate the types of stroke in outcome evaluation is, therefore, clear and has important implications for populations that differ in their stroke profiles. Similarly, selective benefits limited only to non-fatal outcomes, as in the case of CHAOS study which reported a possible benefit of vitamin E administration on non-fatal myocardial infarction,[5] are seldom replicated and cannot influence either public health policy or clinical practice.

The ascertainment of disease-related end points, as the primary outcome, has most often been attempted in large and

long-term cohort studies, or in clinical trials conducted in population groups in whom high event rates were anticipated in a short or medium time frame. Thus, observational cohort studies investigating the long-term impact of diet on primary prevention of cardiovascular disease frequently compete with secondary prevention trials. If the results are discordant, it is difficult to interpret whether the differences are due to methodologic reasons of confounding or due to the fact that exposures occurred at different times and for variable periods in the natural history of the disease. It must, however, be recognized that pathologic processes such as endothelial dysfunction, plaque instability, thrombosis and cardiac arryhythmias can be influenced even by short-term exposures.

Intermediate variables have been frequently utilized in studies evaluating the association of dietary constituents or dietary patterns to cardiovascular diseases (CVD). Most often, these are risk factors like blood pressure or plasma lipids. However, it must be recognized that similar changes in total plasma cholesterol may be associated with variable effects on levels of LDL cholesterol and HDL cholesterol and on the ratio of total to HDL cholesterol. The impact on risk of atherosclerotic CVD may thus vary. The 25 year follow up experience of the Seven Countries Study revealed that while the increase in relative risk of CHD for comparable levels of plasma cholesterol elevation was similar across diverse populations, the absolute risk of CHD varied widely at the same level of plasma cholesterol, possibly due to other dietary and non-dietary influences.[6] Dietary changes may also influence LDL particle size differentially, as also the level of plasma triglycerides, with variable net effects on the atherogenicity of the plasma lipid pool. Such limitations were clearly illustrated in a study by Rudel *et al*[7] where monkeys fed monounsaturated fat had similar lowering of LDL cholesterol as monkeys fed polyunsaturated fat but developed atherosclerosis equivalent to those fed saturated fat. In monkeys fed monounsaturated fatty acids, there was an enrichment of cholesteryl oleate in plasma cholesteryl esters, which correlated with coronary artery cholesteryl ester concentration.[8] Plasma lipids, as intermediate variables, could not also explain the degree of cardiovascular protection conferred by the Mediterranean diet in the Lyon Diet Heart Study.[9] While studies of intermediate variables are useful in identifying mechanistic pathways of dietary harm or benefit and plasma cholesterol has served well so far to explain much of the coronary risk associated with certain diets, there is a need for methodologically strong studies which relate dietary patterns or dietary interventions to hard end points such as total mortality, cardiovascular mortality, and combined fatal and non-fatal cardiovascular events.

Issues involving the exposure variables

These involve the type of exposure selected for study, the methods of measurement employed as well as the duration and dose of exposure. First, the types of dietary exposure assessed for associations with CVD, have varied from specific nutrients (such as saturated fat) to dietary items (such as fish) to food groups (such as fruit and vegetables) to dietary patterns (such "Mediterranean" diet or "Adventist" diet) and composite dietary interventions (such as the DASH diet). A reductionist approach has inherent limitations in the area of diet, because multiple interactions among many nutrients are likely to determine the physiologic effects and pathologic outcomes much more than the individual effects of an isolated nutrient. Multi-component dietary exposures, however, render identification of mechanistic causal pathways difficult to elucidate. While this frustrates efforts to develop and market specific food supplements or nutriceuticals, interests of public health are likely to be better served by a combined food- and food-component-based approach to a causal inquiry exploring the connections between diet and cardiovascular health.

Second, the strengths and limitations of various methods of collecting accurate food consumption data are well recognized.[10] Questionnaire methods of ascertaining information related to habitual food intake pose problems of validity and reproducibility even within well defined populations, but these problems are likely to be magnified when such instruments are applied across different cultures. Even if the nutrient composition of self reported diets is accurately estimated, different cooking methods may alter the final bioavailability of those nutrients as actually consumed. The need for valid and reproducible biomarkers is, therefore, important when studies of specific nutrients are proposed. For example, adipose tissue fatty acid composition is a suitable biomarker for habitual type of dietary fat intake.[11] There may, however, be technical and financial constraints which limit the use of such biomarkers in large epidemiologic studies.

Third, a causal inquiry needs to recognize the lag time effect, wherein a long period of exposure to dietary variables is required before effect is evident on outcome variables (especially disease-related end points of atherosclerotic vascular disorders). Short-term studies may be incapable of identifying true effects even when they exist. This is clearly illustrated by trials evaluating the effect of sodium restriction on blood pressure, where benefit was demonstrated only in trials in which the duration of exposure was at least 5 weeks.[12] The dose of exposure is another critical variable in an area like diet, where many of the nutrients are physiologic requirements at a certain level but may pose risk of cardiovascular dysfunction and disease at other levels. The relationships may vary from linear to J-shaped or threshold, for different variables. Ascertainment of dose-related effects is essential, whether the exposure is salt, alcohol or fish.

Issues related to diet as an independent variable

These relate to the association of dietary behaviors with other behaviors which influence cardiovascular risk and the

impact of diet on several cardiovascular risk factors which may partly or wholly be in the causal pathway to CVD as intermediate variables. Unhealthy dietary behaviors often occur in association with other unhealthy behaviors such as physical inactivity and smoking. Furthermore, unhealthy dietary practices such as high consumption of saturated fats, salt and refined carbohydrates as well as low consumption of fruit and vegetables tend to cluster together. In contrast, persons who habitually adopt one healthy dietary practice are more likely to adopt other healthy dietary habits as well as practice regular physical activity and abstinence from smoking. Dietary behaviors may also reflect patterns influenced by social class and may be influenced by stress levels. Dissociating the specific effects of individual dietary components from other dietary components, physical activity levels, and other behaviors becomes difficult outside the setting of a carefully controlled clinical trial. In observational studies, the question arises whether some dietary practices are merely a surrogate for other dietary practices or for a composite of multiple health behaviors. Whether diet should be considered in dissociation from physical activity or should preferably be studied in combination is also an issue for observational research.

The effects of diet on multiple cardiovascular risk factors, ranging from body weight to blood lipids and blood pressure to thrombotic mechanisms, also poses the question of when and how far to adjust for these variables in evaluating the relationship of diet to CVD. Since many of these are intermediate variables linking diet to CVD, adjustment to exclude their effect would underestimate the effect of diet. However, such variables are also influenced by factors other than diet. In such cases, the decisions related to adjustment should be carefully considered.

Nutrients and CVD

Dietary fats

The relationship between dietary fats and cardiovascular disease (CVD), especially coronary heart disease (CHD), has been extensively investigated, with strong and consistent associations emerging from a wide body of evidence accrued from animal experiments, as well as observational studies, clinical trials, and metabolic studies conducted in diverse human populations. The relationship of dietary fat to CVD was initially considered to be mediated mainly through the atherogenic effects of plasma lipids (total cholesterol, lipoprotein fractions, and triglycerides). The effects of dietary fats on thrombosis and endothelial function as well as the relationship of plasma and tissue lipids to the pathways of inflammation have been more recently understood.[11,13] Similarly, the effects of dietary fats on blood pressure have also become more evident through observational and experimental research.

Cholesterol in the blood and tissues is derived from two sources: diet and endogenous synthesis. Dairy fat and meat are major sources. Egg yolk is particularly rich in cholesterol but, unlike dairy and meat, does not provide saturated fatty acids. Dietary cholesterol raises plasma cholesterol levels.[14] Although both HDL and LDL increase, the effect on the total/HDL ratio is still unfavorable, but small.[15] Observational evidence on an association of dietary cholesterol intake with cardiovascular disease is contradictory.[16,17] The upper limit for dietary cholesterol intake has been prescribed, in most guidelines, to be 300 mg/day. However, since there is no requirement for dietary cholesterol, it is advisable to keep the intake as low as possible.[13] If intake of dairy fat and meat are controlled, there would be no need for a severe restriction of egg yolk intake, although some limitation remains prudent.

Fatty acids are grouped into three classes – saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). While such a classification is useful in providing a structural grouping, it tends to oversimplify the effects of dietary fats. Individual fatty acids, within each group, are now known to have differing effects on lipids, lipoproteins and platelet-vascular homeostasis. SFA and MUFA can be synthesized in the body and hence are not dietary essentials. PUFA are essential fatty acids, since they cannot be synthesized in the body.

Saturated fatty acids (*SFAs*) as a group raise total and LDL cholesterol, but individual SFAs have different effects.[11,18] Myristic and lauric acids have greater effect than palmitic acid, but the latter is more abundant in food supply. The plasma cholesterol raising effects of these three SFAs is higher when combined with high cholesterol diets. Stearic acid has not been shown to elevate blood cholesterol and is rapidly converted to oleic acid (OA) *in vivo*. Metabolic (feeding) studies demonstrate a marked elevation of both HDL and LDL cholesterol induced by SFA diets.[19,20] Replacement of saturated fatty acids by polyunsaturated fat reduces the total to HDL cholesterol ratio but replacement by carbohydrates does not. Also, tropical fats rich in lauric acid (C12) raise total cholesterol strongly, but because of their specific effect on HDL, the ratio of total to HDL cholesterol falls. Thus effects on blood lipids can be variable, depending on which blood lipids are studied, and we need data on actual outcomes to determine the true effects of fats on coronary heart disease.[21] The relationship of dietary saturated fat to plasma cholesterol levels and to CHD was graphically demonstrated by the Seven Countries Study involving 16 cohorts, in which saturated fat intake explained 73% of the total variance in CHD across these cohorts.[22] In the Nurses Health Study[20] the effect of saturated fatty acids was much more modest, especially if saturates were replaced by carbohydrates. The most effective replacement for saturated fatty acids in terms of coronary heart disease outcome is by polyunsaturated fatty acids – that is, linoleic acid. This

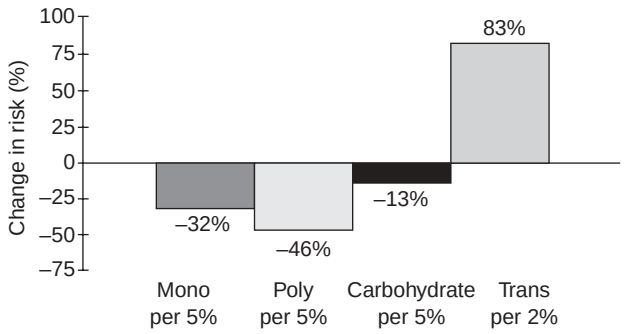

Figure 25.1 Change in CHD risk associated with replacement of saturates by other fats: Nurses Health Study (based on Hu *et al*[22]).

agrees with the outcome of large randomized clinical trials, in which replacement of saturated and *trans* fats by polyunsaturated vegetable oils effectively lowered coronary heart disease risk (see Figure 25.1).[23]

Trans fatty acids (*t-FAs*) are geometrical isomers of unsaturated fatty acids that assume a saturated fatty acid-like configuration. Partial hydrogenation, the process used to create t-FA, also removes essential fatty acids such as linoleic acid and α-linolenic acid. Metabolic studies have demonstrated that t-FAs render the plasma lipid profile even more atherogenic than SFA, by not only elevating LDL cholesterol to similar levels but also decreasing HDL cholesterol.[24] As a result, the ratio of LDL cholesterol to HDL cholesterol is significantly higher with a t-FA diet (2·58) than with a SFA diet (2·34) or an oleic acid diet (2·02). Evidence that intake of t-FA increases the risk of CHD initially became available from large population-based cohort studies in the USA[25,26] and has recently been corroborated in an elderly Dutch population.[27] Levels of t-FA in a biochemical analysis of replicated baseline food composites correlated with the risk of coronary death in the cohorts of the Seven Countries Study. Most t-FAs are contributed by industrially hardened oils, but the dairy and meat fats of ruminants are also a source. Whether these two sources have the same effect on coronary heart disease risk is unclear, but reductions in ruminant fats are already advisable for other reasons. Eliminating t-FAs from the diet would be an important public health strategy to prevent cardiovascular disease. Since these are commercially introduced agents into the diet, policy measures related to the food industry would be required along with public education. *Trans* fatty acids have been eliminated from retail fats and spreads in a large part of the world, but deep-fat fried fast foods and baked goods are a major and increasing source.[28]

The only nutritionally important *monounsaturated fatty acid* (*MUFA*) is oleic acid, which is abundant in olive and canola oils and also in nuts. The epidemiologic evidence related to MUFA and CHD is derived from studies on the Mediterranean diet, as well as from the Nurses Health Study and other similar studies, which investigated the association and controlled for confounding factors.[29] MUFAs have been shown to lower blood glucose and triglycerides in type II diabetic patients and may decrease susceptibility of LDL to oxidative modification.

Polyunsaturated fatty acids (*PUFAs*) are derived from dietary LA (n-6 PUFAs) and dietary ALNA (n-3 PUFAs). The important n-6 PUFAs are arachidonic acid (AA) and dihomogammalinolenic acid (DHGLA), while the important n-3 PUFAs are eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA). Eicasanoids derived from AA have opposing metabolic properties to those derived from DHA. A balanced intake of n-6 and n-3 PUFAs is, therefore, essential for health.

The biologic effects of n-3 PUFAs are wide ranging, involving lipids and lipoproteins, blood pressure, cardiac function, arterial compliance, endothelial function, vascular reactivity, and cardiac electrophysiology as well as potent antiplatelet and anti-inflammatory effects including reduced neutrophil and monocyte cytokine production.[11,30] Recent data have also shown that EPA and DHA have differential effects on many of these. DHA appears to be more responsible for the beneficial effects of fish and fish oils on lipids and lipoproteins, blood pressure, heart rate variability, glycemic control, in comparison to EPA, while a mixture of DHA and EPA significantly reduced platelet aggregation in comparison to ALNA *in vitro*.[11,31] The very long chain n-3 polyunsaturated fatty acids powerfully lower serum triglycerides, but they raise LDL cholesterol.[32] Therefore, their effect on coronary heart disease is probably mediated through pathways other than cholesterol.

Much of the epidemiologic evidence related to n-3 PUFAs is derived from the study of fish consumption in populations or interventions involving fish diets in clinical trials. Fish oils were, however, used in the GISSI study of 11 300 survivors of myocardial infarction.[33] In this factorial design, fish oil (1 g/day) and vitamin E (300 mg/day) were compared, alone and in combination, to placebo. After 3·5 years of follow up, the fish oil group had a statistically significant 20% reduction in total mortality, 30% reduction in cardiovascular death, and 45% decrease in sudden death. While most published studies do not indicate that dietary n-3 PUFA prevent restenosis after percutaneous coronary angioplasty or induce regression of coronary atherosclerosis, one study reported that occlusion of aortocoronary venous bypass grafts was reduced after 1 year by daily ingestion of 4 g fish oil concentrate.[34]

The Lyon Heart Study incorporated an n-3 fatty acid (alpha linolenic acid) into a diet altered to develop a "Mediterranean diet" intervention.[9] In the experimental group plasma ALNA and EPA increased significantly and the trial reported a 70% reduction in cardiovascular mortality at 5 years in its initial report. Total cholesterol and LDL cholesterol were identical

in the experimental and control groups, suggesting that thrombotic and perhaps arrhythmic events may have been favorably influenced by n-3 PUFA. Since the diet altered many other variables, such as fiber and antioxidants (by increasing fruit and vegetable consumption), direct attribution of benefits to n-3 PUFA becomes difficult to establish.

The effect of different fatty acids on cardiac arrhythmias has been an area of great interest. Diets rich in saturated fatty acids increase the risk of ventricular fibrillation and sudden cardiac death in primates. A recent population-based case–control study, using biomarkers, revealed a modest association of *trans* fatty acids in general and a strong association of *trans* isomers of linoleic acid in particular, with primary cardiac arrest in humans.[35] Several studies in different animal models, primate and rodent, have shown that n-3 PUFA are protective against cardiac arrhythmias, especially ventricular fibrillation.[36] It has been suggested that the fall in coronary heart disease mortality in USA and Australia, since 1967, is probably attributable to an increase in polyunsaturated fat consumption in both countries since 1960.[37] The decline in CHD mortality in the Zutphen cohort has similarly been attributed to a decreased consumption, over time, of *trans* fatty acids.[27]

The proportions of SFA, MUFA, and PFA as constituents of total fat intake and total energy consumption have engaged active attention, in view of the strong relationship of these fatty acids to the risk of CVD, especially CHD. The reduction of SFA in the diet has been widely recommended, but its replacement remains an area of debate as to whether the place of reduced SFAs should be taken by MUFA, PUFA or carbohydrate. Both MUFA and PUFA improve the lipoproteins profile, although polyunsaturated fatty acids are somewhat more effective. In view of this, recent US dietary recommendations suggested that SFA should be reduced to 7–8%, MUFA should be increased to 13–15%, and PUFA raised to 7–10% of daily energy, with the total fat contributing to no more than 30% of all calories consumed.[29,38] These may need to be adjusted for populations who consume less quantities of total fat, so as to ensure an adequate intake of MUFA and PUFA even under those circumstances.

The total quantity of fat consumed, as a proportion of daily energy intake, has not shown a relation to CVD that is independent of the SFA content. It has been argued that the type of fat consumed in diet is far more important than the total amount of fat consumed.[39] The compatibility of high fat Mediterranean diets (with total fat contributing >30% of calories) with coronary protection has also been cited as supportive evidence. While the emphasis on the type of fat is well placed, it must be recognized that high fat diets are also high in energy. Whether this contributes substantially to overweight is a subject of much debate.[40]

Enhancing the nutritional quality of dietary fat consumption, to provide greater cardiovascular protection, may be attempted by decreasing the sources of saturated fats and eliminating *trans* fatty acids in the diet, increasing the consumption of foods containing unsaturated fatty acids (both MUFA and PUFA) and decreasing dietary cholesterol consumption. Modification of cooking oils, either through appropriate admixture of different oils[41] or through genetic modification of oilseed crops,[42] may provide methods for improving the quality of dietary fat consumed through edible oils.

Carbohydrates

The relationship of dietary carbohydrates to CVD appears to be mediated through indirect mechanisms: contribution to total energy and its effect on overweight and obesity; influence on central obesity; effects on plasma lipids, especially triglycerides; and effects on glycemic control. The balance between carbohydrates and fat as sources of energy as well as the fiber component of the diet are also areas of interest while considering this relationship. In feeding experiments, an increase in dietary energy from carbohydrates is usually associated with a moderate increase in fasting plasma triglyceride levels in the first few weeks but these return to near original levels in the first few weeks. Epidemiologically, high carbohydrate intakes are associated with low plasma cholesterol and variable plasma triglyceride concentrations.[43]

The effect of a high carbohydrate diet on HDL cholesterol and thereby on the total LDL to HDL cholesterol ratio as well as on the particle size of LDL are matters of interest while considering the influence on vascular function and risk of CVD. High carbohydrate diets appear to reduce HDL cholesterol levels and increase the fraction of small dense LDL, both of which may impact adversely on vascular disease. This dyslipidemic pattern is consistent with the elevation of plasma triglycerides. There is as yet no clear evidence that the risk of CVD is altered independently by the carbohydrate levels in the diet. The glycemic index of foods might also be a determinant of the extent to which carbohydrates can influence the glycemic status. Carbohydrate diets with high glycemic index might adversely impact on glucose control, with associated changes in plasma lipids.[44,45]

Dietary fiber

Dietary fiber is a heterogeneous mixture of polysaccharides and lignin that cannot be degraded by the endogenous enzymes of vertebrate animals.[46] Water soluble fibers include pectins, gums, mucilages, and some hemicelluloses. Insoluble fibers include cellulose and other hemicelluloses. Most soluble fibers reduce plasma total and LDL cholesterol concentrations, as reported by several trials.[47] Pectins, psyllium, gums, mucilages, algal polysaccharides, and some hemicelluloses lower total and LDL cholesterol levels

without affecting HDL cholesterol, the reductions in total cholesterol being usually in the range of 5–10%. Human experiments have clearly shown that oat fiber tends to lower plasma total and LDL cholesterol but wheat fiber does not. Rice, bran, and barley may also lower cholesterol.[48] Fiber consumption predicted insulin levels, weight gain, and cardiovascular risk factors like blood pressure, plasma triglycerides, LDL and HDL cholesterol, and fibrinogen more strongly than other dietary components in the CARDIA cohort study of young adults.[49] However, fiber intake may be confounded with many other determinants of cardiovascular health.

Between 1996 and 2001, five very large cohort studies in the USA, Finland, and Norway have all reported that subjects consuming relatively large amounts of whole grain cereals have significantly lower rates of CHD.[48,50] High intake of fiber from cereal sources was associated with a reduced risk of CHD in the Nurses Health Study[50] and was inversely associated with the risk of hypertension in the Health Professionals Follow-up Study.[51] Available evidence supports a recommendation for consumption of about 15 g/1000 kcal of fiber.[47] Since some of the reported benefits may have arisen from other dietary components occurring in association with fiber in natural foods, dietary consumption of high fiber foods should be recommended rather than isolated fiber. Addition of wheat or cereal bran may be considered, where necessary, to supplement natural foods in order to attain the recommended dietary intake.

Antioxidants

The oxidation of LDL by oxygen free radicals results in the unregulated uptake of modified LDL by macrophages in arterial walls, accelerating the atherosclerotic process. Antioxidant nutrients, which can directly scavenge free radicals, include alpha-tocopherol (vitamin E isomer) and ascorbic acid (vitamin C), which have shown antioxidant activity both *in vitro* and *in vivo*, as well as beta-carotene (a provitamin A carotenoid) which has displayed anti-oxidant activity *in vitro*.[52] These mechanisms suggested that increased dietary intake or supplementation of these nutrients would be protective against atherosclerotic vascular disorders. This was supported by evidence from observational studies for vitamin E and beta-carotene, but results of clinical trials employing supplements have been disappointing.

Observational cohort data suggest a protective role for carotenoids. In a meta-analysis, the pooled relative risk reduction for cardiovascular death in those who ate diets rich in beta-carotene was 31% (95% CI 41–20), when dietary and blood carotene levels were measured to compare high and low consumers. The randomized trials, in contrast, reported a moderate adverse effect of beta-carotene supplementation, with a relative increase in the risk of cardiovascular death of 12% in a meta-analysis of four trials.[53] Cancer risk was also increased.

Several large cohort studies showed significant reductions in the incidence of cardiac events in men and women taking high-dose vitamin E supplements.[52] However, the HOPE trial, a definitive clinical trial relating vitamin E supplementation to cardiovascular outcomes, revealed no effect of vitamin E supplementation (at 400 IU/day, for a mean follow up of 4·5 years) on MI, stroke or death from cardiovascular causes in men or women.[54] Other trials also failed to demonstrate a cardioprotective effect of vitamin E supplements.[55]

The conflict between diet-based observational studies and clinical trials employing supplements may arise because of one or more explanatory factors: confounding, interactions/synergistic activity (among antioxidants – with other nutrients), isomers with differing activity in food compared to supplements, other associated protective elements in natural foods (for example, flavonoids, phytoestrogens) and/or temporal dissociation of antioxidant blood levels from fat intake in meals when administered as once a day pills. While the failure of pill supplementation does not necessarily exclude protective effects of dietary antioxidants, current evidence does not support supplementation of any of these antioxidant vitamins for prevention of CHD. However, intake of their primary food resources, especially fruit and vegetables, may be encouraged.

Folate

The relationship of folate to CVD has been mostly explored through its effect on homocysteine, which has been incriminated as an independent risk factor for CHD and probably stroke.[56–59] Folic acid is required for the methylation of homocysteine to methionine. Reduced plasma folate has been strongly associated with elevated plasma homocysteine levels and folate supplementation has been demonstrated to decrease those levels.[60] However, the role of homocysteine as an independent risk factor for CVD has been subject to debate, in view of the data from several prospective studies which did not find this association to be independent of other risk factors.[61] It has also been suggested that elevation of plasma homocysteine is a consequence and not a cause of atherosclerosis, wherein impaired renal function due to atherosclerosis raises plasma homocysteine levels.[62]

Whether homocysteinemia is the cause or consequence of atherosclerosis, its role in promoting thrombosis makes an intervention with folate appear attractive. There is also recent evidence that suggests that homocysteinemia results in endothelial dysfunction, an effect that is reversed by oral folate supplementation.[63,64] An independent antioxidant role for folate has also been postulated. Data from the Nurses Health Study showed that folate and vitamin B_6, from diet and supplements, conferred protection against CHD (fatal and non-fatal events combined) and suggested

a role for their increased intake as an intervention for primary prevention of CHD.[65] Food grain fortification with folate and cyancobalamin has also been recommended as a cost effective measure for CHD prevention.[66]

Recommendations related to folate supplementation must, however, await the results of ongoing clinical trials. Dietary intake of folate through natural food sources may be encouraged in the meanwhile, especially in individuals at a high risk of arterial or venous thrombosis and elevated plasma homocysteine levels.[67]

Flavonoids and other phytochemicals

Flavonoids are polyphenolic antioxidants which occur in a variety of foods of vegetable origin, such as tea, onions and apples. Data from several prospective studies indicate an inverse association of dietary flavonoids with coronary heart disease.[68] A benefit on stroke risk has also been reported.[69] However, confounding may be a major problem and may explain conflicting results of observational studies on flavonoids and coronary heart disease. Fruit and vegetables also contain other phytochemicals that may have protective properties, including isothiocyanates and indoles (found in cruciferous vegetables), sulfides (found in onions and garlic), terpenes (found in citrus oils), and phytoestrogens.[47] While their role in relation to CVD risk is not clearly established and trial evidence related to garlic supplements is generally not supportive, their consumption in the natural food form may have benefits, which need to be evaluated.

Minerals: blood pressure and cardiovascular disease

Sodium

High blood pressure (HBP) is a major risk factor for coronary heart disease (CHD) and both forms of stroke (ischemic and hemorrhagic). The relative risk of CVD for both systolic and diastolic blood pressures operates in a continuum of increasing risk for rising pressure but the absolute risk of CVD is considerably modified by coexisting risk factors.[70]

Of the many risk factors associated with high blood pressure, the dietary exposure most investigated has been daily sodium consumption. It has been studied extensively in animal experimental models, in epidemiological studies, controlled clinical trials, and in population studies on restricted sodium intake.[70] Salt or sodium intake has been directly correlated with mean blood pressure levels and prevalence of hypertension in many populations. Comprehensive epidemiological evidence was provided by the INTERSALT Study[71,72] which investigated the relationship of 24 hour urinary electrolyte excretion to blood pressure in 52 population groups across 32 countries, using standardized methodology to provide comparable data. In adults aged 20–59 years, there was a significant positive relationship between urinary sodium excretion and blood pressure across the 52 population samples. Further, it was also observed that in four of these populations in whom the mean 24 hour urinary sodium excretion was lower than 100 mmol/day, systolic blood pressure did not rise with age.[73]

The consequences of increased sodium consumption accompanying urbanization, on blood pressure levels, was demonstrated in the Kenyan Luo Migration Study wherein rural farmers who traditionally consumed a low salt diet were observed to have an elevation of blood pressure when they migrated to an urban environment. These migrants exhibited blood pressure levels higher than rural controls and comparable to levels observed in Western populations.[74] This rise in blood pressure was related to an increase in salt consumption and a reduced dietary intake of potassium. An overview of observational data in populations suggested that a difference in sodium intake of 100 mmol/day could be associated with average differences in systolic blood pressure of 5 mmHg at age 15–19 years and 10 mmHg at age 60–69 years.[75] Diastolic blood pressures are reduced by about half as much, but the association increases with age and the magnitude of the initial blood pressure. It was estimated that a universal reduction in dietary intake of salt by 50 mmol/day would lead to a 50% reduction in the number of people requiring antihypertensive therapy, a 22% reduction in number of deaths due to strokes, and a 16% reduction in number of deaths from coronary heart disease.[75]

A recently reported cohort study in Finland prospectively followed up 1173 men and 1263 women aged 25–64 years, with complete data on 24 hour urinary sodium excretion and cardiovascular risk factors.[76] The hazard ratios for CHD, CVD, and all-cause mortality, associated with a 100 mmol increase in 24 urinary sodium excretion, were 1·51 (95% CI 1·14–2·00), 1·45 (95% CI 1·14–1·84) and 1·26 (95% CI 1·06–1·50) respectively, in both men and women. The frequency of acute coronary events, but not acute stroke events, rose significantly with increasing sodium excretion. Disaggregated analyses revealed significant risk ratios in men only and revealed that sodium predicted mortality in men who were overweight. Despite the limitations of such subgroup analyses, the overall association of increasing sodium excretion with CVD and all-cause mortality further support the evidence linking increased sodium intake to adverse cardiovascular health outcomes.

Several clinical intervention trials, conducted to evaluate the effects of dietary salt reduction on blood pressure levels in hypertensive and normotensive individuals, have been systematically reviewed.[12,77] Many of the earlier trials were of limited size, short duration, and deficient in statistical power. Based on an overview of 32 methodologically adequate trials (22 in hypertensive subjects and 12 in

normotensive persons), Cutler *et al*[12] concluded that a daily reduction in intake of sodium by 70–80 mmol was associated with a lowering of blood pressure both in hypertensive and normotensive individuals, with systolic and diastolic blood pressure reductions of 4·8/1·9 mmHg in the former and 2·5/1·1 mmHg in the latter. Clinical trials have also demonstrated the sustained blood pressure lowering effects of sodium restriction in infancy,[78] as well as in the elderly population, in whom it provides a useful non-pharmacologic therapy.[79]

The results of the low sodium – DASH – diet trial[80] further strengthen the conclusion that reduction of daily sodium intake, through salt restricted diets, lowers blood pressure effectively and is additive to the benefits conferred by the DASH diet. This trial revealed that low sodium diets, with 24 hour sodium excretion levels around 70 mmol/day, are effective and safe. Sodium consumption has also been linked to the presence of left ventricular hypertrophy[81,82] and restricted sodium intake has been demonstrated to result in regression of this important indicator of cardiovascular risk.[81,82]

Of three population studies on restriction of salt, two (the Portuguese Salt Trial and the Tianjin trial in China) revealed significant reductions in blood pressure in the intervention group, while the third (the Belgian Salt Intervention Trial) did not reveal success because of difficulties in reducing salt consumption.[83–85] Animal models as well as ecological associations derived from the INTERSALT suggest a direct relationship between sodium consumption and the risk of stroke, though the methodology employed in these studies is not strong.[86,87]

Based on the observational and trial data so far available, it would be justified to recommend a daily salt intake of less than 5 g/day.[80] Such advice would be appropriate even in tropical climates, as sodium homeostasis regulates sodium excretion in sweat and urine without adverse effects under such conditions.

Potassium

Cardioprotective effects of dietary potassium have been hypothesized as the basis for low CVD rates in populations consuming "primitive" diets and in vegetarians in industrialized cultures.[88] The INTERSALT study provided evidence of an inverse association between urinary potassium excretion and blood pressure levels, across diverse populations.[71] Migrant studies also revealed a rise in blood pressure when diets changed to a lower potassium and higher sodium intake.[74]

A protective effect of potassium on blood pressure was suggested by clinical studies reporting that severe short-term potassium restriction induces salt sensitivity in normotensive humans,[89] as well as the blood pressure lowering effect of potassium supplements to the diet (ranging from 24–104 mmol/day) in hypertensive subjects.[88]

Whelton *et al* concluded from a meta-analysis of randomized controlled trials that potassium supplements reduced mean blood pressures (systolic/diastolic) by 1·8/1·0 mmHg in normotensive subjects and 4·4/2·5 mmHg in hypertensive subjects.[90] An increase in dietary intake of potassium, from approximately 60 to 80 mmol/day, was shown to be inversely and significantly related to the incidence of stroke mortality in women.[91]

While dietary potassium has been shown to have protective effects on blood pressure and CVD, there is no evidence to suggest that long-term potassium supplements should be administered for cardiovascular protection. The beneficial effects of fruit and vegetables recommend their regular use in daily diets at a level that should assure an adequate intake of dietary potassium.

Calcium and magnesium

A meta-analysis of studies involving calcium supplements reveal modest effects on blood pressure. The estimated blood pressure reduction was 2·1 mmHg for systolic blood pressure and 1·1 mmHg for diastolic blood pressure.[92] A review of 29 studies of magnesium was inconclusive due to methodological problems but suggested that there was no negative association of blood pressure with magnesium.[93] There is presently no evidence to recommend public health or clinical interventions involving the use of these minerals for cardiovascular protection in populations or individuals, other than in the form of a balanced diet providing an adequate daily intake.

Food items and food groups

Fruit and vegetables

While the consumption of fruit and vegetables has been widely believed to promote good health, evidence related to their protective effect has only been presented in recent years.[94–96] A systematic review reported that nine of ten ecological studies, two of three case–control studies and six of sixteen cohort studies found a significant protective association for coronary heart disease with consumption of fruit and vegetables or surrogate nutrients.[96] For stroke, three of five ecological studies and six of eight cohort studies found a significant protective association.[96]

A 5 year follow up study of 39 876 female health professionals,[97] observed a significant inverse association between fruit and vegetable intake and CVD risk. For increasing quintiles of total fruit and vegetable intake, the relative risks were 1·0, 0·78, 0·72, 0·68, and 0·68. After excluding participants with a self reported history of diabetes, hypertension or high cholesterol at baseline, the multivariate adjusted relative risk was 0·45 when extreme quintiles were compared (95% CI 0·22–0·91). In a 12 year follow up of

15 220 male physicians in the USA,[98] men who consumed at least 2·5 servings of vegetables per day were observed to have an adjusted relative risk of 0·77 for coronary heart disease, compared with men in the lowest category (<1 serving per day). Combining analyses of data from two large prospective cohort studies of women and men respectively, Joshipura *et al* reported that overall fruit and vegetable consumption were inversely related to the risk of ischemic stroke after adjusting for confounders.[99] Assessed as a continuous trend, an increment of 1 serving/day was associated with 6% lower risk of ischemic stroke among men and women combined. When analyzed separately for the type of fruit and vegetables, the lowest risks were observed for high consumption of cruciferous vegetables, green leafy vegetables, citrus fruits, vitamin C-rich fruits and vegetables.

The effects of increased fruit and vegetable consumption on blood pressure alone or in combination with a low fat diet, were assessed in the DASH trial.[100] While the combination diet was more effective in lowering blood pressure, the fruit and vegetable diet too lowered the blood pressure in comparison to the control diet (2·8 mmHg systolic and 1·1 mmHg diastolic). Such reductions, while seeming modest at the individual level, would result in a substantial reduction in population-wide risk of CVD by shifting the blood pressure distribution.

Fish

Most, but not all, population studies have shown that fish consumption in populations is associated with a reduced risk of CHD.[101–103] A systematic review concluded that the discrepancy in the studies may be due to differences in the populations studied, with only high-risk individuals benefitting from increasing their fish consumption.[103] It was estimated that, in high-risk populations, an optimum fish intake estimated at 40–60 g/day would lead to approximately a 50% reduction in death from coronary heart disease. In the Diet and Reinfarction Trial, 2 year mortality was reduced by 29% in survivors of a first myocardial infarction in persons receiving advice to consume fatty fish at least twice a week.[104] While the protective effects of fish on CHD are principally mediated by n-3 PUFA, the contribution of other constituents of fish cannot be ruled out. The effect of dietary fish on the risk of stroke has been investigated in cohort studies, with conflicting results on the risk of ischemic stroke.[105,106] A recent study reported that fish consumption is associated with a reduced risk of death from all causes as well as CHD and stroke mortality, using data from 36 countries.[107]

Nuts

Five large epidemiological studies have, thus far, demonstrated that frequent consumption of nuts was associated with decreased risk of CHD, the best known among them being the Adventist Health Study.[108–111] The relative risk ranged from 0·43 to 0·82 for subjects who consumed nuts more than five times per week compared to those who never consumed nuts. An inverse dose–response relationship was demonstrated between the frequency of nut consumption and the risk of CHD, in men as well as in women. Most of these studies considered nuts as a group, combining many types of nuts.

The effect of specific nuts on lipid and lipoprotein end points were evaluated in several clinical studies. The nuts studied to date include walnuts, almonds, legume peanuts, macadamia nuts, pecans, and pistachio nuts.[108] Collectively, these clinical studies indicate that inclusion of nuts in a lipid lowering diet has favorable effects, but does not provide unequivocal evidence of an additive effect of nuts to the effects of a low saturated fat diet *per se*. The fatty acid profile of nuts (high in unsaturated fatty acids and low in saturated fatty acids) contributes to cholesterol lowering by altering the fatty acid composition of the diet as a whole. Nuts are also a rich source of dietary fiber. It must, however, be recognized that the high fat content of nuts makes them high in calorie content and advice to include nuts in the diet must be tempered in accordance with the desired energy balance. While further research is needed to characterize the independent protective effects of nuts against CVD and identify the mechanisms of such protection, available evidence suggests that nuts should be recommended as part of an energy-appropriate healthy diet which is intended to reduce the risk of CHD.

Soy

Several trials indicate that intake of soy has a beneficial effect on plasma lipids.[112,113] A composite analysis of 38 clinical trials found that an average consumption of 47 g of soy protein a day led to a 9% decline in total cholesterol and a 13% decline in LDL cholesterol in subjects free of CHD.[112] The benefit of soy consumption was associated with baseline cholesterol levels, such that those with the highest cholesterol levels derived the maximum benefit (subjects with total cholesterol >335 mg/dl showed a 19% reduction in total and 24% reduction in LDL cholesterol). Cholesterol lowering of this magnitude could potentially reduce the risk for CAD by 20–40%.

Soy is rich in isoflavones, compounds that are structurally and functionally similar to estrogen. Several animal experiments suggest that intake of these isoflavones may provide protection against CHD,[114] but human data on efficacy and safety are still awaited. Naturally occurring isoflavones, isolated with soy protein, reduced the plasma concentrations of total and LDL cholesterol without affecting the concentrations of triglycerides or HDL cholesterol in mildly hypercholesterolemic individuals, in a casein-controlled clinical trial.[115]

Dairy products

Milk and milk products are important contributors to dietary fat and can be high in saturated fat and cholesterol. They are also sources of minerals like potassium, magnesium, and calcium. Milk protein has been implicated in a study reporting elevated levels of antibodies to milk protein in myocardial infarction patients in comparison with healthy controls.[116] Dairy consumption has been correlated positively, in an ecological study, with blood cholesterol as well as coronary mortality. Milk consumption correlates positively with coronary mortality rates in 43 countries and with myocardial mortality in 19 regions of Europe.[117,118] In contrast, a population-based study in men of Japanese ancestry in Honolulu reported a reduced risk of ischemic stroke in older middle aged men, which could not be explained by the intake of dietary calcium.[119]

On the basis of presently available evidence, reduced intake of high-fat dairy foods should be recommended for cardiovascular protection. Whether milk or milk products modified to substantially lower the content of saturated fat are associated with an increase or decrease in cardiovascular risk cannot be commented upon at present. They formed a component of the DASH diet which significantly lowered blood pressure and may be considered as part of a composite dietary advice.

Alcohol

The relationship of alcohol to overall mortality and cardiovascular mortality has generally been J-shaped, when studied in Western populations in whom the rates of atherothrombotic vascular disorders are high.[120–124] The protective effect of moderate ethanol consumption is primarily mediated through its effect on the risk of coronary heart disease (CHD), as supported by more than 60 prospective studies.[121] A consistent coronary protective effect has been observed for consumption of one to two drinks per day of an alcohol-containing beverage, but heavy drinkers have higher total mortality than moderate drinkers or abstainers, as do binge drinkers. Moderate alcohol consumption (up to two drinks per day) has also been associated with a reduced risk of ischemic stroke in men and women.[125] Long-term heavy alcohol consumption ($>$60 g/day) increases an individual's risk for all stroke subtypes.

Several mechanisms for the cardioprotective effects of alcohol have been proposed: increase in plasma HDL cholesterol; reduced platelet aggregation or clotting; enhanced fibrinolysis; phenolic constituents of some alcoholic beverages acting as antioxidants or platelet inhibitors.[126] Genetic variations which slow alcohol metabolism have been shown to increase HDL cholesterol and reduce the risk of myocardial infarction.[3] Based on current evidence, the benefit of moderate alcohol consumption seems to be a generic effect regardless of the type of beverage.[127] While the specific advantages of red wine over other alcoholic beverages is unproven, the claimed beneficial effects of flavonoids on lipoprotein oxidation are available from grape juice as from wine.[128]

The possible beneficial effects of moderate ethanol consumption must be weighed against the deleterious effects of high intake, including increased risk of hypertension, cardiomyopathy, and hemorrhagic stroke. Alcohol consumption, in excess of three drinks per day, is associated with a rise in blood pressure and plasma triglyceride levels. Reduction or cessation of alcohol consumption is a widely recommended measure for non-pharmacologic therapy of hypertension, in many international guidelines. The recommendations related to alcohol should be made in accordance with the cultural practices of the populations and the clinical profile of individuals, with advice to avoid excess in all cases.

The optimal intake, for cardiovascular protection depends on age, gender, presence of other risk factors or associated diseases, and on the intake of folic acid. However, it is generally recommended to be about two drinks a day for men and one a day for women.

Eggs

Eggs are unique because of their high cholesterol content. Major effects on atherosclerosis are observed in experimental animals but extrapolation to humans is doubtful. A large observational study suggested that there was no increase in the risk of CHD up to one egg per day (except in a diabetic subgroup), in the US population.[129] In terms of global recommendations, it may still be prudent to limit the intake to three to four eggs per week.

Dietary patterns and composite dietary interventions

The Mediterranean diet

The traditional Mediterranean diet has been described to have eight components: (i) high monounsaturated-to-saturated fat ratio; (ii) moderate ethanol consumption; (iii) high consumption of legumes; (iv) high consumption of cereals (including bread); (v) high consumption of fruit; (vi) high consumption of vegetables; (vii) low consumption of meat and meat products; and (viii) moderate consumption of milk and dairy products.[130] Most of these are found in many diets. The characteristic component is olive oil, and many equate a Mediterranean diet with consumption of olive oil.

Based on ecological comparisons, Keys *et al*[131] hypothesized that traditional Mediterranean diet conferred protection against CVD and several other disorders, principally because of a low saturated fat content. Three prospective population studies in Greece, Denmark, and Australia provided supportive evidence of protective effects on overall mortality.[132]

However, this traditional form of "Mediterranean diet" has not been tested in controlled clinical trials.

A secondary prevention trial of dietary intervention in survivors of a first recent myocardial infarction, which aimed to study the cardioprotective effects of a "Mediterranean type" of diet, actually left out its most characteristic component, olive oil.[133] This diet was designed to supply <35% of energy as fat, <10% of energy as saturated fat, <4% of the energy as linoleic acid (n-6) and >0·6% of energy as alpha– linolenic acid (n-3). The main fat source was rapeseed oil. Vegetables and fruit were also increased in the diet. Two major biologic factors were modified by the intervention: plasma levels of alpha-tocopherol and ascorbic acid were elevated and plasma n-3 fatty acids increased along with a decrease in n-6 fatty acids. Other biologic mediators of altered risk, like flavonoids, folate and minerals like potassium were probably altered but not measured. While the initial publication reported a 70% reduction in recurrence of myocardial infarction and cardiac death, the 4 year follow up study reported a 72% reduction in cardiac death and non-fatal myocardial infarction. The risk of overall mortality was lowered by 56%.[9]

Vegetarian diets

A reduced risk of CVD has been reported in populations of vegetarians living in affluent countries[134–136] and in case–control comparisons in developing countries.[137] Reduced consumption of animal fat and increased consumption of fruit, vegetables, nuts and cereals may underlie such a protective effect. However vegetarian diets *per se* need not be healthful.[136] If not well planned, they can contain a large amount of refined carbohydrates and *trans* fatty acids while being deficient in the levels of vegetable and fruit consumption. The composition of the vegetarian diet should, therefore, be defined in terms of its cardioprotective constituents rather than use or endorse the "vegetarian" label as an omnibus category.

"Prudent" *v* "Western" patterns

Using factor analysis on a 131-item food frequency questionnaire, Hu *et al.* identified two major dietary patterns at baseline in 44 875 men followed up for 8 years in the Health Professionals Follow-up Study.[138] The "prudent" pattern was characterized by higher intake of vegetables, fruit, legumes, whole grains, fish, and poultry whereas the "Western" pattern was characterized by higher intake of red meat, processed meat, refined grains, sweets and desserts, French fries, and high fat dairy products. After adjustment for age and other coronary risk factors, relative risks, from the lowest to the highest quintiles of the prudent pattern score, were 1·0, 0·87, 0·79, 0·75, and 0·70. In contrast, the relative risks, across increasing quintiles of the Western pattern, were 1·0, 1·21, 1·36, 1·40, and 1·64. These associations persisted in subgroup analyses according to cigarette smoking, body mass index, and parental history of myocardial infarction.

Japanese diet

The traditional Japanese diet has attracted much attention because of the highest life expectancy and low CHD mortality rates among the Japanese.[139] This diet is low in fat and sugar and includes soy, seaweeds, raw fish, and a predominant use of rice. It has been high in salt, but salt consumption has recently been declining in response to Japanese Health Ministry guidelines. There is also recent trend towards increased fat consumption and plasma cholesterol levels have risen, and their effects on CHD and CVD mortality rates need to be watched.

DASH diets

The effects of composite dietary interventions on blood pressure levels, in "normotensive" and "hypertensive" individuals were studied in well designed clinical trials.[80,100] The initial dietary intervention, used in the Dietary Approaches to Stop Hypertension (DASH) trial, involved a diet that emphasized fruit, vegetables, and low fat dairy products, and included whole grains, poultry, fish, and nuts while reducing the amounts of red meat, sweets, and sugar-containing beverages. Two variants of the intervention diet were used: a fruit and vegetables (F-V) diet and a low fat F-V (DASH) diet. The latter was designed to lower the intake of total and saturated fat as well as dietary cholesterol. In comparison with a "typical" diet in the USA, both intervention diets lowered blood pressure but the DASH diet was more effective in substantially reducing systolic and diastolic blood pressures, both in people with hypertension and in those without hypertension.[80] The DASH diet was also demonstrated to be effective as first line therapy in individuals with stage I isolated systolic hypertension (that is, with a systolic blood pressure of 140–159 mmHg and a diastolic blood pressure below 90 mmHg), with 78% of the persons on the DASH diet reducing their systolic blood pressure to <140 mmHg, in comparison to 24% in the control group.[140] The DASH diet resulted in lowering plasma levels of total cholesterol and LDL cholesterol but these changes were also accompanied by a reduction in HDL cholesterol levels.[141] While the Framingham risk score improved as a result of the impact on total and LDL cholesterol as well as blood pressure, the impact of the associated reduction in HDL cholesterol needs to be assessed.

The DASH trial was followed by a well designed factorial trial combining the DASH diet with high, intermediate, and low levels of sodium consumption and measuring the effects on blood pressure, in comparison to a control diet typical of the USA, administered with similar graded variations in the sodium content.[100] Within each assigned group

(DASH *v* typical), participants ate foods with high intermediate and low levels of sodium for 30 consecutive days each, in random order. Reduction in sodium intake, at each level, resulted in significant lowering of systolic and diastolic blood pressures in both DASH and control groups. The fall was, however, maximal when the DASH diet was modified to reduce the sodium content. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7·1 mmHg lower in participants without hypertension and 11·5 mmHg lower in participants with hypertension (Figure 25.2). There was also a −4·5 mmHg difference in the mean diastolic pressure level, between the low sodium–DASH diet phase and the high sodium–control diet phase of the trial.

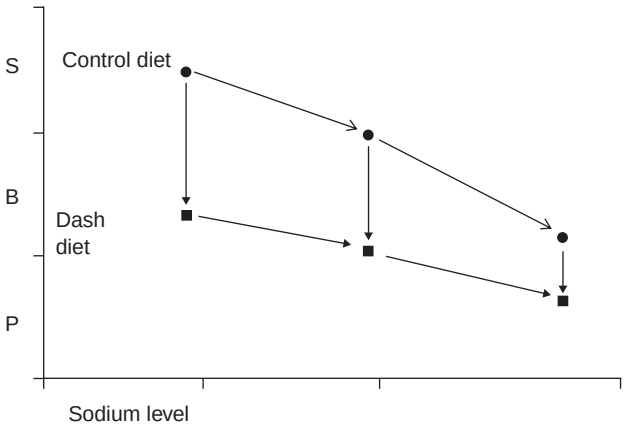

Figure 25.2 Effect of the low sodium–DASH diet on systolic blood pressure (adapted from Sacks *et al*[80])

The effects of the low sodium–DASH diet have a great potential for application in both population-based and individual focused strategies for prevention and control of high blood pressure and associated CVD. Adoption of the low sodium–DASH diet, by populations at large, is likely to be safe and beneficial in shifting the population distributions of blood pressure (and plasma cholesterol) towards lower levels of cumulative risk of CVD in those populations. Similarly, this diet will also provide an effective non-pharmacologic therapeutic intervention in the clinical management of individuals identified to be at an increased risk of CVD because of high blood pressure and associated risk factors.

Dietary recommendations for cardiovascular health

- A low intake of saturated fatty acids (SFA): less than 7% of daily energy intake (within these limits, intake of foods rich in myristic and palmitic acids should be especially reduced). **Grade A**
- A very low intake of *trans* fatty acids (hydrogenated oils and fats): less than 1% of daily energy intake. **Grade B**
- Adequate intake of polyunsaturated fatty acids (PUFA): 6–10% of daily energy intake, with an optimal balance of n-6 PUFA and n-3 PUFA at 5–8% and 1–2% levels of daily energy intake, respectively. **Grade B**
- Intake of monounsaturated fatty acids (MUFA) to make up the rest of daily energy intake from fats, with daily total fat intake ranging between 15% and 30% of daily energy intake (this may be based on current levels of population consumption in different regions and modified in accordance with age, activity and goals of body weight). **Grade A**
- While there is no evidence that links the quantity of dietary fat to CVD, independent of the effects of fat composition and unhealthy weight gain, there are concerns over potential excess energy consumption associated with an unrestricted fat intake. These support a recommendation that fat intake should not exceed 30% of daily energy intake. However, in very active groups with healthy dietary practices and stable healthy weight, fat intake may go up to 35% of energy. **Grade B**
- Restriction of dietary cholesterol consumption: less than 300 mg per day, mainly through the restriction of dairy fats. **Grade B**
- Daily intake of fresh fruit and vegetables (including berries, green leafy and cruciferous vegetables and legumes) in an adequate quantity: 400–500 g per day is recommended to reduce the risk of CHD, stroke and high blood pressure. **Grade A**
- Restriction of daily salt (sodium chloride) intake: less than 5 g per day. This should take into account total sodium intake from all dietary sources. **Grade A**
- Minimization of other forms of sodium consumption such as through food additives or preservatives, such as monosodium glutamate (MSG). **Grade B**
- Potassium intake at a level which will keep the sodium:potassium ratio close to 1: a daily potassium intake level of 70–80 mmol per day. This may be achieved through adequate daily consumption of fruit and vegetables. Such a balance may also be obtained through use of potassium enriched low sodium salt substitutes. **Grade A**
- Consumption of fish and other marine foods to provide over 200 mg per day of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). **Grade A**
- Regular low to moderate consumption of alcohol (that is, 1–2 drinks per day) is protective against CHD, concerns about other cardiovascular and health risks associated with alcohol consumption (including stroke, hypertension, and some cancers) do not favor a general recommendation for its use. **Grade B**

Source: adapted from WHO Expert Consultation on Diet and Prevention of Chronic Diseases, 2002: http://www.who.int/hpr/nutrition/ExpertConsultationGE.htm

Implications for policy

The rising global burden of CVD requires a rapid response that integrates policies and programs which enable effective prevention and control in diverse geographical and resource settings. Diet and nutrition play a critical role in the causation of major CVDs and, along with physical activity, influence many of the biologic variables that mediate the risk of those diseases. There is, therefore, an opportunity to alter the direction and dimensions of the global CVD epidemic through policy interventions (at the local, national, and global levels), which promote the availability, affordability, and acceptability of health promoting diets and restrain the marketing and consumption of unhealthy foods.

Currently available evidence strongly indicates that cardiovascular health is strongly influenced by the quality of dietary fat and the quantity of fruit and vegetables as well as salt consumed daily. While several other food items also contribute to enhanced or decreased risk of CVD, these remain the principal determinants of diet-related CVD risk. Whether the evidence is derived from controlled clinical trials or an ecologic study of reasons for a sharp decline in coronary mortality in Poland since 1991, the evidence suggests that dietary changes can substantially alter the risk of CVD.[142,143] Policies must, therefore, address these directly and decisively.

These measures must encompass a wide range of educational as well as regulatory measures, acting through price and non-price mechanisms. That success in reducing CVD risk factor levels as well as CVD mortality is achievable through such measures that influence usual diet patterns is clear from the experience of developed countries.[144] Developing countries like Mauritius have shown that population levels of CVD risk factors can be altered by a combination of community education and regulatory interventions related to the price of edible oils.[145]

Measures to influence the quality of dietary fat (as well as the total quantity) consumed must address the elimination of *trans* fats and reduction of saturated fats from the daily diet. Governments must work with the food industry to influence production, processing, pricing, and labeling of food products so that these goals can be met. Consumer education must be enhanced so that informed choices can be made, even as the availability of healthier foods is promoted through such measures. As market economy becomes a globally pervasive economic model, it must be recognized that markets are not autonomous entities and should be molded, for public good, by consumer consciousness as well as enlightened regulatory measures.

References

1. Reddy KS. Cardiovascular diseases in the developing countries: dimensions, determinants, dynamics and directions for public health action. *Publ Hlth Nutr* 2002;**5**:231–7.
2. Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001;**358**:1356–60.
3. Hines LM, Stampfer MJ, Ma J *et al.* Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med* 2001;**344**:549–55.
4. Krause BR, Princen HMG. Lack of predictability of classical animal models for hypolipidemic activity: a good time for mice? *Atherosclerosis* 1998;**140**:15–24.
5. Stephens NG, Parsons A, Schofield PM *et al.* Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Anti-Oxidant Study (CHAOS). *Lancet* 1996; **347**:781–6.
6. Verschuren WMM, Jacobs DR, Bloemberg BPM *et al.* Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five year follow-up of the Seven Country Study. *JAMA* 1995:**274**:131–6.
7. Rudel LL, Parks JS, Sowyer JK. Compared with dietary mono unsaturated and saturated fat, poly unsaturated fat protects African green monkeys from coronary artery arteriosclerosis. *Arterioscler Thromb Vasc Biol* 1995;**15**:2101–10.
8. Rudel LL, Hains JL, Sowyer JK *et al.* Hepatic origin of cholesteryl oliate in coronary artery arteriosclerosis in African green monkeys: enrichment by dietary mono unsaturated fat. *J Clin Invest* 1997;**100**:74–83.
9. De Lorgeril M, Salen P, Martin JL et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of Lyon Diet Heart Study. *Circulation* 1999;**99**:779–85.
10. Willett WC. *Nutritional epidemiology.* New York: Oxford University Press, 1990.
11. Kris-Etherton P, Daniels SR, Eckel RH *et al*, for the Nutrition Committee of the American Heart Association. Summary of the Scientific Conference on Dietary Fatty Acids and Cardiovascular Health. *Circulation* 2001;**103**:1034–9.
12. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997; **65**(Suppl. 2):643S–51S.
13. Ghafoorunissa. Dietary lipids and heart disease–the Indian context. *Natl Med J India* 1994;**7**:270–5.
14. Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. *Am J Clin Nutr* 1992;**55**: 1060–70.
15. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *Am J Clin Nutr* 2001;**73**:885–91.
16. Stamler JS, Shekelle RB. Dietary cholesterol and human coronary heart disease. *Arch Pathol Lab Med* 1988;**112**: 1032–40.
17. Hu F, Stampfer MJ, Rimm EB *et al.* A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 1999;**281**:1387–94.
18. Grundy SM, Vega GL. Plasma cholesterol responsiveness to saturated fatty acids. *Am J Clin Nutr* 1998;**47**:822–4.
19. Katan MJ, Zock PL, Mensink RP. Dietary oils, serum lipoproteins and coronary heart disease. *Am J Clin Nutr* 1995; **61**(Suppl):1368S–73S.

20.Hu F, Stampfer MJ, Manson JE *et al.* Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 1994;**337**:1491–9.
21.Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *Am J Cardiol* 1992;**70**:733–7.
22.Kromhout D, Menotti A, Bloemberg B *et al.* Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Prev Med* 1995;**24**:308–15.
23.Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins – a meta-analysis of 27 trials. *Arterioscler Thromb* 1992;**12**:911–19.
24.Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. *N Engl J Med* 1997;**340**:1994–8.
25.Willett WC, Stampfer MJ, Manson JE *et al.* Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* 1993;**341**:581–5.
26.Ascherio A, Rimm EB, Giovannucci EL *et al.* Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ* 1996;**313**:84–90.
27.Oomen CM, Ocke MC, Feskens EDM *et al.* Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet* 2001;**357**:746–51.
28.Katan MB. Trans fatty acids and plasma lipoproteins. *Nutr Rev* 2000;**58**;188–91.
29.Kris-Etherton PM. Monosaturated fatty acids and risk of cardiovascular disease. *Circulation* 1999;**100**:1253–8.
30.Mori TA, Beilin LJ. Long-chain omega 3 fatty acids, blood lipids and cardiovascular risk reduction. *Curr Opin Lipidol* 2001;**12**:11–17.
31.Mori TA, Bao DQ, Burke V *et al.* Purified eicosapentaenoic acid and docosahexaenoic acid have differential effects on serum lipids and lipoproteins, LDL-particle size, glucose and insulin, in mildly hyperlipidaemic men. *Am J Clin Nutr* 2000;**71**:1085–94.
32.Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr* 1997;**65**:1645S–54S.
33.GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI Prevenzione Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1999;**354**:447–55.
34.Von Schacky C. n-3 fatty acids and the prevention of coronary atherosclerosis. *Am J Clin Nutr* 2000;**71**(Suppl. 1): 224S–7S.
35.Lemaitre RN, King IB, Raghunathan TE *et al.* Cell membrane trans-fatty acids and the risk of primary cardiac arrest. *Circulation* 2002;**105**:697–701.
36.McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *Am Heart J* 1998;**116**:709–17.
37.Hetzel BS, Charnock JS, Dwyer T, McLennan PL. Fall in coronary heart disease mortality in USA and Australia due to sudden death: evidence for the role of polyunsaturated fat. *J Clin Epidemiol* 1989;**42**:885–93.
38.Grundy SM. What is the desirable ratio of saturated, polyunsaturated, and monounsaturated fatty acids in the diet? *Am J Clin Nutr* 1997;**66**(Suppl.):988S–90S.
39.Grundy SM. The optimal ratio of fat-to-carbohydrate in the diet. *Annu Rev Nutr* 1999;**19**:325–41.
40.Willett WC. Dietary fat plays a major role in obesity. *Obesity Rev* 2002 (in press).
41.Mendis S, Samarajeewa U, Thattil O. Coconut fat and serum lipoproteins: effects of partial replacement with unsaturated fats. *Br J Nutr* 2001;**85**:583–9.
42.Knutzon DS, Knauf V. Manipulating seed oils for polyunsaturated fatty acid content. In Harwood J, ed. *Plant lipid biosynthesis: fundamentals and agricultural applications*. Cambridge: Cambridge University Press (Society for Experiment Biology Seminar Series), 1998.
43.Truswell AS. Food carbohydrates and plasma lipids – an update. *Am J Clin Nutr* 1994;**59**(Suppl.):710S–18S.
44.Jenkins DJA, Jenkins AL, Wolever TMS *et al.* Low glycemic index: lente carbohydrates and physiological effects of altered food frequency. *Am J Clin Nutr* 1994;**59**(Suppl.):706S–9S.
45.Liu S, Willet WC, Stampfer MJ *et al.* A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000; **71**:1455–61.
46.Marlett JA. Content and composition of dietary fiber in 117 frequently consumed foods. *J Am Diet Assoc* 1992;**92**:175–86.
47.Shikany JM, Ala B, White GL. Dietary guidelines for chronic disease prevention. *South Med J* 2000;**93**:1138–51.
48.Truswell AS. Cereal grains and coronary heart disease. *Eur J Clin Nutr* 2002;**56**:1–14.
49.Ludwig DS, Pereira MA, Kroenke CH *et al.* Dietary fiber, weight gain, and cardiovascular risk factors in young adults. *JAMA* 1999;**282**:1539–46.
50.Liu S, Stampfer MJ, Hu FB *et al.* Whole grain consumption and the risk of coronary heart disease: from the Nurses Health Study. *Am J Clin Nutr* 1999;**70**:412–19.
51.Rimm EB, Ascherio A, Giovannucci E *et al.* Vegetable, fruit and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;**275**:447.
52.Rimm EB, Stampfer MJ. Antioxidants for vascular disease. *Med Clin North Am* 2000;**84**:239–49.
53.Ness AR. Commentary: beyond beta-carotene – antioxidants and cardiovascular disease. *Int J Epidemiol* 2001;**30**:143–4.
54.Yusuf S, Dagenais G, Pogue J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**345**:154–60.
55.Collaborative group of the primary prevention project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001;**357**:89–95.
56.Stampfer MJ, Malinow MR, Willett WC *et al.* A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *JAMA* 1992;**268**:877–81.
57.Selhub J, Jacques PF, Bostom AG *et al.* Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med* 1995;**332**:286–91.
58.Stampfer MJ, Malinow MR, Willett WC *et al.* A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *JAMA* 1992;**268**:877–81.

59.Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Engl J Med* 1998;**338**:1042–50.
60.Brouwer IA, van Dusseldorp M, Thomas CM *et al.* Low dose folic acid supplementation decreases plasma homocysteine concentrations: a randomized trial. *Am J Clin Nutr* 1999; **69**:99–104.
61.Scott JM. Homocysteine and cardiovascular risk. *Am J Clin Nutr* 2000;**72**:333–4.
62.Guttormsen AB, Ueland PM, Svarstad E, Refsum H. Kinetic basis of hyperhomocysteinemia in patients with chronic renal failure. *Kidney Int* 1997;**52**:495–502.
63.Celermajer DS, Sorensen K, Ryalls M *et al.* Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. *J Am Coll Cardiol* 1993;**22**:854–8.
64.Bellamy MF, McDowell IF, Ramsey MW *et al.* Oral folate enhances endothelial function in hyperhomocysteinaemic subjects. *Eur J Clin Invest* 1999;**29**:659–62.
65.Rimm EB, Willett WC, Hu FB *et al.* Folate and vitamin B_6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998;**279**:359–64.
66.Tice JA, Rose E, Coxson PG *et al.* Cost effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease. Effect of grain fortification and beyond. *JAMA* 2001;**286**:936–43.
67.Seshadri N, Robinson K. Homocysteine, B vitamins, and coronary artery disease. *Med Clin North Am* 2000;**84**: 215–37.
68.Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease. The Zutphen elderly study. *Lancet* 1993;**342**:1007–11.
69.Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins and incidence of stroke. *Arch Intern Med* 1996;**154**:637–42.
70.Gibbs CR, Lip GYH, Beevers DG. Salt and cardiovascular disease: clinical and epidemiological evidence. *J Cardiovasc Risk* 2000;**7**:9–13.
71.INTERSALT Cooperative Research Group. INTERSALT; an international study of electrolyte excretion and blood pressure. Results for 24 hr urinary sodium and potassium excretion. *BMJ* 1988;**297**:319–28.
72.Elliott P, Stamler J, Nicholas R *et al*, for the Intersalt Cooperative Research Group. Intersalt revisited: further analyses of 24 hr sodium excretion and blood pressure within and across populations. *BMJ* 1996;**312**:1249–55.
73.Mancilha Carvalho JJ, Baruzzi RG, Howard PF *et al.* Blood pressure in four remote populations in the Intersalt study. *Hypertension* 1989;**14**:238–46.
74.Poulter NK, Khaw KT, Hopwood BEC *et al.* The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 1990;**300**:967–72.
75.Law MR, Frost MD, Wald NJ. By how much does salt reduction lower blood pressure? III. Analysis of data from trials of salt reduction. *BMJ* 1991;**302**:819–24.
76.Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, Nissinen A. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001;**357**:848–51.
77.Law MR, Frost CD, Wald NJ III. Analysis of data from trials of salt reduction. *BMJ* 1991;**302**:819–24.
78.Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension* 1997;**29**: 913–17. (Published erratum in *Hypertension* 1997;**29**:1211.)
79.Whelton PK, Appel LJ, Espeland MA *et al.* Sodium reduction and weight loss in the treatment of hypertension in older persons. *JAMA* 1998;**279**:839–46.
80.Sacks FM, Svetkey LP, Vollmer WM *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;**344**:3–10.
81.Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinent of cardiac involvement in essential hypertension. *Circulation* 1988;**78**:951–6.
82.Liebson PR, Grandits GA, Dianzumba S *et al.* Comparision of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygenic therapy in the Treatment of Mild Hypertension Study (TOHMS). *Circulation* 1995;**91**:698–706.
83.Forte JG, Miguel JM, Miguel MJ *et al.* Salt and blood pressure: a community trial. *J Hum Hypertens* 1989;**3**:179–84.
84.Tian HG, Guo ZY, Hu G *et al.* Changes in sodium intake and blood pressure in a community-based intervention project in China. *J Hum Hypertens* 1995;**9**;959–68.
85.Staessen J, Bulpitt CJ, Fagard R *et al.* Salt intake and blood pressure in the general population: a controlled intervention trial in two towns. *J Hypertens* 1988;**6**:965–73.
86.Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without raising blood pressure. *Hypertension* 1990;**15**:900–3.
87.Xie JX, Sasaki S, Joossens JV, Kesteloot H. The relationship between urinary cations obtained from the INTERSALT study and cerebrovascular mortality. *J Hum Hypertens* 1992;**6**: 17–21.
88.Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. *Am J Physiol* 1995;**268**:R825–R37.
89.Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. *N Engl J Med* 1989;**320**:1177–82.
90.Whelton PK, He J, Cutler JA *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 1996;**275**:1016–22.
91.Khaw KT, Barrett-Connor E. Dietary potassium and stroke associated mortality. *N Engl J Med* 1987;**316**:235–40.
92.Griffith LE, Guyatt GH, Cook RJ *et al.* The influence of dietary and non-dietary calcium supplementation on blood pressure. An updated meta-analysis of randomized controlled trials. *J Hypetens* 1999;**12**:84–92.
93.Mizushima S, Cuppauccio FP, Nichols R, Elliott P. Dietary magnesium intake and blood pressure: a qualitative overview of the observational studies. *J Hum Hypertens* 1998; **12**: 447–53.
94.Nestle M. Animal v. plant foods in human diets and health: is the historical record unequivocal? *Proc Nutr Soc* 1999;**58**:211–18.
95.Law MR, Morris JK. By how much does fruit and vegetable consumption reduce the risk of ischemic heart disease ? *Eur J Clin Nutr* 1998;**52**:549–56.
96.Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol* 1997;**26**:1–13.

97.Liu S, Manson JE, Lee I-M *et al.* Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr* 2000;**72**:922–8.
98.Liu S, Lee I-M, Ajani U *et al.* Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. *Int J Epidemiol* 2001;**30**:130–5.
99.Joshipura KJ, Ascherio A, Manson JF *et al.* Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* 1999; **282**:1233–9.
100.Appel LJ, Moore TJ, Obarzanek E *et al.* A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1998;**336**:1117–24.
101.Kromhout D, Bosschieter Eb, de Lezenne Coulander C. The inverse relation between fish consumption and 20 year mortality from coronary heart disease. *N Engl J Med* 1985;**312**: 1205–9.
102.Daviglus ML, Stamler J, Orencia AJ *et al.* Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997;**336**:1046–53.
103.Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *Eur J Clin Nutr 1*999;**53**:585–90.
104.Burr ML, Fehily AM, Gilbert JF *et al.* Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;**2**:757–61.
105.Gillman MW, Cupples LA, Millen BE *et al.* Inverse association of dietary fat with development of ischemic stroke in men. *JAMA* 1997;**278**:2145–50.
106.Orenica AJ, Daviglus ML, Dyer AR *et al.* Fish consumption and stroke in men. *Stroke* 1996;**27**:204–9.
107.Zhang J, Sasaki S, Amano K, Kesteloot H. Fish consumption and mortality from all causes, ischemic heart disease and stroke: an epidemiological study. *Prevent Med* 1999;**28**: 520–9.
108.Kris-Etherton PM, Zhao G, Binkoski AE *et al.* The effects of nuts on coronary heart disease risk. *Nutr Rev* 2001;**59**: 103–11.
109.Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* 1992; **152**:1416–24.
110.Fraser GE, Lindsted KD, Beeson WL. Effect of risk factor values on lifetime risk of and age at that first coronary event. The Adventist Health Study. *Am J Epidemiol* 1995;**142**:746–58.
111.Hu FB, Stamfer MJ. Nut consumption and risk of coronary heart disease: A review of epidemiologic evidence. *Curr Atheroscler Rep* 1999;**1**:204–9.
112.Anderson JW, Smith BM, Washnok CS. Cardiovascular and renal benefits of dry bean and soybean intake. *Am J Clin Nutr* 1999;**70**(Suppl.):S464–74.
113.Third International Symposium on the role of soy in preventing and treating chronic disease. *J Nutr* 2000;**130**(Suppl.): S653–711.
114.Anthony MS, Clarkson TB, Bullock BC. Soy protein versus soy phytoestrogens (isoflavones) in the prevention of coronary artery atherosclerosis of cyno molgus monkeys (Abstract). *Circulation* 1996;**94**(Suppl. 1):1–265.
115.Crouse JR III, Morgan T *et al.* Randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. *Arch Intern Med* 1999;**159**:2070–6.
116.Davies DF. Cow's milk antibodies and coronary heart disease. *Lancet* 1980;8179:1190–91.
117.Law MR, Wald N. An ecological study of serum cholesterol and ischemic heart disease between 1850 and 1990. *Eur J Clin Nutr* 1994;**48**:305–25.
118.Seely S. Diet and coronary disease. A survey of mortality rates and food consumption statistics of 24 countries. *Med Hypoth* 1981;**7**:907–18.
119.Abbott RD, Curb JD, Rodriguez BL *et al.* Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle aged men. *Stroke* 1996;**27**:813–18.
120.Gaziano JM, Buring JE, Breslow JL *et al.* Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993;**329**:1829–34.
121.Rehm J, Bondy S. Alcohol and all cause mortality: an overview. *Novartis Foundation Symp* 1998;**216**:223–32.
122.Gaziano JM, Godfried S, Hennekens CH. Alcohol and coronary heart disease trends. *Cardiovasc Med* 1996;**329**: 1829–34.
123.Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev* 1993:**15**:328–51.
124.Moore RD, Pearson T. Moderate alcohol consumption and coronary artery disease: a review. *Medicine* 1986;**65**:242–67.
125.Sacco RL, Elkind MM, Boden-Albala B *et al.* The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999;**281**:53–60.
126.Gaziano JM, Buring JE, Brestlow JL, Goldhaber SZ *et al.* Moderate alcohol intake increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993:**329**:1829–34.
127.Gaziano JM, Hennekens CH, Godfried SL *et al.* Type of alcoholic beverage and risk of myocardial infarction. *Am J Cardiol* 1999;**83**:52–7.
128.Miyagi Y, Miwa K, Inoue H. Inhibition of human low-density lipoprotein oxidation by flavonoids in red wine and grape juice. *Am J Cardiol* 1997;**80**:1627–31.
129.Hu FB, Stampfer MJ, Rimm EB *et al.* A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 1999;**281**:1387–94.
130.Trichopoulou A, Kouris-Blazos A, Vassilakou T *et al.* The diet and survival of elderly Greeks; a link to the past. *Am J Clin Nutr* 1995;**61**(Suppl.):1346S–50S.
131.Keys A, Menotti A, Karvonen MJ *et al.* The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol* 1986;**124**:903–15.
132.Trichopoulou A, Vasilopoulou E. Mediterranean diet and longevity. *Br J Nutr* (2000);**84**(Suppl. 2):S205–09.
133.De Lorgeril RS, Mamelle N *et al.* Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;**343**:1454.
134.Rimm EB, Ascherio A, Giovannucci E *et al.* Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;**275**:447.
135.Gilman MW, Cupples LA, Gagnon DJ *et al.* Protective effect of fruits and vegetables on development of stroke in men. *JAMA* 1995;**273**:1113–17.

136. Willett WC. Convergence of philosophy and science: the Third International Congress on Vegetarian Nutrition. *Am J Clin Nutr* 1999;**70**(Suppl.):434S–8S.
137. Pais P, Pogue J, Gerstein H *et al.* Risk factors for acute myocardial infarction in Indians: a case-control study. *Lancet* 1996;**348**:358–63.
138. Hu FB, Rimm EB, Stampfer MJ *et al.* Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr* 2000;**72**:912–21.
139. Shimamoto T, Komachi Y, Inada H *et al.* Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989;**79**:503–15.
140. Moore TJ, Conlin PR, Ard J, Svetkey LP for DASH Collaborative Research Group; DASH (Dietary Approaches to Stop Hypertension) Diet is Effective Treatment for Stage 1 Isolated Systolic Hypertension. *Hypertension* 2001;**38**: 155–8.
141. Obarzanek E, Sacks FM, Vollmer WM *et al.* Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr* 2001;**74**:80–9.
142. Truswell AS. Review of dietary intervention studies: effect on coronary events and on total mortality. *Aust NZ J Med* 1994;**24**:98–106.
143. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality for ischemic heart disease in Poland since 1991. *BMJ* 1998;**317**:678.
144. Pietinen P, Vartianinen E, Seppanen R *et al.* Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Prev Med* 1996;**25**:243–50.
145. Dowsen GK, Gareeboo H, George K *et al.* Changes in population cholesterol concentrations and other cardiovascular risk factor levels after five years of non-communicable disease intervention programme in Mauritius. *BMJ* 1995;**311**:1255–9.

Part IIIa

Specific cardiovascular disorders: Stable coronary artery disease

Bernard J Gersh and John A Cairns, *Editors*

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

26 Anti-ischemic drugs

Lionel H Opie

> A major problem … is the lack of sufficient data comparing antianginal and placebo treatment.[1]

The major anti-ischemic drugs are, in historical order of appearance, the nitrates, the β adrenergic blockers, the calcium-channel antagonists, the metabolic modifiers, and the potassium-channel openers. In addition, there is increasing evidence that the angiotensin converting enzyme (ACE) inhibitors and the statin lipid lowering drugs have indirect anti-ischemic properties. Preservation of endothelial function may also be an indirect anti-ischemic procedure. The antiplatelet agents, including aspirin, clopidogrel, and the GPIIb/IIIb receptor blockers, as well as the antithrombotics and thrombolytics, will not be considered here but in the following section of Part III on acute ischemic syndromes. Special attention will be paid to the potential effect of the standard anti-ischemic drugs not just in giving symptomatic relief of angina, but, in keeping with the aim of this book, on hard outcome end points such as re-infarction and mortality.

What is ischemia?

Ischemia of the myocardium is probably the most important cause of cardiovascular and total mortality and morbidity in Western societies. Although there are many definitions, in the end they come down to an inadequate blood supply to the myocardium.[2] The Greek *ischo* means "to hold back" and *haima* means "blood". The word "ischemia" was, it seems, first used by Rudolf Virchow in 1858, to describe a situation in which limitation of blood flow resulted from an increased resistance to blood flow. The "modern" concept of supply-demand imbalance as a cause of ischemia dates back to observations made nearly two hundred years ago on the exercising limb[3]:

> If we call into vigorous action a limb around which we … applied a ligature, we find then that the member can only support its action for a very short time; for now its supply of energy and its expenditure do not balance each other.

Myocardial ischemia therefore exists when the reduction of coronary flow is so severe that the supply of oxygen is inadequate for the demands of the tissue, which is the generally accepted situation in acute effort angina. Ischemia is often distinguished from infarction, the latter reflecting prolonged irreversible ischemia with myocardial cell death. Therefore the ischemia is also the underlying situation in unstable angina and the very early phase of the clinical syndrome of acute myocardial infarction (AMI), when reperfusion can still reverse the ischemic myocardial damage. Myocardial ischemia is also thought to contribute, together with the underlying anatomical substrate, to the potentially lethal ventricular arrhythmias found in patients with ischemic heart disease.

Myocardial ischemia may also occur chronically, as proposed for hibernation. In the latter case, the proposal is that the myocardium has undergone a chronic adaption to ischemia by downregulation of contraction. The simplified concept is "little blood, little work".[4]

Therefore, there is a wide spectrum of conditions in which myocardial ischemia is clinically relevant (Table 26.1) and for which anti-ischemic drugs can be used. As will be argued, the hard evidence for their long-term benefit is, in general, strikingly absent.

Safety and efficacy

General aspects

Safety and efficacy are ultimately linked: the more pronounced the beneficial effects of a therapeutic regimen, the greater the degree of side effects that may be tolerated. A drug that significantly prolongs life, such as alteplase or streptokinase in AMI, is recommended for use despite an increased incidence of hemorrhagic stroke, because the balance of mortality plus stroke favors the use of the drug. There exists a hierarchy for the significance of end points, the most important primary end point being prolongation of life, with a secondary end point being an improved quality of life, either by reduction of morbidity or by relief of symptoms such as anginal pain. Tertiary end points are those that neither improve the quantity nor the quality of life, but which are expected to prevent disease by reducing risk factors, examples being the treatment of mild asymptomatic arterial hypertension.

Evidence for the first of these end points is, in general, scant in relation to the anti-ischemic drugs. Information gathered in one situation is not necessarily directly relevant to another. Thus, for example, the benefits of β blockade in post-MI prevention[5] do not necessarily show that these

Table 26.1 The clinical spectrum of acute ischemia and the various drugs used

Clinical syndrome	Pathophysiology	Drug therapy	Outcome in RCTs
Effort angina	Imbalance of oxygen supply–demand, transient	Nitrates, β blockers, calcium antagonists, metabolic modifiers, K-channel openers	None for nitrates or metabolic modifiers, limited for β blockers and calcium antagonists, positive for K-opener
Unstable angina, acute NSTE coronary syndrome	As above, prolonged	As above, antithrombins, antiplatelet agents	None for anti-ischemic drugs
Threatened MI	As above prior to start of cell necrosis	β blockade	Possible benefit for β blockade, harm for nifedipine
Ischemic arrhythmias	Ischemia-induced rise in cyclic AMP and cell calcium; increased I_f in Purkinje fibers; lipid changes	β blockade	Indirect evidence strongly favors β blockade, but no RCTs have been directed towards ischemic arrhythmias

Abbreviations: I_f, "funny current"; MI, myocardial infarction; NSTE, non-ST elevation; RCTs, randomized controlled trials

drugs also prolong life in stable effort angina. The present author agrees with Hjemdahl *et al*[1] that the pathophysiologic situation in patients with symptomatic angina is often very different from that in the post-MI setting. In MI, there is a zone of dead tissue, and depending on its size there will be reactive remodeling in the rest of the ventricle, introducing a different pathophysiologic situation and predisposing to left ventricular (LV) failure. Also, the presence of viable and non-viable myocardium creates electrical inhomogeneity that predisposes to re-entry with risks of lethal ventricular arrhythmias. Furthermore, the possibility of the coexistence of stunning, hibernation, and preconditioning, collectively called *the new ischemic syndromes*, all predispose to a highly complex and multifarious spectrum that constitutes ischemic LV dysfunction.[6] Although some of these abnormalities may be found in chronic stable angina because there may be coexisting previous MI, nonetheless the predominant and basic pathology is in the one case transient myocardial ischemia causing effort angina, and in the other case dead tissue with reactive ventricular remodeling. Of note, a sizable portion of patients in studies on chronic stable angina – up to one third – have had previous infarcts.[1] Post-MI angina therefore merits specific consideration, but again outcome studies are missing.

How is safety assessed? The hierarchy of evidence

Safety is not well defined but could be regarded as the absence of significant adverse effects when the drug is used with due regard for its known contraindications.[7] Safety implies the added assurance that there are no hidden dangers in the legitimate use of the drug. Evidence for safety, like evidence for efficacy, can come from a variety of sources. There is a hierarchy of evidence regarding safety, starting from anecdotal case reports as the least reliable, followed by case series, case–control studies, cohort studies, going through to more coherent information with emphasis on large controlled randomized trials (RCTs) and carefully conducted meta-analyses of these trials. These lead to acceptance of the overall evidence as favoring a position where the benefit and the safety of a drug group is well established (which is the most reliable evidence).[7] For example, in the case of calcium antagonists, most of the earlier evidence on adverse effects comes from case–control or cohort studies or small RCTs. Such data are subject to serious intrinsic problems of the methodology, which can generate hypotheses without providing proof or otherwise. On the other hand, in the case of β blockers, there is concordant evidence for benefit in the data on post-MI patients from many large trials,[5] and a very large observational study on over 200 000 patients.[8]

Are there safety concerns regarding calcium antagonists and β blockers?

A number of safety concerns have been raised in relation to calcium antagonists, and to some extent also to β blockers. Many of these are based on case–control or cohort studies,

which are not a reliable source of information.[7,9] There are major contradictions between the various studies. The question of cancer and gastrointestinal hemorrhage as possible side effects is reviewed by the WHO-ISH committee, and by Opie *et al*[7] without a causative association being found.[10] In the case of cancer, one small cohort study is outweighed by two bigger negative studies.[11,12] In the case of hemorrhage, the evidence is incomplete and not supported by prospective studies. In general, it is the short-acting calcium antagonists,[13] and in particular short-acting nifedipine, that have been associated with adverse effects.[7,14]

There is long-standing good evidence that short-acting instant release (IR) nifedipine in capsule form can increase mortality in acute ischemic syndromes[7,15,16] so that it is contraindicated in unstable angina or early phase MI unless accompanied by β blockade. It follows that:

- the mechanism of the adverse effects of IR nifedipine is very probably by reflex adrenergic activation;
- even in stable effort angina, neither short-acting nifedipine nor any other short-acting dihydropyridine should be used in the absence of an accompanying β blocker.

Indirect data from a meta-analysis of effort angina[17] could also suggest that any short-acting dihydropyridine should be avoided in effort angina. Experience in unstable angina would, however, suggest that combination with β blockade would be safe. **Grade B**

Safety concerns have also been raised in relation to β blockers. Case–control studies suggest an increased incidence of sudden cardiac arrest or death in hypertensive patients treated by β blockade.[18,19] In a prospective observational study on 12 550 hypertensive patients over 6 years,[20] those taking calcium antagonists or ACE inhibitors were at no increased risk of diabetes versus hypertensive patients not receiving therapy, whereas with β blockers there was a 28% increase (RR 1·28, 95% CI 1·04–1·57). Although the potential weakness of observational studies must again be emphasized, other short-term studies have shown that β blockade added to thiazide therapy for hypertension has a hyperglycemic effect.[21]

Safety *v* safe use

Whenever a serious side effect of any given drug becomes known, and acted on, then that safety issue should be obviated so that the drug becomes safer. For example, β blockers are no longer given to patients with pre-existing excess bradycardia, sick sinus syndrome, or asthma. In that sense, the increased mortality long known in relation to the use of IR nifedipine in acute ischemic syndromes is a safety issue that should already have been overcome by the appropriate warnings.

RCTs

Calcium antagonists and β blockers in effort angina

Regarding trials with outcome end points, the major studies are two relatively small RCTs comparing calcium antagonists with β blockers in effort angina, neither trial having a placebo arm. In the APSIS[22] study, slow release verapamil was compared with metoprolol, the main prognostic end points being a combination of morbidity and mortality (total and cardiovascular), and non-fatal cardiovascular complications including MI, revascularization, stroke, and peripheral vascular events, as well as treatment failure. These end points did not differ significantly between the treatments, nor were side effects or quality of life indices different between the two drugs. Because of the very low death rate, which was about 2% per year of follow up, it is impossible to exclude that either drug might be better than the other, or that one or the other drugs might be better or worse than placebo (not tested). Studies to settle the mortality issue are unlikely to be undertaken, so we must evaluate the combined end points actually tested. On present evidence there are not enough data to conclude that either the calcium antagonists or the β blockers differ one from the other, or from placebo.

TIBET[23] compared slow release nifedipine (twice daily formulation) with atenolol. As there were three treatment arms including the combination of these drugs, and only 682 patients in total to start with, there were only 450 patient-years in each group. Outcome was assessed by a combination of end points considered either "hard" (cardiac mortality, MI, or unstable angina) or "soft" (revascularization or treatment failure). Thus the major conclusion of this study is that it is underpowered for hard end points and even for combined hard and soft end points. The firm conclusion is the poor tolerance of nifedipine tablets.

The more recent Stanford meta-analysis[24] added 59 short-term studies in which cardiac death or MI were reported during the use of β blockers or calcium antagonists for effort angina, giving 116 extra events, still with no differences between the outcomes and an odds ratio very close to unity.

In addition there are two placebo-controlled trials, ASIST and PREVENT. The ASIST[25] study is the only one in mild effort angina or silent ischemia that compares a β blocker, atenolol, with placebo. Patients with moderate to severe angina were excluded. Over 1 year, atenolol gave better event-free survival, using a mixed bag of end points, including death, resuscitation, non-fatal MI, hospitalization for unstable angina, aggravation of angina, and revascularization. There were only a few serious events and the most evident difference was that there was less aggravation of angina with atenolol (9 of 152 *v* 26 of 154 with placebo, $P = 0{\cdot}003$). This trial, therefore, tells us that atenolol is antianginal, which is not surprising. PREVENT makes

roughly a similar message for the long-acting dihydropyridine (DHP), amlodipine, which reduced unstable angina and revascularizations when added to existing treatment, which often included a β blocker.[26]

The combined message emerging from APSIS, TIBET, ASIST, and PREVENT is this: the real problem is that the incidence of hard end points, such as mortality, infarction, or unstable angina, is so low in chronic stable effort angina that vast trials would be needed to show beyond doubt that calcium antagonists or β blockers do more than relieve symptoms. For example, it can be estimated that a study of 600 total deaths in effort angina, even with a risk reduction of one quarter, would need about 30 000 patients in a long-term trial (60 000 if the end point is cardiac mortality) to show any differences between calcium antagonists and β blockers. Trials of this size are, in the view of the present author, unlikely ever to be undertaken. Rather, it makes much more sense to select high-risk patients (see section on nicorandil) with clusters of risk factors, such as age, male gender, hypertension, smoking, and hypercholesterolemia. Alternatively, trials carefully designed to establish whether or not two treatments have an equivalent effect may be considered because fewer numbers are required than in mega-trials.[27] From the point of view of evidence-based medicine, and except for nicorandil the data currently available are insufficient.

Therefore the author has argued that the choice of drug between β blocker and calcium-channel blocker should be geared to the needs and the pathophysiology of the individual patient.[28] For example in a middle-aged man athletically active and anxious to avoid impotence, a calcium-channel blocker would be first choice. **Grade B** In a person with a compromised myocardium or with a previous MI, a β blocker appropriately titrated would be first choice. **Grade A** In someone at high risk of MI, antihypertensive therapy started with a β blocker is somewhat safer than starting with a calcium-channel blocker, while, if the major aim is prevention of stroke and hence intellectual integrity, a calcium-channel blocker may be preferable (Figure 26.1).[29]

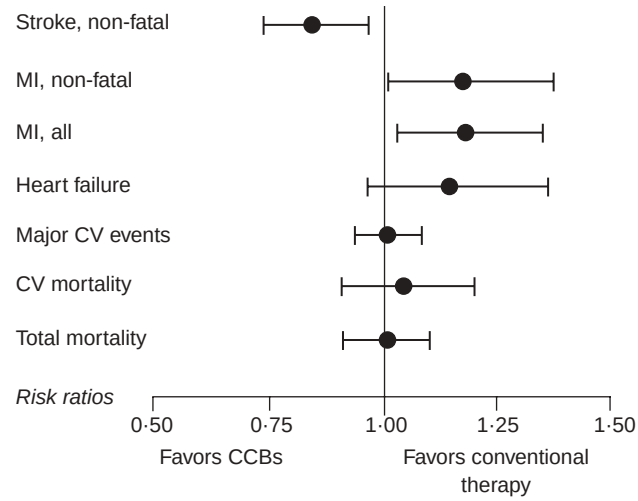

Figure 26.1 Outcomes in a meta-analysis of hypertension trials, comparing calcium-channel blocker (CCB)-based therapy *v* therapy conventional therapy (starting with either diuretic or β blocker). Note decrease ($P = 0{\cdot}013$) in non-fatal stroke, the increase in non-fatal myocardial infarction (MI) ($P = 0{\cdot}036$), and unchanged cardiovascular (CV) and total mortality. Figure corrected from error in original publication of Opie and Schall.[29]

Combination therapy: calcium antagonist added to β blocker in higher risk effort angina

ACTION is a large trial testing the outcome efficacy of long-acting nifedipine (GITS, gastro-intestinal tract system) in higher risk patients with chronic effort angina.[30] It is powered both for efficacy (death, AMI, heart failure, stroke) and for safety (death, AMI, stroke). Of the 7720 entrants, 78% were already taking β blockade. Therefore this trial is chiefly going to tell us about changes in hard end points when nifedipine GITS is added to a β blocker. Extrapolating from what little is already known from unstable angina, but with only 48 hour re-infarction as the outcome, the combination of nifedipine with a β blocker is likely to improve outcome. The trail will terminate in late 2003. There may be enough of a difference in the subgroup of those not receiving a β blocker to help judge on the efficacy of long acting nifedipine alone.

Nitrates in effort angina

There are no such trials reported and none is being planned. Nitrates therefore remain strictly in the realm of agents that provide symptomatic relief, without evidence for outcome benefit. **Grade C** Theoretically, the reflex tachycardia that they invoke might adversely affect the long-term outcome in ischemic states. Equally theoretically, their capacity to act as nitric oxide donors might protect the vascular endothelium and provide protective preconditioning.[31]

Unstable angina as an example of prolonged ischemia

This condition has two major components: acute myocardial ischemia and a disturbance of the thrombotic mechanism. Antianginal drugs therefore constitute only part of the therapy. In contrast to the good data on the benefit of heparin and aspirin, and now on clopidogrel, there is again no good evidence for the benefit of nitrates in unstable angina. Compared with intravenous diltiazem, intravenous nitroglycerin was less effective on short-term end points such as refractory angina and MI.[32] Furthermore, there was still a benefit in favor of diltiazem-treated patients at 1 year

of follow up.[33] Regarding long-term outcome with nitrates in unstable angina, there has been only one trial, which compared transdermal nitroglycerin with placebo therapy over 4 months, each arm receiving in addition conventional medical treatment. Outcome events such as death, MI or refractory angina were similar in the nitrate and placebo arms.[34]

There is a difference in the safety profile of the dihydropyridines (DHPs) and the non-DHPs (such as verapamil and diltiazem). Of the DHPs, only IR nifedipine has been well tested, with an adverse outcome in two trials. In the HINT study,[27] IR nifedipine was inferior to placebo with MI within 48 hours as an end point (OR 2·0, 95% CI 1·1–3·6) so that the trial was stopped,[35] while in the other study[36] there was an increase in early mortality. The heart rate-increasing effect of IR nifedipine[36] was probably the result of adrenergic activation because a benefit for the addition of IR nifedipine to prior β blockade was shown in both these trials and also by Gerstenblith *et al.*[37] By contrast, the non-DHP diltiazem was successfully used in comparison with a nitrate, both agents being given intravenously with a relative risk of 0·49 in favor of diltiazem for short-term events, chiefly recurrent pain.[32] Diltiazem decreased the heart rate whereas the nitrate increased it. Although there has been no similar trial with verapamil, several smaller trials suggest efficacy.[38–40] While it is possible that long-acting DHPs such as amlodipine that do not increase the heart rate might be safe in unstable angina, no such trials are likely to be done. The conclusion from the safety point of view is that the non-DHP diltiazem is best tested without the trial being large enough to yield outcome data, that verapamil may be similar in its effects though even less well tested, and that the DHPs as a group are relatively contraindicated in the absence of β blockade, with short-acting nifedipine (and nicardipine) totally contraindicated.

In the case of β blockade, there are no good studies in unstable angina, the only one available showing an insignificant trend to short-term benefit as measured by the decrease in recurrent ischemia or MI within 48 hours.[35] Neither of two older studies had hard end points.[41,42]

Prinzmetal's variant angina

This type of angina at rest is caused by coronary spasm and is specifically relieved by calcium antagonists. There are no outcome studies with hard end points, perhaps because the condition is potentially fatal and therefore placebo-controlled trials would be impossible. Some of the studies with remission of attacks as end point are reviewed by Opie and Maseri.[43] **Grade B** Short-acting agents are standard. Of these, nifedipine should not be used unless the diagnosis is firm and it is sure that the patient does not have unstable angina or threatened MI.

Threatened infarction

In this situation where ischemia is threatening to develop into infarction, IR nifedipine had adverse short-term (2 week) effects in a relatively small randomized trial, in which mortality was increased from 0 of 82 placebo patients to 7 of 89 nifedipine patients ($P = 0{\cdot}018$).[15] By contrast, in another relatively small trial with propranolol started intravenously within 4 hours of the onset of symptoms of AMI and then continued orally, there were fewer completed infarcts as shown by a limitation of blood enzyme rise,[42] and the incidence of ventricular fibrillation was less.[44] **Grade B** When given in a pilot study to patients with clinically threatened MI, atenolol reduced eventual infarction but, as the authors point out, the small numbers mean that the statistics are far from robust.[45] These small trials do not provide definitive information but are in agreement with the general concept that adrenergic activation is harmful in threatened infarction[42] so that β blockade is the preferred mode of therapy. This recommendation is, however, not based on good trial data.

Postinfarct effort angina

Two large RCTs suggest that long-term post-AMI therapy by instant release capsular nifedipine in standard doses is not beneficial or possibly harmful.[16,46] **Grade A** The presumed mechanism is reflex sympathetic stimulation. Angina was not a specific end point. Even though evidence from cohort studies is contradictory,[47,48] this agent is far from ideal for post-MI patients with angina.

Only one of the post-MI trials with calcium antagonists specifically reported on the incidence of angina pectoris in a subgroup of the postinfarct DAVIT II study,[49] in which verapamil 360 mg/day was started 7–15 days following infarct and continued for up to 18 months. Verapamil was significantly antianginal.[50] Regarding the outcome of the DAVIT II study as a whole, in the verapamil group there was a reduction (RR 0·80, 95% CI 0·64–0·99) in the combined end point predetermined as death and/or re-infarction. Although total mortality did not fall, the RR was also 0·80 (95% CI 0·61–1·05), and the lack of significance could possibly be ascribed to the relatively small numbers involved. Regarding heart failure, analysis of predetermined subgroups, undertaken before the code was broken, showed that in patients without prior heart failure during their stay in the coronary care unit, there was a mortality reduction ($P = 0{\cdot}024$). There was no effect of verapamil, either beneficial or harmful, in those with prior (not concurrent) heart failure. However, subgroup analysis even with predetermined end points is open to criticism. **Grade B**

Regarding diltiazem, the MDPIT post-MI study, in which diltiazem was given as 240 mg/day for a mean of 25 months,

did not report on effort angina.[51] An earlier study in which diltiazem was given for 14 days after non-Q wave infarction found no difference in the incidence of chest pain "recognized as angina pectoris".[52] Outcome evidence that this drug increases cardiac events (cardiac deaths and/or nonfatal infarction) in post-MI patients with congestive heart failure cannot be disputed.[51] **Grade A**

Regarding β blockers, there is impressive evidence that these drugs prolong life in post-MI patients.[5] Furthermore, in a very large observational study on over 200 000 post-MI patients, mortality was reduced by about 40% in all subgroups of those receiving β blockers, including those with prior revascularization.[8] **Grade A** Therefore, although there appear to be no formal trials on antianginal properties in post-MI patients, the large number of post-MI trials and the many patients studied, mean that these drugs have more overall compelling evidence in their favor in the postinfarct situation than does verapamil and much more compelling evidence than for the DHP calcium antagonists. First principles suggest it is likely that they are exerting their benefit at least in part by an anti-ischemic effect, although benefits on remodeling and postinfarct heart failure are a reasonable alternative.[53,54]

Ischemic arrhythmias

The Cape Town hypothesis is that β blockers have a ventricular antiarrhythmic effect in AMI by limiting metabolic changes, such as increased levels of cyclic AMP in the ischemic tissue.[55] Nonetheless, other modes of action are possible, for example by inhibition of the current I_f that initiates pacemaker activity in injured Purkinje cells. A meta-analysis has shown that β blockade is effective when given as prophylactic antiarrhythmic therapy in the context of AMI, and that it reduces mortality with an odds ratio of 0·81 in 55 trials.[56] Further evidence for outcome benefit for β blockers, as in postinfarct patients, comes from the Cardiac Arrhythmia Suppression Trial (CAST) in which prior β blockade therapy was associated with a one third reduction in arrhythmic death or cardiac arrest.[54] By contrast, calcium antagonists had a slightly increased relative risk, albeit not of statistical significance. Yet these findings do not prove that the β blockers were acting as anti-ischemic agents, and only provide indirect evidence that β blockers are safe when deliberately chosen as anti-ischemic drugs in other clinical situations.

Calcium antagonists in stable angina after angioplasty

There still is no convincing evidence that pharmacologic therapy by any of the anti-ischemic drugs alters the incidence of restenosis. There is some evidence from a meta-analysis that calcium antagonists as a group may help to prevent restenosis,[57] which should mean lessened effort angina – a possibility that was not reported. In one specific study over 6 months, twice daily verapamil reduced restenosis following percutaneous transluminal coronary angioplasty (PTCA), but only in patients with stable angina.[58] **Grade B** β blockers appear to be untested in this situation.

Congestive heart failure and effort angina

There are no studies with this combination as a predetermined end point. In view of the consistent benefit that accrues to patients with heart failure, already receiving a diuretic and an ACE inhibitor when a β blocker is carefully phased in, such added therapy can be expected to improve angina. However, direct evidence is missing. **Grade C**

ACE inhibitors as potential anti-ischemic drugs

There are at least four potentially anti-ischemic mechanisms whereby ACE inhibitors may operate. First, angiotensin II is known to facilitate sympathetic adrenergic transmission, also in humans.[59] Second, ACE inhibitors, by formation of bradykinin, indirectly promote the formation of nitric oxide, which in turn inhibits myocardial oxygen consumption.[60] Third, ACE inhibitors are potentially antihypertensive and thereby reduce the afterload. Fourth, in 15 hypertensive patients of whom 11 had effort angina, ACE inhibitors improved coronary flow reserve after long-term therapy.[61] The mechanism may be by reversal of endothelial dysfunction. Not surprisingly, these agents have a documented antianginal effect in hypertensive patients with angina[62,63] without, however, any outcome data. In patients with low ejection fractions, below 35%, chronic therapy by enalapril in the Studies of Left Ventricular Dysfunction (SOLVD) trials led to less hospital admissions for unstable angina, and therefore might well have reduced stable effort angina, but the data are not clear on this point.[64] In the SAVE study there was an unexpected reduction in recurrent MI in the group given captopril.[65]

The hypothesis that ACE inhibitors can protect against manifestations of ischemic heart disease in those at high risk was tested in HOPE,[66] in which one of the predetermined secondary or other outcomes was reduction of revascularization (RR 0·85, 95% CI 0·77–0·94) and of worsening angina (RR 0·89, 95% CI 0·82–0·96). However, what is controversial is the mechanism: is it just blood pressure reduction,[67] or an additional explanation specific to ACE inhibition such as an increased formation of bradykinin? Objective anti-ischemic effects can be found in hypertensive but not normotensive people.[68] **Grade A** In "standard"

angina of effort, without hypertension or heart failure, ACE inhibitors have an inconstant effect, as reviewed elsewhere.[69] Logically, the expected benefit would be more in patients with more severe ischemia and a greater activation of the adrenergic and renin–angiotensin systems.[70]

Metabolic modifiers

Trimetazidine and ranolazine are antianginals that act metabolically, probably through multiple mechanisms including partial fatty acid oxidation. While there is no doubt about their antianginal efficacy, supported by the recent oral presentation of data on 800 patients in the case of ranolazine, there are no outcome trials.

Nicorandil

This antianginal drug acts through several mechanisms including nitric oxide formation and potassium channel opening, the latter leading to preconditioning and to an antiadrenergic effect during experimental ischemia.[71] In a large prospective trial on higher risk patients with stable effort angina,[72] the primary composite end point was achieved, namely a reduction of coronary heart disease death, non-fatal MI, or unplanned hospitalization for cardiac chest pain. The secondary end point, coronary heart disease death or non-fatal MI, showed a strong trend to reduction without significance being reached. This trial is remarkable because it shows that a trial testing hard end point reduction in effort angina can be undertaken. Nicorandil is thus, in the view of the present author, the only antianginal that has strong evidence-based data in its favor. It is licensed in the UK, Japan, and several other countries, but not in the USA. **Grade A**

Statins as potential anti-ischemic drugs

Statins have made a considerable difference to the mortality of patients with ischemic heart disease in several studies. In the West of Scotland Coronary Prevention Study (WESCOPS), pravastatin was able to reduce hard end points in middle-aged hypercholesterolemic men without prior MI. In this group, the occurrence of angina pectoris was highly correlated ($P < 0{\cdot}0001$) with the primary end point, which was definite coronary heart disease death or non-fatal MI.[73] Therefore, in hypercholesterolemic males with angina, statins are able to reduce hard end points. That they have a direct anti-ischemic effect is shown by reduction of ST segment deviations on 48 hour Holter traces in patients with stable angina pectoris, documented coronary artery disease and pre-existing antianginal therapy, the latter not being specified.[74] **Grade A** Statin therapy can improve endothelial function, measured in the brachial artery, within 3 days in high-risk patients (elderly patients).[75] Formal prospective proof that cholesterol lowering by a statin has clinical antianginal efficacy is provided by the MIRACL study (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) in which a high daily dose of atorvastatin (80 mg/day) reduced symptomatic ischemia and hospitalization in patients within 16 weeks of an acute coronary syndrome.[76]

Diuretics as potential anti-ischemic drugs

Short-term diuretic therapy has an antianginal effect, possibly by reduction of the left ventricular preload.[77] No outcome data are available. Some case–control studies on hypertensive patients have suggested increased mortality on diuretics when given in high doses and without potassium supplementation.[18,19]

Conclusions

There are few if any satisfactory outcome studies available with the conventional antianginal drugs in effort angina. There are no trials at all on nitrates, and only rather small trials comparing β blockers and calcium antagonists. Some indirect evidence suggests that the ACE inhibitors may have antianginal properties. Statins are indirectly antianginal. Adequately powered outcome trials in patients with cardiac death and non-fatal MI as end points in effort angina would require mega-trials in view of the low incidence of these events. It would be more practicable to select high-risk categories or to aim trials at showing drug equivalence. Thus in higher risk patients with effort angina, the relative new antianginal nicorandil gave a positive outcome with a reduction in the primary end point of coronary heart disease death, non-fatal MI and hospitalization, or unplanned cardiac chest pain. In unstable angina, where ischemia is prolonged, there are no good trials showing that nitrates, β blockers or calcium antagonists – all commonly used drugs – have outcome benefit. Although β blockers have good evidence favoring their use as prophylactic antiarrhythmic drugs in AMI, with a reduction in mortality shown by meta-analysis, it is not certain that they are acting as anti-ischemic drugs in this situation.

Key points

- Standard anti-ischemic drugs (nitrates, β blockers, calcium antagonists) relieve anginal pain but their effect on outcome in effort angina is not known. Two relatively small trials and a meta-analysis suggest equivalence between calcium antagonists and β blockers. It is desirable but

unlikely that mega-trials will be conducted to settle this issue.

- Nicorandil is a relatively new anti-anginal with hard outcome data in its favor when tested in higher risk patients with effort angina.
- Likewise in unstable angina, outcome data for the anti-ischemic agents are lacking.
- An exception is short-acting nifedipine, which in two trials in acute ischemic syndromes has increased mortality, probably by reflex adrenergic activation.
- The closer the patient is to AMI, the stronger are the data for the safety of β blockers.
- In the postinfarct phase the data for safety and efficacy of β blockers are especially strong. The only calcium antagonist with good evidence for safety is verapamil, but without mortality benefit in the relatively small trials conducted.
- In acute ischemic ventricular arrhythmias, there is indirect evidence for the prophylactic effect of β blockers on mortality, even though there is no formal trial.
- Indirect evidence suggests that angiotensin converting enzyme inhibitors have some anti-ischemic properties without clear evidence for antianginal efficacy except in hypertensive patients. A large prospective study shows that ramipril protects from worsening angina in high-risk patients.
- In one trial, early use of high-dose statin following an acute coronary syndrome reduced symptomatic ischemia within 16 weeks.

References

1. Hjemdahl P, Eriksson SV, Held C, Rehnqvist N. Prognosis of patients with stable angina pectoris on antianginal drug therapy. *Am J Cardiol* 1996;**77**:6D–15D.
2. Hearse DJ. Myocardial ischaemia: can we agree on a definition for the 21st century? *Cardiovasc Res* 1994;**28**:1737–44.
3. Burns A. Observations on some of the most frequent and important diseases of the heart; on aneurysm of the thoracic aorta; on preternatural pulsation in the epigastric region; and on the unusual origin and distribution of some of the large arteries of the human body. Edinburgh: Bryce, 1809.
4. Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989;**117**:211–21.
5. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Dis Cardiovasc Dis* 1985;**27**:335–71.
6. Opie LH. The multifarious spectrum of ischemic left ventricular dysfunction: relevance of new ischemic syndromes. *J Mol Cell Cardiol* 1996;28:2403–14.
7. Opie LH, Yusuf S, Kübler W. Current status of safety and efficacy of calcium-channel blockers in cardiovascular diseases. A critical analysis based on 100 studies. *Prog Cardiovasc Dis* 2000;**43**:171–96.
8. Gottlieb SS, McCarter MJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;**339**:489–97.
9. Yusuf S, Garg R, Zucker D. Analyses by the intention-to-treat principle in randomized trials and databases. *PACE* 1991;**14**: 2078–82.
10. WHO-ISH Committee. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997;**15**:105–15.
11. Jick H, Jick S, Derby LE, Vasilakis C, Myers M. Calcium-channel blockers and risk of cancer. *Lancet* 1997;**349**:525–8.
12. Olsen JH, Sorensen HT, Friis S, McLaughlin JK, Steffensen FH. Cancer risk in users of calcium-channel blockers. *Hypertension* 1997;**29**:1091–4.
13. Alderman MH, Cohen H, Roque R, Medhaven S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet* 1997;**349**: 594–8.
14. Pahor M, Guralnik JM, Corti M, Foley DJ, Carbonin P, Havlik RJ. Long term survival and use of antihypertensive medications in older persons. *J Am Geriat Soc* 1995;**43**:1191–7.
15. Muller J, Morrison J, Stone P *et al*. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. *Circulation* 1984;**69**:740–7.
16. SPRINT II Study. Goldbourt U, Behar S, Reicher-Reiss H *et al*. Early administration of nifedipine in suspected acute myocardial infarction. The Secondary Prevention Reinfarction Israel Nifedipine Trial 2 Study. *Arch Intern Med* 1993;**153**: 345–53.
17. Glasser SP, Clark PI, Lipicky RJ, Hubbard JM, Yusuf S. Exposing patients with chronic, stable, exertional angina to placebo periods in drug trials. *JAMA* 1991;**265**:1550–4.
18. Hoes AW, Grobbee DE, Lubsen J, Man in 't Veld AJ, van der Does E, Hofman A. Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995;**123**:481–7.
19. Siscovick DS, Raghunathun TE, Psaty BM. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;**330**:1852–7.
20. Gress TW, Nieto J, Shahar E, Wofford MR, Brancati FL. For the Atherosclerosis Risk in Communities Study. Hypertension and antihypertensives therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000;**342**:905–12.
21. Swislocki ALM, Hoffman BB, Reaven GM. Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am J Hypertens* 1989;**2**:419–23.
22. Rehnqvist N, Jjemdahl P, Billing E, Bjokander I, Eriksson SV. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J* 1996;**17**:76–81.
23. Dargie HJ, Ford I, Fox KM. On behalf of the TIBET Study Group. Total Ischaemic Burden European Trial (TIBET) Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. *Eur Heart J* 1996;**17**:104–12.
24. Heidenreich PA, McDonald KM, Hastie T *et al*. Meta-analysis of trials comparing β-blockers, calcium antagonists, and nitrates for stable angina. *JAMA* 1999;**281**:1927–36.
25. Pepine C, Cohn PF, Prakash C *et al*. Effects of treatment on outcome in mildly symptomatic patients with ischemia during

daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation* 1994;**90**:762–8.
26. Pitt B, Byington R, Furberg C *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000;**102**:1503–10.
27. Hampton JR. Alternatives to mega-trials in cardiovascular disease. *Cardiovasc Drugs Ther* 1996;**10**:759–65.
28. Opie LH. First line drugs in chronic stable effort angina – the case for newer, longer-acting calcium-channel blocking agents. *J Am Coll Cardiol* 2000;**36**:1967–71.
29. Opie LH, Schall R. Evidence-based evaluation of calcium-channel blockers (CCBs) for hypertension. Equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002;**39**:315–*22* (correction in press).
30. Lubsen J, Poole-Wilson PA, Pocock SJ *et al.* Design and current status of ACTION: a coronary disease trial investigating outcome with nifedipine GITS. *Eur Heart J* 1998;**19**:1202.
31. Bolli R. Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research. *J Mol Cell Cardiol* 2001;**33**:1897–918.
32. Göbel EJ, Hautvast RW, van Gilst WH *et al.* Randomised, double-blind trial of intravenous diltiazem versus glyceryl trinitrate for unstable angina pectoris. *Lancet* 1995;**346**:1653–7.
33. Göbel EJ, van Gilst WH, de Kam PJ, ter Napel MGJ, Molhoek GP, Lie KI. Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris. *Eur Heart J* 1998;**19**:1208–13.
34. Ardissino D, Merlini PA, Savonitto S, Demicheli G, Zanini P. Effect of transdermal nitroglycerin on N-acetylcysteine, or both, in the long-term treatment of unstable angina pectoris. *J Am Coll Cardiol* 1997;**29**:941–7.
35. HINT Study. Early treatment of unstable angina in the coronary care unit, a randomised, double-blind placebo controlled comparison of recurrent ischemia in patients treated with nifedipine or metoprolol or both. The Netherlands Inter-university Nifedipine Trial. *Br Heart J* 1986;**56**:400–13.
36. Muller J, Turi Z, Pearl D *et al.* Nifedipine and conventional therapy for unstable angina pectoris: a randomized, double-blind comparison. *Circulation* 1984;**69**:728–33.
37. Gerstenblith G, Ouyang P, Achuff SC, Bulkley BH, Becker LC. Nifedipine in unstable angina. A double-blind, randomized trial. *N Engl J Med* 1982;**306**:885–9.
38. Mauritson DR, Johnson SM, Winniford MD, Cary JR, Willerson JT. Verapamil for unstable angina at rest: a short-term randomized, double-blind study. *Am Heart J* 1983;**106**:652–8.
39. Mauri F, Marfici A, Briaghi M, Cerri P, de Biase AM. Effectiveness of calcium antagonist drugs in patients with unstable angina and proven coronary artery disease. *Eur Heart J* 1988;**9**:158–63.
40. Capucci A, Bassein L, Bracchetti D, Carini G, Maresta A. Propranolol v. verapamil in the treatment of unstable angina. A double-blind cross-over study. *Eur Heart J* 1983;**4**:148–54.
41. Fischl SJ, Herman MV, Gorlin R. The intermediate coronary syndrome. Clinical, angiographic and therapeutic aspects. *N Engl J Med* 1973;**288**:1193–8.
42. Norris RM, Sammel NL, Clarke ED, Smith WM. Protective effect of propranolol in threatened myocardial infarction. *Lancet* 1978;**2**:907–9.
43. Opie LH, Maseri A. Vasospastic angina. In: Krebs R, ed. *Treatment of cardiovascular disease by Adalat (nifedipine).* Stuttgart: Schattauer, 1986.
44. Norris RM, Brown MA, Clarke ED, Barnaby PF, Geary GG. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. *Lancet* 1984:883–6.
45. Yusuf S, Sleight P, Rossi R *et al.* Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983;**67**(Suppl. I):I-32–I-41.
46. SPRINT Study. Secondary Prevention reinfarction Israeli Nifedipine Trial. A randomized intervention trail of nifedipine in patients with acute myocardial infarction. *Eur Heart J* 1988;**9**:354–64.
47. Braun S, Boyko V, Behar S *et al.* Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11 575 patients. *J Am Coll Cardiol* 1996;**28**:7–11.
48. Koenig W, Lowel H, Lewis M, Hormann A. Long-term survival after myocardial infarction: relationship with thrombolysis and discharge medication. Results of the Augsburg myocardial infarction follow-up study. *Eur Heart J* 1996;**17**: 1199–206.
49. Jespersen CM, Hansen JF, Mortensen LS. Danish Study Group on Verapamil in Myocardial Infarction. The prognostic significance of post-infarction angina pectoris and the effect of verapamil on the incidence of angina pectoris and prognosis. Results of the Survival and Ventricular Enlargement trial. *Eur Heart J* 1994;**15**:270–6.
50. DAVIT Study. Danish Study Group of Verapamil in Myocardial Infarction. Verapamil in acute myocardial infarction. *Eur Heart J* 1984;**5**:516–28.
51. MDPIT Study. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;**319**: 385–92.
52. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. *N Engl J Med* 1986;**315**:423–9.
53. Lichstein E, Hager D, Gregory JJ, Fleiss JL, Rolnitzky L, Bigger JT. Relation between beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure. *J Am Coll Cardiol* 1990;**16**: 1327–32.
54. Kennedy HL, Brooks MM, Barker AH, Bergstrand R, Huther ML. β-blocker therapy in the cardiac arrhythmia suppression trial. *Am J Cardiol* 1994;**74**:674–80.
55. Lubbe WH, Podzuweit T, Opie LH. Potential arrhythmogenic role of cyclic adenosine monophosphate (AMP) and cytosolic calcium overload: implications for prophylactic effects of beta-blockers in myocardial infarction and proarrhythmic effects of phospodiesterase inhibitors. *J Am Coll Cardiol* 1992;**19**:1622–33.
56. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. *JAMA* 1993;**270**:1589–95.
57. Hillegass WB, Ohman M, Leimberger JD, Califf RM. A meta-analysis of randomized trials of calcium antagonists to reduce restenosis after coronary angioplasty. *Am J Cardiol* 1994;**73**: 835–9.
58. Hoberg E, Kubler W. Prevention of restenosis after PTCA: role of calcium antagonists. *J Cardiovasc Pharm* 1991;**18** (Suppl. 6):S15.

59.Lyons D, Webster J, Benjamin N. Angiotensin II. Adrenergic sympathetic constriction action in humans. *Circulation* 1995; **91**:1457–60.
60.Zhang X, Xie Y-W, Nasjletti A, Xu X, Wolin MS, Hintze TH. ACE inhibitors promote nitric oxide accumulation to modulate myocardial oxygen consumption. *Circulation* 1997;**95**: 176–82.
61.Motz W, Strauer BE. Improvement of coronary flow reserve after long-term therapy with enalapril. *Hypertension* 1996; **27**:1031–8.
62.Akhras F, Jackson G. The role of captopril as single therapy in hypertension and angina pectoris. *Int J Cardiol* 1991;**33**: 259–66.
63.Stumpe KO, Overlack A. On behalf of the Perindopril Therapeutic Safety Study Groups (PLUTS). A new trial of the efficacy, tolerability and safety of angiotensin-converting enzyme inhibition in mild systemic hypertension with concomitant diseases and therapies. *Am J Cardiol* 1993;**71**:32E–37E.
64.Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;**340**: 1173–8.
65.Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;**327**:669–77.
66.HOPE Investigators. Yusuf S, Sleight P *et al*. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**:145–53.
67.Staessen JA, Wang J-G, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001;**358**: 1305–15.
68.Prasad A, Mincemoyer R, Quyyumi AA. Anti-ischemic effects of angiotensin-converting enzyme inhibition in hypertension. *J Am Coll Cardiol* 2001;**38**:1116–22.
69.Opie LH. *Angiotensin converting enzyme inhibitors: scientific basis for clinical use, 3rd ed*. New York: Author's Publishing House, 1999.
70.Remme WJ, Kruyssen DA, Look MP, Bootsma M, de Leeuw PW. Systemic and cardiac neuroendocrine activation and severity of myocardial ischemia in humans. *J Am Coll Cardiol* 1994;**23**:82–91.
71.Miura T, Kawamura S, Tatsuno H *et al*. Ischemic preconditioning attenuates cardiac sympathetic nerve injury via ATP-sensitive potassium channels during myocardial ischemia. *Circulation* 2001;**104**:1053–8.
72.IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;**3509**:1262–9.
73.WESCOPS Study. The West of Scotland Coronary Prevention Study Group. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 1997;**79**:756–62.
74.van Boven AJ, Jukema W, Zwinderman AH, Crijns HJ, Lie KI, Bruschke AV. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. *Circulation* 1996;**94**: 1503–5.
75.Tsunekawa T, Hayashi T, Kano H *et al*. Cerivastatin a hydroxymethylgutaryl coenzyme A reductase inhibitor, improves endothelial function in elderly diabetic patients within 3 days. *Circulation* 2001;**104**:376–9.
76.Schwartz GG, Olsson AG, Ezekowitz MD *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–18.
77.Parker JD, Parker AB, Farrell B, Parker JO. Effects of diuretic therapy on the development of tolerance to nitroglycerin and exercise capacity in patients with chronic stable angina. *Circulation* 1996;**93**:691–6.

27 Impact of revascularization procedures in chronic coronary artery disease on clinical outcomes: a critical review of the evidence

Charanjit S Rihal, Dominic Raco, Bernard J Gersh, Salim Yusuf

Coronary artery disease (CAD) is the leading cause of death worldwide and a major determinant of morbidity, use of healthcare resources, and lost productivity from illness. Since the original descriptions of surgical[1] and percutaneous[2] revascularization, the number of revascularization procedures has increased yearly (Figure 27.1). By 1998, 1 202 000 cardiac catheterizations, 926 000 percutaneous transluminal coronary angioplasty (PTCA) procedures, and 553 000 coronary artery bypass graft (CABG) operations were being performed annually in the USA alone.[3] An equivalent number are likely being performed in the rest of the world. Because the immediate risks of invasive procedures must be balanced against future potential benefits, it is important to critically evaluate the evidence supporting the use of these procedures, and to define the types of patients most likely to benefit and those unlikely to have any substantial benefit.

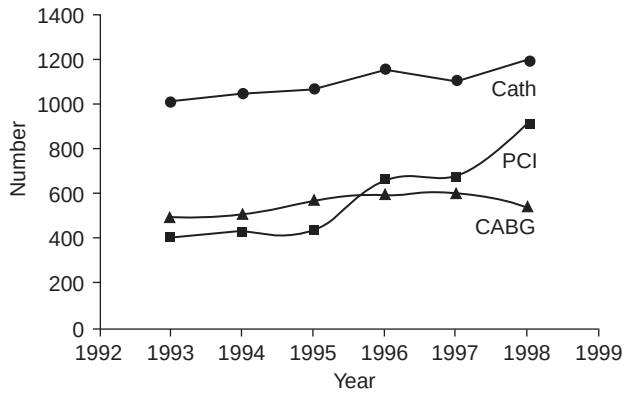

Figure 27.1 Annual growth in number of invasive cardiac procedures performed in the USA 1993–1998. Data are from the annual National Hospital Discharge Surveys 1993–1998. National Center for Health Statistics, Hyattsville, Maryland (www.cdc.gov/nchs). Values represent total number of discharges, not patients, with the indicated procedure listed as the primary procedure. Because federal, military, and Veterans Affairs hospitals are not included, the numbers may be underestimated. CABG, coronary artery bypass graft surgery (ICD-9 Code 36.1); Cath, catheterization; PCI, percutaneous coronary intervention.

Considered empirically, there are three broad potential reasons to recommend myocardial revascularization:

- to alleviate symptoms caused by myocardial ischemia;
- to improve the likelihood of long-term survival; and
- to reduce the risk of future non-fatal cardiac events such as myocardial infarction, serious arrhythmias, or congestive heart failure.

Within these categories, the potential and magnitude of benefit must be balanced against the intrinsic risk of invasive procedures. These considerations require thorough knowledge of both the technical aspects and the pertinent evidence, in particular relative efficacies with respect to outcomes of interest, estimation of individual risk-to-benefit ratios, and an understanding of the limitations and potential harm of each procedure. This chapter reviews the evidence comparing CABG surgery, PTCA, stents, and medical therapy for chronic CAD with respect to both fatal and non-fatal clinical outcomes. By building a conceptual framework, this chapter attempts to place the evidence from more recent trials of percutaneous revascularization into the context of previous trial data that compared CABG with medical therapy. Limitations of the available data and application to clinical practice are also discussed.

CABG surgery versus medical therapy

The first generation of randomized clinical trials of chronic CAD tested CABG surgery against medical therapy. Three moderate sized, prospective randomized studies conducted two decades ago provide the bulk of the data: the European Coronary Surgery Study (ECSS), the Veterans Administration (VA) Coronary Artery Bypass Surgery Cooperative Study Group, and the Coronary Artery Surgery Study (CASS).[4–6] These trials and numerous retrospective studies from associated registries demonstrated that the benefits of CABG were proportional to the long-term risk among patients who

received medical therapy.[5–7] Although both the VA study and CASS failed to demonstrate a difference in overall mortality between the medical and surgical groups that was statistically significant, subgroups in which CABG appeared to be superior to medical therapy were identified early. These subgroups included patients with left main CAD,[8,9] so-called left main equivalent disease,[10] and three vessel disease with left ventricular dysfunction.[11] Because each trial was relatively small (350–400 patients per treatment arm), only the ECSS trial demonstrated a decrease in mortality overall that was statistically significant.[4,9]

The three major trials (CASS, VA, and ECSS) plus four smaller trials (50 patients per treatment arm), in which patients were followed for 10 years, have been subjected to meta-analysis.[7] In all, 2649 patients randomly allocated to CABG or medical therapy were included. Original clinical and angiographic data were collected and analyzed according to uniform definitions. Enrolled patients had stable angina pectoris, whereas those with medically refractory or unstable angina generally were not included. The baseline angiographic and clinical characteristics are listed in Table 27.1. Of note, the majority had three vessel (50·6%) or left main CAD (6·6%), most of the patients were between 40 and 60 years old, almost all were male, and only 20% had an ejection fraction less than 50%. About half of the patients were taking β adrenergic blockers, but only 3·2% were receiving antiplatelet drugs at enrollment.

Table 27.1 Clinical and angiographic characteristics of patients enrolled in randomized trials of CABG versus medical therapy

Characteristic[a]	% of patients
Age distribution (years)	
≤40	8·5
41–50	38·2
51–60	46·0
>60	7·3
Ejection fraction (n = 2474)	
<40	7·2
40–49	12·5
50–59	28·0
≥60	52·3
Male	96·8
Severity of angina	
none	11·2
class I or II	53·8
class III or IV	35·0
History	
myocardial infarction	59·6
hypertension	26·0
heart failure	4·0
diabetes mellitus	9·6
smoking (*n* = 1949)	83·5
current smokers (*n* = 2298)	45·5
ST-segment depression > 1 mm	
resting (*n* = 2423)	9·9
exercise (*n* = 1985)	70·5
Drugs at baseline	
β blockers (*n* = 2308)	47·4
antiplatelet agents (*n* = 1195)	3·2
digitalis (*n* = 2319)	12·9
diuretics (*n* = 1940)	12·6
Number of vessels diseased	
left main coronary artery	6·6
one vessel[b]	10·2
two vessels[b]	32·4
three vessels[b]	50·6
Location of disease	
proximal left anterior descending	59·4
left anterior descending diagonal	60·4
circumflex	73·8
right coronary	81·6

Abbreviation: CABG, coronary artery bypass graft
[a] Data on some characteristics are not available for all patients.
[b] Without left main artery. (From Yusuf *et al*[7] by permission of *The Lancet* Ltd.)

Mortality

Cumulative mortality after initial medical therapy or initial CABG over 12 years of follow up is shown in Figure 27.2. Because of the perioperative mortality associated with CABG, 1 year mortality was not different between the groups and a net benefit in favor of CABG was not observed for 2 to 3 years (Figure 27.2). The advantage in favor of an initial strategy of CABG substantially widened at 5 to 7 years, before narrowing again by 10 to 12 years. At 5, 7, and 10 years, 10·2%, 15·8%, and 26·4% of patients, respectively, assigned to CABG had died, compared with 15·8%, 21·7%, and 30·5% of their medically assigned counterparts. Risk reductions were significant at all three time points (relative risk [RR], 0·61, 0·68, 0·83), even though 40% of patients initially assigned to medical treatment had delayed CABG surgery by 10 years. Because such crossovers tend to occur in the highest risk medical patients (left main coronary artery or three vessel disease, unstable angina), these trials may underestimate the real benefits of CABG surgery compared with medical therapy alone, and this underestimation would be greatest among high-risk subsets. This tendency for the relative – but not the absolute – benefit to converge is likely due to high rates of crossover to surgery among the highest risk medical patients, the development of graft atherosclerosis, and progression of underlying native vessel disease.

Significant heterogeneity of treatment effect was observed between various angiographic and clinical subgroups (Table 27.2). In general, the survival advantage of CABG over medical therapy was proportional to the

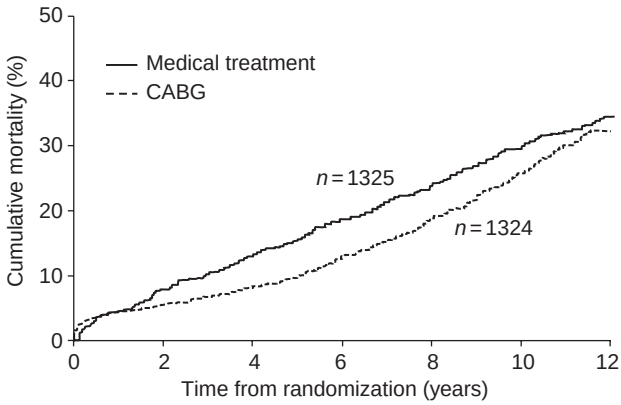

Figure 27.2 Overall survival after random allocation to medical treatment or coronary artery bypass graft (CABG). (From Yusuf *et al*[7] by permission of *The Lancet* Ltd.)

number of diseased coronary arteries (three vessel RR, 0·58; $P < 0 \cdot 001$, or left main RR, 0·32; $P = 0 \cdot 004$), particularly if the left anterior descending artery was involved (RR, 0·58). Although the relative benefits were similar regardless of left ventricular function (RR, 0·61 if normal and 0·59 if abnormal), the *absolute* benefit was greater among patients with an abnormal ejection fraction, because the risk of death was twice as high in this group (5 year medical mortality rate of 25·2% with an ejection fraction <50% *v* 13·3% if it was >50%). Similarly, absolute (and to some extent relative) mortality benefits were greater among patients with evidence of myocardial ischemia (abnormal exercise test results or severe angina).

To put the relative and absolute benefits of CABG further into the perspective of baseline risk, a score stratified by clinical and angiographic markers was developed. This indicated that patients at high risk (5 year medical mortality, 23%) experienced a clinically and statistically highly significant

Table 27.2 Outcomes of various subgroups in medical therapy versus CABG trials at 5 years

Subgroup	Overall number		Medical therapy mortality rate (%)	Odds ratio (95% CI)	*P* for CABG *v* medical treatment	*P* for interaction
	Deaths	Patients				
Vessel disease						
one vessel	21	271	9·9	0·54 (0·22–1·33)	0·180	0·19
two vessels	92	859	11·7	0·84 (0·54–1·32)	0·450	
three vessels	189	1341	17·6	0·58 (0·42–0·80)	<0·001	
left main artery	39	150	36.5	0·32 (0·15–0·70)	0·004	
No LAD disease						
one or two vessels	50	606	8·3	1·05 (0·58–1·90)	0·880	0·06
three vessels	46	410	14·5	0·47 (0·25–0·89)	0·020	
left main artery	16	51	45·8	0·27 (0·08–0·90)	0·030	
overall	112	1067	12·3	0·66 (0·44–1·00)	0·050	
LAD disease present						
one or two vessels	63	524	14·6	0·58 (0·34–1·01)	0·050	0·44
three vessels	143	929	19·1	0·61 (0·42–0·88)	0·009	
left main artery	22	96	32·7	0·30 (0·11–0·84)	0·020	
overall	228	1549	18·3	0·58 (0·43–0·77)	0·001	
LV function						
normal	228	2095	13.3	0·61 (0·46–0·81)	<0·001	0·90
abnormal	115	549	25·2	0·59 (0·39–0·91)	0·020	
Exercise test status						
missing	102	664	17·4	0·69 (0·45–1·07)	0·100	0·37
normal	60	585	11·6	0·78 (0·45–1·35)	0·380	
abnormal	183	1400	16.8	0·52 (0·37–0·72)	<0·001	
Severity of angina						
class 0, I, II	178	1716	12·5	0·63 (0·46–0·87)	0·005	0·69
class III, IV	167	924	22·4	0·57 (0·40–0·81)	0·001	

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; LAD, left anterior descending; LV, left ventricle (From Yusuf *et al*[7] by permission of *The Lancet* Ltd.)

improvement in survival (RR, 0·50; $P = 0·001$). Those at moderate risk (5 year medical mortality, 11·5%) also benefitted (RR, 0·63; $P = 0·05$), but the absolute benefits were smaller. No evidence of a survival benefit was observed among those at low risk (5 year medical mortality, 5·5%; RR, 1·18; $P = 0·70$).

Myocardial infarction and other non-fatal end points

Registry studies have suggested a favorable effect on late myocardial infarction only among the highest risk subsets, such as patients with three vessel disease and severe angina pectoris.[12] In the meta-analysis, no overall effect of CABG on subsequent infarction could be demonstrated, primarily because of an excess of infarction in the perioperative period (10·3% incidence of death or myocardial infarction at 30 days) among those assigned to surgery.[7] Although the risk of subsequent myocardial infarction was lower during extended follow up, this was not statistically significant (24·4% incidence of death or myocardial infarction at 5 years for the CABG group *v* 30·7% for the medical group).[7] Most trials did not prospectively collect data on rehospitalization for unstable angina, stroke, quality of life, or cost.

Recent trials

Few randomized data from the modern era compare CABG surgery with medical therapy. The Asymptomatic Cardiac Ischemia Pilot (ACIP) prospectively assigned 558 patients with asymptomatic ischemia to one of two medication strategies or to routine revascularization with CABG or PTCA.[13,14] Despite the relatively small sample size, mortality (1·1% *v* 6·6% and 4·4% for the two medical groups, $P < 0·02$), and death or myocardial infarction (4·7% revascularization *v* 12·1% and 8·8%, $P < 0·04$) was significantly lower after 2 years of follow up among the patients assigned to routine revascularization.[15] Rates of non-protocol revascularization procedures and hospital admission were also lower among the routine revascularization group (29% of medically assigned patients "crossed over" to invasive procedures).

The Medicine, Angioplasty, or Surgery Study (MASS) prospectively enrolled 214 patients with proximal left anterior descending artery stenoses to CABG surgery with an internal thoracic arterial conduit ($n = 70$), to PTCA ($n = 72$), or to medical therapy alone ($n = 72$). Rates of death (one in each group) or non-fatal myocardial infarction (one CABG, two PTCA) were very low over a mean 3 year follow up. After 3 years, 98% of patients assigned to CABG and 82% assigned to PTCA were free of angina, compared with only 32% of those in the medical group; however, 21 patients (29%) in the PTCA group required repeat procedures. No patient in any treatment group had severe angina (class III or IV).

Because previous trials have systematically tended to exclude elderly patients, precise estimates of relative risks and benefits are not available and must be extrapolated from other data. A recently published Swiss study focused on elderly patients. Patients older than 75 years (mean age, 80 years; 44% women) who had chronic, severe angina pectoris were randomly assigned to either an invasive approach or continued medical therapy.[16] Of 155 patients assigned to the invasive approach, 80 received PTCA, 33 CABG surgery, and 34 continued medical treatment. A third of the medical group required non-protocol revascularization for symptom control. By 6 months, angina severity and quality of life measures had improved in both groups but to a significantly greater extent in the invasive group. In the invasive group, 16·3% of patients had either died or had a non-fatal infarction, compared with 15·5% in the medical group. A greater proportion of the medical group (49% *v* 9·8%) required hospital admission during the ensuing 6 months. Although this was a relatively small trial, the findings affirmed the role of revascularization in improving symptoms and quality of life among elderly patients, the most important goal of treatment in this group.

Although the findings described above were derived from relatively small trials, they suggest that among patients with evidence of myocardial ischemia, modern revascularization techniques may be more effective than previously thought. These data point to a need for larger, more definitive randomized trials that test current revascularization techniques against modern medical therapy so that reliable estimates of effect of size on clinical outcomes with narrower confidence intervals can be made.

Conclusions

The available data suggest that a strategy of early CABG surgery improves long-term survival in a broad spectrum of patients at moderate to high risk with medical therapy. Relative reductions in mortality risk of about 40% over 5 years can be expected in comparison with the alternative of medical therapy. Absolute benefits are proportional to the risk expected with medical therapy. Clinical and angiographic markers of risk, including severity of CAD, left ventricular dysfunction, and myocardial ischemia, can identify patients in various risk strata. The benefits of CABG are greatest among those who are at highest risk with medical therapy (5 year mortality greater than 20%).

Limitations of first generation randomized clinical trials

During the last two decades, advances have occurred in both surgical and medical treatments that potentially could alter the results if trials were repeated today. These advances include the use of left internal thoracic artery

conduits that have long-term patency rates markedly superior to venous bypass grafts, and aggressive lipid lowering and chronic antiplatelet therapies.[17,18] The CABG surgery versus medical therapy trials were confined to patients 65 years or younger, but more than 50% of CABG procedures are now performed on patients 65 years or older.[3] Similarly, only CASS enrolled women, whereas women now commonly undergo CABG surgery. The use of internal thoracic conduits was limited to only 14% of the patients in CASS, and this conduit was not used in the other trials. Lipid lowering agents were not widely used, HMG-CoA reductase inhibitors were not available, and aspirin was not widely used in either the medical or surgical groups. High-risk patients, such as those with severe angina and left main coronary artery stenosis, were underrepresented in these trials. These considerations and the results of the small recent trials suggest that the benefits of CABG surgery on clinical outcomes are likely to be larger than in the old randomized trials, especially among subsets of high risk patients.

PTCA versus medical therapy

PTCA was first introduced in the late 1970s as a treatment for single vessel CAD,[2] and it has become one of the most commonly performed major procedures. Most PTCA procedures are still performed for single vessel disease,[19,20] but its role in multivessel disease is expanding, and rates of procedural success and complications[19,20] have been described in large observational databases. Six prospective trials have enrolled patients to strategies of initial medical therapy versus balloon angioplasty.[21–26]

The first of such trials, A Comparison of Angioplasty With Medical Therapy in the Treatment of Single-Vessel Coronary Artery Disease (ACME), was published in 1992,[21] 13 years after the first report of PTCA.[2] In this trial, 212 patients with stable, single vessel CAD and exercise induced myocardial ischemia were randomly assigned to PTCA or medical therapy. The proportion of patients free of angina at 6 months was greater in the PTCA arm (64% *v* 46%, $P < 0{\cdot}01$), and the number of monthly anginal episodes was fewer among those with angina despite a low (by current standards) technical success rate of only 80% with PTCA. These patients required fewer medications and had better improvement in treadmill exercise duration (increase, 2·1 *v* 0·5 minutes; $P < 0{\cdot}0001$) and psychologic wellbeing scores. However, these symptomatic improvements came at a considerable price, which included two emergency CABG operations and five myocardial infarctions. An accompanying trial from the ACME group enrolled 328 patients with double vessel disease and was reported in 1997. In this trial, functional improvement occurred in both the medical and angioplasty treated groups, and without statistically significant differences between the groups.[25]

The largest prospective trial of PTCA versus medical therapy was the multicenter Randomized Intervention Treatment of Angina (RITA) 2 trial.[23] Most of the patients had mild symptoms (80% Canadian Cardiovascular Society class 0 to II), 60% had single vessel CAD, and 33% had two vessel disease; only 6% had marked left ventricular dysfunction. The primary end point of death or myocardial infarction occurred in 6·3% of the PTCA group and 3·3% of the medical therapy group (absolute difference, 3·0%, 95% CI 0·4–5·7; $P = 0{\cdot}02$). The combined rates of death, myocardial infarction, and non-protocol revascularization were about 25% in both groups by 3 years of follow up, and were primarily due to repeat procedures in the PTCA group and progression of symptoms in the medical group (Figure 27.3). Angina pectoris and treadmill exercise time improved significantly in both groups. Patients with grade 2 or worse angina appeared to benefit more from PTCA; they had a lower incidence of angina and longer treadmill

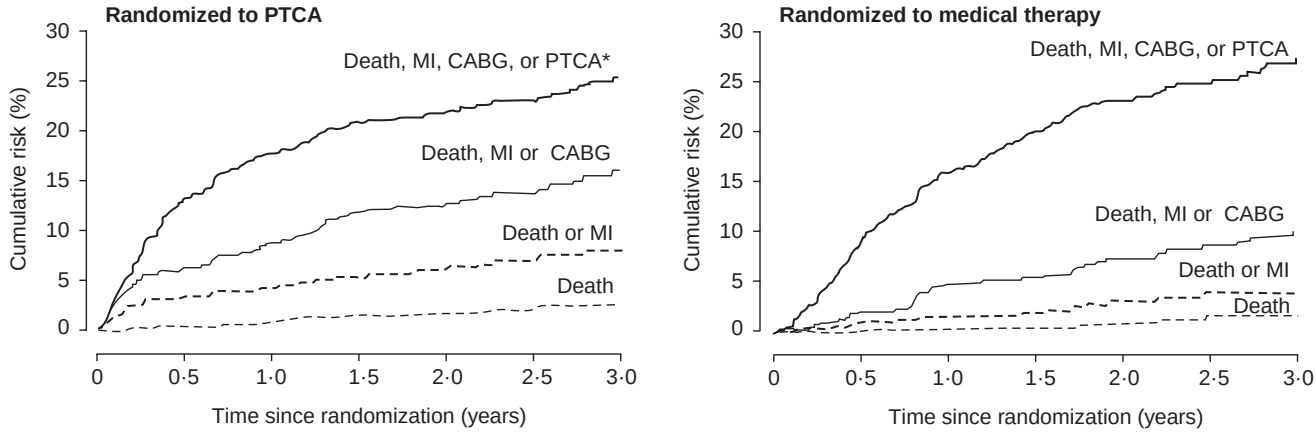

Figure 27.3 Cumulative risk of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) for myocardial infarction (MI), or death. * denotes PTCA in addition to randomized PTCA. (From RITA-2 Trial participants[23] by permission of *The Lancet* Ltd.)

exercise times than that of the medical therapy group. Patients with mild symptoms at enrollment had no measurable improvement from PTCA. Quality of life measures were assessed at 6 months and at 1 and 3 years with the SF-36 instrument.[1] Both groups experienced improvement, with PTCA producing greater improvement in physical functioning, vitality, and general health at 3 months and 1 year; 33% of the PTCA group and 22% of the medical therapy group rated their health much improved ($P = 0 \cdot 008$). These improvements were related to breathlessness, angina, and treadmill exercise time. By 3 years, no intergroup differences were observed, which may be explained partly by the 27% crossover to PTCA among the medical therapy group.[27]

The Atorvastatin Versus Revascularization Treatment (AVERT) trial[26] randomly assigned 341 patients with low risk CAD (99% of patients had stable Canadian Cardiovascular Society class 0 to II angina) to percutaneous revascularization plus usual medical care, or to medical care including aggressive therapy with atorvastatin. Over a mean follow up of 18 months, the PTCA group experienced more cardiac events (cardiac death or arrest, revascularization, stroke, or worsening angina) overall than the atorvastatin group (21% *v* 13% for PTCA and atorvastatin groups, respectively, $P = 0{\cdot}048$). However, a greater proportion of the PTCA group had improvement in anginal symptoms (54% *v* 41%, $P = 0{\cdot}009$).

The findings of the individual trials are reinforced by a systematic review of PTCA versus medical treatment for stable CAD.[28] The review included data from six randomized clinical trials that enrolled 953 patients given balloon angioplasty and 951 given medication. Treatment with PTCA resulted in significant improvement in angina (RR, 0·70, 95% CI 0·50–0·98); however, patients who had PTCA required CABG more frequently (RR, 1·59, 95% CI 1·09–2·32). No differences in death (RR, 1·32, 95% CI 0·65–2·70) or myocardial infarction (RR, 1·42, 95% CI 0·90–2·25) were observed (Figure 27.4). Because a substantial proportion of patients enrolled in medical arms required PTCA for symptom control, the overall odds of non-protocol PTCA did not differ despite the occurrence of restenosis after initial PTCA (RR, 1·29, 95% CI 0·72–3·36).

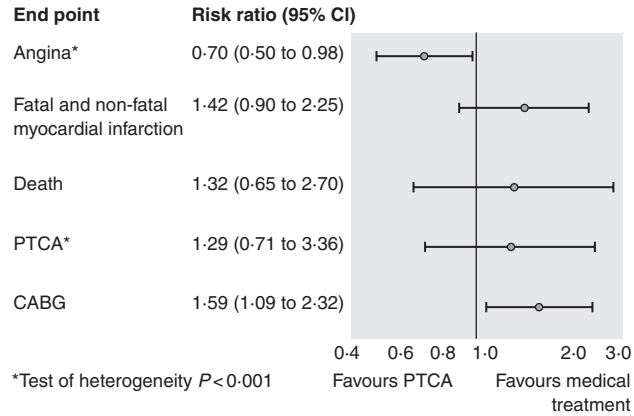

Figure 27.4 Pooled risk ratios for various end points from six randomized controlled trials comparing percutaneous transluminal coronary angioplasty (PTCA) with medical treatment in patients with non-acute coronary heart disease. CABG, coronary artery bypass grafting; n=953 for PTCA and 951 for medical treatment. (From Bucher *et al*[28] by permission of BMJ Publishing Group.)

Conclusions: PTCA versus medical therapy

On the basis of the results of the above trials, it is evident that among patients with low risk symptomatic CAD (Canadian Cardiovascular Society class II or greater and average mortality of <1% per year), PTCA can improve symptoms and measures of quality of life compared with medication alone. No apparent reduction can be expected in overall mortality, need for subsequent PTCA, myocardial infarction, or CABG (which may be higher than with medical therapy). These data suggest that PTCA is indicated if the desired level of anginal relief and physical activity cannot be achieved with medical therapy. Aggressive lipid lowering therapy is indicated for all patients with stable CAD. With the excess risk of cardiac events seen in several trials, PTCA purely for the treatment of an anatomical coronary artery stenosis or for ischemia without symptoms cannot be recommended. Similarly, PTCA for prevention of myocardial infarction is not indicated.

Theoretic considerations for comparison of CABG, PTCA, and medical therapy

Although PTCA was conceived originally as an alternative to CABG, rates of both PTCA and CABG have increased consistently and in parallel.[3] This and the fact that most PTCA procedures have been performed for single vessel disease suggest that PTCA has been used primarily as an alternative to medical therapy rather than to CABG. More recently, with increased experience and technical advances, the pattern of use of PTCA has increasingly included subsets of patients previously referred for CABG. Several prospective randomized clinical trials have compared multivessel PTCA, CABG, and stents. Before the results of these trials are reviewed (which compare two active invasive therapies without medical or placebo controls), several methodologic issues need to be considered.

Moderate- to high-risk patients

As mentioned above, several outcomes can be assessed in comparing PTCA with CABG: mortality, non-fatal events (such as non-fatal myocardial infarction), symptoms, cost, and

surrogate laboratory end points (such as left ventricular function). Because neither PTCA nor CABG has been shown to decrease the incidence of non-fatal myocardial infarction compared with medical therapy, this end point is unlikely to be sensitive to a possible differential effect of the two procedures. Indeed, considering non-fatal infarction in a composite end point may dilute event rates sufficiently to preclude detection (by lowering statistical power). Similarly, inclusion of low-risk subgroups in which CABG has *not* been shown to improve survival compared with medical therapy, such as single vessel disease, would decrease the ability to demonstrate mortality differences. An exception would occur if PTCA were significantly worse than medical therapy or substantially superior to CABG (both of which can be considered unlikely).

It has been demonstrated that CABG is associated with a 30–50% mortality risk reduction in moderate- and high-risk subgroups at 5 years compared with medical therapy. The detection of a difference in relative risk difference of half this magnitude (15–25%) between CABG and PTCA would be clinically relevant. If such a comparison indicated superiority of PTCA over CABG, it could reasonably be concluded that PTCA was superior to both medical therapy (indirect extrapolation) and CABG (direct inference). However, if a 20% difference in the relative risk of mortality in favor of CABG existed, surgical revascularization generally would be preferred over PTCA for such patients if the goal were improvement in prognosis. If the available data from such a comparison were large, the confidence interval of any observed difference would be narrow enough (for example, 20% ± 10%) to suggest that PTCA was superior to medical therapy to a clinically worthwhile extent, an indirect extrapolation that would be necessary in the absence of a medical control arm.

If no difference were observed between CABG and PTCA, it could be concluded that PTCA is equivalent to CABG only if trials were large enough to reliably detect or exclude relative differences in mortality of about 20% (with narrow confidence intervals) and included a large number of patients for whom CABG has been shown to improve prognosis. Because approximately 600 deaths would be needed in the "control" group to exclude a relative risk difference of 20% with 90% power, trials with about 8000 moderate- to high-risk patients would be needed. If a 30% risk difference were considered the smallest clinically important difference, then trials of about 4000 patients would be required. Moreover, in such a comparison, if the confidence limits of any difference included the possibility that PTCA was worse than CABG by 50% (relative risk), it could not be inferred that PTCA had any favorable effect on survival compared with medical therapy.

Low-risk patients

Among low-risk patients (annual mortality <2%), it may be moot to assess mortality differences between PTCA and CABG, because CABG has not been shown to decrease mortality. Conducting a trial to detect clinically important differences in such patients would be extremely difficult because of the large number of patients that would be required. For example, if a control group annual mortality rate of 1% is assumed, 8000 patients would need to be followed for 5 years to detect reliably a 30% risk reduction (or 16 000 patients to detect a 20% risk reduction). In such low-risk patients, any absolute benefit is likely to be too small to justify the costs and risks associated with revascularization. A large difference (for example, a 50% risk reduction that could be demonstrated with about 4000 randomized patients) would be extremely unlikely.

Therefore, among low-risk patients, the most relevant comparison is between PTCA and medical therapy. Such trials are unlikely to demonstrate a difference in mortality between PTCA and medical therapy (unless PTCA were harmful), and symptom improvement is the most relevant outcome of interest. Effects on a combined clinical variable could be compared, potentially including other non-fatal events such as myocardial infarction, severe angina, cost, and need for further revascularization procedures. Non-fatal events in a composite end point would need to be chosen carefully. As mentioned above, neither CABG nor PTCA has been shown to decrease the risk of subsequent non-fatal myocardial infarction, and inclusion of such an end point would dilute relative differences and decrease the likelihood of detecting differences. Both PTCA and CABG are effective in relieving angina and myocardial ischemia, and a relevant composite end point could include death plus severe angina. Such trials are feasible and could provide clinically relevant answers. It must be borne in mind that invasive procedures may increase rates of myocardial infarction, because of periprocedural risks, while decreasing subsequent angina pectoris.

Conclusions

These considerations indicate that to reliably compare the relative effect of PTCA versus CABG and to avoid missing clinically important differences, the following conditions need to be met:

- inclusion of subgroups in which surgery has been shown to be superior to medical therapy;
- inclusion of a sufficient number of patients (that is, adequate statistical power);
- follow up of at least 4–5 years to accrue a sufficient number of end points and to obtain data well beyond the early period when periprocedural events predominate; and
- a high rate of compliance to the original treatment allocation.

If a substantial proportion of patients crossover (30–40% by 5 years), the ability to detect differences in survival decreases markedly.

Trials of PTCA versus CABG

Technologic advances in the last 5–7 years have increasingly allowed wider application of PTCA, and a number of prospective, randomized trials have directly compared PTCA with CABG. A systematic review of eight of these trials[29] has been published.

Single vessel disease

In patients with single vessel CAD, medical therapy generally is indicated first, but revascularization may be indicated for symptom relief. Both PTCA and CABG offer a high rate of procedural success in such patients. Three randomized trials have provided data comparing PTCA and CABG for single vessel disease. The largest of these was the British RITA trial, which included 456 patients with single vessel disease.[30,31] After a median 6·5 years of follow up, no significant difference in death plus myocardial infarction was found (16·7% CABG *v* 19·3% PTCA, $P = 0{\cdot}56$) among patients with single vessel disease. Patients randomly assigned to PTCA required a significantly greater number of repeat interventional procedures (38% *v* 12%, $P = 0{\cdot}01$).

The results of MASS, the only three-way randomization among PTCA, CABG, and medical therapy to date, have been reviewed above. A second, single-center Swiss study was published in 1994.[32] In this trial, 134 patients with isolated proximal left anterior descending coronary artery stenosis were randomly assigned to angioplasty or CABG with a left internal thoracic artery conduit. Over 2·5 years of follow up, only one cardiac death occurred in the CABG group and none in the PTCA group, confirming the generally low-risk status of these patients. No significant difference was found in cardiac death or myocardial infarction (4·5% CABG *v* 11·7% PTCA, $P = 0{\cdot}21$), and the only significant difference between the two groups was a higher rate of repeat revascularization in the PTCA group (34%) because of restenosis. Relief of angina was achieved in a high proportion of each group (more than 95% of patients were in Canadian Cardiovascular Society class I at 1 year), and no difference in the duration of the exercise test was found.

The meta-analysis of Pocock *et al*[29] included 732 patients with single vessel disease. Results of an updated meta-analysis, including the RITA long-term follow up data, are presented in Table 27.3. No significant differences were found in overall mortality. Rates of death or myocardial infarction favored CABG but did not reach statistical significance. Rates of additional revascularization procedures were significantly higher after PTCA.

In summary, the data available suggest that both PTCA and CABG are effective in providing symptom relief for patients with severe single vessel CAD. Rates of myocardial infarction may be higher after PTCA, likely because of periprocedural events; however, because no such difference was found for multivessel disease (see below), caution is needed to avoid overinterpretation of these data. Patients undergoing PTCA unequivocally have a greater likelihood of repeat procedures because of restenosis. If this is acceptable to patients and their physicians, then PTCA offers a simpler and less invasive method of revascularization. Of note, the meta-analysis of CABG versus medical therapy trials suggested a mortality benefit for CABG in one or two vessel disease with involvement of the proximal left anterior descending coronary artery (odds ratio, 0·58, 95% CI 0·34–1·01).[7] These patients have a large area of myocardium at jeopardy and are at higher risk for death than those with other forms of single vessel disease and may represent a group that merits special consideration. For single vessel disease, the current conclusions and recommendations are based on a relatively small number of patients and events ($n = 731$, with 44 deaths), and the possibility that potentially important differences between therapies were missed cannot be excluded.

Multivessel disease

For multivessel disease, CABG has remained the mainstay of therapy, especially for moderate- and high-risk patients such as those with severe two or three vessel disease with concomitant left ventricular dysfunction. The group of patients with multivessel disease is a heterogeneous group, with marked heterogeneity in the location and extent of anatomical stenosis, clinical symptoms, ventricular function, and coexistent disease. Thus, characteristics of patients enrolled need to be evaluated carefully when comparing trial results.

Nine prospective randomized clinical trials have compared PTCA (that is, balloon angioplasty) with CABG surgery in the treatment of multivessel disease.[24,30,32–38] These trials have enrolled 5200 patients and, although they vary in design, methods, and stage of follow up, they are broadly comparable and it is instructive to consider them together. The main characteristics of these trials are compared in Tables 27.3 and 27.4. All trials shared important features: treatment allocation to PTCA or CABG was randomly assigned, a high degree of compliance with the assigned therapy was achieved (more than 95%), and follow up data describing vital status, incidence of myocardial infarction, and prevalence of angina pectoris (or measures of myocardial ischemia) were collected. No trial individually was powered to detect or to exclude differences in mortality, and various composite clinical end points were used. Length of follow up varied, and in some instances, additional follow up is planned.

The largest of the PTCA versus CABG trials, the Bypass Angioplasty Revascularization Investigation (BARI), was published in 1996.[39] Designed as an "equivalence" trial,

Table 27.3 Main characteristics of nine prospective randomized trials of PTCA versus CABG

	BARI[37]	CABRI[35]	EAST[33]	ERACI[36]	GABI[34]	MASS[24]	RITA[30]	Swiss[32]	Toulouse[38]
Location	North America, multicenter	Europe, multicenter	Emory University (Atlanta, GA), single-center	Argentina, single-center	Germany, multicenter	Brazil, single-center	Britain, multicenter	Switzerland, single-center	France, single-center
Patients screened (*n*)	25 200	?	5118	1409	8981	?	17 237	?	?
Randomized (%)	1829 (7·3)	1054	392 (7·7)	127 (9·0)	359 (4·0)	214	1011 (4·8)	142	152
Equivalent revascularization required	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Follow up									
Planned duration (years)	10	5–10	3	3	1	3·5	5	2·5	3
Completed	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Primary end point	Mortality, MI	Mortality, non-fatal MI, angina, functional capacity	Combined death, MI, and large thallium defect	Combined death, MI, and angina	Freedom from angina at 1 year (>CCS 2)	Combined cardiac death, MI, refractory angina	Combined death and MI	Death, MI, repeat revascularization	?

Abbreviations: CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty
(Adapted from Raco D, Rihal CS, Yusuf S. Randomized trials of percutaneous transluminal coronary angioplasty: comparison of medical and surgical therapy. In: Grech ED, Ramsdale DR, eds. *Practical interventional cardiology*. St. Louis: Mosby, 1997. By permission of Martin Dunitz)

Table 27.4 Patient profiles in nine randomized trials of PTCA versus CABG

	BARI[37]	CABRI[35]	EAST[33]	ERACI[36]	GABI[34]	MASS[24]	RITA[30]	Swiss[32]	Toulouse[38]
Number of stenotic vessels (%)									
one	0	0	0	0	0	100	45	100	–
two	56	58	60	55	81	–	43	–	49
three	43	40	40	45	19	–	12	–	14
Mean ejection fraction (%)	58	63	61	61	?	75	?	?	?
Average age (years)	61	61	62	57	59	56	57	56	?
CCS class 3 or 4 angina (%)	?	65	80	?	65	?	60	89	?
Mammary artery used (% of CABG procedures)	82	?	90	77	37	100	74	100	?
Male:female	74:26	63:37	74:26	54:46	80:20	58:42	81:19	80:20	?
Previous MI (%)	?	41	41	32	47	?	43	0	?

Abbreviations: CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; MI, myocardial infarction
(Adapted from Raco D, Rihal CS, Yusuf S. Randomized trials of percutaneous transluminal coronary angioplasty: comparison of medical and surgical therapy. In: Grech ED, Ramsdale DR, eds. *Practical interventional cardiology*. St. Louis: Mosby, 1997. By permission of Martin Dunitz)

sample size calculations were predicated on an estimated cumulative 5 year mortality of about 5%, with the goal that the upper 95% confidence limit for any observed difference would not exceed 2·5%.[37] Approximately 30% of screened angiograms of patients with multivessel disease were considered eligible and 1829 patients were enrolled. About 40% of these patients had three vessel disease, and 22% had an ejection fraction less than 50%. Assignment to PTCA or CABG was randomly allocated, and follow up was continued for 5 years before the first results were presented. Five year mortality among patients assigned to CABG was 10·7%, and 13·7% among those assigned to PTCA (absolute difference 3·0%, 95% CI −0·2–6·0; $P = 0·19$). The study was interpreted as negative because the 22% relative risk reduction in favor of CABG did not reach statistical significance, but the study had less than 40% power to detect the observed difference. Extension of follow up to 7 years demonstrated a mortality advantage to CABG that was nominally significant (15·6% *v* 19·1% for PTCA, $P = 0·043$).[40] The entire difference appears to be confined to the subgroup of 353 (19% of total enrollees) patients with diabetes mellitus (7 year mortality 23·6% CABG *v* 44·3% PTCA, $P = 0·0011$). No difference in survival was noted among the remaining 1476 (81%) patients (7 year mortality, 13·6% CABG *v* 13·2% PTCA, $P = 0·72$). Implications of the findings in the diabetic subgroup are discussed in more detail below; however, considerable caution should be applied to interpretation of these findings unless they are confirmed by other randomized clinical trials.

A systematic review of eight of these trials has been published;[29] however, BARI was published after the initial meta-analysis. Results of updated systematic reviews of all-cause mortality (death or myocardial infarction) and non-protocol revascularization after the initial randomly assigned treatment are presented in Table 27.3. Inclusion of late follow up data, particularly from BARI, yielded a nominally significant difference in total mortality in favor of CABG (11·1% PTCA *v* 9·5% CABG; odds ratio 1·20, 95% CI 1·00–1·45; $P = 0·05$). The combined end point of death or myocardial infarction, however, did not differ (17·2% PTCA, 16·8% CABG; odds ratio 1·04, 95% CI 0·89–1·20). Rates of repeat procedures were much higher after PTCA (52% *v* 11%; odds ratio 9·15, 95% CI 7·9–10·6).

Substudies have demonstrated that PTCA and CABG produce similar benefits on quality of life measures and return to employment, and are roughly equivalent in cost over 3–5 years of follow up.[41–44] CABG is associated with more complete revascularization, but differences in degree of revascularization of major lesions are less pronounced.[43]

Conclusions: PTCA (balloon angioplasty) versus CABG

In summary, 5200 patients with multivessel CAD have been enrolled in nine trials of PTCA versus CABG. When long-term follow up data are considered, cumulative mortality rates are lower with CABG than with PTCA, and fewer patients require repeat procedures. However, the initial morbidity is less with PTCA, rates of myocardial infarction are similar, and overall anginal relief is nearly equivalent by 3 years. Restenosis continues to be a major limitation of PTCA. These data suggest that for patients at high risk for death, CABG is preferred. For other patients, PTCA is a reasonable alternative if a higher rate of repeat procedures is acceptable.

Can it be concluded, then, that PTCA and CABG are roughly equivalent modes of revascularization for multivessel disease among angiographically eligible patients, except for the unsolved problem of restenosis? To answer this question, it is necessary to consider the marked heterogeneity of what is termed "multivessel disease". Although discrete lesions of the right coronary and circumflex arteries in a patient who has a normal left ventricle or diffuse three vessel disease in a patient with an ejection fraction of 30% can rightly be classified under the term "multivessel disease", the prognoses, risks, and potential benefits of revascularization vary considerably.

In the recent PTCA versus CABG trials, enrolled patients were relatively low risk: fewer than 20% had left ventricular dysfunction and almost 70% had one or two vessel disease. In the meta-analysis of Pocock *et al*,[29] for example, the observed first year mortality of 2·6% and 1·1% per year thereafter confirms the relatively low-risk status of these patients. (However, no medical control arms were present.) Patients enrolled in BARI had higher observed mortality rates and more closely approximated moderate-risk patients, in part because of the higher proportion of patients with diabetes mellitus. Even in BARI, however, nearly 60% of patients had two vessel coronary artery disease. In contrast, patients enrolled in the earlier CABG versus medical therapy trials had a 20% prevalence of left ventricular dysfunction and 60% had three vessel or left main CAD.[7] Thus, the current PTCA versus CABG trials include a high proportion of patients in whom CABG has *not* been shown to be superior to medical therapy. Moreover, the total enrollment of 5200 patients falls short of the roughly 8000 needed to demonstrate clinically important differences in mortality of 20–30% among low- and moderate-risk patients. It is reasonable to surmise that, if CABG were superior to PTCA in moderate- and high-risk patients, the current PTCA versus CABG trials would have low power to reliably detect significant differences, and that such a difference cannot be ruled out. Large mortality differences on the order of 40–50%, however, are unlikely, given the current data. Also, these trials were performed before the wide use of intracoronary stents, and whether stents may change the observed outcomes is discussed below.

Relative effect of PTCA and CABG in patients with diabetes

BARI findings

On 21 September 1995, the National Heart, Lung, and Blood Institute took the unusual measure of issuing a Clinical Alert to physicians in the United States about the observed superiority of CABG over PTCA among the 353 treated diabetic patients enrolled in the BARI randomized trial.[45] After 5 years of follow up, the cumulative mortality after CABG was 19% among patients with diabetes compared with 35% for those treated with PTCA ($P < 0{\cdot}0024$). The findings, however, were unexpected. At the initiation of the trial, patients were categorized into four subgroups for purposes of analysis: by anginal status, left ventricular function, extent of ischemia, and angiographic risk. Patients with diabetes were not among the original four pre-assigned subgroups, but within 1 year after the trial began, the Data and Safety Monitoring Board requested that these patients be monitored separately.[46] The magnitude of the difference favoring CABG met the pre-specified significance criteria ($P < 0{\cdot}005$) for subgroup analyses and led to the Clinical Alert.

The recently published 7 year outcome data have extended these observations.[40] Among the patients with diabetes in the BARI randomized trial, estimated 7 year survival was 76·4% after CABG and 55·7% after PTCA ($P = 0{\cdot}0011$). The difference in outcome was confined to diabetic patients who received at least one internal mammary arterial graft (7 year survival 83·2%, $n = 140$), whereas diabetic patients who received only saphenous vein grafts had a 7 year survival (54·5%, $n = 33$), similar to those who had PTCA (55·5%, $n = 170$).[40] Long-term follow up from the much smaller Emory Angioplasty versus Surgery Trial (EAST) that included 59 patients with diabetes was consistent with these results, although it did not attain statistical significance (8 year survival, 75·5% after CABG and 60·1% after PTCA; $P = 0{\cdot}23$).[47] Of course, the key question is whether the BARI outcomes among diabetic patients were real or only a play of chance. Several lines of evidence suggest it is real, and they have been reviewed in detail.[46]

In a combined analysis from the BARI trial and registry of 641 diabetic patients and 2962 non-diabetic patients, 5 year death (20% *v* 8%) and Q wave myocardial infarction (8% *v* 4%) rates were significantly higher among those with diabetes.[48] Multivariate analysis identified insulin treated diabetes, heart or renal failure, black race, and older age as most strongly associated with high overall mortality.[49] The only significant interaction term was between treatment and insulin treated diabetes ($P = 0{\cdot}042$).[49] Overall, CABG did not have a protective effect against the incidence of Q wave myocardial infarction; however, CABG greatly decreased the risk of death among diabetic patients when infarction occurred (RR 0·09, 95% CI 0·03–0·29; $P < 0{\cdot}001$). This effect may account for up to 50% of the overall reduction in mortality after CABG observed in the diabetic subgroup of BARI.

An independent, angiographic case–control study has suggested a significantly higher propensity for the development of new coronary vascular lesions among patients with diabetes, both when previously instrumented (16·9% *v* 12·7% of non-diabetic arteries) and *de novo* (13·2% *v* 7·3%).[50] Unpublished 5 year angiographic follow up data from BARI 1 (Frye RL, read at the American College of Cardiology 50th Annual Scientific Sessions, Orlando, Florida, 20 March 2001) have suggested similar findings. These data suggest that

CABG, particularly with internal mammary artery conduits, confers a protective shield against the complications of progression of the underlying vascular disease in patients with diabetes. Whether intensive medical therapy for diabetes can influence progression of macrovascular complications in this group is not known.

The results of the BARI subgroup have not been reproduced in other large trials, and observational data sets and caution must be exercised in the interpretation of the BARI diabetic data.[51–55] Retrospective analysis of small subgroups may overestimate or even misdirect the treatment effect. A Duke University study of 3230 patients (24% with diabetes), selected for similarity to BARI enrollees, found that diabetes was a marker of a worse prognosis after both CABG and PTCA, but with no clear superiority of one procedure over the other.[52]

The largest database study of patients with diabetes undergoing revascularization is from Emory University, where 2639 such patients with multivessel coronary artery disease who underwent PTCA or CABG between 1981 and 1994 were examined. CABG was superior only among the 889 patients treated with insulin, but confidence intervals were wide (hazard ratio for mortality after PTCA 1·35, 95% CI 1·01–1·79 compared with CABG). This finding is consistent with the BARI trial, in which CABG superiority was more pronounced among patients with diabetes who were taking insulin.[54] In the BARI observational registry, which accompanied the randomized trial, a clear difference in outcomes after CABG or PTCA was not observed.[53] Five year mortality among diabetic patients after PTCA ($n=182$) was 14·4% and 14·9% after CABG ($n=117$; RR 1·10, $P=0·86$).[54] Significant differences in adverse socioeconomic and angiographic characteristics (such as number of significant lesions and presence of diffuse disease) between patients treated with PTCA or CABG were present. Generally, patients who had PTCA had fewer adverse risk factors than those assigned to CABG. After adjustment for these differences, the hazard ratio for mortality after PTCA rose to 1·41 but did not attain significance (95% CI 0·60–3·29).

Conclusions: revascularization in patients with diabetes

In both trials and observational data sets, diabetes mellitus is clearly a marker for high risk and, in comparison with non-diabetic patients, the prognosis is worse after either PTCA or CABG. In the largest randomized trial of PTCA versus CABG, patients with diabetes who received internal mammary artery grafts had better outcomes than those treated with PTCA. However, large non-randomized registry data suggest equivalent outcomes after either procedure as long as the sicker patients are triaged to surgery. One conclusion that may resolve the apparent dilemma is that selected patients with diabetes, such as those with favorable angiographic characteristics, may do as well with PTCA and CABG, whereas those with more diffuse or advanced coronary artery disease do better with CABG as initial therapy. Because 5200 patients have been enrolled in trials of PTCA versus CABG surgery, collaborative meta-analysis based on individual patient data may allow more definitive characterization of outcomes after revascularization among diabetic patients. It remains to be determined whether the use of stents, particularly in combination with parenteral antiplatelet drugs and aggressive metabolic management, will change these conclusions.

Although no prospective randomized trial of myocardial revascularization in patients with diabetes exists, the BARI 2 trial will test the hypothesis that revascularization for diabetic patients early in the stages of CAD may significantly decrease 5 year mortality. This study will incorporate strict metabolic and risk factor control and test both insulin-providing and insulin-sensitizing agents.

Effect of stents on outcome after revascularization

Since first approved by the US Food and Drug Administration in 1993, coronary stents have been adopted rapidly and widely as the main method of percutaneous revascularization, although the pace of adoption has outstripped the pace of the accompanying clinical investigation and regulatory approval.[56,57] Likely, more than 1 000 000 patients now receive intracoronary stents in the USA annually, with an equivalent number in the rest of the world, primarily Europe.

The first indication for stents was for the treatment of severe coronary artery dissection with acute or threatened vessel closure. The National Heart, Lung and Blood Institute 1985–86 PTCA registry documented the risks of balloon angioplasty before the development of stents. Abrupt vessel closure occurred in 6·8% of all procedures, with 32% of these patients requiring emergency CABG and 42% having a myocardial infarction; the case fatality rate was 5%.[58] A prospective multicenter registry of 518 patients with acute or threatened vessel closure after PTCA treated with stents was reported in 1993.[59] Successful stent deployment occurred in 95·4% of cases. The rates of inhospital emergency CABG and myocardial infarction among these patients with severe coronary artery dissections were 4·3% and 5·5%, respectively, markedly lower than the historical control rates mentioned above. Although not randomized, this study and others[60] established the role of stents in the treatment of arterial dissections after PTCA.

Numerous prospective, randomized trials published over the past 10 years have compared elective stenting to balloon angioplasty under various circumstances. These studies have enrolled patients with various lesion types, including elective procedures for single discrete lesions in vessels

of 3·0 mm or larger,[61–71] restenosis lesions after previous balloon angioplasty,[72] lesions of saphenous vein grafts,[73] small caliber vessels,[74–77] and chronic total occlusions.[78–84] The effect of stents versus balloon angioplasty on the clinical outcomes of death, death or myocardial infarction, and repeat procedures, and the angiographic outcome of restenosis are shown in Table 27·5. In total, almost 7000 patients have been randomly allocated in published trials of stent versus balloon angioplasty, including 4694 who had systematic angiographic follow up. As shown in Table 27·5, overall mortality was low (1·5% *v* 1·9% for stent versus balloon angioplasty patients, respectively; odds ratio 0·83, 95% CI 0·57–1·21), as were death or myocardial infarction rates (6·1% *v* 6·5%; odds ratio 0·93, 95% CI 0·77–1·14). The impact of stenting on clinical end points was related to the need for repeat revascularization (14·7% after stenting *v* 23·9% after balloon angioplasty; 9·2% absolute risk reduction; odds ratio 0·53, 95% CI 0·46–0·60). A significant decrease in the incidence of angiographic restenosis was found (27·5% *v* 42·2%; odds ratio 0·50, 95% CI 0·44–0·57) among patients who had systematic follow up angiography (26·6% stent *v* 41·6% PTCA; odds ratio 0·48, 95% CI 0·42–0·56).

As with any rapidly evolving therapy, advances have occurred in techniques of stenting – for example, high pressure inflations[85] and improved antiplatelet therapy with oral[86,87] and parenteral antiplatelet[69] agents – that have allowed wider application.

A novel approach to the further optimization of results – the use of local drug delivery to inhibit the restenotic process after intracoronary stenting – is being evaluated in multiple trials. The first published trial tested a metal stent coated with the macrolide antibiotic sirolimus, an immunosuppressive agent that is a potent inhibitor of lymphocyte and smooth muscle cell proliferation.[88] In animal studies, sirolimus has been shown to be a potent inhibitor of restenosis.[89] The trial enrolled 238 patients with standard clinical indications for stenting and randomly assigned them to receive stents

Table 27.5 Summary of meta-analyses of revascularization for chronic coronary artery disease

PTCA[a] *v* CABG

Variable	PTCA (%)	CABG (%)	Trials (*n*)	Patients (*n*)	OR (95% CI)
Single vessel disease					
All cause mortality	5·6	6·4	3	732	0·86 (0·47–1·59)
Death or MI	15·0	11·7	3	732	1·33 (0·87–2·05)
Repeat revascularization	33·8	8·1	3	732	4·73 (3·32–6·77)
Overall					
All cause mortality	16·2	14·6	9	5200	1·14 (0·98–1·34)
Death or MI	17·2	16·8	9	5200	1·04 (0·89–1·20)
Repeat revascularization	52·6	13·1	9	5200	8·24 (7·14–9·52)

Stents *v* PTCA

Variable	Stents (%)	PTCA (%)	Trials (*n*)	Patients (*n*)	OR (95% CI)
Mortality	1·5	1·9	21	6929	0·83 (0·57–1·21)
Death or MI	6·1	6·5	21	6929	0·93 (0·77–1·13)
Repeat revascularization	14·7	23·9	21	6929	0·53 (0·44–0·57)
Angiographic restenosis > 50%	27·5	42·2	20	4694	0·50 (0·77–1·33)

Stents *v* CABG

Variable	Stents (%)	CABG (%)	Trials (*n*)	Patients (*n*)	OR (95% CI)
Mortality	5·5	5·6	5	3218	0·98 (0·72–1·34)
Death or MI	7·9	8·9	4	2764	0·87 (0·67–1·14)
Repeat revascularization	19·0	4·5	5	3218	5·00 (3·83–6·51)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; OR, odds ratio; PTCA, percutaneous transluminal coronary angioplasty

[a] Meta-analyses were performed using RevMan 5·0 software (Cochrane Collaboration). To accrue the largest number of events possible, data used represent the longest term follow up available for each trial included, whether published or presented orally; 1 was added to all zero cells. Data are presented in summary form only. Details of each meta-analysis are beyond the scope of the current review.

coated with a sirolimus-polymer matrix or uncoated stents. Results were assessed by routine angiography at 6 months. None of the patients who received a sirolimus-coated stent had restenosis, as defined by at least 50% stenosis within the stent, compared with 26·6% of those who had a bare metal stent ($P < 0{\cdot}001$). After 1 year of clinical follow up, there were no episodes of stent thrombosis, and 5·8% of the sirolimus group experienced an adverse cardiac event (death, MI, CABG, or revascularization of the original target vessel) compared with 28·8% of control stent group ($P < 0{\cdot}001$). Although the decrease in restenosis rate and the corresponding reduction in need for further procedures are striking, the trial was only a relatively small single study with follow up limited to 1 year. Whether potent intra-arterial immunosuppression will have unanticipated long-term problems related to impaired arterial healing is unknown.

Several prospective randomized trials have compared multivessel stenting with multivessel CABG, although follow up periods remain short. The Arterial Revascularization Therapy Study (ARTS)[90] enrolled 1205 patients with multivessel disease (average, 2·7 treated lesions) to either stenting or CABG. At 12 months of follow up, 2·5% of the 600 stent patients and 2·8% of the 605 CABG patients had died. Kaplan–Meier estimated rates of the irreversible end points of death, stroke, or myocardial infarction at 1 year were 9·5% for the stent group and 11·2% for the CABG group (RR 0·92, 95% CI 0·62–1·35; $P = 0{\cdot}65$). Stent patients required more follow up procedures than those assigned to CABG, with cumulative event rates at 1 year of 26·2% for the stent group and 12·2% for the CABG group (absolute difference, 14%). Within the stent group, the incremental 16·7% event rate at 1 year attributable to repeat revascularization was about half of the corresponding 33·7% 1 year repeat revascularization rate after balloon angioplasty in a meta-analysis of the balloon versus CABG trials,[29] and was consistent with the findings of the stent versus balloon trials described above. For comparison, 1 year rates of repeat revascularization after CABG have remained constant: 3·3% in the meta-analysis and 3·5% in ARTS.

Data from four other trials of stents versus CABG have been published or presented, including Stents or Surgery (Sigwart U, read at the American College of Cardiology 50th Annual Scientific Sessions, Orlando, Florida, 20 March 2001), a multicenter European study of nearly 1000 patients; Argentine Randomized Trial of PTCA Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI) II,[91] a multicenter Argentinian study of 450 patients; and Stenting versus Internal Mammary Artery (SIMA),[92] a Swiss–Italian study of 123 patients. Findings are summarized in the accompanying meta-analyses in Table 27.3 and are consistent with those of ARTS. Data from Angina With Extremely Serious Operative Mortality Evaluation (AWESOME),[93] a prospective randomized clinical trial conducted at 16 Veterans Affairs Medical Centers that assigned 454 patients with refractory angina and markers of high risk to either percutaneous coronary intervention or CABG, are included because a high proportion of the patients in the percutaneous coronary intervention group received stents. Together, these randomized clinical trials have enrolled 3218 patients. No significant differences in mortality (5·45% after percutaneous coronary intervention *v* 5·61% after CABG; odds ratio 0·98, 95% CI 0·98–1·34), or death or myocardial infarction (7·9% after percutaneous coronary intervention *v* 8·9% after CABG; odds ratio 0·87, 95% CI 0·67–1·14) were found. The need for repeat procedures remains higher after stenting (19% *v* 4·5% after CABG; odds ratio 5·54, 95% CI 3·83–6·51), although lower than the rates reported earlier after multivessel balloon angioplasty.

Longer follow up and accrual of events is necessary before final conclusions can be drawn. Similarly, the number of patients with diabetes enrolled was small and no specific conclusions can be drawn yet.

Miscellaneous interventional device trials

Numerous devices have been developed to allow or facilitate percutaneous revascularization. After balloon angioplasty, the directional atherectomy catheter was the first such device, gaining FDA approval in 1990. This device allows cutting and removal of coronary plaque in a controlled ("directional") manner. The hypothesis was that plaque removal would cause less trauma to the artery, incite a less vigorous neointimal response, and, ultimately, significantly decrease rates of restenosis and repeat procedures. Although marginal benefits regarding angiographic restenosis were observed in some trials (CAVEAT, BOAT),[94,95] this was not so in others (CCAT).[96] Worrisome increases in rates of myocardial infarction, death, and other major complications were noted in several trials (BOAT, CAVEAT, CAVEAT-II).[97,98] The rapid ease of use and rapid adoption of intracoronary stents have made directional atherectomy a so-called niche device, used only for particular anatomic circumstances.

Rotational atherectomy is another procedure that can be used for performing lesion debulking. It is performed with a high-speed rotating, diamond-tipped abrasive burr. The device allows recanalization of heavily calcified lesions or fibrotic lesions as well as debulking. No tissue is removed, and the device pulverises atherosclerotic plaque into tiny particles that pass through the microcirculation and are removed by the reticuloendothelial system. The device is associated with a relatively high incidence of poor flow after use and non-Q wave myocardial infarction and has had no particular benefit on restenosis (ERBAC).[99–101] Currently it is used primarily to facilitate stent deployment when this would otherwise be impossible because of severe calcification or fibrosis of the target lesion.

Intracoronary brachytherapy, or the local delivery of radiation to inhibit the restenotic process, was approved for the treatment of in-stent restenosis, a vexing problem that is difficult to treat initially and has high recurrence rates. Two

competing systems, one capable of delivering beta radiation, and the other, gamma radiation, have been widely used. These devices have been demonstrated to significantly lower the rates of subsequent recurrent restenosis (14·6% *v* 60·8% in pooled data from three studies totalling 442 patients) and adverse cardiac events (24·5% *v* 70% $P < 0{\cdot}001$).[102–6] A triple-blind design with dummy radiation sources was used in some studies.[104] A delayed risk of stent thrombosis, particularly when a new stent was placed at the time of the procedure, was observed in follow up (6·2% of brachytherapy patients with a new stent *v* 0·7% of control patients with a new stent).[102] Avoidance of placement of new stents and continuation of dual antiplatelet therapy with aspirin and clopidogrel for 6–12 months has largely obviated this problem. If local drug-elution essentially eliminates or greatly reduces the incidence of in-stent restenosis, utilization of coronary brachytherapy is expected to decrease.

Database studies

Prospective randomized trials provide the highest level of evidence for clinical decision making; nonetheless, information from trials frequently must be supplemented and enhanced by observational studies. Long-term survival for 9263 patients with angiographically documented CAD has been reported recently from Duke University Medical Center.[107,108] Although treatment assignment was non-random, the 97% complete follow up of this consecutive series has provided insight into the outcomes after various treatments (2449 patients, medical only; 2924, PTCA; and 3890, CABG), with concurrent controls. Nine risk strata based on the number and extent of diseased coronary arteries were identified (left main CAD and stenoses less than 75% were excluded). Long-term survival comparisons between treatments were assessed with Cox proportional hazards models and Kaplan–Meier survival analysis. CABG was significantly associated with improved long-term outcomes in comparison with medical therapy for patients in moderate-and high-risk strata (for three vessel disease [$n = 2771$]: odds ratio, 0·44, 95% CI 0·42–0·80) (Figure 27.5). PTCA, however, was superior to medical therapy only among low-risk strata.[108] In comparison with PTCA, CABG was associated with improved outcomes among high-risk strata, namely, all patients with three vessel disease and two vessel disease with

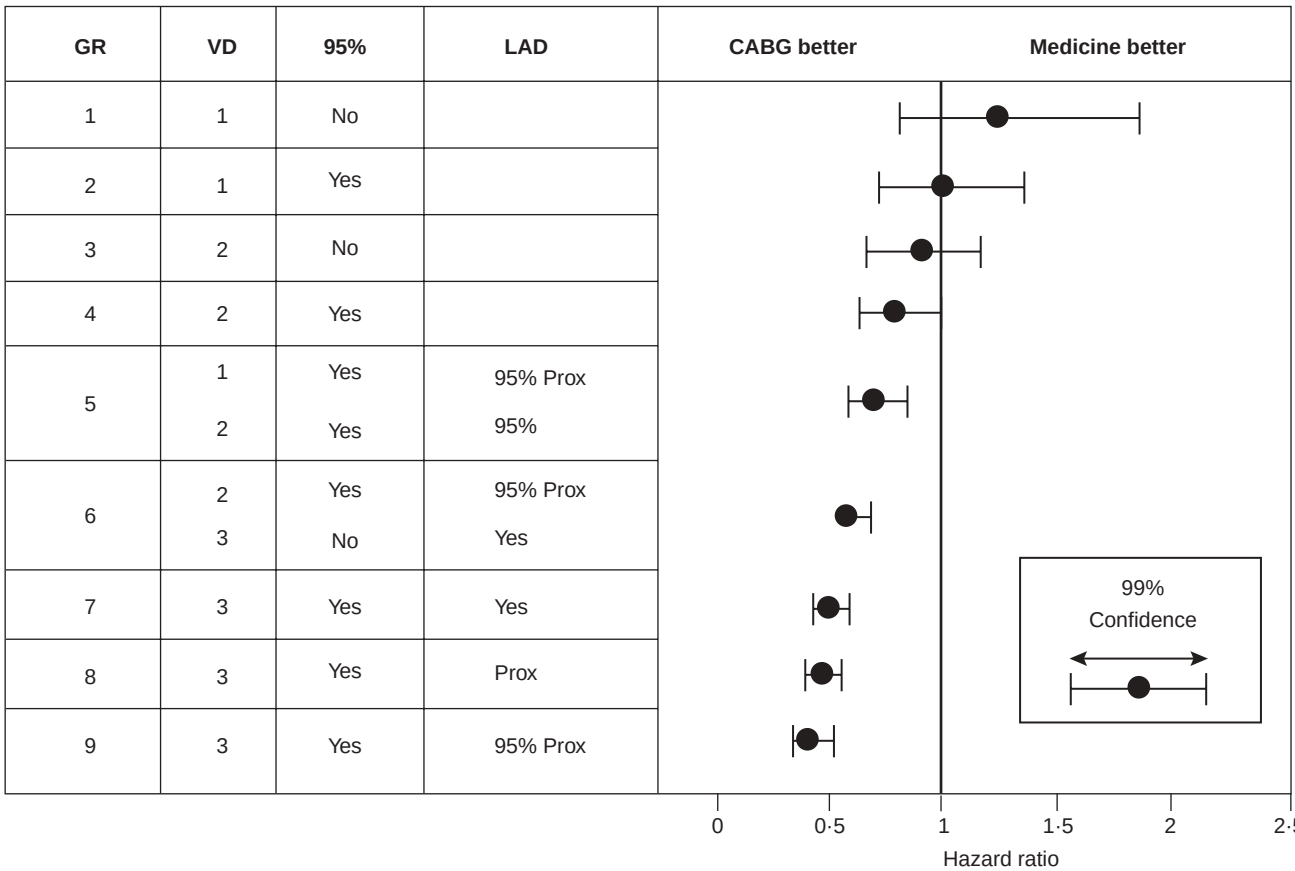

Figure 27.5 Adjusted hazard ratios comparing coronary artery bypass graft (CABG) and medicine for the nine coronary anatomy groups. GR, group; LAD, left anterior descending coronary artery; Prox, proximal; VD, number of diseased vessels; 95%, ≥95% coronary artery stenosis. (From Jones *et al*[108] by permission of Mosby-Year Book, Inc.)

GR	VD	95%	LAD
1	1	No	
2	1	Yes	
3	2	No	
4	2	Yes	
5	1	Yes	95% Prox
	2	Yes	95%
6	2	Yes	95% Prox
	3	No	Yes
7	3	Yes	Yes
8	3	Yes	Prox
9	3	Yes	95% Prox

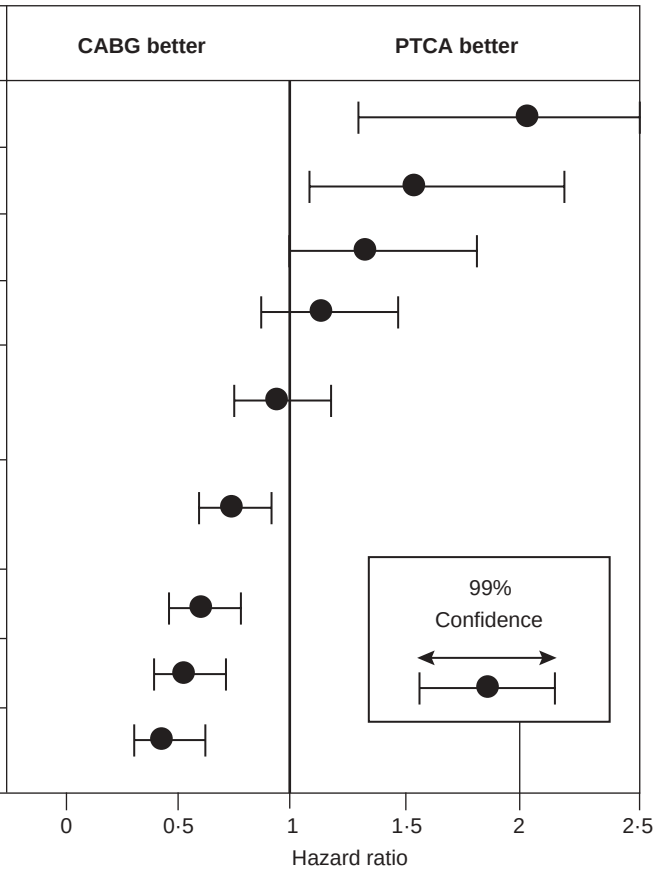

Figure 27.6 Adjusted hazard ratios comparing coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA) for the nine coronary anatomy groups. GR, group; LAD, left anterior descending coronary artery; Prox, proximal; VD, number of diseased vessels; 95%, ≥95% coronary artery stenosis. (From Jones *et al*[108] by permission of Mosby-Year Book, Inc.)

95% involvement of the proximal left anterior descending coronary artery. Conversely, adjusted hazard ratios demonstrated superiority of PTCA over CABG among low-risk patients (Figure 27.6) and a trend toward superiority among moderate-risk patients.

These prospective observational data are broadly consistent with the previously presented framework placing PTCA versus CABG trials in the context of CABG versus medical therapy trials. Although a definitive benefit of CABG over medical therapy for one and two vessel disease could not be demonstrated in the randomized trials (with the possible exception of proximal left anterior descending CAD), non-significant trends favoring CABG were found. The relatively low number of observed events (113 deaths over 5 years) in these trials may have precluded detection of even a large benefit (type II error). The Duke observational data extended the randomized trials and, by virtue of the much larger number of events (related to the larger number of patients and longer duration of follow up), allow further characterization of possible treatment differences. As with any non-randomized study, important limitations related to intrinsic biases in patient selection remain, and definitive conclusions require performance of larger randomized trials. For example, determination of time zero is a problem and deaths occurring while awaiting revascularization were assigned to medical therapy, which would tend to inflate event rates among medical patients.

Limitations of current data

In an evolving field, all trials designed to address specific clinical questions at a specific time should be interpreted in the context of relevant changes in the procedures and complementary treatments. This is especially notable for the CABG versus medical therapy trials performed 20 to 25 years ago. The wide application of antiplatelet, antihyperlipidemic, and ACE inhibitor therapy in current practice may substantially mitigate the published results. Temporal changes in angioplasty and surgical techniques are continuing and, in some cases, accelerating. The development of new interventional devices designed to deal with procedural complications, specific high-risk lesions, or previously unapproachable lesions

has broadened the feasibility of percutaneous procedures. Coronary stents have decreased the incidence of both emergency and late CABG and lower restenosis. New adjunctive medical therapies such as platelet IIb/IIIa receptor antagonists reduce the risk of non-fatal myocardial infarction and emergency CABG with interventional procedures. CABG, too, has undergone considerable technologic advances. Internal thoracic arterial conduits with excellent long-term patency are now widely used. Improved myocardial preservation techniques, adjunctive medical therapies, and less invasive surgical approaches have been developed.

Specific methodologic concerns also exist about the available data. All the trials discussed above compared two active treatments and were not placebo controlled, decreasing the chances of detecting differences among arms. Invasive or surgical trials are logistically very complex, tend to be small compared with drug therapy trials, and are inherently open label. The possibility of missing potentially important differences, even when one exists, is always higher for small trials. Although systematic reviews, preferably based on individual patient data, can provide some redress, larger definitive trials (along with meta-analysis of their results) are preferable. In trials of invasive treatments, crossover to the other therapy occurs with increasing frequency during the course of follow up, necessitating consideration of therapeutic strategies rather than specific treatments. As with many large surgical trials, applicability of results to medical centers with lower volume and different levels of experience remains unproven.[109–111]

The greatest limitation of the currently available data is the low statistical power to detect potential differences in clinical outcomes, in particular the PTCA trials, whereas PTCA rates have grown dramatically. This situation could be rectified partly by long-term follow up of the trials that have been completed, accompanied by a collaborative meta-analysis based on individual patient data. Even if this were done, however, the lack of large trials incorporating all three major approaches to patients with coronary artery disease – medical, interventional, and surgical – would limit comprehensive comparisons to observational databases.[107]

Summary: overview of the evidence for myocardial revascularization in patients with chronic stable angina

CABG surgery versus medical therapy

- Among patients with medically refractory angina pectoris, CABG is indicated for symptom improvement. **Grade A1a**
- Among patients with medically stable angina pectoris, CABG is indicated for left main coronary artery or three vessel disease, regardless of left ventricular function, for prolongation of life. **Grade A1a**
- CABG may be indicated for prolongation of life if the proximal left anterior descending coronary artery is involved, regardless of the number of diseased vessels. **Grade A1c**

Percutaneous coronary intervention versus medical therapy

- Among patients with medically refractory angina pectoris, PTCA is indicated for symptom improvement. **Grade A**
- In the absence of symptoms or myocardial ischemia, PTCA is not indicated merely for the presence of an anatomical stenosis. **Grade A**
- Stents are indicated for the treatment of arterial dissections with abrupt or threatened vessel closure after balloon angioplasty. **Grade B**
- Electively placed stents are superior to balloon angioplasty for reducing the need for repeat procedures and, likely, the risks of periprocedural myocardial infarction and emergency CABG surgery. **Grade A1a**

Percutaneous coronary intervention versus CABG

- For single vessel disease, both PTCA and CABG provide excellent symptom relief, but repeat revascularization procedures are required more frequently after PTCA. **Grade A**
- For multivessel disease, the higher the baseline risk of the patient, the more CABG is to be preferred. **Grade A1c** This includes both diabetic and non-diabetic patients with three vessel or diffuse disease or with left ventricular dysfunction. The following caveats should be considered:
  - Large differences in mortality (40–50%) between PTCA and CABG are unlikely, but smaller differences in mortality (on the order of 20–30%) cannot be excluded given the available data.
  - CABG is associated with more complete revascularization and superior early relief of angina, but these differences are lessened after 3–5 years.
  - No significant differences in rates of myocardial infarction have been demonstrated.
  - Repeat revascularization procedures are required significantly more often after PTCA, an effect partly mitigated by the use of stents.
  - The cost, quality of life, and return to work are initially more favorable with PTCA than CABG, but these variables roughly equalize over 3–5 years.

References

1. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. *Ann Thorac Surg* 1968;**5**:334–9.
2. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;**301**:61–8.
3. Hall MJ, Popovic JR. *1998 Summary: National Hospital Discharge Survey. Advance data from Vital and Health Statistics; no. 316*. Hyattsville, Maryland: National Center for Health Statistics, 2000.
4. European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;**2**:1173–80.
5. The VA Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for stable angina. *Circulation* 1992;**86**:121–30.
6. Alderman EL, Bourassa MG, Cohen LS *et al.* Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation* 1990;**82**: 1629–46.
7. Yusuf S, Zucker D, Peduzzi P *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–70.
8. Caracciolo EA, Davis KB, Sopko G *et al.* Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. *Circulation* 1995;**91**:2325–34.
9. European Coronary Surgery Study Group. Prospective randomised study of coronary artery bypass surgery in stable angina pectoris. Second interim report by the European Coronary Surgery Study Group. *Lancet* 1980;**2**:491–5.
10. Caracciolo EA, Davis KB, Sopko G *et al.* Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation* 1995;**91**:2335–44.
11. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med* 1985;**312**: 1665–71.
12. Myers WO, Schaff HV, Fisher LD *et al.* Time to first new myocardial infarction in patients with severe angina and three-vessel disease comparing medical and early surgical therapy: a CASS registry study of survival. *J Thorac Cardiovasc Surg* 1988;**95**:382–9.
13. Chaitman BR, Stone PH, Knatterud GL *et al.* Asymptomatic Cardiac Ischemia Pilot (ACIP) study: impact of anti-ischemia therapy on 12-week rest electrocardiogram and exercise test outcomes. The ACIP Investigators. *J Am Coll Cardiol* 1995; **26**:585–93.
14. Rogers WJ, Bourassa MG, Andrews TC, *et al.* Asymptomatic Cardiac Ischemia Pilot (ACIP) study: outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. The ACIP Investigators. *J Am Coll Cardiol* 1995;**26**:594–605.
15. Davies RF, Goldberg AD, Forman S *et al.* Asymptomatic Cardiac Ischemia Pilot (ACIP) study 2-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997;**95**: 2037–43.
16. The TIME Investigators. Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary-Artery Disease (TIME): a randomised trial. *Lancet* 2001;**358**:951–7.
17. The Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
18. West of Scotland Coronary Prevention Study. Identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* 1996;**348**:1339–42.
19. Detre K, Holubkov R, Kelsey S *et al.* One-year follow-up results of the 1985–1986 National Heart, Lung, and Blood Institute's Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1989;**80**:421–8.
20. Detre K, Holubkov R, Kelsey S *et al.* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. The National Heart, Lung, and Blood Institute Registry. *N Engl J Med* 1988;**318**:265–70.
21. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med* 1992;**326**:10–16.
22. Sievers B, Hamm CW, Herzner A, Kuck KH. Medical therapy versus PTCA: a prospective, randomized trial in patients with asymptomatic coronary single vessel disease (abstract). *Circulation* 1993;**88**(Suppl. 1):I-297.
23. RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997;**350**:461–8.
24. Hueb WA, Bellotti G, de Oliveira SA *et al.* The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol* 1995;**26**:1600–5.
25. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs cooperative randomized trial. Veterans Affairs ACME Investigators. *J Am Coll Cardiol* 1997;**29**:1505–11.
26. Pitt B, Waters D, Brown WV *et al.* Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;**341**:70–6.
27. Pocock SJ, Henderson RA, Clayton T, Lyman GH, Chamberlain DA. Quality of life after coronary angioplasty or continued medical treatment for angina: three-year follow-up in the RITA-2 trial. Randomized Intervention Treatment of Angina. *J Am Coll Cardiol* 2000;**35**:907–14.
28. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ* 2000;**321**:73–7.
29. Pocock SJ, Henderson RA, Rickards AF *et al.* Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;**346**:1184–9.

30. Coronary angioplasty versus coronary artery bypass surgery: The Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;**341**:573–80.
31. Henderson RA, Pocock SJ, Sharp SJ *et al.* Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. *Lancet* 1998; **352**:1419–25.
32. Goy JJ, Eeckhout E, Burnand B *et al.* Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. *Lancet* 1994; **343**:1449–53.
33. King SB III, Lembo NJ, Weintraub WS *et al.* A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med* 1994;**331**:1044–50.
34. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med* 1994;**331**:1037–43.
35. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *Lancet* 1995;**346**:1179–84.
36. Rodriguez A, Boullon F, Perez-Baliño N, Paviotti C, Liprandi MI, Palacios IF. Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. *J Am Coll Cardiol* 1993;**22**:1060–7.
37. Williams DO, Baim DS, Bates E *et al.* Coronary anatomic and procedural characteristics of patients randomized to coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Cardiol* 1995;**75**:27C–33C.
38. Puel J, Karouny E, Marco F *et al.* Angioplasty versus surgery in multivessel disease: immediate results and in-hospital outcome in a randomized prospective study (abstract). *Circulation* 1992;**86**(Suppl. 1):I-372.
39. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;**335**:217–25.
40. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000;**35**: 1122–9.
41. Pocock SJ, Henderson RA, Seed P, Treasure T, Hampton JR. Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial. *Circulation* 1996;**94**:135–42.
42. Zhao XQ, Brown BG, Stewart DK *et al.* Effectiveness of revascularization in the Emory Angioplasty versus Surgery Trial. A randomized comparison of coronary angioplasty with bypass surgery. *Circulation* 1996;**93**:1954–62.
43. Weintraub WS, Mauldin PD, Becker E, Kosinski AS, King SB III. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty versus Surgery Trial (EAST). *Circulation* 1995;**92**:2831–40.
44. Rodriguez A, Ahualli P, Pérez Baliño N *et al.* Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI): late cost and three years follow up results (abstract). *J Am Coll Cardiol* 1994;**23**:469A.
45. Ferguson JJ. NHLI BARI clinical alert on diabetics treated with angioplasty. *Circulation* 1995;**92**:3371.
46. Kelsey SF. Patients with diabetes did better with coronary bypass graft surgery than with percutaneous transluminal coronary angioplasty: was this BARI finding real? *Am Heart J* 1999;**138**:S387–93.
47. King SB III, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol* 2000;**35**:1116–21.
48. Detre KM, Lombardero MS, Brooks MM *et al.* The effect of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. Bypass Angioplasty Revascularization Investigators. *N Engl J Med* 2000;**342**:989–97.
49. Brooks MM, Jones RH, Bach RG *et al.* Predictors of mortality and mortality from cardiac causes in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial and registry. For the BARI Investigators. *Circulation* 2000;**101**: 2682–9.
50. Rozenman Y, Sapoznikov D, Mosseri M *et al.* Long-term angiographic follow-up of coronary balloon angioplasty in patients with diabetes mellitus: a clue to the explanation of the results of the BARI study. Balloon Angioplasty Revascularization Investigation. *J Am Coll Cardiol* 1997;**30**:1420–5.
51. Kurbaan AS, Bowker TJ, Ilsley CD, Sigwart U, Rickards AF. Difference in the mortality of the CABRI diabetic and nondiabetic populations and its relation to coronary artery disease and the revascularization mode. *Am J Cardiol* 2001; **87**:947–50.
52. Barsness GW, Peterson ED, Ohman EM *et al.* Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997;**96**:2551–6.
53. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997;**96**:1761–9.
54. Detre KM, Guo P, Holubkov R *et al.* Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1999;**99**: 633–40.
55. Weintraub WS, Stein B, Kosinski A *et al.* Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. *J Am Coll Cardiol* 1998;**31**:10–19.
56. Pepine CJ, Holmes DR Jr. Coronary artery stents. American College of Cardiology. *J Am Coll Cardiol* 1996;**28**:782–94.
57. Topol EJ. Coronary-artery stents – gauging, gorging, and gouging. *N Engl J Med* 1998;**339**:1702–4.
58. Detre KM, Holmes DR Jr, Holubkov R *et al.* Incidence and consequences of periprocedural occlusion. The 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1990;**82**:739–50.

59. George BS, Voorhees WD III, Roubin GS *et al.* Multicenter investigation of coronary stenting to treat acute or threatened closure after percutaneous transluminal coronary angioplasty: clinical and angiographic outcomes. *J Am Coll Cardiol* 1993; **22**:135–43.
60. Herrmann HC, Buchbinder M, Clemen MW *et al.* Emergent use of balloon-expandable coronary artery stenting for failed percutaneous transluminal coronary angioplasty. *Circulation* 1992;**86**:812–19.
61. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;**336**:817–22.
62. Serruys PW, de Jaegere P, Kiemeneij F *et al.* A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;**331**:489–95.
63. Fischman DL, Leon MB, Baim DS *et al.* A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994;**331**:496–501.
64. George CJ, Baim DS, Brinker JA *et al.* One-year follow-up of the Stent Restenosis (STRESS I) Study. *Am J Cardiol* 1998; **81**:860–5.
65. Kiemeneij F, Serruys PW, Macaya C *et al.* Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 2001; **37**:1598–603.
66. Serruys PW, van Hout B, Bonnier H *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673–81.
67. Betriu A, Masotti M, Serra A *et al.* Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. *J Am Coll Cardiol* 1999;**34**:1498–506.
68. Lincoff AM, Califf RM, Moliterno DJ *et al.* Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. *N Engl J Med* 1999;**341**:319–27.
69. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
70. Eeckhout E, Stauffer JC, Vogt P, Debbas N, Kappenberger L, Goy JJ. Comparison of elective Wiktor stent placement with conventional balloon angioplasty for new-onset lesions of the right coronary artery. *Am Heart J* 1996;**132**:263–8.
71. Witkowski A, Ruzyllo W, Gil R *et al.* A randomized comparison of elective high-pressure stenting with balloon angioplasty: six-month angiographic and two-year clinical follow-up. On behalf of AS (Angioplasty or Stent) trial investigators. *Am Heart J* 2000;**140**:264–71.
72. Erbel R, Haude M, Hopp HW *et al.* Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. Restenosis Stent Study Group. *N Engl J Med* 1998;**339**:1672–8.
73. Savage MP, Douglas JS Jr, Fischman DL *et al.* Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 1997;**337**:740–7.
74. Park SW, Lee CW, Hong MK *et al.* Randomized comparison of coronary stenting with optimal balloon angioplasty for treatment of lesions in small coronary arteries. *Eur Heart J* 2000; **21**:1785–9.
75. Kastrati A, Schomig A, Dirschinger J *et al.* A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. ISAR-SMART Study Investigators. Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. *Circulation* 2000;**102**:2593–8.
76. Koning R, Eltchaninoff H, Commeau P *et al.* Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. *Circulation* 2001;**104**:1604–8.
77. Doucet S, Schalij MJ, Vrolix MC *et al.* Stent placement to prevent restenosis after angioplasty in small coronary arteries. *Circulation* 2001;**104**:2029–33.
78. Sirnes PA, Golf S, Myreng Y *et al.* Stenting in Chronic Coronary Occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. *J Am Coll Cardiol* 1996;**28**:1444–51.
79. Rubartelli P, Niccoli L, Verna E *et al.* Stent implantation versus balloon angioplasty in chronic coronary occlusions: results from the GISSOC trial. Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche. *J Am Coll Cardiol* 1998;**32**:90–6.
80. Buller CE, Dzavik V, Carere RG *et al.* Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 1999;**100**: 236–42.
81. Hancock J, Thomas MR, Holmberg S, Wainwright RJ, Jewitt DE. Randomised trial of elective stenting after successful percutaneous transluminal coronary angioplasty of occluded coronary arteries. *Heart* 1998;**79**:18–23.
82. Sievert H, Rohde S, Utech A *et al.* Stent or angioplasty after recanalization of chronic coronary occlusions? (The SARECCO Trial.) *Am J Cardiol* 1999;**84**:386–90.
83. Hoher M, Wohrle J, Grebe OC *et al.* A randomized trial of elective stenting after balloon recanalization of chronic total occlusions. *J Am Coll Cardiol* 1999;**34**:722–9.
84. Lotan C, Rozenman Y, Hendler A *et al.* Stents in total occlusion for restenosis prevention. The multicenter randomized STOP study. The Israeli Working Group for Interventional Cardiology. *Eur Heart J* 2000;**21**:1960–6.
85. Colombo A, Hall P, Nakamura S *et al.* Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995;**91**:1676–88.
86. Schomig A, Neumann FJ, Kastrati A *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**: 1084–9.
87. Leon MB, Baim DS, Popma JJ *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;**339**:1665–71.

88. Morice MC, Serruys PW, Sousa JE *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**:1773–80.
89. Gallo R, Padurean A, Jayaraman T *et al.* Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;**99**: 2164–70.
90. Serruys PW, Unger F, Sousa JE *et al.* Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;**344**:1117–24.
91. Rodriguez A, Bernardi V, Navia J *et al.* Argentine Randomized Study: Coronary Angioplasty with Stenting Versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol* 2001;**37**:51–8.
92. Goy JJ, Kaufmann U, Goy-Eggenberger D *et al.* A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Stenting vs Internal Mammary Artery. *Mayo Clin Proc* 2000;**75**:1116–23.
93. Morrison DA, Sethi G, Sacks J *et al.* Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study 385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 2001;**38**:143–9.
94. Topol EJ, Leya F, Pinkerton CA *et al.* A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. *N Engl J Med* 1993;**329**:221–7.
95. Baim DS, Cutlip DE, Sharma SK *et al.* Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). *Circulation* 1998; **97**:322–31.
96. Adelman AG, Cohen EA, Kimball BP *et al.* A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. *N Engl J Med* 1993;**329**:228–33.
97. Elliott JM, Berdan LG, Holmes DR *et al.* One-year follow-up in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I). *Circulation* 1995;**91**:2158–66.
98. Holmes DR Jr, Topol EJ, Califf RM *et al.* A multicenter, randomized trial of coronary angioplasty versus directional atherectomy for patients with saphenous vein bypass graft lesions. CAVEAT-II Investigators. *Circulation* 1995;**91**:1966–74.
99. Reifart N, Vandormael M, Krajcar M *et al.* Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison (ERBAC) Study. *Circulation* 1997;**96**: 91–8.
100. Reisman M, Harms V, Whitlow P, Feldman T, Fortuna R, Buchbinder M. Comparison of early and recent results with rotational atherectomy. *J Am Coll Cardiol* 1997; **29**:353–7.
101. MacIsaac AI, Bass TA, Buchbinder M *et al.* High speed rotational atherectomy: outcome in calcified and noncalcified coronary artery lesions. *J Am Coll Cardiol* 1995;**26**:731–6.
102. Sapirstein W, Zuckerman B, Dillard J. FDA approval of coronary-artery brachytherapy. *N Engl J Med* 2001;**344**:297–9.
103. Waksman R, White RL, Chan RC *et al.* Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;**101**: 2165–71.
104. Leon MB, Teirstein PS, Moses JW *et al.* Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;**344**:250–6.
105. Verin V, Popowski Y, de Bruyne B *et al.* Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. *N Engl J Med* 2001;**344**:243–9.
106. Teirstein PS, Massullo V, Jani S *et al.* Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 2000;**101**:360–5.
107. Mark DB, Nelson CL, Califf RM *et al.* Continuing evolution of therapy for coronary artery disease: initial results from the era of coronary angioplasty. *Circulation* 1994;**89**:2015–25.
108. Jones RH, Kesler K, Phillips HR III *et al.* Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg* 1996;**111**:1013–25.
109. Ellis SG, Omoigui N, Bittl JA *et al.* Analysis and comparison of operator-specific outcomes in interventional cardiology. From a multicenter database of 4,860 quality-controlled procedures. *Circulation* 1996;**93**:431–9.
110. Ellis SG, Weintraub W, Holmes D, Shaw R, Block PC, King SB III. Relation of operator volume and experience to procedural outcome of percutaneous coronary revascularization at hospitals with high interventional volumes. *Circulation* 1997;**95**: 2479–84.
111. Jollis JG, Peterson ED, Nelson CL *et al.* Relationship between physician and hospital coronary angioplasty volume and outcome in elderly patients. *Circulation* 1997;**95**: 2485–91.

28 Adjunctive medical therapy in percutaneous coronary intervention

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Introduction

The introduction of percutaneous transluminal coronary angioplasty (PTCA) has proven to be a major step forward in the treatment of coronary heart disease. Unfortunately, the gain has not come without a price: frequent and serious complications can occur, acute as well as chronic. In 1977, when Gruentzig introduced PTCA, it was clear that the technique required pharmacologic support. Since then, the development of adjunctive therapy has come a long way. Great progress has been made, but some major problems still wait to be resolved.

The goal of this chapter is to provide the reader with a general overview of adjunctive therapy directed primarily against acute complications, and the pathophysiologic principles involved in percutaneous coronary interventions (PCI).

Key points

Acute complications of PCI

- Intimal dissection with or without thrombus
- Plaque rupture with thrombus
- Spasm
- Perforation
- Distal embolization

Acute complications

The complications in the key points box can each lead to abrupt vessel closure. This occurs in 6·8–8·3% of PTCA procedures and is responsible for a sizeable mortality (up to 1·7%), acute myocardial infarction (1·3–8·6%), emergency bypass surgery (1·3–3·6%), and emergency re-PTCA (4·5%).[1–5] Abrupt vessel closure usually happens in the catheterization laboratory, with the great majority taking place within 6 hours post-PTCA. If it is not possible to open the vessel rapidly, major problems can be expected: persisting anginal pain and myocardial infarction, hemodynamic instability and arrhythmias. Rather unexpectedly, these difficulties can also arise with the abrupt re-closure after opening a chronically occluded vessel. The incidence of abrupt vessel closure is more frequent in unstable coronary syndromes and in angiographically complicated lesions.

Intimal dissection is caused by intravascular maneuvering of guidewires, balloons or other devices. It occurs in a wide variety, from minor and acceptable to major and occlusive. It is usually but not always accompanied by thrombus formation. At present, the only feasible therapy for a significant dissection is mechanical. The most widely used therapy used to be prolonged balloon inflation at the site of the dissection, preferably with a perfusion catheter, but this has to a large extent been replaced by the application of stents.[6,7]

Plaque rupture results from pressure applied to an atherosclerotic lesion. The fibrous cap of the plaque ruptures, uncovering highly thrombogenic plaque contents, in many ways resembling the events in the acute coronary syndromes. This probably happens in a large number of angioplastic maneuvers, often without deleterious consequences. It is only harmful if excessive flow limitation and thrombus formation takes place, leading to coronary occlusion or near occlusion. Antiplatelet strategies usually prevent thrombus formation to a large extent. However, it may still occur and treatment often proves to be difficult. Though often used, thrombolysis in the form of intracoronary urokinase,[8] streptokinase or intravenous or intracoronary rTPA has not been proven to be effective in a randomized fashion. Furthermore, it may complicate an ensuing emergency bypass operation. It is likely that abciximab can be helpful in these often-awkward situations and it is indeed frequently used for this indication, but its beneficial effect has not yet been demonstrated in a randomized trial.[9]

Spasm can be caused by the mere touch of the intracoronary guidewire. Isolated spasm, without dissection or plaque rupture, can rarely lead to abrupt vessel closure. More often, spasm is associated with dissection and/or plaque rupture. Antispasmodic therapy usually consists of intracoronary nitroglycerin.[10,11] In refractory cases a calcium antagonist can be given.[12,13]

Chronic sequelae

Restenosis is an indirect sequela of angioplastic trauma to the endovascular structures. Six months after successful conventional angioplasty, it is angiographically present in approximately 40% of cases. Causal factors of chronic restenosis are shown in the key points box.

Key points

Events leading to chronic restenosis
- Elastic recoil
- Formation of mural thrombus
- Intimal proliferation and synthesis of intracellular matrix
- Pathological arterial remodeling

Many drugs have been named as potentially valuable in the prevention of chronic restenosis. A host of trials have been conducted but only a few have reported a positive outcome. It was shown in a double-blind, placebo-controlled, randomized trial that probucol, an antioxidant, was effective in reducing the restenosis rate.[14] One month before PTCA, 317 patients were randomly assigned to receive one of four treatments: placebo, probucol (500 mg bid), multivitamins (30 000 IU of betacarotene, 500 mg of vitamin C, and 700 IU of vitamin E, bid), or both probucol and multivitamins (bid). Patients were treated for 4 weeks before and 6 months after angioplasty. Follow up angiography 6 months after PTCA showed restenosis in 20·7% in the probucol group, 28·9% in the combined treatment group, 40·3% in the multivitamin group, and 38·9% in the placebo group. The difference between the probucol and non-probucol groups is statistically highly significant ($P = 0{\cdot}003$). More recently, a double-blind, placebo-controlled, randomized trial of folate treatment revealed a reduction in restenosis. A total of 205 patients were randomized after successful PCI to folate treatment (folic acid 1 mg, vitamin B_{12} 400 micrograms and pyridoxine 10 mg) or placebo for a total of 6 months. Follow up angiography was carried out at 6 months (or earlier if clinically indicated). The rate of restenosis was significantly reduced in the folate group (19·6% *v* 37·6%, $P = 0{\cdot}01$), as was the need for revascularization (10·8% *v* 22·3%, $P = 0{\cdot}047$).[15] These results need confirmation in other trials before probucol or folate treatment can be advocated as an indispensable adjunct to PTCA.

Pharmacologic suppression of restenosis is, however, still under intense research. Trials are presently being conducted with new pharmacologic agents, systemically or locally delivered. Promising new strategies include drug-eluting stents. Stents alone have been successful, at least in large vessels.[16,17] Effects in smaller coronary arteries are awaited, but seem to be less promising. Stenting prevents recoil and pathological remodeling to a large extent, but leaves formation of mural thrombus and intimal proliferation unhampered. Stenting is therefore at best a partial remedy to the problem of chronic restenosis, reducing the incidence of restenosis but not abolishing it. However, drug-eluting stents may provide the ability to localize therapy without systemic effects. Rapamycin, an anti-rejection drug, has shown the most promise to date. The recent RAVEL study, a double-blind, placebo-controlled, randomized trial of rapamycin drug-eluting stent versus bare stents revealed a significant decrease in both restenosis (0% *v* 26·6%, $P < 0{\cdot}001$) and major adverse events (5·8% *v* 28·8%, $P < 0{\cdot}001$) at 6 months. A total of 238 patients were randomized of which 88·7% underwent 6 month angiograms.[18] However promising these agents appear, more studies are required to fully evaluate the efficacy, safety and cost effectiveness of drug-eluting stents.

Thrombus, platelets, and thrombin

Thrombus formation

This plays a leading role in abrupt vessel closure and may be of importance in chronic restenosis. The composition of arterial thrombi ("white thrombi"), with their predominance of platelets, shows that thrombocytes are central in angioplasty-related thrombus formation and acute vessel occlusion. A second agent of great importance is thrombin.

Platelets, physiology, and pathophysiology

The properties of platelets relevant to the formation of thrombus are shown in the key points box and are discussed in some detail below. Platelets are produced by the megakaryocyte. Through processes yet unexplained, this cell fragments into many platelets, which are disk-shaped cells with a diameter of 2–3 μm derived from the cytoplasm of the megakaryocyte without a nucleus. They do contain platelet-specific granules and a dense tubular system as well as a skeleton consisting of actin. The surface has a host of receptors for a wide variety of agents all playing a role in the very complex processes of adhesion, aggregation, and release of granules.

Normally, platelets are in contact solely with the other blood components and the endothelial lining of the blood vessels. Any other contact is inducive to platelet adhesion, with the potential to escalate to aggregation. As long as the endothelial lining of the blood vessels is intact, platelets are not activated. This does not mean that they are inert. Platelets produce substances responsible for the maintenance of the integrity of the vessel walls.

Platelets are normally heterogeneous, both physically and functionally. Younger platelets seem to be larger and more responsive to thrombin than older ones.[19] The lifespan of the platelet is 7–10 days. They are not distributed evenly throughout the lumen; the arterial flow pattern is such that platelets tend to concentrate near the wall, while red blood cells are present predominantly in the central part of the vessel.

Key points

Platelet properties relevant to thrombus formation
- Adhesion
- Aggregation
- Synthesis and release of prostaglandins, thromboxane, and intracellular granules

Adhesion

Platelets contacting surfaces other than erythrocytes, leukocytes or intact endothelium can adhere to them. They adhere to subendothelial structures, macrophages, activated leukocytes, and endothelial cells activated by inflammatory cytokines, and through the expression of membrane integrins, a subset of the glycoprotein receptors situated on the platelet membrane. The main endothelial adhesive protein is the von Willebrand factor, but many others can play a role. Adhesion denotes the deposition of thrombocytes on a surface perceived as foreign, involving a monolayer of platelets and, at least theoretically, having the effect of providing a more natural environment for the other blood corpuscles. Often, however, aggregation ensues.

The most frequently encountered foreign structure is subendothelial tissue that is exposed when endothelium is damaged, for example, during angioplasty. The level of platelet adherence is dependent on the nature of the foreign structure; deeper seated structures are a stronger stimulus than those just under the endothelial lining,[20] and on the presence of the von Willebrand factor. The von Willebrand factor can bind to certain types of collagen and form complexes that bind to the platelet membrane glycoprotein GP IIb and thus cause adhesion.[21] Adhesion involves one single layer of thrombocytes only.

On adhesion, contact with subendothelial collagen can initiate the following physiologic events:

- intracellular platelet granules are released into the extracellular space;
- P-selectin, a platelet membrane glycoprotein, expresses itself on the platelet surface, mediating adhesion to white blood corpuscles;
- activation of the intraplatelet eicosanoid pathway, starting with the emanation of arachidonic acid;
- a profound change in the shape of the platelets, from a smooth disc to a spiculated structure.

These reactions together constitute the activation of the platelets which leads to platelet aggregation, a process that accelerates itself considerably in a short passage of time.

Aggregation

More extensive vessel damage induces platelets to aggregate. Activation and ensuing aggregation can be caused by many factors including adenosine diphosphate (ADP) and serotonin, which are produced (among many others) by the release of platelet granules, thromboxane A_2 (TXA_2), which is generated in the interior of the platelet as an end product of the eicosanoid pathway, and platelet activating factor, which is produced by injured endothelial cells. Adrenaline, noradrenaline, and thrombin (most powerful) also activate platelets, and vice versa; platelet activation catalyzes the conversion of prothrombin to thrombin, thereby accelerating the process of activation and aggregation. Fibrillar collagen, which is exposed when the vessel is damaged, not only promotes adhesion, but also induces aggregation.

After the specific agents have made contact with the platelet membrane, the platelet changes in shape from disc to spiculated sphere. This change in shape is regulated by a skeleton of actin situated interior to the plasmalemma. The filopodial projections that constitute the spiculae probably facilitate contact between GP IIb/IIIa, the receptor on the platelet surface which is the final common pathway responsible for aggregation, and crucial proteins: fibrinogen and von Willebrand factor. In the next stage the GP IIb/IIIa receptor changes in conformation, allowing fibrinogen and von Willebrand factor to bind simultaneously to the GP IIb/IIIa receptors on the surface of two platelets, thus creating a link between them. This usually irreversible linkage is called aggregation. A plug of linked platelets constitutes a thrombus and may obstruct a vessel lumen.

Synthesis and release of prostacyclin, thromboxanes, and intracellular granules

The eicosanoid pathway exists in endothelial cells as well as in the interior of the platelet. Arachidonic acid is converted by cyclo-oxygenase to endoperoxides that form prostacyclin in the endothelial cells but generate TXA_2 in the platelet. TXA_2 enhances aggregation, and is a vasoconstrictor; prostacyclin, on the other hand, has strong vasodilatory and antiaggregant properties. Platelets contain at least three different types of intracellular storage granules. These granules contain a host of substances that can be liberated from the activated platelets by an exocytotic mechanism.[22] The various materials are able to potentiate platelet aggregation and blood coagulation and increase vascular permeability.

Thrombin

Thrombin is the second major player in the pathogenesis of acute coronary thrombosis. It is at the center of reactions essential to thrombus formation. It can activate platelets strongly and independently.[23] Thrombin can cause the release of the von Willebrand factor from endothelium, and facilitates the activation of factor V and VIII and the transition of fibrinogen to fibrin. It promotes the formation of a fibrin mesh around thrombi. Thrombin is abundantly generated during angioplasty.[24]

Antiaggregatory strategies

Four major classes of antiaggregatory agents can be discerned:

- cyclo-oxygenase inhibitors, for example, aspirin;
- thienopyridines, for example, ticlopidine, clopidogrel;

- glycoprotein IIb/IIIa inhibitors, for example, abciximab (Reopro), eptifibatide (Integrilin) and tirofiban (Aggrastat);
- thrombin inhibitors, for example, heparin, LMWH and hirudin.

Aspirin

Platelet aggregability can be inhibited to some extent by aspirin. In thrombocytes, aspirin irreversibly inhibits cyclooxygenase and thereby the generation of TXA_2 which is an aggregation promotor. Aspirin thus inhibits platelet aggregation and thrombus formation. However the production of antiaggregatory prostacyclin is also reduced in the endothelium. Possibly this unfavorable side effect becomes more pronounced with higher doses of aspirin, rendering the lower doses relatively more effective.[25] Aspirin leaves other platelet activation pathways untouched. It is therefore a relatively weak antiaggregatory agent.

Aspirin has been used as premedication to angioplasty since its debut in 1977 and is a universally used adjunctive,[26] but with few prospective trials ever having proven the efficacy. In one trial, a daily dose of 990 mg aspirin combined with dipyridamole (225 mg daily) showed no effect on restenosis compared to placebo, but periprocedural infarctions were significantly less in the treatment group.[27] Among the 376 randomized patients, there were periprocedural Q wave infarctions in 6·9% in the placebo group and 1·6% in the active drug group, the difference reaching statistical significance ($P = 0{\cdot}0113$). A retrospective angiographic study also showed a clear periprocedural advantage of aspirin and dipyridamole.[28] After doubts had been raised concerning the contribution of dipyridamole to the antithrombotic action of aspirin,[29] this drug disappeared from the adjunctive armamentarium.

The optimal daily dosage of aspirin with a reliable effect in angioplasty is not known. In the USA, 325 mg is usual, while in Europe 100 mg or 80 mg is accepted. The higher dosages (over 100 mg) are associated with more, predominantly gastrointestinal, side effects but not convincingly with greater efficacy. Aspirin is rapidly absorbed from the stomach and upper small intestine. Following ingestion, peak plasma levels are reached 20 minutes after ingestion.[30] Clinically relevant inhibition of platelet aggregation requires 80–90% blockade of TXA_2 synthesis.[31] With daily oral dosages of 80 mg it takes 48 hours to develop this effect on TXA_2 production and aggregation.[32] In higher dosages effective inhibition is reached earlier. It is therefore advisable to start oral aspirin at a low dose at least 48 hours before the angioplasty. Often time is lacking to prepare the patient along these lines. If an immediate procedure has to be performed and the patient is not on aspirin, chewing of enteric coated aspirin results in a sufficient antiplatelet effect after 30 min.[33] Intravenous injection of 250 or 500 mg aspirin results in an even more immediate platelet inhibition, however this is not readily available in many countries.[34]

Ticlopidine and clopidogrel

Ticlopidine is metabolized to an as yet unknown substance, which inhibits ADP-induced platelet aggregation but has no effect on TXA_2-induced aggregation. It leads to a remarkable prolonging of the bleeding time. An effect on platelet aggregation is demonstrable only after 3–5 days of medication.

Ticlopidine has proven its usefullness in conjunction with aspirin in the prevention of acute and subacute stent thrombosis. This complication occurs after insertion of an intracoronary stent in 2–8% of cases, usually between days 2 and 14 with a peak between days 5 and 7 after stent placement. Very extensive regimens, consisting of vitamin K antagonists, dipyridamole, and dextran as well as aspirin and heparin, did not positively influence this complication and led to unacceptable bleeding complications.[16] However, the combination of aspirin and ticlopidine achieved a significant decrease of stent thrombosis as well as bleeding complications.[35] Simultaneously, significant improvement of stent delivery technique such as high pressure implantation also affected results. Until recently, the standard of practice was to administer ticlopidine daily, beginning 7 days before scheduled stent placement. If a stent is inserted as a bailout procedure or because of a suboptimal result, it is customary to start the drug immediately after the procedure. It is continued for 30 days in a regimen of 250 mg bid. The main untoward but reversible effect is bone marrow depression, especially of the neutrophil granulocytes, occurring in less than 2% of patients.[36] In less than 1%, thrombocytopenia is encountered. Two weeks after starting ticlopidine, a white blood cell and thrombocyte count should be performed.

However, clopidogrel is now utilized for most patients treated by PCI in North America and Europe. While in many respects similar to ticlopidine (though it differs in its chemical structure and shares no common metabolites), it displays a lesser tendency to bone marrow depression and other adverse side effects, prompting its use in lieu of ticlopidine.[37] Multiple studies of clopidogrel versus ticlopidine have been carried out.[38–47] Initially, evidence for clopidogrel use in PCI came from non-randomized, single center registries.[38–44] These centers initially had altered their practices from ticlopidine to clopidogrel due to the belief that the benefits of the two drugs would be similar, but the side effects of ticlopidine were significantly worse. Moderate-sized randomized trials were subsequently carried out comparing ticlopidine (plus aspirin) and clopidogrel (plus aspirin) in PCI. These included the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), the Ticlid Or Plavix Post-Stent (TOPPS) trial and another by Muller *et al.*[45–47] CLASSICS was the largest study and the only one that was double-blinded. None of these individual studies revealed any significant differences in terms of 30 day major adverse cardiac events. A meta-analysis of these registries and trials reveals that clopidogrel is associated with a lower adverse cardiac event

rate (2·1% *v* 4·0%, OR 0·51; $P = 0·001$) and mortality (0·48% *v* 1·09%, OR 0·44; $P = 0·001$) at 30 days.[48] Overall, given the totality of evidence, clopidogrel appears as effective if not more effective at reducing adverse events in standard PCI.

Patients with unstable angina or non-ST elevation myocardial infarction undergoing PCI are a known higher-risk subset with regard to adverse cardiac events. Pretreatment with 300 mg and continued treatment after one month with 75 mg per day of clopidogrel (in addition to aspirin) prior to PCI in the CURE-PCI study decreased adverse cardiac events at both 30 days (adjusted relative risk 0·65, $P = 0·01$) and long-term follow up at 12 months (adjusted relative risk 0·72, $P = 0·03$).[49]

IIb/IIIa receptor blockers

Although there are many ways to activate the platelet, all converge into the same final common pathway, the IIb/IIIa receptor. Blockade of this receptor impedes aggregation to a very large extent, if not completely, with all modes of platelet activation using the final common pathway.

Presently, IIb/IIIa blockers are known in four forms:

- a chimeric monoclonal antibody (derived from murine antibodies), abciximab, which is commercially available;
- naturally occurring snake venom polypeptides. These non-enzymatic peptides have a low potency and short half life, diminishing their therapeutic value;[50]
- synthetic peptides, for example, integrilin and tirofiban;
- non-peptide IIb/IIIa inhibitors, which have not been efficacious until now.

Relevant large scale clinical investigations have been conducted with abciximab, integrilin, and tirofiban.

Abciximab was tested in the CAPTURE, EPILOG, EPIC and EPISTENT trials. All were prospective, multicenter, randomized, double-blind, placebo-controlled, Phase III studies, with over 8500 patients. Table 28.1 shows the main results of these studies.

EPIC studied 2099 patients at increased risk for ischemic complications during or after PTCA[51]: unstable angina and/or recent non-Q wave infarction, acute Q wave infarction within 12 hours of symptom onset, and clinical and angiographic characteristics predictive of increased risk of ischemic complications according to AHA Medical/Scientific Statement Guidelines.[52] Patients were randomized to one of the following regimens:

- placebo bolus+infusion;
- abciximab bolus 0·25 mg/kg IV+12 hour infusion of placebo;
- abciximab bolus 0·25 mg/kg IV+12 hour infusion of abciximab 10 migrograms/min.

Treatment started at least 10 min before PTCA, all patients received 325 mg aspirin orally and 10 000–12 000 IU heparin intravenously. Abciximab dosages were devised to reach a receptor blockade of at least 80%. Patients were followed for 30 days, 6 months and 3 years post-procedure. The 30 day composite end point, as in the other two studies, comprised death from any cause, acute infarction or the need for urgent coronary intervention and was statistically significantly reduced by 34·8% in the group treated with bolus and infusion of abciximab as compared to placebo bolus and infusion ($P = 0·008$). Thirty days emergency repeat PTCA was necessary in 6% of the placebo group and in 1% of the bolus plus infusion group ($P = 0·002$). At 6 months and after 3 years, the 30 day benefits were sustained.

Thrombocytopenia (<100 000/ml) was seen more often in the bolus plus infusion than in the placebo group (respectively 5·2% and 3·4%; $P = 0·01$). Of the patients who received abciximab, 6·5% developed human antichimeric antibody, mostly in low titers; none showed allergic reactions. Major hemorrhagic complications immediately after angioplasty, predominantly involving the access site, were higher in the abciximab treated patients. Hemorrhage was especially prominent in patients with a body weight under 75 kg receiving abciximab bolus plus infusion, suggesting that the fixed dose heparin was to blame.

This concept was tested in EPILOG.[53] A total of 2792 patients undergoing elective angioplasty were allocated among three regimens. In the EPIC trial an abciximab regimen was used almost similar to the bolus plus infusion in two of the three groups: one with standard dose heparin (100 IU/kg with a maximum of 10 000 IU) and one with low dose heparin (70 IU/kg, with a maximum of 7000 IU). A third cohort received placebo with standard dose heparin. In all groups additional heparin was administered to keep ACT above 300 seconds.

It was demonstrated that the efficacy of abciximab was preserved under the low dose regimen of heparin. It was also shown that the rate of major bleeding could be reduced to acceptable values: 2·0% in the low dose heparin group versus 3·1% and 3·5% in the heparin-only and the standard heparin with abciximab groups respectively (P = NS). Minor bleeding was 3·7% in the heparin-only group, 4·0% in the low dose heparin with abciximab and 7·4% in the standard heparin and abciximab group ($P = 0·01$). In this study, too, the benefit of abciximab was preserved after 6 months: primary end points after 30 days were reached in 11·7% in the heparin-only group, 5·2% in the standard dose heparin with abciximab group, and 5·4% in the low dose heparin with abciximab group ($P < 0·0001$).

In the CAPTURE trial, 1265 patients with refractory unstable angina were randomized to abciximab (bolus and infusion 18 hours preceding angioplasty) or placebo. Abciximab was given as a bolus and an infusion during 18–24 hours preceding the PTCA procedure. This infusion was stopped 1 hour after PTCA. Heparin was administered prior to randomization, until at least 1 hour after PTCA and

Table 28.1 Main results of CAPTURE, EPILOG, EPIC and EPISTENT trials

	CAPTURE (Refractory angina)			EPIC (High-risk PTCA)					EPILOG (Elective PTCA)					EPISTENT (PCI with STENT)				
	Placebo	Abciximab	*P* value	Placebo	Bolus	*P* value	Bolus + infusion	*P* value	Placebo	Abciximab + low heparin	*P* value	Abciximab + normal heparin	*P* value	Stent + placebo	Stent + abciximab	*P* value	PTCA + abciximab	*P* value
	n = 635	*n* = 635		*n* = 696	*n* = 695		*n* = 708		*n* = 939	*n* = 918		*n* = 935		*n* = 809	*n* = 794		*n* = 796	
30 day MAE	15·9%	11·3%	0·012	12·8%	11·5%	ns	8·3%	0·008	11·7%	5·4%	<0·001	5·2%	<0·001	10·8%	5·3%	<0·001	6·8%	ns
Mortality	1·3%	1·0%	ns	1·7%	1·3%	ns	1·7%	ns	0·8%	0·3%	ns	0·4%	ns	0·6%	0·3%	ns	0·8%	ns
Myocardial infarction	8·2%	4·1%	0·002	8·6%	6·2%	ns	5·2%	0·01	8·7%	3·7%	<0·001	3·8%	<0·001	4·5%	9·6%	<0·05	5·3%	<0·05
Emergency revascularization	10·9%	7·8%	0·054	7·8%	6·4%		4·0%	0·003	5·2%	2·3%	0·001	1·6%	<0·001	2·2%	1·5%	ns	1·45%	ns
Major bleeding	1·9%	3·8%	0·043	6·6%	11·1%	0·003	14·0%	<0·001	3·1%	2·0%	ns	3·5%	ns					
6 month MAE	30·8%	31·0%	ns	35·1%	32·6%	ns	27·0%	0·001	25·8%	22·8%	ns	22·3%	0·004					
3 year MAE	–			47·2%	41·1%	0·009												

Abbreviations: CAPTURE, C7E3 Anti Platelet Therapy in Unstable Refractory Angina; EPIC, Evaluation of C7E3 to Prevent Ischemic Complications; EPILOG, Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; MAE, major adverse events, comprising death, myocardial infarction, urgent revascularization of any sort, in percentages

adjusted to keep APTT between 2·0 and 2·5 times normal or an ACT of 300 s.[54]

It should be noted that EPILOG and CAPTURE were terminated early, interim analyses demonstrating a significant reduction in end points in the abciximab treated groups.

The relative reduction of primary end points was of the same magnitude as in EPIC. The difference in primary end points between CAPTURE (placebo *v* active drug: 15·9% *v* 11·3%; $P = 0{\cdot}012$) and EPIC (12·8% *v* 8·3%; $P = 0{\cdot}008$) can be explained by inclusion of more severely unstable patients in CAPTURE ("refractory" *v* "high risk"). The significance of the difference in regimens – abciximab being administered before and during angioplasty in CAPTURE, and during and after in EPIC – is not clear.

Stent use was low in these early studies. However, practice patterns changed with increased stent use and less PTCA alone or "plain old balloon angioplasty" (POBA). The Evaluation of Platelets IIb/IIIa Inhibitor for Stenting (EPISTENT) was initiated to evaluate the use of abciximab in PCI with stent implantation.[55] A total of 2399 patients were randomized to one of three treatment arms; stent plus abciximab, PTCA plus abciximab or stent plus placebo. Patients were otherwise treated with standard medications including aspirin, ticlopidine, and heparin. The primary end point was a composite of death, myocardial infarction and the need for urgent target revascularization in the first 30 days. Patients randomized to the stent/abciximab therapy had a lower event rate compared to stent/placebo (5·3% *v* 10·8%, $P < 0{\cdot}001$, hazard ratio 0·48) and PTCA/abciximab (5·3% *v* 6·9%, $P = 0{\cdot}007$, hazard ratio 0·63). Major bleeding complications were not significantly different, but this study was not powered to detect this. The benefits of abciximab appear to be maintained over time.[56] Debate over the implications of the results continues to occur. Many of the events prevented were troponin and CK rises which may or may not be an accurate surrogate of mortality. As with any therapeutic intervention, higher-risk patients probably benefit most from abciximab. In the case of PCI, diabetic patients appear to benefit both in the short-term and longer follow up. However, evidence from EPISTENT is a substudy analysis with different baseline characteristics. Other non-randomized studies have confirmed the 30 day but not the long-term results.[57]

Eptifibatide was tested in the IMPACT II study,[58] which involved 4010 patients undergoing angioplasty or atherectomy. The incidence of major ischemic complications or emergency revascularization at 24 hours was lower in two groups treated with integrilin (135 micrograms/kg bolus plus 0·5 micrograms/ kg/min or 0·75 micrograms/kg/min, both for 20–24 hours) than in the placebo treated patients, but this was not statistically significant after 30 days (11·4% *v* 9·2% *v* 9·9% respectively for placebo, low-dose, and high-dose eptifibatide; $P = 0{\cdot}063$ placebo *v* low-dose eptifibatide). There was no difference in the occurrence of major bleeding. The IMPACT II study displayed statistically non-significant results. However, it was felt that platelet inhibition was not optimal. The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial compared eptifibatide to placebo in stable patients undergoing PCI with stent.[59] Patients in this study were deemed appropriate not to necessarily need GP IIb/IIIa inhibitor, therefore considered lower risk than patients in the abciximab trials. Furthermore, patients were excluded if they were pretreated with clopidogrel greater than 24 hours. The ESPRIT study utilized a significantly higher dose of eptifibatide (2 boluses 180 micrograms/kg 10 min apart plus 2·0 micrograms/kg/min for 18–24 hours). The primary end point was the composite of death, myocardial infarction, urgent target vessel revascularization and bailout glycoprotein IIb/IIIa inhibitor use at 48 hours. ESPRIT was terminated early due to efficacy. The primary end point was reduced in the eptifibatide group (6·6% *v* 10·5%, $P = 0{\cdot}0015$). There appeared to be continued benefit out to 6 months.[60] However, many of the events in the ESPRIT trial were arguably of borderline significance such as enzymatic rise and bailout use of glycoprotein IIb/IIIa inhibitor.

Tirofiban was tested in the RESTORE (Randomized Efficacy of Tirofiban for Outcomes and Restenosis) study in 2139 patients with unstable angina or acute myocardial infarction, undergoing PTCA or atherectomy. Tirofiban (bolus of 10 micrograms/kg + 0·15 micrograms/kg/min for 36 hours) was compared with placebo, both groups receiving aspirin and heparin. At 30 days, the incidence of a composite end point of death, acute infarction, urgent or emergent PTCA or CABG was 10·5% in the placebo group and 8·0% in the tirofiban group ($P = 0{\cdot}052$). Here also, the incidence of major bleeding did not differ significantly.[61] The RESTORE study did not conclusively prove that tirofiban provided protection from adverse events peri-PCI. However, since there were differences between the small-molecule inhibitors (eptifibatide and tirofiban) and monoclonal antibodies (abciximab) in both structure and cost, a direct comparison was carried out. The TARGET (do Tirofiban And ReoPro Give similar Efficacy Trial) was designed as a non-inferiority trial of tirofiban and abciximab. This was a double-blind, double-dummy randomized trial of 4809 patients undergoing PCI with stent. Primary end point was a composite of death, non-fatal myocardial infarction, and urgent target vessel revascularization at 30 days. A significantly higher number of patients treated with tirofiban reached the primary end point (7·6% *v* 6·0%, $P = 0{\cdot}038$). Importantly, pretreatment with clopidogrel was associated with fewer adverse events in both treatment arms.[62]

Comparison of abciximab, eptifibatide, and tirofiban shows that abciximab is probably the most effective in reducing ischemic complications. This can be possibly explained by the tightness of the abciximab-IIb/IIIa binding, while eptifibatide and tirofiban are loosely bound. Also, actual dosages of the small molecule GP IIb/IIIa inhibitors

may be inadequate. Furthermore, it is probable that only abciximab also binds to the vitronectin receptor (which shares an epitope with IIb/IIIa), extending its blocking capacities. Unfortunately, a direct comparison of abciximab and eptifibatide is not currently available.

Antithrombins

The most widely used thrombin antagonist is heparin. In its unfractionated form, it has been used in PTCA since its introduction. Its effect on peri-procedural complications has never been demonstrated unequivocally.

Heparin is not a simple substance but consists of a combination of agents that all bind to antithrombin III (ATIII). Its molecular weight is 15 000. Through a reversible binding with ATIII, a naturally occurring inhibitor of activated blood coagulation factors,[63,64] heparin converts ATIII from a slow inhibitor to a rapid inhibitor of factors XIIa, XIa, IXa, Xa, and thrombin. Thrombin is more sensitive to the effects of heparin than is Xa and in keeping with this, unfractionated heparin exerts its action mainly through inhibition of thrombin-induced activation of factors V and VIII.[65] For thrombin inhibition it is necessary that both thrombin and ATIII bind to heparin. This requires a minimum chain length of 18 monosaccharides.

Heparin also comes in fractionated forms. These low molecular weight heparins (LMWH) have a molecular weight of 4000–5000 and a chain length >18 monosaccharides. These LMWH, when compared to the heavier components of unfractionated heparin, are more prone to bind to ATIII. They cannot bind to thrombin but they retain anti-Xa activity. The heavier components, on the other hand, are probably responsible for heparin-associated thrombocytopenia and possibly for some platelet activation. LMWH can be administered subcutaneously once daily.

In accordance with the better binding to ATIII, LMWH are more effective than unfractionated heparin in the prevention of deep venous thrombosis.[66] Hopes for a better safety profile did not materialize: in a meta-analysis of 62 studies with a total of over 20 000 patients, it was shown that LMWH are associated with a higher bleeding risk than heparin.[67]

In the treatment of unstable angina, LMWH were proven valuable in various trials as compared to unfractionated heparin, without excessive bleeding.[68–70] LMWH inhibits *in vitro* smooth muscle cell migration and proliferation without affecting endothelial cell growth.[71] However, *in vivo*, one LMWH, enoxaparin, did not show any effect on the incidence of restenosis nor did another,[72] reviparin, compared to unfractionated heparin in patients undergoing PTCA.[73] Reviparin was not associated with a decrease in the incidence of bleeding complications nor did it show any advantage in the occurrence of acute complications during and after PTCA. Further studies have been carried out by the National Investigators Collaborating on Enoxaparin (NICE) utilizing enoxaparin with (NICE-4) and without (NICE-1) abciximab. These were registries, but the results appear promising. Presently, there are no compelling evidence-based arguments to replace unfractionated heparin with LMWH as an adjunctive to PTCA.

Heparin is a relatively weak antiplatelet agent, in part because it does not inhibit the other platelet activators that operate independently from thrombin. Also, it tends to bind to the platelet surface, thus increasing platelet activity.[74,75] Furthermore, thrombin is incorporated into a developing thrombus and binds to fibrin. This fibrin bound thrombin can generate activated factors V and VIII, producing additional thrombin and promoting thrombus growth.

The heparin-ATIII complex is a potent inhibitor of free thrombin but only weakly inhibits fibrin bound thrombin. Heparin therefore can only inhibit but not completely prevent the growth of thrombi.[76,77] Moreover, heparin can only exert its influence in the presence of adequate levels of antithrombin III.

Direct thrombin inhibitors have been developed to circumvent the need for antithrombin III. Hirudin is a natural antithrombin, produced by the salivary glands of the European leech. A recombinant form is equipotential. Both inhibit all known functions of thrombin,[50] at least theoretically overcoming many of the disadvantages of heparin. However, in contrast to heparin, thrombin generation is left intact. In the HELVETICA (Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA) trial hirudin was compared with heparin in patients with unstable angina undergoing PTCA.[78] This study in 1141 patients was designed to evaluate the effect of hirudin on chronic restenosis. In the occurrence of early cardiac events, a clear advantage could be attributed to hirudin: after 96 hours a combination of death, myocardial infarction, bypass surgery and second angioplasty occurred in 11% of the group treated with heparin, 7·9% in the intravenous hirudin group and 5·6% in the intravenous and subcutaneous hirudin group ($P = 0{\cdot}023$). There was a particular benefit in patients in Braunwald class III angina;[79] in patients who had angina at rest during the 48 hours before randomization, the event rate was 21·6% in the heparin group as compared with 5·3% in the patients receiving intravenous hirudin and 12·3% among the patients receiving intravenous and subcutaneous hirudin ($P = 0{\cdot}006$). After 7 months, however, there was no difference in major end points between the three cohorts, nor was there any difference in the angiographic degree of restenosis. Bleeding complications did not differ significantly. It was argued that the hirudin dosage was sufficient to limit acute thrombin mediated platelet aggregation and thus could affect acute complications, but insufficient to produce an adequate level of anticoagulation to influence restenosis.

In the GUSTO IIb study, in acute myocardial infarction, immediate angioplasty was performed in a subgroup. Patients were randomized to heparin and hirudin and to

immediate angioplasty and thrombolysis. No beneficial effect of hirudin over heparin was found.[80]

Hirulog is a synthetic peptide designed on the structure of hirudin. Its effectiveness in angioplasty was studied in a prospective double-blind randomized trial of 4098 patients with unstable angina who were treated with either heparin or bivalirudin (hirulog).[81] No difference was demonstrated in short- and long-term complications. Bivalirudin was associated with a lower incidence of major hemorrhage.

At present, neither a direct thrombin inhibitor nor LMWH can be advocated to take the place of heparin in PTCA.

Recommendations

Preventive

Aspirin is indispensable as an adjunct to PTCA. It is safe, cheap, and effective as well as easy to administer. It should be given in a single daily dose of at least 80 or 100 mg for at least 3 days before PTCA. It should be continued afterwards indefinitely. **Grade A1a**

If a stent is inserted, ticlopidine (250 mg bid) or clopidogrel (75 mg od) preferably starting 7 days before and continuing at least 2–4 weeks after the procedure should be added to the regimen. **Grade A1a**

Heparin is the thrombin inhibitor of choice in all PTCA procedures; dosage is a bolus of 70–100 IU/kg bodyweight or 5000 IU IV at the start of the procedure, with repeated bolus injections during procedure to maintain therapeutic APTT (around 70 sec) or ACT (above 200 sec). It is still not clear as to the ideal ACT, but clear heparin required for PCI. Other anticoagulants such as LMWH or direct thrombin inhibitors can also be utilized during PCI, but there is still no significant evidence they are more efficacious than standard heparin. **Grade A1a**

In high-risk procedures, as in unstable angina or angiographically complicated lesions (type B2, C), abciximab should be considered, before PCI, followed by a 12 hour infusion. Heparin should be rigorously weight adjusted. Abciximab, eptifibatide or tirofiban can be considered for lower risk PCI, but overall absolute benefit may not be significant. **Grade A1a**

Therapeutic

Spasm can be countered with nitroglycerin or nifedipine. **Grade B2**

Acute or threatened closure due to dissection/thrombus can be treated with thrombolytics or glycoprotein IIb/IIIa inhibitors, but there is weak evidence that this is useful. **Grade B2**

References

1. Myler RK, Shaw RE, Stertzer SH *et al.* Lesion morphology and coronary angioplasty: current experience and analysis. *J Am Coll Cardiol* 1992;**9**:1641–52.
2. Detre KM, Holmes DR, Holubkov R *et al.* Incidences and consequences of periprocedural occlusion: the 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1990;**82**: 739–50.
3. De Feyter PJ, van den Brand M, Laarman GJ *et al.* Acute coronary artery occlusion during and after percutaneous transluminal coronary angioplasty: frequency, prediction, clinical course, management and follow up. *Circulation* 1991;**83**:927–36.
4. Lincoff AM, Popma JJ, Ellis SG *et al.* Abrupt vessel closure complicating coronary angioplasty: clinical angiographic, and therapeutic profile. *J Am Coll Cardiol* 1992;**19**:926–35.
5. Ellis SG, Roubin GS, King SB III *et al.* Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988;**77**:372–9.
6. Roubin GS, Cannon AD, Agrawol SK *et al.* Intracoronary stenting for acute and threatened closure complicating PTCA. *Circulation* 1992;**85**:916–21.
7. Scott NA, Weintraub WS, Carlin SF *et al.* Recent changes in the management and outcome of acute closure after PTCA. *J Am Coll Cardiol* 1993;**71**:1159–63.
8. Schachinger V, Kasper W, Zeiker AM. Adjunctive intracoronary urokinase therapy during PTCA. *J Am Coll Cardiol* 1996;**77**:1174–8.
9. Velianou JL, Strauss BH, Kreatsoulas C, Pericak D, Natarajan MK. Evaluation of the role of abciximab (Reopro) as a rescue agent during percutaneous coronary interventions: in-hospital and six-month outcomes. *Cathet Cardiovasc Intervent* 2000; **51**:138–44.
10. Margolis JR, Chen C. Coronary artery spasm complicating percutaneous transluminal angioplasty: role of intracoronary nitroglycerin. *Z Kardiol* 1989;**78**(Suppl. 2):41–7.
11. Fischell TA, Derby G, Tse TM, Stadius ML. Coronary artery vasoconstriction routinely occurs after PTCA: a quantitative arteriographic analysis. *Circulation* 1988;**78**:323–4.
12. McIvor ME, Undemir C, Lawson J, Reddinger J. Clinical effects and utility of intracoronary diltiazem. *Cathet Cardiovasc Diagn* 1995;**35**:287–91.
13. Pomerantz RM, Kuntz RE, Diver DJ, Safian RD, Baim DS. Intracoronary verapamil for the treatment of distal microvascular coronary artery spasm following PTCA. *Cathet Cardiovasc Diagn* 1991;**24**:283–5.
14. Tardif JC, Cote G, Lesperance J *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997;**337**:418–19.
15. Schnyder G, Roffi M, Pin R *et al.* Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001;**345**:1593–600.
16. Serruys PW, de Jaegere P, Kiemeney F *et al.* A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease (Benestent I). *N Engl J Med* 1994;**331**:489–95.
17. Fischman DL, Leon MB, Baim DS *et al.* A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease (STRESS). *N Engl J Med* 1994;**331**:496–501.
18. Morice M-C, Serruys PW, Sousa JE *et al.* A randomized comparison of sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–80.

19.Peng JP, Friese P, Heilmann E, George JN, Burstein SA, Dale GL. Aged platelets have an impaired response to thrombin. *Blood* 1994;**83**:161–6.
20.Kehrel B. Platelet-collagen interactions. *Semin Thromb Hemost* 1995;**21**:123–9.
21.Stel HV, Sakariassen KS, de Groot PG *et al.* Von Willebrand factor in the vessel wall mediates platelet adherence. *Blood* 1985;**65**:85–90.
22.Heptinstall S, Hanley SP. Blood platelets and vessel walls. In: Walter Bowie EJ, Sharp AA, eds. *Hemostasis and thrombosis*. London: Butterworths, 1985.
23.Coughlin SR, Vu TK, Hung DT, Wheaton VI. Characterization of a functional thrombin receptor: issues and opportunities. *J Clin Invest* 1992;**89**:351–5.
24.Marmur JD, Merlini PA, Sharma SK *et al.* Thrombin generation in human coronary arteries after percutaneous transluminal balloon angioplasty. *J Am Coll Cardiol* 1994;**24**:1484–91.
25.Verheugt FWA, van der Laarse A, Funke Kupper AJ *et al.* Effects of early intervention with low-dose aspirin (100 mg) on infarct-size, reinfarction and mortality in anterior wall acute myocardial infarction. *Am J Cardiol* 1990;**66**:267–70.
26.Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. II. Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994;**308**:159–68.
27.Schwartz L, Bourassa MG, Lesperance J *et al.* Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988; **318**:1714–19.
28.Barnathan ES, Sanford Schwartz J, Taylor L *et al.* Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation* 1987;**76**: 125–34.
29.Fitzgerald GA. Dipyridamole. *N Engl J Med* 1987;**316**: 1247–57.
30.Hirsh J, Dalen J, Fuster V, Harker LB, Salzman EW. Aspirin and other platelet-active drugs: the relationship between dose, effectiveness, and side effects. *Chest* 1992;**102**: 327–36.
31.Reilly IAG, Fitzgerald GA. Aspirin in cardiovascular disease. *Drugs* 1988;**35**:154–76.
32.Ridker PM, Hebert PR, Fuster V *et al.* Are both aspirin and heparin justified as adjuncts to thrombolytic therapy for acute myocardial infarction? *Lancet* 1993;**341**:1574–7.
33.Jimenez AH, Stubbs ME, Tofler GH, Winther K, Williams GH, Muller JE. Rapidity and duration of platelet suppression by enteric coated aspirin in healthy young men. *Am J Cardiol* 1992;**69**:258–62.
34.Husted SE, Kristensen SD, Vissinger H, Mann B, Schmidt EB, Nielsen HK. Intravenous acetyl-salicylic acid – dose related effects on platelet function and fibrinolysis in healthy males. *Thromb Haemost* 1992;**68**:226–9.
35.Schomig A, Neumann FJ, Kastrati A *et al.* A randomized comparison of platelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334**:1084–9.
36.Bonita R. Epidemiology of stroke. *Lancet* 1992;**339**:342–4.
37.CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
38.Calver AL, Blows LJ, Harmer S *et al.* Clopidogrel for the prevention of major cardiac events after coronary stent implantation: 30-day and 6-month results in patients with smaller stents. *Am Heart J* 2000;**140**:483–91.
39.Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999;**34**:1884–90.
40.Allier PL, Aronow HD, Cura FA *et al.* Short-term mortality lower with clopidogrel than ticlopidine following coronary artery stenting. *J Am Coll Cardiol* 2000;**35** (Suppl. 66A):
41.Berger PB, Bell MR, Rihal CS *et al.* Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999;**34**:1891–4.
42.Moussa I, Oetgen M, Roubin G *et al.* Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation* 1999;**99**:2364–6.
43.Dangas G, Mehran R, Abizaid AS *et al.* Combination therapy with aspirin plus clopidogrel versus aspirin plus ticlopidine for prevention of subacute thrombosis after successful native coronary stenting. *Am J Cardiol* 2001;**87**:470–2.
44.Plucinski DA, Scheltema K, Krusmark J, Panchyshyn N. A comparison of clopidogrel to ticlopidine therapy for the prevention of major adverse events at thirty days and six months following coronary stent implantation. *J Am Coll Cardiol* 2000;**35** (Suppl. 67A):
45.Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel ASpirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000;**102**:624–9.
46.Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;**104**: 539–43.
47.Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;**101**:590–3.
48.Bhatt DL, Bertrand ME, Berger PB *et al.* Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol* 2002;**39**:9–14.
49.Mehta SR, Yusuf S, Peters RJ *et al.* Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**:527–33.
50.Verstraete M, Zoldhelyi P. Novel antithrombotic drugs in development. *Drugs* 1995;**49**:856–84.
51.The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;**330**: 956–61.
52.AHA Medical/Scientific Statement Guidelines for percutaneous transluminal coronary angioplasty. 1993;**88**: 2987–3007.
53.The EPILOG Investigators. Effect of the platelet glycoprotein IIb/IIIa receptor inhibitor abciximab with lower heparin dosages on ischemic complications of percutaneous coronary revascularization. *N Engl J Med* 1997;**336**: 1689–96.

54.The CAPTURE Investigators. Refractory unstable angina; reduction of events by treatment with abciximab prior to coronary intervention. *Lancet* 1997;**349**:1429–35.
55.Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
56.Topol EJ, Mark DB, Lincoff AM *et al.* Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicenter randomised trial. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1999;**354**:2019–24.
57.Velianou JL, Mathew V, Wilson SH, Barsness GW, Grill DE, Holmes DR Jr. Effect of abciximab on late adverse events in patients with diabetes mellitus undergoing stent implantation. *Am J Cardiol* 2000;**86**:1063–8.
58.Tcheng JE, Lincoff AM, Sigmon KN, Califf RM, Topol EJ. Platelet glycoprotein IIbIIIa inhibition with Integrelin during percutaneous coronary intervention: the IMPACT II Trial (Integrilin to Manage Platelet Aggregation to Prevent Coronary Thrombosis II). *Circulation* 1995;**92**(Suppl. 1): 543.
59.The ESPRIT Investigators. Novel dosing regimen of eptifabitide in planned coronary stent implantation (ESPRIT): a randomized, placebo-controlled trial. *Lancet* 2000;**356**: 2037–44.
60.O'Shea JC, Hafley GE, Greenberg S *et al.* Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. *JAMA* 2001;**285**:2468–73.
61.Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;**96**:1445–53.
62.Topol EJ, Herrmann HC, Powers ER *et al.* TARGET Investigators. Comparison of two platelet glycoprotein IIb/ IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888–94.
63.Rosenberg RD, Rosenberg JS. Natural anticoagulant mechanisms. *J Clin Invest* 1984;**74**:1–6.
64.Salzman EW, Rosenberg RD, Smith MH, Lindon JN, Favreau L. Effect of heparin and heparin fractions on platelet aggregation. *J Clin Invest* 1980;**65**:64–73.
65.Ofusu FA, Hirsh J, Esmon CT *et al.* Unfractionated heparin inhibits thrombin-catalysed amplifications of coagulation more efficiently than those catalysed by Xa. *Biochem J* 1989;**257**: 143–50.
66.Kakkar VV, Murray WJG. Efficacy and safety of low molecular weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a cooperative study. *Br J Surg* 1985;**72**: 786–91.
67.Rosendaal FR, Nurmohamed MT, Buller HR, Dekker E, Vandenbroucke JP. Low molecular weight heparins in the prophylaxis of venous thrombosis: a meta-analysis. *Haemost Thromb* 1991;**65**:927.
68.Gurfinkel EP, Manos EJ, Mejail RI *et al.* Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 1995;**26**:313–18.
69.Klein W, Buchwald A, Hillis SE *et al.* Comparison of low-molecular weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease (FRIC). *Circulation* 1997; **96**:61–8.
70.FRISC Study Group. Low-molecular weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561–8.
71.Roth D, Betz E. Kultivierte Gefasswandzellen des Menschen. *Vasa* 1992;**35**:125–7.
72.Faxon DP, Spiro TE, Minor S *et al.* Low molecular weight heparin in prevention of restenosis after angioplasty. Results of the Enoxaparin Restenosis (ERA) trial. *Circulation* 1994; **90**:908–14.
73.Karsch KR, Preisack MB, Baildon R *et al.* Low molecular weight heparin (Reviparin) in PTCA: results of a randomized, double-blind unfractionated heparin and placebo-controlled, multicenter trial (REDUCE trial). *J Am Coll Cardiol* 1996; **28**:1437–43.
74.Coller BS. Antiplatelet agents in the prevention and therapy of thrombosis. *Annu Rev Med* 1992;**43**:171–80.
75.O'Reilly RA. Anticoagulant antithrombotic and thrombolytic drugs. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics, 7th edn.* New York: Macmillan, 1985.
76.Hirsh J, Fuster V. Guide to anticoagulant therapy. I. Heparin. *Circulation* 1994;**89**:1449–68.
77.Hull RD, Delamore T, Genton E *et al.* Warfarin sodium versus low dose heparin in the long term treatment of venous thromboembolism. *N Engl J Med* 1979;**301**:855–8.
78.Serruys PW, Herrman JR, Simon R *et al.* for the HELVETICA Investigators. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995;**333**:757–63.
79.Braunwald E. Unstable angina: a classification. *Circulation* 1989;**80**:410.
80.Angioplasty Substudy Investigators. The global use of strategies to open occluded coronary arteries in acute coronary syndromes (GUSTO IIb). A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621–8.
81.Bittl JA, Strony J, Brinker JA *et al.* Treatment with Bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. *N Engl J Med* 1995;**333**:764–9.

29 Restenosis: etiologies and prevention

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Introduction

Percutaneous coronary interventions have revolutionized the treatment of coronary atherosclerosis, creating an alternative strategy to medical and surgical therapy for myocardial ischemia and acute coronary events. The concept was that atherosclerotic plaque can be fractured, removed or ablated within the vessel by different device technologies. However, it was quickly understood that following the intervention, a healing response, known as restenosis, significantly reduced the long-term success of the procedure.

Restenosis is a substantial medical problem, both because it occurs in 40–50% of patients undergoing coronary revascularization procedures, with increased patient morbidity, but also for the significant burden of medical costs,[1,2] which is estimated to be of nearly $2·0 billion per year.[3] Restenosis may be effectively treated by repeat angioplasty. However, further interventional procedures entail additional cost, and the redilated lesions are more prone to the development of restenosis than native lesions.

Because of this unacceptably high restenosis rate and the huge health cost implications, it is not surprising that in the past ten years or so there have been intense efforts to elucidate the pathophysiologic mechanisms of this process and, most importantly, extensive clinical trials aimed at a wide array of strategies to prevent restenosis. Today, while the cellular mechanisms and interactions involved in the pathobiology of restenosis have been better understood, and powerful effects have been obtained in some animal models with the use of different drugs and devices, the search for successful therapeutic effects continues, because when transferred into clinical practice, restenosis is still a shadow over the broad use of the interventional techniques. The introduction of the drug-eluting stent has recently offered a light at the end of the tunnel. As we stand on the verge of a "cure" for restenosis, it is interesting to ask, "Why has it taken so long?"

Since the late 1970s, enormous efforts and resources have been directed to the problem of restenosis. Our understanding of restenosis evolved slowly, but major components in the evolution of the restenosis process have been identified, and in the early 1990s several pivotal studies distinguished basic restenosis mechanisms such as early recoil, negative remodeling, and proliferative response to injury.[4,5] Other landmark studies established the concept that the extent of luminal "late loss" at follow up is proportional to the amount of "acute gain" achieved during the initial procedure.[6] Although this strategy provided incremental reduction in restenosis under the philosophy of "bigger is better", the scientific community soon realized that restenosis could not be eliminated using only mechanical devices like bare stents. Thus, the fertile soil for the development of drug-eluting stents was created. This also required the development of predictable animal models to allow precise, quantitative documentation of the *in vivo* response to injury.[7] The initial stent coatings, however, were dismal failures.[8] Only recently, biocompatible materials have been developed that maintain adequate patency in the animal model. Another problem was applying coating to stent struts and then sterilizing the combination without altering the properties of the coating or the drug.

With these aspects kept in mind, this chapter will review four aspects of the restenosis problem. First, it will highlight the mechanisms of restenosis, including neointimal hyperplasia, acute recoil, and vascular remodeling. These, in turn, influence the response of the vessel wall to mechanical injury. Second, the issue of mural thrombus in restenosis will be addressed for both stenting and balloon angioplasty, since blood elements and factors produced by circulating cells play a key role in the initiation and propagation of neointima formation. The importance of antithrombotic agents such as GPIIb/IIIa receptor antagonists in reducing morbidity and mortality after percutaneous transluminal angioplasty (PTCA) and their potential in reducing the restenosis process will be reviewed. Third, emerging concepts in gene therapy and moreover in drug-eluting stents and their clinical trials will be reviewed.

The problem of restenosis

Defining restenosis

Restenosis studies have suffered to various degrees from methodological problems. Since native coronary atherosclerotic and restenotic lesions are both identified and treated with the use of angiography, one would hope that a uniform angiographic definition of restenosis exists. Unfortunately, such definitions are currently lacking, representing a major limitation in comparing different studies.

The numerous angiographic definitions used in clinical studies,[9] and more recently, definitions based on absolute changes in minimal lumen diameter at follow up,[10] have led to confusion and hampered investigations in this field[11] (Box 29.1).

Box 29.1 Angiographic definitions of restenosis

- An increase of ≥30% from immediate postangioplasty diameter stenosis to follow up stenosis
- An initial diameter stenosis <50% after angioplasty, increasing to ≥70% at follow up angiography
- An increase in diameter stenosis at follow up angiography to within 10% of the preangioplasty value
- A loss of >50% of the initial diameter stenosis gain achieved by angioplasty, from immediate postangioplasty to follow up angiography
- A postangioplasty diameter stenosis <50% increasing to >50% at follow up angiography
- A decrease in the minimal lumen diameter at the lesion of >0·72 mm from immediate postangioplasty to follow up angiography
- Cumulative distribution of MLD

Using clinical criteria, restenosis may be defined by evidence of recurrent myocardial ischemia after the revascularization procedure discovered during clinical tests by the presence of symptoms (that is, recurrence of angina, need for target vascular revascularization). Difficulties occur with a discordance between angiography and clinical status. A patient with a lesion fitting the angiographic criteria for restenosis but who is asymptomatic and/or has negative tests for ischemia will likely not be recatheterized on the basis of clinical criteria alone.

Moreover, restenosis has been previously characterized as an "all or none" phenomenon and, by subsequent studies, as a continuous variable that takes place to a different extent in all treated lesions.[12] Many studies have been small, and the timing and methods of follow up have been variable,[1,13] introducing the selection biases and misleading interpretations of the data.

It is clear that a more uniform definition, that includes a combination of angiographic and clinical criteria, and studies with more uniform groups of patients, may provide a more accurate picture of the restenosis phenomenon.[14]

Predicting restenosis

While many clinical studies have been performed to identify correlates of restenosis,[1,13,15–19] the ability to predict an excessive healing response after percutaneous interventions has remained particularly difficult.[20]

Three different categories of variables are related to an increased risk of restenosis. These include clinical patient-related factors, anatomic-related factors, and interventional procedure-related factors. Patient-related variables include older age, male gender, diabetes, hypertension, hyperlipidemia, unstable angina prior to angioplasty, vasospastic angina, and continued smoking after angioplasty. Anatomical and procedural factors include ostial lesions, longer lesions, total occlusions, multilesion and multivessel angioplasty procedures, saphenous vein graft location, left anterior descending location, presence of calcium, balloon-to-artery ratio, suboptimal results with significant residual stenosis, and extent of dissection.

However, no variables have yet been found that predict restenosis with absolute certainty. Of all the factors, the most consistent in predicting a better long-term outcome appears to be a large postprocedural lumen diameter.[21] This finding has led to the current aphorism "bigger is better",[6] which has been widely applied as a therapeutic strategy of angioplasty and which may explain the improved long-term outcome observed with coronary stents or directional atherectomy.[22,23]

Other factors that are not yet fully evaluated may also predict restenosis. Angioscopic observations suggest that coronary thrombus is an important determinant of the late outcome.[24] Recent clinical studies using the glycoprotein IIb/IIIa receptor antagonist 7E3 have shown in support of the role of thrombus a significative reduction in the incidence of restenosis.[25] Experimental evidences suggest that oxidative stress may be important in the restenotic process, and the results of the MVP study[26] indicate that probucol is effective in reducing restenosis by means of low density lipoprotein oxidation prevention, decreasing platelet aggregation and modulation of prostaglandin and leukotriene synthesis.[27–29]

Studying restenosis

Traditionally, animal models are the cornerstone to test strategies aimed at developing treatments for pathologic conditions and for understanding pathophysiologic mechanisms that may cause that particular condition. In this respect, restenosis is no exception and several animal models have been developed during the past decade in an attempt to reproduce restenotic lesions and find a therapeutical strategy to reduce neointimal formation. Unfortunately, although several models of restenosis have been evaluated in the past 15 years, there is no perfect animal model for human restenosis. Common models include the rat carotid air desiccation or balloon endothelial denudation model,[30,31] the rabbit femoral or iliac artery balloon injury model with or without cholesterol supplementation,[32] and the porcine carotid and coronary artery model.[33]

The rat model, based on elastic arteries, does not develop severe stenotic neointimal lesions, and is therefore very permissive in terms of efficacy of pharmacological interventions. The cholesterol-fed rabbit model has been criticized for the high level of hyperlipidemia required for the

development of lesions. The latter results in a large macrophage foam cell component, resembling fatty streaks rather than human restenotic lesions. Conversely, the histopathologic features of neointima obtained in porcine models closely resemble the human neointima, and the amount of neointimal thickening is proportional to injury severity. This has allowed the creation of an injury–neointima relationship that can be used to evaluate the response to different therapies. However, the repair process in the pig coronary artery injury model using normal coronary arteries is certainly more rapid and may be different from the response to balloon angioplasty that characterizes human coronary atherosclerotic plaques.

The major limitation in the use of animal models of restenosis is that agents effective in reducing neointima in those models are ineffective when transferred into the clinical arena. Many explanations might support those differences. Different animal species, types of artery, degree of arterial injury, volume of neointima, drug dosages and timing regimens, and atherosclerotic substrate might be considered.

To address this concern, we believe that before transferring the results obtained in animal models into clinical trials, standardization of injury type, the method of measurement, and the dose and timing of drug administration among different animal models is necessary.

Other issues in the study of restenosis are the limitations in the design of restenosis clinical trials. Incomplete angiographic follow up leading to the occurrence of selection and withdrawal biases, followed by inadequate power due to small patient sample leading to the potential of β (type II) errors, are the most common problems. Non-uniform definitions of angiographic restenosis and poor correlation between angiographic and clinical outcome are other problems that need to be resolved when comparing different trial results. Future restenosis studies should utilize composite clinical outcomes as primary end points, with multiple, simultaneous treatment approaches and careful choice of the appropriate regimen. These studies should also include an angiographic or IVUS subset to allow assessment of mechanisms of action, and using these data can help limit sample size necessary to detect efficacy at reducing neointima.

Understanding restenosis

To better understand the mechanisms of restenosis, it is useful briefly to review the potential mechanisms by which coronary interventional procedures increase lumen patency. Since the explanation given by Dotter and Judkins,[34] who ascribed the enlargement of vessel lumen by balloon angioplasty to compression of atheromatous plaque against the arterial wall, several morphologic and histologic observations have been made both in human necropsy studies[35–37] and experimental models.[38] Different mechanisms of action have been identified. The original concept of plaque compression is unlikely to occur because the majority of atherosclerotic plaques are composed of dense fibrocollagenous tissue with hard calcium deposits, and thus, are difficult to compress. However, this mechanism can play a major role in the dilation of newly formed atherosclerotic plaque – that is, soft plaques – or recently formed thrombus.

Subsequent data suggest that the major mechanisms of action of coronary angioplasty are breaking, cracking, and splitting of the intimal plaque with partial disruption of the media and stretching of the plaque-free vessel wall.[39–41] In particular, intravascular ultrasound studies have shown that those mechanisms may vary depending on the histologic plaque composition, with more plaque dissection in calcified lesions and more vessel expansion in non-calcified plaques.[42]

Conversely, directional and rotational coronary atherectomy improve lumen caliber by tissue removal, with little disruption and expansion of the vessel wall. Finally, the mechanism of laser angioplasty is related to atherosclerotic tissue photoablation and dissection associated with vessel expansion.

Based on these clinical and experimental observations, the presumed healing and repair processes leading to arterial restenosis may be categorized as follow: (a) exaggerated cell proliferation at the site of injury; (b) incomplete plaque dissection by balloon angioplasty or incomplete tissue removal by directional coronary atherectomy (DCA), rotational atherectomy, and laser angioplasty; (c) thrombus formation and organization at the site of injury; (d) favorable or unfavorable artery wall remodeling.

Pathobiologic events in restenosis: from growth regulatory factors to cell cycle genes

It has been more than a decade since Essed *et al* first documented intimal proliferation after PTCA as a cause of restenosis.[43] During this interval, enormous progress has been made in defining the pathogenetic mechanisms of human restenotic lesions. At the same time, molecular techniques coupled with increasing understanding of the regulatory events at the level of nucleic acids have been applied to investigation of the restenotic process. Today, there is a general consensus that restenosis involves the interactions of cytokines, growth factors, vascular elements, blood cells, and the extent of injury.

Based on the experiences derived from experimental models, cell culture, human pathologic evidence as well as angiographic, angioscopic, and intravascular ultrasound observations, the sequence of events that take place in the artery and that characterize the restenotic process can be divided into three phases (Figures 29.1 and 29.2). **Grade A**

1. A first phase of elastic recoil, usually occurring within 24 hours of the procedure.

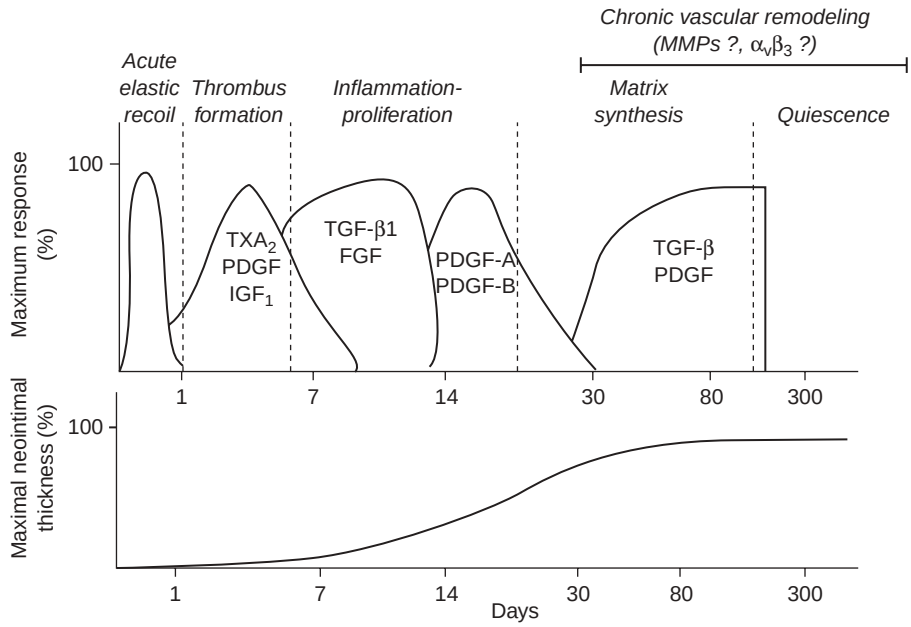


Figure 29.1 Different phases of the restenotic process. The lower panel indicates the increase in neointimal thickening and the upper panel the associated expression of growth factors (for abbreviations see text).

2. A second phase of mural thrombus formation and organization associated with inflammatory infiltrate at the site of vascular injury in the subsequent 2 weeks. In this phase, immediately after stent implantation, activation, adhesion, aggregation, and deposition of platelets and neutrophils occurs. The platelet thrombus formed can even become large enough to occlude the vessel. Within hours the thrombus at the injured site becomes fibrin-rich and also fibrin/red cell thrombus adheres to the platelet mass. From day 3 the thrombus is covered by a layer of endothelial-like cells and intense cellular infiltration begins at the injury site with monocytes (which become macrophages after migration into the mural thrombus) and lymphocytes. In the process these cells progressively migrate deeper into the mural thrombus and vessel wall.
3. A third phase of cell activation, proliferation, and extracellular matrix formation, which usually lasts from 2 to 3 months. In this phase, smooth muscle cells from different vessel wall layers proliferate and migrate and thereafter resorb the residual thrombus until all of it is gone and replaced by neointimal cells. For several weeks proliferative activity can be detected in the endothelial layer, the intimal layer, the medial layer, and in the adventitia. Thereafter a more or less quiescent fourth state will ensue, characterized by further buildup of extracellular matrix.[33,44]

Therefore, several factors may influence the production of excessive neointimal volume, including the amount of platelet–fibrin thrombus at the injury site, the total number of smooth muscle cells (SMC) within the neointima, and the amount of extracellular matrix elaborated by neointimal cells. Limiting one of those steps, either individually or in combination, might perhaps reduce the neointimal response following mechanical injury (Table 29.1).

Phase I: elastic recoil

The vessel wall itself can participate in acute lumen loss observed in some patients just after coronary interventions by a mechanism termed "recoil". Elastic recoil occurs within minutes to hours following balloon angioplasty and seems to be the consequence of the "spring-like" properties of the non-diseased vascular wall responding to its overstretching.[45–47] Other possible explanations are vasoconstriction due to vessel endothelial disruption[48] or platelet activation and thrombus formation with consequent release of vasoconstrictive substances.[49,50] Whenever the normal wall is significantly stretched, recoil may be the predominant mechanism of restenosis. Different studies, indeed, have shown that this very early vessel wall recoil increases the likelihood of subsequent restenosis with a rate of 73·6% for the lesions that had lumen loss >10% and only 9·8% for lesions that diminished by <10%.[51,52] Early recoil may possibly have a significant importance in restenosis when the vessel has not been severely injured and the lesion consists of SMC. When the vessel wall injury is more severe, thrombus formation with consequent activation of growth factors

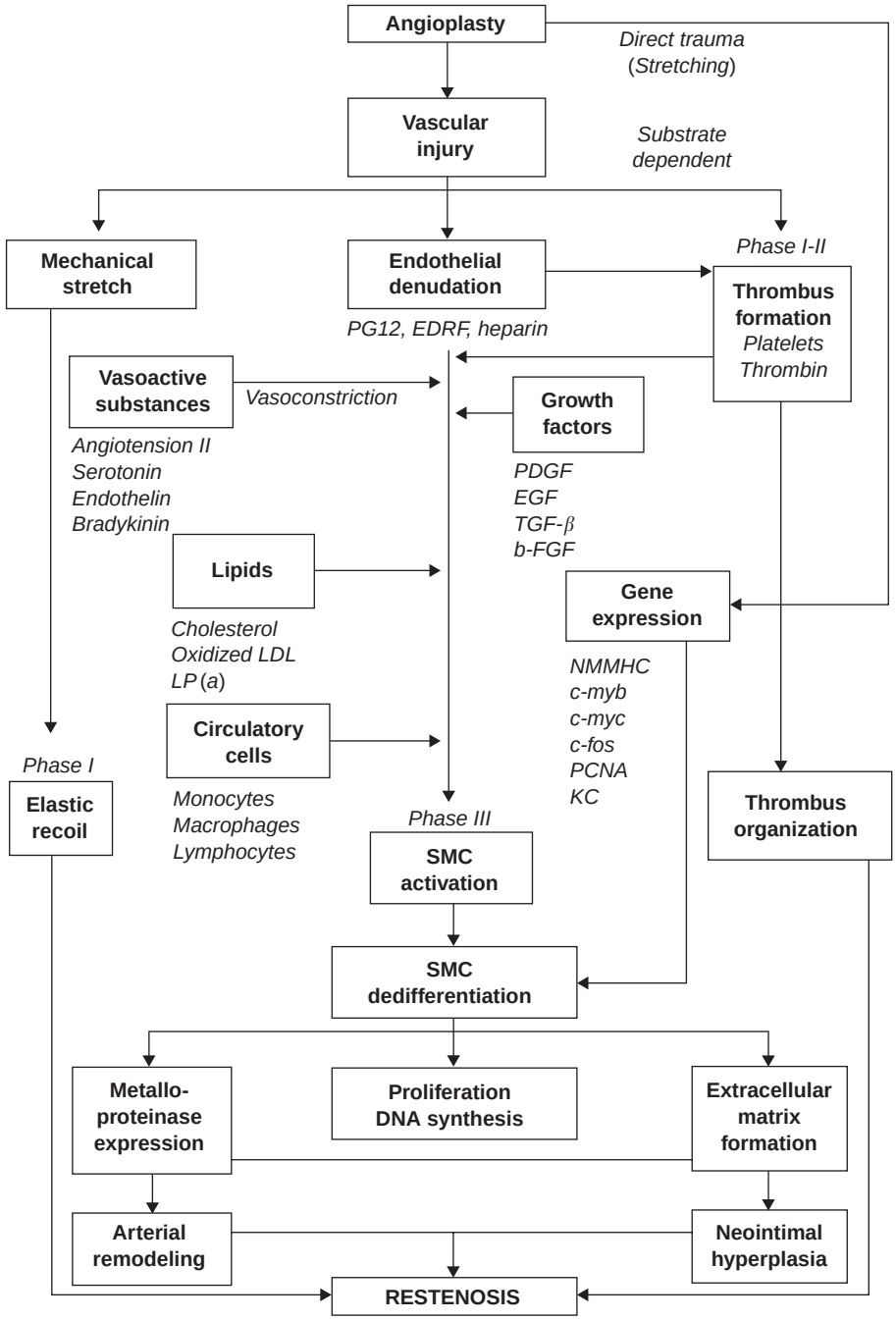


Figure 29.2 Sequence of events resulting in restenosis after vessel injury (for abbreviations see text)

and release of cytokines may be, instead, the predominant mechanism of restenosis.

Prevention of phase I: mechanical *v* pharmacologic approaches

It is clear that the utilization of methods to minimize the angioplasty injury, reduce the elastic recoil and enlarge the lumen size should result in a lower incidence of restenosis.

Balloon angioplasty allows manipulation of only few parameters that cause injury or recoil. Several studies have evaluated the number of balloon inflations,[53,54] duration of inflation,[53,55–57] inflation pressure,[58–60] and balloon–artery ratio.[54,59,61,62] Although higher inflation pressures and larger balloon size have been related to a small decrease in restenosis rate, they also cause a substantial increase in acute complications such as rate of emergency surgery and myocardial infarction.[59,63]

Table 29.1 Potential therapeutic approaches for the treatment of the different phases of the restenotic process

Response to vessel injury	Potential therapy
Early elastic recoil	Achievement of greater MLD by stents
Thrombus formation	Antithrombotic agents Antiplatelet agents Rapid re-endothelization Molecular therapies
Inflammation	Coated/drug-eluting stents
Neointimal proliferation	
SMC activation	Molecular therapies, coated/drug-eluting stents
SMC migration	Rapid re-endothelization, MMP inhibitors, coated/drug-eluting stents
SMC proliferation	Antiproliferative agents, brachytherapy, rapid re-endothelization, molecular therapies, coated/drug-eluting stents
ECM formation	Antiproliferative agents, rapid re-endothelization, molecular therapies, coated/drug-eluting stents
Chronic vascular remodeling	Stents

Abbreviations: ECM, extracellular matrix; MLD, minimal lumen diameter; MMP, metalloproteinase; SMC, smooth muscle cells

Coronary stents, by means of their rigid structure, significantly decrease acute recoil. One of the most important advantages of intracoronary stents is that those devices represent the "bigger is better" approach. Stents address restenosis from the direction of greater luminal gain and a decrease in the elastic recoil. By this radial support, the technique results in increased residual lumen and expansion of the artery at the long-term follow up.[6,64] Furthermore, coronary stents limit the exposure of deep vessel wall tissue to blood elements, diminishing the activation of unfavorable rheological factors and allowing a higher anterograde flow through a smooth contoured lumen.

Randomized studies such as the Stent in Restenosis Study (STRESS)[65] and the European Belgian–Netherlands Stent trial (BENESTENT)[22] have both shown a significant decrease in restenosis in the groups with stent placement compared with conventional balloon angioplasty.[22,66] **Grade A** The STRESS investigators reported a 10% decrease in restenosis rate with Palmaz–Schatz stent compared with balloon angioplasty (32% *v* 42% respectively), and the BENESTENT trial also demonstrated a 10% decrease in restenosis (22% in the stent group *v* 32% in the PTCA group), with better event-free survival and fewer revascularization procedures at 8 month follow up. Stenting technique has continued to evolve and other trials have compared conventional balloon angioplasty with contemporary stenting techniques – high pressure deployment,[67] IVUS,[68] reduced anticoagulation,[68] ostial placement,[69] – always demonstrating a reduction of restenosis rate in patients receiving coronary stents. **Grade B** The pilot phase of a new study, the BENESTENT-II trial, has shown that the rate of restenosis was impressively reduced to less than 13% when heparin coated stents were placed with high pressure delivery.[70] These results were confirmed by the BENESTENT-II trial,[71] which demonstrated that use of a heparin coated stents plus antiplatelet therapy resulted in better event-free survival at 6 months compared to standard balloon angioplasty. However, with respect to an antiproliferative effect of heparin, data of preclinical studies as well as from the BENESTENT-II trial suggest no reduction of neointimal hyperplasia within the stent in comparison to uncoated stents.[71–74] **Grade A**

Other devices, such as directional atherectomy, rotational atherectomy, and TEC atherectomy, improve lumen patency by tissue removal and are associated with less vessel wall recoil and dissection.[75,76] The CAVEAT-I and the C-CAT trials did not show a significative advantage of atherectomy over conventional balloon angioplasty.[77–79] This was a surprising finding since experimental and clinical studies have shown that a larger final lumen correlates with lower restenosis rates. However, it is important to note that in those trials the final lumen achieved with atherectomy did not differ compared with that obtained by balloon angioplasty. Indeed, a prospective multicenter registry of 199 patients treated by optimal DCA (<15% residual stenosis), the OARS study,[80] demonstrated a 6 month restenosis rate of 28·9% with a target lesion revascularization rate of 17·8% at 1 year follow up. These results have been recently confirmed by the Balloon versus Optimal Atherectomy Trial (BOAT),[81] which randomized 1000 patients with single *de novo*, native vessel lesions to DCA (<20% short-term post-treatment residual stenosis) or PTCA and demonstrated that optimal DCA provided lower angiographic restenosis than conventional PTCA (31·4% *v* 39·8%, respectively) at 6 month follow up. **Grade B** Other debulking modalities, such as aggressive rotational atherectomy utilized in the STRATAS study, demonstrated a trend toward increasing late loss index, restenosis, and target revascularization.[82]

Phase II: platelet aggregation/thrombus formation and inflammation

As an integral part of the dilation mechanism, coronary angioplasty results in injury to the arterial wall, including

endothelial damage with loss of antithrombotic properties (EDRF, PGI2, t-PA), induction of procoagulant factors (thrombin, tissue factor) and inflammatory infiltrate at the site of vascular injury. In addition, rupture of the internal elastic lamina and medial disruption, with exposure of the blood elements to wall constituents like collagen, von Willebrand factor, and extracellular matrix components, stimulates the interaction with platelet surface receptors (primarily glycoprotein Ib and IIb/IIIa integrins), resulting within minutes to hours after the intervention in platelet activation and deep mural thrombus formation[83–86] inaccessible to the action of heparin.[87,88] Experimental and clinical studies have also shown that platelets are activated by contrast medium.[89,90] Activated platelets secrete several substances from their α granules that stimulate vasoconstriction, chemotaxis, and activation of neighboring platelets.[91,92] In addition, platelet aggregation releases or stimulates the production of several factors and cytokines including thrombin, tromboxane A2, serotonin, plasminogen activator inhibitor (PAI-1), platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (b-FGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1), interleukin-1, and monocyte chemoattractant protein-1 (MCP-1) (Box 29.2).[93–95] These factors are believed to be responsible for neointimal growth by attracting and stimulating SMC migration and proliferation at the site of injury. (Figure 29.3).[96–99] The severity of the thrombogenic response depends on the degree of vascular injury, the surface area of exposure, the type of substrate exposed in the underlying vessel wall, and the rheological conditions such as shear stress and time of exposure.

Platelet activation leads to the recruitment of glycoprotein IIb/IIIa integrin surface receptors, which mediate platelet aggregation and thrombus formation by binding fibrinogen molecules between adjacent receptors.[93,100,101] Aggregated platelets accelerate the conversion of prothrombin to thrombin, which in turn stimulates further platelet activation.[102] Thrombin is involved in both thrombus formation, upregulation of E-selectin and P-selectin expression on endothelial cells, monocyte and neutrophil migration in the injured wall,[103] and stimulation of endothelin and tissue factor release from endothelial cells with a mitotic effect on SMC.[104] Of interest, there is also evidence that monocyte-macrophage recruitment may contribute to thrombus myofibrotic organization.[105] Genes for the PDGF ligands and receptor components are expressed in normal and injured rat carotid arteries.[106] Basic FGF and FGF receptor Type 1 are both expressed by endothelial cells and SMC after mechanical injury and inhibition of this growth factor reduces neointimal formation.[94,107,108] TGF-β seems to be the principal growth factor involved in the regulation and synthesis of proteoglycans, the major components of the extracellular matrix.[109–111] TGF-β induces both migration and proliferation of vascular cells and recent evidences suggest that this is an important factor in the vascular remodeling process associated with restenosis.[112,113]

Box 29.2 Extracellular factors involved in restenosis

- Angiotensin-II
- Collagen
- Collagenase
- Colony stimulating factors (CSFs)
- Elastic fibers
- Endothelins (ETs)
- Epidermal growth factor/transforming growth factor α (EGF/TGF-α)
- Fibroblast growth factors, acidic and basic (a-FGF, b-FGF)
- Heparin
- Heparin-binding epidermal growth factor (HB-EGF)
- Insulin-like growth factor 1 (IGF-1)
- Interferon γ (IFN-γ)
- Interleukin-1 (IL-1)
- Low density lipoprotein, oxidized (oxLDL)
- Monocyte-macrophage colony stimulating factor (M-CSF)
- Monocyte chemotactic protein 1 (MCP-1/MCAF-1)
- Nitric oxide/endothelium-derived relaxing factor (NO/EDRF)
- Plasmin
- Plasminogen activator inhibitor (PAI-1)
- Platelet derived growth factor A (endothelium, PDGF-AA)
- Platelet derived growth factor B (smooth muscle cells, PDGF-BB)
- Prostacyclin (PGI_2)
- Prostaglandin E
- Proteoglycans
- Thrombin
- Thromboxane A_2 (TXA_2)
- Tissue plasminogen activator (tPA)
- Transforming growth factor β (TGF-β)
- Tumor necrosis factor α (TNF-α)

Following platelet activation, circulating inflammatory cells adhere to the site of injury and migrate into the thrombus. Neutrophils, lymphocytes, and monocytes have been observed within the mural thrombus 1–5 days following angioplasty in an atherosclerotic rabbit model,[114] and presence of leukocytes and macrophages has been demonstrated by scanning electron microscopy adherent to the luminal surface of stented arteries in different animal models.[115,116] Stent deployment can also cause a foreign body reaction due to deeper arterial injury compared to balloon angioplasty.[117] Karas *et al* found reactive inflammatory infiltrates and multinucleated giant cells surrounding the stent wires at 4 week follow up in a porcine model of coronary injury.[118] Recently, the present authors demonstrated in a large

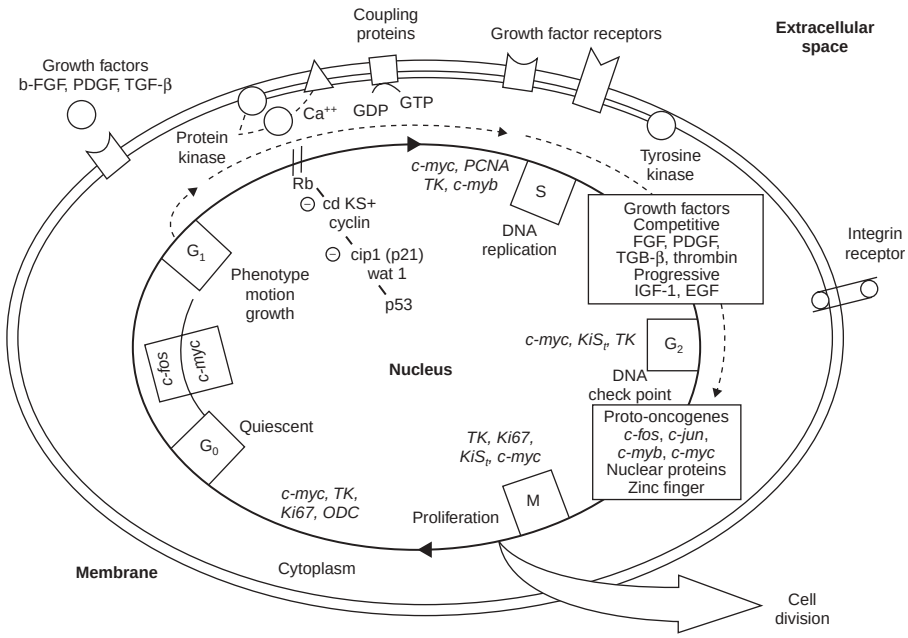


Figure 29.3 Cytoplasmatic and nuclear control points for SMC division and proliferation: CDKS, cyclin-dependent kinases; ODC, ornithine decarboxylase gene; Rb, retinoblastoma protein; TK, tyrosine kinase (for other abbreviations see text)

autopsy series that acute inflammation (mainly composed by neutrophils) linked to the extent and location of vessel injury and that chronic inflammation (lymphocytes and macrophages) was frequently observed around metallic struts at different time points following stent placement in humans.[119] Furthermore, it has been demonstrated that the extent of inflammatory reaction is significantly correlated, both independently and in combination with the degree of arterial injury, with the amount of neointimal formation.[120] The inflammatory response after stent deployment is also related to the material, design, and surface of the stent.[8,121–124]

In summary, the extent of vessel wall injury, amount of thrombus formation, and likelihood of neointimal proliferation are interrelated. Although the relationship of thrombus formation to restenosis remains to be elucidated, evidence suggests that thrombus contributes directly to restenosis by vessel occlusion[125] and indirectly by mediating the release of several factors, which in turn are also involved in the third phase of the restenotic process.[126]

Prevention of phase II: the role of new antithrombotic drugs

Since platelet function and consequent thrombus formation are important in the vascular response to injury, they have been logical targets of several therapeutic strategies. In addition to existing antithrombotic and anticoagulant drugs (that is, heparin and aspirin), antiplatelet therapies to prevent restenosis have been recently boosted by the development of newer agents that specifically inhibit critical steps in the coagulation cascade and proteins on the surface of platelets. These new drugs include inhibitors of thrombin generators (factor Xa inhibitors),[127,128] thrombin action (direct thrombin inhibitors),[129] or platelet aggregation (Gp IIb/IIIa receptor antagonists).[130]

Although aspirin,[131] dypiridamole,[132] ticlopidine,[133] warfarin,[134–136] thromboxane antagonists,[137–139] and prostacyclin analogs,[140,141] have been shown to be effective in animal models of restenosis, these drugs have failed to show any benefit in clinical practice. **Grade B** However, several factors may confound the interpretation of those studies. For example, differences in the lesion substrate, inappropriate drug doses, or incomplete block of the target, may explain the discrepancy between animal models and human studies. Moreover, while the magnitude of injury and thrombus formation correlate with the degree of neointimal formation in animals, the relationship in humans is by no means established. In addition, specific anticoagulant agents such as heparin,[142–145] low molecular weight heparin,[146,147] hirudin and hirulog,[148–151] did not show any favorable effect either on angiographic or clinical outcome related to restenosis. Recently, dietary fish oils have been demonstrated to inhibit platelet aggregation and thromboxane synthesis.[152] It has also been shown that fish oil intake reduces blood and red cell viscosity and reduces the inflammatory response to injury.[153,154] However, the two largest trials designed to test the hypothesis that restenosis could be reduced by fish oil intake have definitively demonstrated the lack of efficiency of these agents in the clinical arena.[155,156] **Grade A**

Both animal models of restenosis and clinical trials demonstrated a reduction of neointimal proliferation by blocking the platelet Gp IIb/IIIa ($\alpha_{IIb}\beta_3$) or the vitronectin receptors ($\alpha_v\beta_3$).[25,157–160] By using a chimeric 7E3 antibody directed against the platelet membrane IIb/IIIa receptor complex, the EPIC trial demonstrated a reduction in the onset of acute complications and clinical restenosis in high-risk angioplasty.[25] Since this trial was published, other studies have evaluated the effect at 6 month follow up of IIb/IIIa antagonists versus placebo. Unfortunately, IMPACT[161], IMPACT-II[160], RESTORE[162], EPILOG, and CAPTURE trials,[163,164] that studied the efficacy of integrilin, tirofiban, and abciximab, respectively, did not demonstrate a reduction in target vessel revascularization compared to placebo treatment. The EPISTENT trial demonstrated lower need for repeat target vessel revascularization among diabetic patients receiving abciximab compared to placebo,[165,166] as previously noted at 6 months.[167] **Grade A**

Aggarwal *et al* reported results of platelet Gp IIb/IIIa antibody eluting from cellulose polymer coated stents, implanted in iliac arteries of rabbits after balloon injury. There was a significant improvement in patency rates after both 2 hours and 28 days, but no difference in mean neointimal thickness at 28 days.[168] **Grade C** A clinical trial has been planned (UK RESOLVE trial), but thus far clinical results have not been reported. Alt *et al* coated a Palmaz-Schatz stent with a 10 μm layer of biocompatible and biodegradable high molecular weight poly-l-lactic acid and incorporated in this coating recombinant polyethylene glycol (r-PEG)-hirudin and the prostacyclin analog iloprost. Both drugs have antithrombotic and potentially antiproliferative effects. Stents were implanted in the non-overstretch model in sheep and in the overstretch pig model and compared to non-coated controls. At 28 days a greater luminal diameter was seen with a significant reduction of mean restenosis area of 22·9% in the sheep and 24·8% in the pig model, independently of the extent of vascular injury.[169] **Grade C**

Prevention of phase II: the role of anti-inflammatory approaches

The inflammatory reaction in restenosis relates to neointimal formation and arterial remodeling. Therefore, inhibition of the inflammatory response after vascular injury may have some beneficial effects on restenosis.

P-selectin, a protein stored in the α granules of platelets and Weibel–Palades bodies of endothelial cells, and binding to circulating monocytes and leukocytes, plays a crucial role in the early inflammatory response. Manka *et al* reported that apolipoprotein E-deficient mice with targeted disruption of the P-selectin gene exhibited dramatically decreased monocyte infiltration into the arterial wall and significantly decreased neointimal formation in a carotid artery injury model.[170] Mac-1 (CD11b/CD18, $\alpha_M\beta_2$), a leukocyte integrin, promotes adhesion and transmigration of leukocytes and monocytes at the site of vascular injury. Upregulation of Mac-1 in patients is associated with increased restenosis.[171,172] M1/70, a CD11b blocking Mab, was shown to inhibit neutrophil infiltration and medial SMC proliferation in a balloon denudation model.[173] Administration of recombinant human interleukin-10 (rhuIL-10), an anti-inflammatory cytokine, inhibited monocytes and macrophage infiltration in hypercholesterolemic rabbits, which was associated in turn with dramatic reduction in neointimal hyperplasia.[174] In addition, due to a broad range of anti-inflammatory and immunosuppressive activities, dexamethasone stent coating has been shown to reduce neointima hyperplasia compared to uncoated stents in canine femoral arteries.[175] Tranilast, a novel anti-inflammatory agent, has been shown to interfere with the PDGF-induced proliferation and migration of SMCs. This drug has been evaluated in the largest interventional anti-restenosis trial conducted to date, the Prevention of Restenosis with Tranilast and Its Outcome (PRESTO) trial,[176] which enrolled more than 11 500 patients after successful percutaneous coronary intervention. Unfortunately, this trial provided unequivocal evidence that this compound has no effect on both restenosis and clinical events. **Grade A/C**

Phase III: smooth muscle cell activation and synthesis of extracellular matrix

This final phase of vascular healing is predominantly characterized by neointimal formation due to SMC proliferation and extracellular matrix accumulation produced by the neointimal cells at the injury site.[45,177–180] The healing response is a normal process which is essential in maintaining vascular integrity after an injury to the vessel wall, but varies in the degree to which it occurs. One pathogenetic explanation of restenosis is, indeed, an exaggeration of this healing response.

Phase III could be further divided into three different waves.[44] In the *first wave* (days 1–4 after vessel injury), medial SMC from the site of injury and possibly from adjacent areas are activated and stimulated by the triggering factors mentioned earlier. In addition to mitogenic factors released by endothelial cells, stretching of the arterial wall is a potent stimulus for SMC activation and growth.[181] Once activated, SMC undergo characteristic phenotypic transformation, from a "contractile" to a "synthetic" form,[178] which is responsible for the production of extracellular matrix rich in chondroitin sulfate and dermatan sulfate seen in the first 6 months after injury. The *second wave* (3–14 days after vessel injury) and the *third wave* (14 days to months after vessel injury) are respectively characterized by the migration of SMC through breaks in the internal elastic lamina into the intima, the local thrombus,[182] and

SMC proliferation followed by extracellular matrix formation.[126,183–186] Those events are characterized by complex interactions between growth factors, second messengers, and gene regulatory proteins resulting in phenotypic change from a quiescent state to a proliferative one.[96] The peak of proliferation is observed 4–5 days after balloon injury but the duration of migration is not known, nor is it known whether a phase of cellular replication is required before SMC migration. Few studies have been done to identify the matrix molecules involved in the migration into the intima. Osteopontin is expressed in sites of marked remodeling,[187] and antibodies to osteopontin inhibit SMC migration into the intima after balloon angioplasty.[188] Proteoglycans may also be important for the formation of neointima. CD44, a receptor for hyaluronic acid, seems to play a role in the migration of cells into fibrin or osteopontin.[189,190] SMC migration presumably requires degradation of the basement membrane surrounding the cells. Several metalloproteinases, including tissue type plasminogen activator, plasmin, MMP-2, and MMP-9, may be responsible for this process,[191,192] and the administration of a protease inhibitor reduces SMC migration into the intima.[193] Cell migration is probably initiated by recognition of extracellular matrix proteins by a family of cell surface adhesion receptors known as integrins.[194,195] *In vitro* and *in vivo* studies have demonstrated that the selective blockage of the $\alpha_v\beta_3$ integrin inhibits SMC migration and reduces neointimal formation.[158,196]

Experimental studies have suggested that endothelin-1 (ET-1) and endothelin receptors may also be indirectly implicated in the SMC migration and matrix synthesis.[197–199] Immunohistochemical studies demonstrate a time-dependent increase in endothelin immunoreactivity after balloon angioplasty in the rat model.[200] The administration of endothelin receptor antagonists in different animal models of balloon injury has been shown to be effective in reducing neointimal formation.[197,201,202]

Several *in vitro* studies have suggested that different growth factors, such as PDGF-AA, PDGF-BB, β-FGF, IGF, EGF, FGF, TGF-β, and angiotensin II, may also play a major role in this process.[96,185,203–207] Control of SMC proliferation is regulated by the actions of mitogens (that is, PDGF) and the opposing effect of inhibitors (that is, TGF-β). The growth factors bind to cell surface receptors and initiate a cascade of events which leads to cell migration and division. Components of the cascade include different tyrosine kinases, coupling proteins, and membrane-associated and cytoplasmic protein kinases (see Figure 29.3). On stimulation by growth factors, proto-oncogenes are transiently activated and together with other cell cycle-dependent proteins such as zinc finger proteins, mediate the effects within the nucleus. Several studies have demonstrated that stimulation of SMC *in vitro* is associated with an increase of the proto-oncogenes *c-myc*, *c-myb*, and *c-fos*.[208–210] The ornithine decarboxylase (ODC) gene and the thymidine kinase (TK) messenger RNA are both expressed in stimulating cells and in continuously cycling cells.[210] SMC proliferation may also result from a reduction in an inhibitory factor which normally prevents cell division. Proteins such as p21 are inhibitors of the cyclin-dependent kinases (cdks) which regulate the entry of the cell in the cycle (see Figure 29.3). Stimulation of these proteins, indeed, inhibits SMC proliferation and neointima formation after balloon injury.[211]

As smooth muscle cells decrease their proliferation rate, they begin to synthesize large quantities of proteoglycan matrix. The extracellular matrix production continues for up to 20–25 weeks and over time it is gradually replaced by collagen and elastin, while the SMC turn into quiescent mesenchymal cells. The resulting neointima is composed of a fibrotic extracellular matrix with few cellular constituents. The endothelial cells proliferate and cover the denuded area resulting in a re-endothelization process, and the new endothelium begins to produce large quantities of heparan sulfate and nitric oxide, both of which inhibit SMC proliferation.[86] However, whether SMC proliferation and extracellular matrix production cease after re-endothelization is still unknown at this time.

Prevention of phase III: the past and the future

Multiple experimental and clinical trials[212,213] have been carried out specifically to target what seemed the key in the restenosis process: smooth muscle cell proliferation. To date, with only few exceptions, no pharmacologic or mechanical agent has been conclusively shown to reduce restenosis.

Antiproliferative approaches

The aim of an antiproliferative approach to restenosis is to control and modulate the action of possible mediators of proliferation at any point in the biologic pathway in which they are involved or to enable the cell to respond appropriately to the proliferative stimulus. Two different strategies to inhibit neointima hyperplasia are available:

1. the cytostatic approach, by which regulation and expression of cell cycle modulating proteins at any level along the pathway is performed;
2. the cytotoxic approach, by which proliferating cells are killed and eliminated.

The latter approach has the disadvantage of necrosis induction, associated with inflammation, which may contribute to vessel wall weakening. Hence, the cytostatic approach is conceptually more attractive.

Several antiproliferative agents targeting SMC migration and proliferation have been evaluated, including glucocorticoids, colchicine, somatostatin, hypolipidemic drugs, antineoplastic agents, and angiotensin-converting enzyme (ACE) inhibitors. Both natural and synthetic corticosteroids are potent inhibitors of SMC proliferation, leukocyte migration, and degranulation, PDGF and macrophage derived growth factor release, and matrix production.[214] While experimental and preclinical studies[215–217] have reduced SMC proliferation with the use of local glucocorticoids delivery, three different human trials using oral steroid dosage have failed to shown any reduction in restenosis rate.[131,218,219] **Grade A**

Contradictory results have been obtained as well with antineoplastic agents such as methotrexate, cytarabine, azathioprine, etoposide, vincristine, taxol, and doxorubicin. While some *in vitro* and *in vivo* studies show an attenuation of vascular SMC proliferation,[220,221] other studies show no efficacy in reducing the incidence of restenosis after PTCA.[222–224] Colchicine, which has an antimitotic and anti-inflammatory action in addition to an inhibitory effect on platelet aggregation and release of secretory products, has been shown to reduce restenosis in animals.[225] However, no clinical benefit has been seen with colchicine in two randomized placebo-controlled clinical trials.[226,227] **Grade A** As with other chemotherapeutic agents, the narrow therapeutic index of these drugs may be of concern. However, the recent availability of new local delivery systems (Box 29.3), such as drug eluting stents, has increased interest in the antiproliferative approach and has led to the evaluation of a multitude of compounds with antiproliferative properties. Furthermore, local therapy offers the combined advantages of high local concentrations at the injury site and diminished systemic levels, with decreased risk of adverse effects. The problem of systemic toxicity may be overcome.[228–233]

Box 29.3 Local drug delivery systems

- Double balloon system
- Iontophoretic porous balloon
- Balloon with hydrophilic polyacrylic polymer (hydrogel)
- Channel catheter
- Transport porous catheter
- Dispatch catheter
- Rheolytic system
- Ultrasonic energy and radiofrequency
- Balloon over a stent
- Biodegradable drug eluting polymer stent
- Dacron stent
- Silicone stent
- High molecular weight poly-l-lactic acid stent
- Nitinol stent with polyurethane coating
- Fibrin coated stent
- Stent with cell layer
- Stent with radioactive substance

After verification of an inhibitory effect on neointimal hyperplasia in animal models,[234–236] ACE inhibitors have been extensively studied to assess the clinical effect on restenosis. Unfortunately, two large clinical studies (MERCATOR and MARCATOR), with over 2129 patients enrolled, failed to show any impact on clinical or angiographic restenosis.[237,238] **Grade A** Intensive treatment with cholesterol lowering agents such as the HMG-CoA (3-hydroxy-3methylglutaryl coenzyme A) reductase inhibitors lovastatin, pravastatin, simvastatin, and fluvastatin, reduces intimal hyperplasia in the rat and rabbit models,[224,239,240] probably for serum lipid reduction and decreased platelet aggregation. Despite this promising preliminary data, chronic high-dose lovastatin treatment does not attenuate the incidence of clinical restenosis.[241] Antioxidant agents such as probucol, ascorbic acid and α-tocopherol may be useful in limiting restenosis by reducing platelet aggregation, and modulating prostaglandin and leukotriene synthesis. Both animal[242,243] and clinical[26,244] studies have recently shown a reduction in restenosis with the use of such agents. **Grade B**

Paclitaxel is a cytostatic drug which is extensively used in cancer therapy. It is a micro-tubule stabilizing agent with antiproliferative activity as well as inhibition of migration of smooth muscle cells. *In vitro* studies with cultured human vascular smooth muscle cells (VSMC) and endothelial cells show strong antiproliferative effects on the VSMC.[245] In rabbits an antiproliferative effect was seen at 1 month, which was dose-related. However, in this *in vivo* model more inflammation was seen in the paclitaxel group as well as a poor endothelization.[246] Herdeg *et al* have reported a significant reduction in neointimal stenosis after balloon dilation and subsequent local paclitaxel delivery with a double balloon catheter, compared to balloon dilation alone in rabbit carotid arteries. **Grade C** They observed marked enlargement of vessel size with positive remodeling after paclitaxel treatment (at 7, 28, and 56 days).[247] Phosphorylcholine (PC) coated stent with incorporated angiopeptin has also been tested (Table 29.2). This is a somatostatin analog which is hypothesized to prevent myointimal thickening after vessel injury mainly by inhibiting secretion of growth factors. After balloon injury effective inhibition of intimal hyperplasia has been shown in porcine coronary arteries.[248] In a randomized clinical trial including 553 patients with 742 lesions the incidence of events was significantly reduced in the angiopeptin treatment group, despite no difference in angiographic variables at follow up.[249] **Grade B** De Scheerder *et al* demonstrated the feasibility of loading a polymer coated stent with angiopeptin and significant reduction of neointimal proliferation was found 6 weeks after stenting in porcine coronary arteries.[250] Armstrong *et al* demonstrated in pig coronary arteries using 125-I angiopeptin loaded PC stents that the drug was still detectable in the vessel wall after 28 days.[251] Impressive

Table 29.2 Stent coating and covering categories

Material type	Examples
(In)-organic/ceramic materials	Gold, iridium oxide, silicium carbide, diamond-like carbon, biogold
Synthetic and biologic polymers	PC, PU, PLA, PE, cellulose
Human polymers	Chondroitin sulfate, hyaluronic acid, fibrin, elastin, endothelial cells
Immobilized drugs	Heparin, paclitaxel, abciximab
Eluting, degradable matrices	PLA-hirudin-iloprost, PLA-paclitaxel, PC-angiopeptin, cellulose-abciximab, PU-forskolin, PLA-PC-viral vector, PE-DNA
Covering substances	PTFE, autologous vein

Different materials can be used to cover a stent surface using an array of techniques such as dipping, (plasma) spraying, plating, sputtering, and surface induced mineralization. Some materials have been used as coatings *per se*, while others have been tested as a platform for local drug delivery.
Abbreviations: PC, metacrylyl phosphorylcholine lauryl-methacrylate; PE, polyester; PLA, poly-l-lactic acid; PTFE, polytetrafluoroethylene; PU, polyurethane.

results have been demonstrated in the RAVEL trial[252,253] using rapamycin coated stent (Sirolimus). **Grade A** Rapamycin is a potent immunosuppressive agent that inhibits vascular SMC proliferation by blocking cell cycle progression. Significant reduction of arterial proliferative response after systemic administration of rapamycin was already shown in the porcine coronary model by Gallo *et al.*[254] Finally, other drugs, such as tranilast, a novel inflammatory agent, batimastat, a matrix metalloproteinases inhibitor, and nitric oxide-eluting polymer coated stents are currently under investigation and the clinical results are eagerly awaited. In the case of the Batimast-coated stent, preliminary results are negative.

The concept and technique of applying ionizing radiation to the arterial wall (brachytherapy) during percutaneous coronary intervention procedures has emerged and gained considerable momentum,[255–261] including entry in clinical trials.[262,263] Ionizing radiation affects dividing cells by chromosomal damage in the vascular smooth muscle cells, fibroblasts, and, when present, endothelial cells, resulting in the loss of cells' ability to reproduce, with mitotic cell death.[264] Radiation may also reduce neointima proliferation by increasing the rate of apoptosis within the intima.[265] External beam radiotherapy involves the generation of a beam of radiation from a source external to the patients, for example linear accelerator or ^{60}Co unit. Brachytherapy is a method of delivering radiation to a target organ by placing radioactive sources, for example ^{90}Yt or ^{192}Ir sources, close to or within an organ. This method is well suited (as opposed to external beam radiation) to deliver high doses of radiation to a small defined region. Both γ and β emitters have been utilized in clinical trials of intracoronary radiation therapy.[266–269] However, γ emitters deliver a more uniform dose to the arterial wall than β emitters, but at the cost of increased radiation risk. In addition, radioactive stents, made either by bombardment with subatomic particles, ion implantation of the stents with radioisotopes, or by chemical methods that incorporate the radioactive material into the metallic stents, have been evaluated.[270] Encouraging results from small human clinical studies utilizing both γ and β emitters have set the stage for human clinical trials. The SCRIPPS trial[263] was the first randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of coronary brachytherapy with a γ radiation source (^{192}Ir) in reducing restenosis. At 6 months, the angiographic restenosis rate was 53·6% in the control versus 16·7% in the irradiated group. The clinical benefit was maintained at 2 year follow up with target vessel revascularization of 15·4% as against 44·8% of the placebo group.[271] The GAMMA-1 trial randomized 252 patients with in-stent restenosis to placebo or gamma irradiation. The restenosis rate was 22% in the irradiated arm compared to 51% for the placebo arm.[272]

Several clinical trials (ARREST, Angiorad Radiation for REStenosis trial; ARTISTIC, Angiorad Radiation Therapy for In-Stent Restenosis Intra-Coronary trial; SMART, Smart Artery Radiation Therapy trial; WRIST-SVG, Washington Radiation for In-Stent Restenosis-Saphenous Vein Graft trial) are still ongoing and the results as awaited. BETA CATH, which is the largest multicenter placebo-controlled trial assessing intracoronary β radiation therapy (^{90}Sr/Y source) for restenosis prevention, recently started the enrollment phase. In this trial, clinical end points will be MACE at 8 months, 1 and 2 years follow up. BRIE (Beta Radiation in Europe) is a European trial in 180 patients with encouraging interim results.[270] Finally, European trials on radioactive stents, such as the ^{32}P-Isostent BX^{TM} stent, resulted in an increased restenosis rate (43–50% of the lesions treated) due to neointimal hyperplasia development at the stent edge, the so called "candy wrapper effect".[273]

Growth factor approaches

For the reason that several growth factors have been implicated in the pathogenesis of restenosis, interference with the cellular processes that control cellular migration, replication, and matrix deposition has attracted much interest in the continuous search for pharmacologic agents to reduce the incidence of restenosis.

Angiopeptin, an analog of somatostatin, prevents the mitotic effect of several growth factors, including somatomedin-C, epidermal growth factor, insulin-like growth factor, and PDGF. It inhibits SMC proliferation and reduces neointimal hyperplasia in different experimental models.[274–276] A multicenter trial in which 1246 patients were randomized to receive placebo or three different doses of angiopeptin showed no reduction in clinical events and restenosis rates between the different groups.[277] **Grade A** On the other hand, in a smaller randomized study, angiopeptin treatment reduced restenosis after PTCA (7·5% *v* 37·8% of the placebo group).[278] However, using the same drug regimen, this promising finding was not confirmed by another multicenter European study.[279] Questions remain whether a more prolonged dosing of this agent is needed to affect neointimal growth.

Trapidil is a potent thromboxane-A2 and PDGF antagonist which significantly reduces neointimal formation in animal models of restenosis.[280] The STARC trial randomized 305 patients to receive trapidil versus aspirin and showed a reduction in restenosis rate by 40%, and reduction in clinical symptoms at 6 month follow up in the trapidil treatment group.[281] **Grade B** The efficacy of trapidil in the prevention of restenosis after balloon angioplasty has also been reported in a meta-analysis by Serruys and coauthors.[282] However, results from a randomized trial of trapidil versus aspirin (performed in the stent era) showed no benefit in terms of late restenosis in patients treated systemically with trapidil compared to the aspirin control group.[283]

Molecular approaches

With the growing understanding that the failure of several antiproliferative agents to reduce neointima hyperplasia may be related to the amplification and redundancy present in the membrane and nuclear protein signaling, several attempts have been made to control and transform the gene expression at the molecular level.[284] The mechanisms by which genetic material is transferred into the target tissue include:

1. *in vivo* gene transfer by infusion of naked DNA or antisense oligonucleotides;[285]
2. transport by hybrid liposomes containing viral coat particles;[286]
3. transport by cationic liposomes containing the DNA;[287]
4. via viral vectors using retro- or adenoviruses.[288,289]

Besides the potential safety concern of gene therapy, there are also problems of transfection efficiency and which gene should be delivered. In previous years, in agreement with the restenosis hypothesis, SMC have been the preferential target. In more recent years, however, with the improved knowledge of the pathogenetic mechanisms involved in the restenosis phenomenon, other targets have been selected, including endothelial cells, thrombus formation, growth factors, matrix production, and vascular remodeling.[290–294] In addition, increased extracellular growth inhibitors of SMC proliferation might be another potential approach.[211,295,296] Other future approaches may include enhancement of re-endothelization and repair by cell seeding,[297–300] and photodynamic therapy with light which shows cytotoxic properties on SMC and cell membranes through the production of activated singlet oxygen species.[301–304]

New etiologies in restenosis: the role of chronic vascular remodeling and adventitia

Vascular remodeling, first described in relation to atherosclerosis,[305,306] has assumed great importance as a cause of coronary restenosis in the past few years in non-stented patients.[307] In atherosclerotic vessels a chronic focal enlargement of the artery occurs in response to plaque increase, in order to preserve blood flow.[308–312] Artery size changes also occur following coronary angioplasty[313] and the artery may exhibit three different remodeling responses:

1. compensatory enlargement;[314]
2. absence of compensation;[315] or
3. vascular constriction.[316,317]

Intravascular ultrasound (IVUS) has become an important means to understand the concept of remodeling. IVUS imaging has shown that after PTCA there is an axial plaque redistribution, and that failure to cause dissection is one of the causes of early lumen loss by elastic recoil.[39,42] More recently, serial IVUS studies indicated that the restenotic lesion led to contraction of the artery and late lumen narrowing.[5,318–320] While the mechanisms of chronic remodeling are poorly understood, several explanations have been postulated to explain the late lumen narrowing after PTCA: fibrosis of the vessel wall underlying the lesion, rearrangement of extracellular matrix composition and structure, and response to increased shear stress.[4,321–323] A recent paper suggests that $\alpha_v\beta_3$ may regulate contraction of the vessel wall.[324] The integrins may therefore play a role in active contraction as well as migration of SMC. Animal studies indicate that after PTCA, stretching of the adventitia may result in the proliferation and synthesis of extracellular matrix by myofibroblasts within the adventitia, itself with consequent scar-like contraction and compression of the underlying vascular wall.[325–327] This mechanism, however, does not seem relevant for late lumen narrowing in human coronary arteries subjected to balloon angioplasty.[328]

The potential impact of neointimal hyperplasia and geometric remodeling on restenosis requires further studies. Methods to prevent constrictive remodeling or to promote compensatory enlargement should be investigated. The metallic stent or drugs like cytokalasin B, which seems to function as a biologic stent, may serve this function.[329]

Conclusions: is the end of restenosis possible?

The failure effectively to circumvent the problem of restenosis, after 15 years of research, underscores the complexity of this biological process, which, to date, has not yet been fully understood. The elimination of the intimal healing response to injury is probably not achievable, nor is it desirable, considering that this physiologic response to preserve vascular integrity has been maintained across millions of years in different species. The more we delve into it, the more complex and redundant this process appears.

From the above description of the postulated model of restenosis, although SMC proliferation and neointima formation undoubtedly play a central role in restenosis, it is more likely that multifactorial mechanisms, involving different stimuli, interacting in a synergistic manner, are responsible for the restenosis phenomenon. Given the multimechanistic nature of restenosis, it is too simplistic to expect that a single drug or mechanical device will solve this problem completely. The solution, as the problem, will most likely be multifactorial, possibly involving the use of drug therapy in conjunction with adjunctive second-generation mechanical devices. Of these devices, coronary stents are the most promising, especially for their ability to achieve the best post-treatment luminal size in comparison with other devices.

In the history of medicine, human attempts to interfere with the natural course of a disease by active interventions have often led to undesired consequences. Restenosis is a new disease, one of the many that medicine has encountered trying to solve an old disease. Enormous progress has been made in the past years in understanding the pathogenetic mechanisms of restenosis and in the search for a cure. If the efficacy of drug eluting stents was to be confirmed, this would lead to a repositioning of the indications for percutaneous coronary interventions. Most of the events observed after balloon angioplasty, with or without stent implantation, in recent multicenter trials were linked to the problem of restenosis in the first months of evolution. It may well be that in the future new clinical trials could demonstrate that percutaneous coronary intervention is proven to be superior to surgical revascularization techniques. To some it may seem a nightmare, to us, as interventional cardiologists, and to our patients, it may indeed seem like a dream.

References

1. Califf RM, Fortin DF, Frid DJ *et al.* Restenosis after coronary angioplasty: an overview. *J Am Coll Cardiol* 1991;**17**: 2B–13B.
2. Franklin SM, Faxon DP. Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials. *Coronary Artery Dis* 1993;**4**:232–42.
3. Topol EJ, Ellis SG, Cosgrove DM *et al.* Analysis of coronary angioplasty: practice in the United States with an insurance-claims database. *Circulation* 1993;**87**:1489–97.
4. Glagov S. Intimal hyperplasia, vascular remodeling, and the restenosis problem. *Circulation* 1994;**89**:2888–91.
5. Mintz GS, Popma JJ, Pichard AD *et al.* Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;**94**:35–43.
6. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 1993;**21**:15–25.
7. Schwartz RS, Murpphy JG, Edwards WD *et al.* Restenosis after balloon angioplasty: a practical proliferative model in porcine coronary arteries. *Circulation* 1990;**82**:2190–200.
8. van der Giessen WJ, Lincoff AM, Schwartz RS *et al.* Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996;**94**:1690–7.
9. Holmes DR, Vlietstra RE, Smith HC *et al.* Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;**53**:77C–81C.
10. Serruys PW, Luijten HE, Beat KJ *et al.* Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1,2,3, and 4 months. *Circulation* 1988;**77**:361–71.
11. Serruys PW, Rensing BJ, Hermans WRM, Beatt KJ. Definition of restenosis after percutaneous transluminal coronary angioplasty: a quickly evolving concept. *J Interv Cardiol* 1991; **4**:256–76.
12. Beatt KJ, Luijten HE, de Feyter PJ, van den Brand M, Reiber JH, Serruys PW. Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty: failure of percent diameter stenosis measurement to reflect morphologic changes induced by balloon dilation. *J Am Coll Cardiol* 1988;**12**:315–23.
13. Kuntz RE, Keaney KM, Senerchia C, Baim DS. A predictive method for estimating the late angiographic results of coronary intervention despite incomplete ascertainment. *Circulation* 1993;**87**:815–30.
14. Kuntz RE, Baim DS. Defining coronary restenosis: newer clinical and angiographic paradigms. *Circulation* 1993;**88**:1310–23.
15. Renkin J, Melin J, Robert A *et al.* Detection of restenosis after successful coronary angioplasty: improved clinical decision making with use of a logistic model combining procedural and follow-up variables. *J Am Coll Cardiol* 1990;**16**: 1333–40.
16. Weintraub W, Ghazzal Z, Liberman H, Cohen C, Morris D. Long term clinical follow-up in patients with angiographic restudy after successful angioplasty. *Circulation* 1991;**84**: II-364.
17. Weintraub WS, Kosinski AS, Brown CL, King SB. Can restenosis after coronary angioplasty be predicted from clinical variables? *J Am Coll Cardiol* 1993;**21**:6–14.
18. Mick MJ, Piedmonte MR, Arnold AM, Simpfendorfer C. Risk stratification for long-term outcome after elective coronary angioplasty: a multivariate analysis of 5,000 patients. *J Am Coll Cardiol* 1994;**24**:74–84.

19.Melkert R, Violaris AG, Serruys PW. Luminal narrowing after percutaneous transluminal coronary angioplasty: a multivariate analysis of clinical , procedural and lesion related factors, affecting long-term angiographic outcome in the PARK study. *J Invas Cardiol* 1994;**6**:160–71.
20.Peters RJC, Wouter EM, Kok MD *et al.*, for the PICTURE study group. Prediction of restenosis after coronary balloon angioplasty: results of PICTURE (post-intracoronary treatment ultrasound result evaluation), a prospective multicenter intracoronary ultrasound imaging study. *Circulation* 1997;**95**:2254–61.
21.Farb A, Virmani R, Atkinson JB, Anderson PG. Long-term histologic patency after percutaneous transluminal coronary angioplasty is predicted by the creation of a greater lumen area. *J Am Coll Cardiol* 1994;**24**:1229–35.
22.Serruys PW, de Jaegere P, Kiemeneij F *et al.*, for the BENESTENT study group. A comparison of balloon expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;**331**:489–95.
23.Fischman DL, Leon MB, Baim DS *et al.*, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;**331**:496–501.
24.Feld S, Ganim M, Carrel ES *et al.* Comparison of angioscopy, intravascular ultrasound imaging and quantitative coronary angiography in predicting clinical outcome after coronary interventions in high risk patients. *J Am Coll Cardiol* 1996; **28**:97–105.
25.Topol EJ, Califf RM, Weisman HF *et al.* Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC investigators. *Lancet* 1994;**343**:881–6.
26.Tardif JC, Cote G, Lesperance J *et al.* Prevention of restenosis by pre- and post-PTCA probucol therapy: a randomized clinical trial. *Circulation* 1996;**94**(Suppl. I):I-91 (Abstract).
27.Godfried SL, Deckelbaum LI. Natural antioxidants and restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1995;**129**:203–10.
28.Chisolm G. Antioxidants and atherosclerosis: a current assessment. *Clin Cardiol* 1991;**14**:125–30.
29.Schneider J, Berk B, Santoian E *et al.* Oxidative stress is important in restenosis: reduction of neointimal formation by the antioxidant probucol in a swine model of restenosis. *Circulation* 1992;**86**(Suppl. I):I-186.
30.Clowes AV, Karnovsky MJ. Suppression by heparin of smooth muscle cell proliferation in injured arteries. *Nature* 1977;**265**:625–6.
31.Olson LV, Clowes AW, Reidy MA. Inhibition of smooth muscle cell proliferation in injured rat arteries. *J Clin Invest* 1992;**90**:2044–9.
32.Faxon DP, Weber VJ, Haudenschild C, Bottsman SB, McGovern WA, Ryan TJ. Acute effect of transluminal angioplasty in three experimental models of atherosclerosis. *Arteriosclerosis* 1982;**2**:125–33.
33.Schwartz RS, Edwards WD, Huber KC *et al.* Coronary restenosis: prospects for solution and new perspectives from a porcine model. *Mayo Clin Proc* 1993;**68**:54–62.
34.Dotter CT, Judkins MP. Transluminal treatment of atherosclerotic obstruction: desciption of new technique and a preliminary report of its application. *Circulation* 1964;**30**:654–70.
35.Baughman KL, Pasternak RC, Fallon JT, Block PC. Transluminal coronary angioplasty of post mortem human hearts. *Am J Cardiol* 1981;**48**:1044–7.
36.Block PC, Myler RK, Stertzer S, Fallon JT. Morphology after transluminal angioplasty in humans. *N Engl J Med* 1981;**305**:382.
37.Waller BF. Pathology of transluminal balloon angioplasty used in the treatment of heart disease. *Hum Pathol* 1987;**18**: 476–84.
38.Sanborn TA, Faxon DP, Haudenschild C, Gottsman SB, Ryan TJ. The mechanism of coronary angioplasty: evidence for formation of aneurysms in experimental atherosclerosis. *Circulation* 1983;**68**:1136–40.
39.Potkin BN, Roberts WC. Effects of coronary angioplasty on atherosclerotic plaque composition and arterial size to outcome. *Am J Cardiol* 1988;**62**:41–50.
40.Kohchi K, Takebayashi S, Block PC *et al.* Arterial changes after percutaneous coronary angioplasty: results at autopsy. *J Am Coll Cardiol* 1987;**10**:592–9.
41.Mizuno K, Kurita A, Imazeki N. Pathologic findings after percutaneous transluminal coronary angioplasty. *Br Heart J* 1984;**52**:588–90.
42.Potkin BN, Keren GN, Mintz GS *et al.* Arterial responses to balloon coronary angioplasty: an intravascular ultrasound study. *J Am Coll Cardiol* 1992;**20**:942–51.
43.Essed CE, van der Brand M, Becker AE. Transluminal coronary angioplasty and early restenosis: fibrocellular occlusion after wall laceration. *Br Heart J* 1983;**49**:393–6.
44.Fuster V, Erling F, Fallon JT, Badimon L, Chesebro JH, Badimon JJ. The three processes leading to post PTCA restenosis: dependence on the lesion substrate. *Thromb Haemostas* 1995;**74**:552–9.
45.Nobuyoshi M, Kimura T, Nosaka H *et al.* Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol* 1988;**12**:616–23.
46.Sanders M. Angiographic changes thirty minutes following percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *Angiology* 1985;**36**: 419–24.
47.Daniel WC, Pirwitz MJ, Willard JE *et al.* Incidence and treatment of elastic recoil occurring in the 15 minutes following successful percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1996;**78**:253–9.
48.Fischell TA, Derby G, Tse TM, Stadius ML. Coronary artery vasoconstriction routinely occurs after percutaneous transluminal angioplasty. *Circulation* 1988;**78**:1323–34.
49.Mabin TA, Holmes DR, Smith HC *et al.* Intracoronary thrombus: role in coronary occlusion complicating percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1985; **5**:198–202.
50.Arora RR, Platko WP, Bhadwar K, Simpfendorfer C. Role of intracoronary thrombus in acute complications during percutaneous transluminal coronary angioplasty. *Cath Cardiovasc Diagn* 1989;**16**:226–9.
51.Rodriguez AE, Santaera O, Larribeau M, Sosa MI, Palacios IF. Early decrease in minimal luminal diameter after successful percutaneous transluminal angioplasty predicts late restenosis. *Am J Cardiol* 1993;**71**:1391–5.

52.Rodriguez AE, Santaera O, Larribeau M *et al.* Coronary stenting decreases restenosis in lesions with early loss in luminal diameter 24 hours after successful PTCA. *Circulation* 1995;**91**:1397–402.
53.Rupprecht HJ, Brennecke R, Bernhard G *et al.* Analysis of risk factors for restenosis after PTCA. *Cath Cardiovasc Diagn* 1990;**19**:151–9.
54.Guiteras V, Bourassa MG, David PR *et al.* Restenosis after percutaneous transluminal coronary angioplasty: the Montreal Heart Institute experience. *Am J Cardiol* 1987;**60**:50B.
55.Staudacher RA, Hess KR, Harris SL, Abu-Khalil J, Heibig J. Percutaneous transluminal coronary angioplasty utilizing prolonged balloon inflations: initial results and six-month follow-up. *Cath Cardiovasc Diagn* 1991;**23**:239–44.
56.Kaltenbach M, Beyer J, Walter S *et al.* Prolonged application of pressure in transluminal coronary angioplasty. *Cath Cardiovasc Diagn* 1984;**10**:213–19.
57.Douglas GS, King SBI, Roubin GS. Influence of methodology of percutaneous transluminal coronary angioplasty on restenosis. *Am J Cardiol* 1987;**60**:29B.
58.Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JG, Serruys PW. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: a quantitative angiographic study in 1445 successfully dilated lesions. *J Am Coll Cardiol* 1992;**19**:939–45.
59.Meier B, Gruntzig AR, King SBI, Douglas GS, Hollman J, Ischinger T. Higher balloon dilatation pressure in coronary angioplasty. *Am Heart J* 1984;**107**:619–22.
60.Shaw RE, Myler RK, Fishman-Rosen J *et al.* Clinical and morphologic factors in prediction of restenosis after multiple vessel angioplasty. *J Am Coll Cardiol* 1986;**7**:63A.
61.Detre K, Holubkov R, Kelsey S *et al.* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981; the NHLBI registry. *N Engl J Med* 1988;**318**:265.
62.Mata LA, Bosch X, David PR, Rapold HJ, Corcos T, Bourassa MG. Clinical and angiographic assessment 6 months after double vessel percutaneous coronary angioplasty. *J Am Coll Cardiol* 1985;**6**:1239–44.
63.Roubin GS, Douglas JSJ, King SBI *et al.* Influence of balloon size on initial success, acute complications and restenosis after percutaneous coronary angioplasty: a prospective randomized study. *Circulation* 1988;**78**:557–65.
64.Sangiorgi G, Nunez BD, Keelan E, Berger P, Schwartz RS, Holmes DRJ. Detailed restenosis angiographic analysis after "crackers, stretchers, drillers, shavers and burners". *J Invas Cardiol* 1995;**7**(Suppl. c): (Abstract).
65.Schatz RA, Penn IM, Baim DS *et al.* for the STRESS investigators. Stent Restenosis Study (STRESS): analysis of in-hospital results. *Circulation* 1993;**88**:I-594.
66.Serruys P, Macaya C, de Jaegere P *et al.* Interim analysis of the BENESTENT-trial. *Circulation* 1993;**88**:594.
67.Colombo A, Maiello L, Almagor Y *et al.* Coronary stenting: single institution experience with the initial 100 cases using the Palmaz–Schatz stent. *Cath Cardiovasc Diagn* 1992;**26**:171–6.
68.Colombo A, Hall P, Nakamura S. Intracoronary stenting without anti-coagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995;**91**:1676–88.
69.Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA. A comparison of coronary stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;**336**:817–22.
70.Serruys PW, Emanuellsson H, van der Giessen W *et al.* Heparin-coated Palmaz–Schatz stents in human coronary arteries: early outcome of the Benestent-II Pilot Study. *Circulation* 1996;**93**:412–22.
71.Serruys PW, van Hout B, Bonnier H *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673–81.
72.van der Giessen WJ, van Beusekom HMM, Larsson R, Serruys PW. Heparin-coated coronary stents. *Curr Intervent Cardiol Rep* 1999;**1**:234–40.
73.Serruys PW, Kay IP *et al.* Benestent II, a remake of Benestent I? Or a step towards the era of stentoplasty? *Eur Heart J* 1999;**20**:779–81 (Hotline Editorial).
74.Vrolix MC, Legrand VM, Reiber JH *et al.* Heparin-coated Wiktor stents in human coronary arteries (MENTOR trial). *Am J Cardiol* 2000;**86**:385–9.
75.Tanaglia AN, Buller CE, Kisslo KB *et al.* Mechanisms of balloon angioplasty and directional atherectomy as assessed by intracoronary ultrasound. *J Am Coll Cardiol* 1992;**20**:685–91.
76.Kimball BP, Bui S, Cohen EA. Comparison of acute elastic recoil after directional coronary atherectomy vs standard balloon angioplasty. *Am Heart J* 1992;**124**:1459–66.
77.Elliot JM, Berdan LG, Homes DR *et al.* One year follow-up in the coronary angioplasty versus excisional atherectomy trial (CAVEAT I). *Circulation* 1995;**91**:2158–66.
78.Topol EJ, Leya F, Pinkerton CA *et al.* A comparison of patients with coronary artery disease. *N Engl J Med* 1993;**329**:221–7.
79.Adelman AG, Cohen EA, Kimball BP *et al.* A comparison of directional atherectomy with balloon angioplasty in the treatment of coronary artery disease for lesions of the left anterior descending arteries. *N Engl J Med* 1993;**329**:228–33.
80.Simonton CA, Leon MB, Baim DS *et al.* "Optimal" Directional Coronary Atherectomy. Final Results of the Optimal Atherectomy Restenosis Study (OARS). *Circulation* 1998;**97**:332–9.
81.Baim DS, Cutlip DE, Sharma SK *et al.* Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). *Circulation* 1998;**97**:322–31.
82.Whitlow PL, Bass TA, Kipperman RM *et al.* Results of the Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS). *Am J Cardiol* 2001;**87**:699–705.
83.Uchida Y, Hasegawa K, Kawarmura K, Shibuya I. Angioscopic observation of the coronary luminal changes induced by percutaneous transluminal coronary angioplasty. *Am Heart J* 1989;**117**:769–76.
84.Miller DD, Boulet AJ, Tio FO *et al. In vivo* technetium-99 m S12 antibody imaging of platelet al.pha granules in rabbit endothelial neointimal proliferation after angioplasty. *Circulation* 1991;**83**:224–36.
85.den Heijer P, van Dijk RB, Hillege HL, Pentinga ML, Serruys PW, Lie KI. Serial angioscopic and angiographic observations during the first hour after successful coronary angioplasty: a preamble to a multicenter trial addressing angioscopic markers for restenosis. *Am Heart J* 1994;**128**:656–63.
86.Ip JH, Fuster V, Israel D, Badimon L, Badimon J, Chesebro JH. The role of platelets, thrombin and hyperplasia in

restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991;**17**:77B–88B.
87. Weitz JI, Huboda M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990;**86**:385–91.
88. Bar-Shavit R, Eldor A, Vlodavsky I. Binding of thrombin to subendothelial extracellular matrix: protection and expression of functional properties. *J Clin Invest* 1989;**84**:1096–104.
89. Chronos NAF, Goodall AH, Wilson DJ, Sigwart U, Buller NP. Profound platelet degranulation is an important side effect of some type of contrast media used in interventional cardiology. *Circulation* 1993;**88**:2035–44.
90. Kolarov P, Tschoepe D, Nieuwenhuis HK, Gries FA, Strauer B, Schultheiss HP. PTCA: periprocedal platelet activation. Part II of the Dusseldorf PTCA Platelet Study (DPPS). *Eur Heart J* 1996;**17**:1216–22.
91. Fukami MH, Salganicoff L. Human platelet storage organelles. *Thromb Haemostas* 1977;**38**:963–70.
92. Holmsen H. Secretable storage pools in platelets. *Annu Rev Med* 1979;**30**:119–34.
93. Le Breton H, Plow EF, Topol EJ. Role of platelets in restenosis after percutaneous coronary revascularization. *J Am Coll Cardiol* 1996;**28**:1643–51.
94. Lindner V, Reidy MA. Expression of basic fibroblast growth factor and its receptor by smooth muscle cells and endothelium in injured rat arteries: an enface study. *Circ Res* 1993;**73**:589–95.
95. Shimokawa H, Ito A, Fukumoto Y *et al.* Chronic treatment with interleukin-1 induces coronary intimal lesions and vasospastic responses in pigs *in vivo*. *J Clin Invest* 1996; **97**:769–76.
96. Casscells W. Migration of smooth muscle and endothelial cells. Critical events in restenosis. *Circulation* 1992;**86**: 723–9.
97. Rekhter MD, O'Brien E, Shah N, Schwartz SM, Simpson JB, Gordon D. The importance of thrombus organization and stellate cell phenotype in collagen I gene expression in human coronary atherosclerosis and restenotic lesions. *Cardiovasc Res* 1996;**32**:496–502.
98. Poole JCF, Cromwell SP, Benditt EP. Behavior of smooth muscle cells and formation of extracellular structures in the reaction of the arterial walls to injury. *Am J Pathol* 1971; **62**:391–413.
99. Jeong MH, Owen WG, Staab ME *et al.* Porcine model of stent thrombosis: platelets are the primary component of acute stent closure. *Cath Cardiovasc Diagn* 1996;**38**:38–43.
100. Plow EF, McEver RP, Coller SW *et al.* Related binding mechanisms for fibrinogen, fibronectin, von Willebrand factor and thrombospondin on thrombin-stimulated human platelets. *Blood* 1985;**66**:724–7.
101. Weiss HG, Hawiger J, Ruggeri ZW, Turitto VT, Thiagarajan P, Hoffmann T. Fibrinogen-independent platelet adhesion and thrombus formation on subendothelium mediated by glycoprotein IIb/IIIa complex at high share rate. *J Clin Invest* 1989;**83**:288–97.
102. Unterberg C, Sandrock D, Nebendhal K, Buchwald AB. Reduced acute thrombus formation results in decreased neointimal proliferation after coronary angioplasty. *J Am Coll Cardiol* 1995;**26**:1747–54.
103. Sugama Y, Malik A. Thrombin receptor 14-aminoacid peptide mediates endothelial hyperadhesivity and neutrophil adhesion by P-selectin-dependent mechanism. *Circ Res* 1992; **71**:1015–19.
104. Shi Y, Hutchinson HG, Hall DG, Zalewsky A. Downregulation of c-myc expression by antisense oligonuleotides inhibits proliferation of human smooth muscle cells. *Circulation* 1993;**88**:1190–95.
105. Moreno P, Falk E, Palacios I, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. *Circulation* 1994;**90**:775–8.
106. Majesky MW, Reidy MA, Bowen-Pope DF, Hart CE, Wilcox JN, Schwartz SM. PDGF ligand and receptor genes expression during repair of arterial injury. *J Cell Biol* 1990;**111**:2149–58.
107. Nabel EG, Yang ZY, Plautz G, Forough R, Zhan X *et al.* Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries *in vivo*. *Nature* 1993;**362**:844–6.
108. Lindner V, Reidy MA. Proliferation of smooth muscle cells after vascular injury is inhibited by an antibody against basic fibroblast growth factor. *Proc Natl Acad Sci USA* 1991; **88**:3739–43.
109. Chen JK, Hoshi H, McKeehan WL. Transforming growth factor type beta specifically stimulates synthesis of proteoglycan in human adult arterial smooth muscle cells. *Proc Natl Acad Sci USA* 1987;**84**:5287–91.
110. Nikol S, Weir L, Sullivan A, Sharaf B, White CJ *et al.* Persistently increased expression of the transforming growth factor beta 1 gene in human vascular restenosis: analysis of 62 patients with one or more episodes of restenosis. *Cardiovasc Pathol* 1992;**3**:57–62.
111. Nabel EG, Shum L, Pompili VJ *et al.* Direct transfer of transforming growth factor beta 1 into arteries stimulates fibrocellular hyperplasia. *Proc Natl Acad Sci USA* 1993;**90**:10759–763.
112. Shi Y, O'Brien J, Fard A, Zalewski A. Adventitial myofibroblasts contribute to neointimal formation following coronary arterial injury. *Circulation* 1995;**92**:I-34 (Abstract).
113. Shi Y, Pieniek M, Fard A, O'Brien J, Mannion JD, Zalewski A. Adventitial remodeling after coronary arterial injury. *Circulation* 1996;**93**:340–8.
114. Wilensky RL, March KL, Gradus-Pizlo I *et al.* Vascular injury, repair, and restenosis after percutaneous transluminal angioplasty in the atherosclerotic rabbit. *Circulation* 1995; **92**:2995–3005.
115. Rodgers GP, Minor ST, Robinson K *et al.* Adjuvant therapy for intracoronary stents. Investigation in atherosclerotic swine. *Circulation* 1990;**82**:560–9.
116. Whelan DM, van der Giessen WJ, Krabbendam SC *et al.* Biocompatibility of phosporylcholine coated stents in normal porcine coronary arteries. *Heart* 2000;**83**:338–45.
117. Kollum M, Kaiser S, Kinscherf R *et al.* Apoptosis after stent implantation compared with balloon angioplasty in rabbits: role of macrophages. *Arterioscler Thromb Vasc Biol* 1997; **17**:2383–88.
118. Karas SP, Gravanis MB, Santoian EC *et al.* Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. *J Am Coll Cardiol* 1992;**20**:467–74.

119. Farb A, Sangiorgi G, Carter AJ *et al.* Pathology of acute and chronic coronary stenting in humans. *Circulation* 1999;**99**:44–52.
120. Kornowski R, Hong MK, Tio FO *et al.* In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol* 1998;**31**:224–30.
121. Tanigawa N, Sawada S, Kobajashi M. Reaction of the aortic wall to six metallic stent materials. *Acad Radiol* 1995; **2**:379–84.
122. Rogers C, Edelman E. Endovascular stent design dictates experimental restenosis and thrombosis. *Circulation* 1995; **91**:2995–3001.
123. Edelman E, Seifert P, Groothuis A *et al.* Gold-coated NIR stents in porcine coronary arteries. *Circulation* 2001;**103**:429–34.
124. McKenna CJ, Camrud A, Sangiorgi G *et al.* Fibrin-film stenting in porcine coronary injury model: efficacy and safety compared with uncoated stents. *J Am Coll Cardiol* 1998; **31**:1434–8.
125. Violaris AG, Melkert R, Hermann JPR, Serruys PW. Role of angiographically identifiable thrombus on long-term luminal renarrowing after coronary angioplasty: a quantitative angiographic analysis. *Circulation* 1996;**93**:889–97.
126. Schwartz RS, Holmes DRJ, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. *J Am Coll Cardiol* 1992;**20**:1284–93.
127. Yamazaki M. Factor Xa inhibitors. *Drugs Future* 1995;**20**: 911–18.
128. Schwartz RS, Holder DJ, Holmes DRJ *et al.* Neointimal thickening after severe coronary artery injury is limited by short-term administration of a factor Xa inhibitor: results in a porcine model. *Circulation* 1996;**94**:2998–3001.
129. Deutsch E, Rao AK, Colman RW. Selective thrombin inhibitors: the next generation of anticoagulants. *J Am Coll Cardiol* 1993;**22**:1089–92.
130. Fitzgerald GA, Meagher EA. Antiplatelets drugs. *Eur J Clin Invest* 1994;**24**:46–9.
131. Hillegas WB, Ohman EM, Califf RM. Restenosis: the clinical issues. In: Topol EJ ed. *Texbook of interventional cardiology, 2nd edn*. Philadelphia, PA: WB Saunders, 1994.
132. Schwartz L, Bourassa MG, Lesperance J *et al.* Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988;**318**:1714–19.
133. White C, Knudson M, Schmidt D. Neither ticlopidine nor aspirin-dipyridamole prevents restenosis post PTCA: results from a randomized placebo-controlled multicenter trial. *Circulation* 1987;**76**:IV-213 (Abstract).
134. Thomton MA, Gruentzig AR, Hollman J *et al.* Coumadin and aspirin in prevention of restenosis after transluminal coronary angioplasty: a randomized study. *Circulation* 1984;**69**: 721–7.
135. Urban P, Buller N, Kox K, Shapiro L, Bayliss J, Richards A. Lack of effect of warfarin on the restenosis rate or on clinical outcome after balloon coronary angioplasty. *Br Heart J* 1988;**60**:485–8.
136. Bertrandt ME, Allain H, Lablanche JM. Results of a randomized trial of ticlopidine vs placebo for the prevention of acute closure and restenosis after coronary angioplasty: the TACT study. *Circulation* 1990;**82**:190 (Abstract).
137. Serruys PW, Rutsch W, Heyndrickx GR *et al.* Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A2-receptor blockade. A randomized, double-blind, placebo-controlled trial. Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism Study (CARPORT). *Circulation* 1991;**84**: 1568–80.
138. Feldman RL, Bengston JR, Pryor DB, Zimmerman MB, from the GRASP Study Group. Use of a thromboxane A_2 receptor blockers to reduce adverse clinical events after coronary angioplasty. *J Am Coll Cardiol* 1992;**19**:259A.
139. Bove A, Savage M, Deutsch E *et al.* Effects of selective and non-selective thromboxane A2 blockade on restenosis after PTCA: M-Heart II. *J Am Coll Cardiol* 1992;**19**:259A (Abstract).
140. Knudtson ML, Flintoft VF, Roth DL, Hansen JL, Duff HJ. Effect of short-term prostacyclin administration on restenosis after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1990;**15**:691–7.
141. Raitzner AE, Holman J, Abukhalil J, Demke D. Ciprostene for restenosis revisited: quantitative analysis of angiograms. *J Am Coll Cardiol* 1993;**21**:321A (Abstract).
142. Ellis SG, Roubin GS, Wilentz J, Douglas JSJ, King SB. Effect of 18- to 24-hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. *Am Heart J* 1989;**117**:777–82.
143. Ellis S, Roubin G, Wilentz J *et al.* Results of a randomized trial of heparin and aspirin vs. aspirin alone for prevention of acute closure (AC) and restenosis (R) after angioplasty (PTCA). *Circulation* 1987;**76**:213 (Abstract).
144. Dryski M, Mikat E, Bjornsson TD. Inhibition of intimal hyperplasia after arterial injury by heparins and heparinoids. *J Vasc Surg* 1988;**8**:623–33.
145. Lehmann KG, Doria RJ, Feuer JM *et al.* Paradoxical increase in restenosis rate with chronic heparin use, final results of randomized trials. *J Am Coll Cardiol* 1991;**17**:181A (Abstract).
146. Currier JW, Pow TK, Haudenschild CC, Minihan AC, Faxon DP. Low molecular weight heparin (Enoxaparin) reduces restenosis after iliac angioplasty in the hypercholesterolemic rabbit. *J Am Coll Cardiol* 1991;**17**:118B–25B.
147. Faxon D, Spiro T, Minor S *et al.* Low molecular weight heparin in the prevention of restenosis after angioplasty: results of enoxaparin restenosis (ERA) trial. *Circulation* 1994;**90**:908–14.
148. Topol EJ, Bonar R, Jewitt D *et al.* Use of a direct antithrombin, hirulog, in place of heparin during coronary angioplasty. *Circulation* 1993;**87**:1622–9.
149. Serruys PW, Herrman JR, Simon R *et al.* Investigators for the HELVETICA. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995;**333**:757–63.
150. Heras M, Chesebro JH, Penny WJ, Bailey KR, Badimon L, Fuster V. Effects of thrombin inhibition on the development of acute platelet-thrombus deposition during angioplasty in pigs. Heparin versus recombinant hirudin, a specific thrombin inhibitor. *Circulation* 1989;**79**:657–65.
151. van den Boss AA, Deckers JW, Heyndrickx GR *et al.* Safety and efficacy of recombinant hirudin (CGP 39393) vs heparin in

patients with stable angina undergoing coronary angioplasty. *Circulation* 1993;**88**:2058–66.
152. Thorwest M, Balling E, Kristensen SD *et al.* Dietary fish oil reduces microvascular thrombosis in a porcine experimental model. *Thromb Res* 2000;**99**:203–8.
153. Baumann KH, Hessel F, Larass I *et al.* Dietary omega-3, omega-6, and omega-9 unsaturated fatty acid and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A randomized volunteer study. *Arterioscler Thromb Vasc Biol* 1999;**19**:59–66.
154. Kuiper KK, Muna ZA, Erga KS, Dyroy E *et al.* Tetradecylthioacetic acid reduces stenosis development after balloon angioplasty injury of rabbit iliac arteries. *Atherosclerosis* 2001;**158**:269–75.
155. Cairns JA, Gill J, Morton B *et al.*, for the EMPAR collaborators. Fish oils and low- molecular- weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR study. *Circulation* 1996;**94**:1153–60.
156. Leaf A, Jorgensen MB, Jacobs AK *et al.* Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994;**90**:2248–57.
157. Matsuno H, Stassen JM, Vermylen J, Deckmyn H. Inhibition of integrin function by a cyclic RGD-containing peptide prevents neointimal formation. *Circulation* 1994;**90**:2203–6.
158. Choi ET, Engel L, Callow AD, Sun S, Trachtenberg J, Santoro S, Ryan US. Inhibition of neointimal hyperplasia by blocking $\alpha_v\beta_3$ integrin with a small peptide antagonist GpenGRGDSPCA. *J Vasc Surg* 1994;**19**:125–34.
159. The EPIC investigators. Use of monoclonal antibody direct against the platelet glycoprotein IIa/IIIb receptor in high risk coronary angioplasty. *N Engl J Med* 1994;**14**:956–61.
160. Lincoff AM, Tcheng JE, Ellis SG *et al.* IMPACT-II investigators. Randomized trials of platelet glycoprotein IIb/IIIa inhibition with Integrelin for prevention of restenosis following coronary interventions: the IMPACT-II angiographic substudy. *Circulation* 1995;**92**:I-607.
161. Tcheng JE, Harrington RA, Kottke-Marchant K *et al.* Multicenter, randomized, double-blind placebo-controlled trial of the platelet integrin glycoprotein IIb/IIIa inhibition blocker integrelin in elective coronary intervention. *Circulation* 1995;**91**:2151–7.
162. Tcheng JE. Glycoprotein IIb/IIIa receptor inhibitors: putting the EPIC, IMPACT II, RESTORE and EPILOG trials into perspective. *Am J Cardiol* 1996;**78**:35–40.
163. van der Werf F. More evidence for a beneficial effect of platelet glycoprotein IIb/IIIa – blockade during coronary interventions: latest results from the EPILOG and CAPTURE trials. *Eur Heart J* 1996;**17**:325–6 (Editorial).
164. Ferguson J Jr. EPILOG and CAPTURE trials halted because of positive interim results. *Circulation* 1996;**93**:637 (news).
165. Topol EJ, Mark DB, Lincoff AM *et al.* Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicenter randomized trial. *Lancet* 1999;**354**: 2019–24.
166. Cura FA, Deepak LB, Lincoff AM, Kapadia SR *et al.* Pronounced benefit of coronary stenting and adjunctive platelet glycoprotein IIb/IIIa inhibition in complex atherosclerotic lesions. *Circulation* 2000;**102**:28–34.
167. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade: evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
168. Aggarwal RK, Ireland DC, Azrin MA *et al.* Antithrombotic potential of polymer-coated stents eluting platelet glycoprotein IIb/IIIa receptor antibody. *Circulation* 1996;**94**: 3311–17.
169. Alt E, Haehnel I, Beilharz C *et al.* Inhibition of neointima formation after experimental coronary artery stenting: a new biodegradable stent coating releasing hirudin and the prostacyclin analogue Iloprost. *Circulation* 2000;**101**:1453–8.
170. Manka D, Collins RG, Ley K *et al.* Absence of P-selectin but not intercellular adhesion molecule-1, attenuates neointimal growth after arterial injury in apolipoprotein E-deficient mouse. *Circulation* 2001;**103**:1000–5.
171. Inoue T, Sakai Y, Morooka S *et al.* Expression of polymorphonuclear leukocyte adhesion molecules and its clinical significance in patients treated with percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1996;**28**: 1127–33.
172. Mickelson JK, Lakkis NM, Villareal-Levy G *et al.* Leukocyte activation with platelet adhesion after coronary angioplasty: a mechanism for recurrent disease? *J Am Coll Cardiol* 1996;**28**:345–53.
173. Rogers C, Edelman ER, Simon DI. A mAb to the beta2-leukocyte integrin Mac-1 (CD11/CD18) reduces intimal thickening after angioplasty or stent implantation in rabbits. *Proc Natl Acad Sci USA* 1998;**95**:10134–9.
174. Feldman LJ, Aguirre L, Ziol M *et al.* Interleukin-10 inhibits intimal hyperplasia after angioplasty or stent implantation in hypercholesterolemic rabbits. *Circulation* 2000;**101**:908–16.
175. Strecker EP, Gabelmann A, Boos I *et al.* Effect of intimal hyperplasia of dexamethasone released from coated metal stents compared with non-coated stents in canine femoral arteries. *Cardiovasc Intervent Radiol* 1998;**21**:487–96.
176. Holmes DRJ, Fitzgerald P, Goldberg S *et al.* Prevention of Restenosis with Tranilast and its Outcome (PRESTO) protocol: a double-blind, placebo-controlled trial. *Am Heart J* 2000;**139**:23–31.
177. Ueda M, Becker AE, Tsukada T, Numano F, Fujimoto T. Fibrocellular tissue response after percutaneous transluminal coronary angioplasty. An immunocytochemical analysis of the cellular composition. *Circulation* 1991;**83**:1327–32.
178. Nobuyoshi M, Kimura T, Ohishi H *et al.* Morphologic studies: restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. *J Am Coll Cardiol* 1991;**17**:433–9.
179. Garratt KN, Edwards WD, Kaufmann UP, Vlietstra RE, Holmes DR. Differential histopathology of primary atherosclerotic and restenotic lesion in coronary arteries and saphenous vein bypass grafts: analysis of tissue obtained from 73 patients by directional atherectomy. *J Am Coll Cardiol* 1991;**17**: 442–8.
180. van Beusekom H, van der Giessen W, van Suylen R, Bos E, Bosman FT, Serruys PW. Histology after stenting of human saphenous vein bypass grafts: observations from surgically excised grafts 3 to 320 days after stent implantation. *J Am Coll Cardiol* 1993;**21**:45–54.

181.Clowes A, Clowes M, Fingerle J, Reidy M. Kinetics of cellular proliferation after arterial injury V. Role of acute distension in the induction of smooth muscle proliferation. *Lab Invest* 1989;**49**:360–4.
182.Clowes AW, Schwartz SN. Significance of quiescent smooth muscle cell migration in the injured rat carotid artery. *Circ Res* 1985;**56**:139–45.
183.Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm of restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol* 1991;**17**:758–69.
184.Clowes AW, Reidy MA, Clowes MM. Kinetics of cellular proliferation after arterial injury. I. Smooth muscle growth in the absence of endothelium. *Lab Invest* 1983;**49**:327–33.
185.Clowes AW, Clowes MM, Fingerle J, Reidy MA. Kinetics of cellular proliferation after arterial injury. V. Role of acute distension in the induction of smooth muscle proliferation. *Lab Invest* 1989;**60**:360–4.
186.Clowes A, Clowes M, Reidy M. Kinetics of cellular proliferation after arterial injury: endothelial and smooth muscle growth in chronically denuded vessels. *Lab Invest* 1986; **54**:295–303.
187.Thayer JM, Giachelli PM, Mirkes PE, Schartz SM. Expression of osteopontin in the head process late in gastrulation in the rat. *J Exp Zool* 1995;**272**:240–4.
188.Liaw L, Lombardi DM, Almeida MM, Schwartz SM. Neutralizing antibodies direct against osteopontin inhibit rat carotid neointimal thickening following endothelial denudation. *Arterioscler Thromb Vasc Biol* 1997;**17**:188–93.
189.Weber GF, Ashkar S, Glimcher MJ, Cantor H. Receptor-ligand interaction between CD44 and osteopontin (Eta-1). *Science* 1996;**271**:509–12.
190.Jain M, He Q, Lee WS *et al.* Role of CD44 in the reaction of vascular smooth muscle cells to arterial wall injury. *J Clin Invest* 1996;**97**:596–603.
191.Bendeck M, Zempo N, Clowes A, Galardy R, Reidy M. Smooth muscle cell migration and matrix metalloproteinase expression after injury in the rat. *Circulation Res* 1994;**75**: 539–45.
192.Schwartz SM. Smooth muscle migration in atherosclerosis and restenosis. *J Clin Invest* 1997;**99**:2814–17.
193.Bendeck MP, Irvin C, Reidy MA. Inhibition of matrix metalloproteinase activity inhibits smooth muscle cell migration but not neointimal thickening after arterial injury. *Circ Res* 1996;**78**:38–43.
194.Ruoslahti E. Integrins. *J Clin Invest* 1991;**87**:1–5.
195.Hynes RO. Integrins: versatility, modulation, and signalling in cell adhesion. *Cell* 1992;**69**:11–25.
196.Samanen J, Ali FE, Romoff T *et al.* Development of a small RGD-peptide fibrinogen receptor antagonist with potent antiaggregatory activity *in vitro*. *J Med Chem* 1991;**34**: 3114–125.
197.Douglas S, Ohlstein E. Endothelin-1 promotes neointima formation after balloon angioplasty in the rat. *J Cardiovasc Pharmacol* 1993;**22**(Suppl. 8):S371–3.
198.Helset E, Sildnes T, Seljelid R, Konoski ZS. Endothelin-1 stimulates human monocytes in vitro to release TNFα, IL-1β and IL-6. *Mediat Inflamm* 1993;**2**:417.
199.Scott-Burden T, Resink TJ, Hahn AWA, Vanhoutte PM. Induction of endothelin secretion by angiotensin II: effects on growth and synthetic activity of vascular smooth muscle cells. *J Cardiovasc Pharmacol* 1991;**17**:S96.
200.Wang X, Douglas SA, Louden C, Vickery-Clark LM, Feuerstein GZ, Ohlstein EH. Expression of endothelin-1, endothelin-3, endothelin-converting-enzyme-1, endothelin-A and endothelin-B receptor mRNA following angioplasty-induced neointima formation in the rat. *Circ Res* 1996;**78**: 322–8.
201.Tsjuno M, Hirata Y, Eguchi S, Watanabe T, Chatani F, Marumoi F. Nonselective ETA/ETB receptor antagonist blocks proliferation of rat vascular smooth muscle cells after balloon angioplasty. *Life Sci* 1995;**56**:PL449.
202.Wessale J, Adler A, Novosad E, Burke S, Dayton B, Opgenorth T. Endothelin antagonism reduces neointima formed following balloon injury in rabbit. In: *Fourth International Conference on Endothelin*. London, UK, 1995:153.
203.Ferns GA, Raines EW, Sprugel KH, Motani AS, Reidy MA, Ross R. Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. *Science* 1991;**253**:1129–32.
204.Clowes AW, Clowes MM, Fingerle J, Reidy MA. Regulation of smooth muscle cell growth in injured artery. *J Cardiovasc Pharmacol* 1989;**14**:S12–15.
205.Nabel EG, Yang Z, Plautz *et al.* rFGF-1 gene expression in porcine arteries induces intimal hyperplasia and angiogenesis *in vivo*. *Nature* 1993;**362**:844–6.
206.Nabel EG, Liptay S, Yang *et al.* r-PDGF gene expression in porcine arteries induces intimal hyperplasia *in vivo*. *J Clin Invest* 1993;**91**.
207.Scott-Burden T, Vanhoutte PM. Regulation of smooth muscle cell growth by endothelium-derived growth factors. *Text Heart Inst J* 1993;**21**:91–7.
208.Kindy MS, Sonenshein GE. Regulation of oncogene expression in cultured aortic smooth muscle cells: post-transcriptional control of c-myc m-RNA. *J Biol Chem* 1986;**261**: 12865–8.
209.Simons M, Edelman ER, DeKeyser JL, Langer R, Rosenberg RD. Antisense c-myb oligonucleotides inhibit intimal arterial smooth muscle cell accumulation *in vivo*. *Nature* 1992; **359**:67–70.
210.Campan M, Desgranges C, Gadeau AP, Millet D, Belloc F. Cell cycle dependent gene expression in quiescent stimulated and asynchronously cycling arterial smooth muscle cells in culture. *J Cell Physiol* 1992;**150**:493.
211.Chang MW, Barr E, Lu MM, Barton K, Leiden JM. Adenovirus-mediated over-expression of the cyclin/cyclin-dependent kinase inhibitor, p21 inhibits vascular smooth muscle cell proliferation and neointima formation in the rat carotid artery model of balloon angioplasty. *J Clin Invest* 1995;**96**:2260–8.
212.Paranandi SN, Topol EJ. Contemporary clinical trials of restenosis. *J Invas Cardiol* 1994;**6**:109–24.
213.Dangas G, Fuster V. Management of restenosis after clinical intervention. *Am Heart J* 1996;**132**:428–36.
214.Berk BC, Gordon JB, Alexander RW. Pharmacologic roles of heparin and glucocorticoids to prevent restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991;**17**:111B–17B.
215.Longenecker JP, Kilty LA, Johnson LK. Glucocorticoid inhibition of vascular smooth muscle cells proliferation: influence of

homologous extracellular matrix and serum mitogens. *J Cell Biol* 1984;**98**:534–40.
216. Longeneker JP, Kilty LA, Johnson LK. Glucocorticoid influence on growth of vascular cells in culture. *J Cell Physiol* 1982;**113**:197–202.
217. Stone GW, Rutherford BD, McConahay DR *et al.* A randomized trial of corticosteroids for the prevention of restenosis in 102 patients undergoing repeat coronary angioplasty. *Cath Cardiovasc Diagn* 1989;**18**:227–31.
218. Pepine CJ, Hirshfield JW, MacDonald RG *et al.* A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. *Circulation* 1990;**81**: 1753–61.
219. Villa AE, Guzman LA, Chen W, Golomb G, Levy RJ, Topol EJ. Local delivery of dexamethasone for prevention of neointimal proliferation in a rat model of balloon angioplasty. *J Clin Invest* 1994;**93**:1243–9.
220. Voisard R, Dartsch PC, Seitzer U *et al.* The in-vitro effect of antineoplastic agents on proliferative activity and cytoskeletal components of plaque-derived smooth muscle cells from human coronary arteries. *Coronary Artery Dis* 1993;**4**: 935–42.
221. Sollott SJ, Cheng L, Pauly RR *et al.* Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 1995;**95**:1869–76.
222. Murphy JG, Schwartz RS, Edwards WD *et al.* Methotrexate and azathioprine fail to inhibit porcine coronary restenosis. *Circulation* 1990;**82**:III-429.
223. Cox DA, Anderson PG, Roubin GS, Chou C-Y, Agrawal SK, Cavender C. Effect of local delivery of heparin and methotrexate on neointimal proliferation in stented porcine coronary arteries. *Coronary Artery Dis* 1992;**3**:237–48.
224. Mullett DW, Topol EJ, Abrams GD, Gallagher KP, Ellis SG. Intramural metrotrexate therapy for the prevention of the neointimal thickening after balloon angioplasty. *J Am Coll Cardiol* 1992;**20**:460–6.
225. Muller D, Ellis S, Topol E. Colchicine and antineoplastic therapy for the prevention of restenosis after percutaneous coronary interventions. *J Am Coll Cardiol* 1991;**17**:126B–31B.
226. O'Keefe J, McCallister B, Bateman T, Kuhnlein D, Ligon R, Hartzler G. Colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991;**17**:181A (Abstract).
227. Grines CL, Rizik D, Levine A *et al.* Colchicine angioplasty restenosis trial (CART). *Circulation* 1991;**84**:II-365 (Abstract).
228. Wolinsky H, Thung SN. Use of perforated balloon catheter to deliver concentrated heparin into the wall of the normal canine artery. *J Am Coll Cardiol* 1990;**15**:475–81.
229. Santoian EC, Gravanis MB, Schneider JE *et al.* Use of the porous balloon in porcine coronary arteries: rationale for low pressure and volume delivery. *Cath Cardiovasc Diagn* 1993;**31**:240–5.
230. Murphy JG, Schwartz RS, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR Jr. Percutaneous polymeric stents in porcine coronary arteries. Initial experience with polyethylene terephthalate stents. *Circulation* 1992;**86**:1596–604.
231. van der Giessen WJ, Slager CJ, van Beusekom HMM *et al.* Development of a polymer endovascular prosthesis and its implantation in porcine arteries. *J Interv Cardiol* 1992;**5**: 175–85.
232. Bier JD, Zalesky P, Li ST *et al.* A new bioabsorbable intravascular stent: *in vitro* assessment of hemodynamic and morphometric characteristics. *J Interv Cardiol* 1992;**5**:187–94.
233. Riessen R, Isner JM. Prospects for site-specific delivery of pharmacologic and molecular therapies. *J Am Coll Cardiol* 1994;**23**:1234–44.
234. Powell JS, Clozel JP, Muller RK *et al.* Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989;**245**:186–8.
235. Huber KC, Schwartz RS, Edwards WD, Camrud AR, Bailey K. Effects of angiotensin converting enzyme inhibition on neointimal hyperplasia in a porcine coronary injury model. *Am Heart J* 1993;**125**:695–701.
236. Janiak P, Libert O, Vilaine JP. The role of the renin-angiotensin system in neointima formation after injury in rabbits. *Hypertension* 1994;**24**:671–8.
237. The Multicenter European Research Trial with Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR Study. *Circulation* 1992;**86**:100–10.
238. Faxon DP, on behalf of the MARCATOR investigators. Angiotensin converting enzyme inhibition and restenosis: the final results of the MARCATOR trial. *Circulation* 1992;**88**: 506 (Abstract).
239. Rogler G, Lacknet KJ, Schmitz G. Effects of fluvastatin on growth of porcine and human vascular smooth muscle cells in vitro. *Am J Cardiol* 1995;**76**:114A–6A.
240. Gellman J, Ezekowitz MD, Sarembock IJ *et al.* Effect of lovastatin on intimal hyperplasia after balloon angioplasty: a study in an atherosclerotic hypercholesterolemic rabbit. *J Am Coll Cardiol* 1991;**17**:251–9.
241. Weintraub WS, Boccuzzi SJ, Klein JL *et al.* Lack of effect of lovastatin on restenosis after coronary angioplasty: lovastatin restenosis trial study group. *N Engl J Med* 1994; **331**:1331–7.
242. Lafont AM, Chai Y-C, Cornhill JF, Whitlow PL, Howe PH, Chisolm GM. Effect of alpha-tocopherol on restenosis after angioplasty in a model of experimental atherosclerosis. *J Clin Invest* 1995;**95**:1108–25.
243. Schneider JE, Berk BC, Gravanis MB *et al.* Probucol decreases neointimal formation in a swine model of coronary artery balloon injury. *Circulation* 1993;**88**:628–37.
244. Watanabe K, Sekiya S, Miyagawa M, Hashida K. Preventive effects of probucol on restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1996;**132**: 23–9.
245. Haehnel I, Pfeifer U, Resch A *et al.* Differential effect of a local paclitaxel release from a biodegradable stent coating on vascular smooth muscle cells and endothelial cells in a co-culture model (Abstract). *J Am Coll Cardiol* 1999; **33**(Suppl. A):1011–24.
246. Farb A, Heller PF, Shroff S, Cheng L *et al.* Pathological analysis of local drug delivery of paclitaxel via a polymer-coated stent. *Circulation* 2001;**104**:473–9.

247.Herdeg C, Oberhoff M, Baumbach A *et al.* Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy *in vivo*. *J Am Coll Cardiol* 2000;**35**:1969–76.
248.Santoian ED, Schneider JE, Gravanis MB *et al.* Angiopeptin inhibits intimal hyperplasia after angioplasty in porcine coronary arteries. *Circulation* 1993;**88**:11–14.
249.Emanuelsson H, Beatt KJ, Bagger JP *et al.* Long-term effects of angiopeptin treatment in coronary angioplasty: Reduction of clincial events but not angiographic restenosis. *Circulation* 1995;**91**:1689–96.
250.De Scheerder I, Wilczek K, van Dorpe J *et al.* Local angiopeptin delivery using coated stents reduces neointimal proliferation in overstretched porcine coronary arteries. *J Invas Cardiol* 1996;**8**:215–22.
251.Armstrong J, Gunn J, Holt CM *et al.* Local angiopeptin delivery from coronary stents in porcine coronary arteries (Abstract). *Eur Heart J* 1999;**20**(Suppl.):366.
252.Morice MC, Serruys PW, Sousa JE *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;**346**:1773–80.
253.Sousa JE, Costa MA, Abizaid A *et al.* Sustained suppression of neointimal proliferation by sirolimus eluting stents: one year angiographic follow-up and intravascular ultrasound follow-up. *Circulation* 2001;**104**:2007–11.
254.Gallo R, Padurean A, Jayaraman T *et al.* Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;**99**:2164–70.
255.Schwartz RS, Koval TM, Edwards WD *et al.* Effect of external beam irradiation on neointimal hyperplasia after experimental coronary artery injury. *J Am Coll Cardiol* 1992;**19**:1106–13.
256.Waksman R, Robinson KA, Crocker IR *et al.* Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation* 1995;**92**:3025–31.
257.Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol* 1994;**23**:1491–8.
258.Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces neointimal proliferation after balloon angioplasty in swine: persistent benefit at 6-month follow-up. *J Am Coll Cardiol* 1995;**25**:1451–6.
259.Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation* 1995;**91**:1533–9.
260.Verin V, Popowski Y, Urban P *et al.* Intra-arterial beta irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. *Circulation* 1995;**92**: 2284–90.
261.Liermann D, Boettcher HD, Schopohl B *et al.* Is there a method to prevent intimal hyperplasia after stent implantation in peripheral vessels? *Angiology* 1992;**92**:269–70.
262.Condado JA, Waksman R, Gurdiel O *et al.* Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation in humans. *Circulation* 1997;**96**:727–32.
263.Teirstein PS, Masullo V, Jani S *et al.* Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;**336**:1697–703.
264.Hall EJ, Millers RC, Bvenner DJ. The basic radiobiology of intravascular irradiation. In: Waksman R, ed. *Vascular brachytherapy*. Armonk NY: Futura Publishing Co, Inc, 1999.
265.Sangiorgi G, Kline RW, Bonner JA *et al.* 17 kilovolt beta-radiation induce apoptosis following experimental balloon angioplasty: results in a tissue culture model. In: *Restenosis summit IX*; 1997.
266.Popowski Y, Verin V, Papirov I *et al.* High dose rate brachytherapy for prevention of restenosis after percutaneous transluminal coronary angioplasty: preliminary dosimetric tests of a new source presentation. *Int J Radiat Oncol Biol Phys* 1995;**33**:211–15.
267.Condado JA, Gurdiel O, Espinoza R *et al.* Percutaneous transluminal coronary angioplasty (PTCA) and intracoronary radiation therapy (IRT): a possible new modality for treatment of coronary restenosis. A preliminary report of the first 10 patients treated with intracoronary radiation therapy. *J Am Coll Cardiol* 1995;**38**:228A (Abstract).
268.Liermann D, Bottcher HD, Kollath J *et al.* Prophylactic endovascular radiotherapy to prevent intimal hyperplasia after stent implantation in femoropopliteal arteries. *Cardiovasc Intervent Radiol* 1994;**17**:12–16.
269.Bottcher HD, Schopohl B, Liermann D, Kollath J, Adamietz IA. Endovascular irradiation – a new method to avoid recurrent stenosis after stent implantation in peripheral arteries: technique and preliminary results. *Int J Radiat Oncol Biol Phys* 1994;**29**:183–6.
270.Salame MY, Verheye S, Croker IR *et al.* Intracoronary radiation therapy. *Eur Heart J* 2001;**22**:629–47.
271.Teirstein PS, Massullo V, Jani S *et al.* Two-year follow-up after catheter-based radiotherapy to inhibit coronary restenosis. *Circulation* 1999;**99**:243–7.
272.Leon MB, Tierstein PS, Moses JW. Localized intracoronary gamma-radiation therapy to inhibit the occurrence of restenosis after stenting. *N Engl J Med* 2001;**344**:250–6.
273.Albiero R, Di Mrio C, De Gregorio J. Intravascular ultrasound (IVUS) analysis of beta-particle emitting radioactive stent implantation in human coronary arteries. Preliminary immediate and intermediate-term results of the MILAN study (Abstract). *Circulation* 1998;**98**:I-780.
274.Grant MB, Wargovich TJ, Ellis EA, Caballero S, Mansour M, Pepine CJ. Localization of insulin growth factor I and inhibition of coronary smooth muscle cell growth by somatostatin analogues in human coronary smooth muscle cells: a potential treatment for restenosis? *Circulation* 1994;**89**:1511–17.
275.Lundergan CF, Foegh ML, Ramwell PW. Peptide inhibition of myointimal proliferaion by angiopeptin, a somatostatin analogue. *J Am Coll Cardiol* 1991;**17**:132B–136B.
276.Santoian EC, Schneider JE, Gravanis MB *et al.* Angiopeptin inhibits intimal hyperplasia after angioplasty in porcine coronary arteries. *Circulation* 1993;**88**:11–14.
277.Kent KM, Williams DO, Cassagneau B *et al.* Double blind, controlled trial of the effect of angiopeptin on coronary restenosis following balloon angioplasty. *Circulation* 1993; **88**:506 (Abstract).

278. Eriksen UH, Amtorp, Bagger JP *et al.* Angiopeptin Study Group. Continuous angiopeptin infusion reduces coronary restenosis following coronary angioplasty. *Circulation* 1993;**88**:594 (Abstract).
279. Emanuelsson H, Beatt KJ, Bagger JP *et al.* Long-term effect of angiopeptin treatment in coronary angioplasty: reduction of clinical events but not angiographic restenosis. *Circulation* 1995;**91**:1689–96.
280. Liu MW, Roubin GS, Robinson KA *et al.* Trapidil in preventing restenosis after balloon angioplasty in the atherosclerotic rabbit. *Circulation* 1990;**81**:1089–93.
281. Maresta A, Balducelli M, Cantini L *et al.* Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty: results of the randomized, double-blind STARC study. *Circulation* 1994;**90**:2710–15.
282. Serruys PW, Banz K, Darcis T *et al.* Results of a meta-analysis of trapidil, a PDGF inhibitor. A sufficient reason for a second look at the pharmacologic approach to restenosis. *J Invas Cardiol* 1997;**9**:505–12.
283. Galassi AR, Tamburino C, Nicosia A *et al.* A randomized comparison of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, versus aspirin in prevention of angiographic restenosis after coronary artery Palmaz–Schatz stent implantation. *Cath Cardiovasc Interv* 1999;**46**:162–8.
284. Ohno T, Gordon D, San H, Pompili VJ, Imperiale MJ, Nabel GJ, Nabel EG. Gene therapy for vascular smooth muscle cell proliferation after arterial injury. *Science* 1994;**265**:781–4.
285. Chapman G, Lim CS, Gammon RS *et al.* Gene transfer into coronary arteries of intact animals with a percutaneous balloon catheter. *Circ Res* 1992;**71**:27–33.
286. Morishita R, Gibbons GH, Kaneda Y, Ogihara T, Dzau VJ. Novel *in vitro* gene transfer method for study of local modulators in vascular smooth muscle cells. *Hypertension* 1993; **21**:894–9.
287. Mazur W, Ali NM, Geske RS *et al.* Lipofectin-mediated versus adenovirus-mediated gene transfer in vitro and *in vivo*: comparison of canine and porcine models systems. *Coronary Artery Dis* 1994;**5**:779–86.
288. Kahn ML, Lee SW, Dichek D. Optimization of retroviral vector-mediated gene transfer into endothelial cells in vitro. *Circ Res* 1992;**71**:1508–17.
289. French BA, Mazur W, Ali NM *et al.* Percutaneous transluminal *in vivo* gene transfer by recombinant adenovirus in normal porcine coronary arteries, atherosclerotic arteries, and two models of coronary restenosis. *Circulation* 1994;**90**:2402–13.
290. Epstein S, Siegall C, Biro S, Fu Y, Fitzgerald D, Pastan I. Cytotoxic effects of a recombinant chimeric toxin on rapidly proliferating vascular smooth muscle cells. *Circulation* 1991;**84**:778–87.
291. Pickering G, Weir L, Jekanowski J, Isner J. Inhibition of proliferation of human vascular smooth muscle cells using antisense oligonucleotides to PCNA. *J Am Coll Cardiol* 1992; **19**:165A (Abstract).
292. Pickering JC, Bacha P, Weir L, Jekanowski J, Nichols JC, Isner JM. Prevention of smooth muscle cells outgrowth from human atherosclerotic plaque by a recombinant cytotoxin specific for epidermal growth factor receptor. *J Clin Invest* 1993;**91**:724–9.
293. Biro S, Siegall CB, Fu YM, Speir E, Pastan I, Epstein SE. *In vitro* effects of a recombinant toxin targeted to the fibroblast growth factor receptor on rat vascular smooth muscle and endothelial cells. *Circ Res* 1992;**71**:640–5.
294. Casscells W, Lappi DA, Olwin BB *et al.* Elimination of smooth muscle cells in experimental restenosis: targeting of fibroblast growth factor receptors. *Proc Natl Acad Sci USA* 1992;**89**: 7159–63.
295. Chang MW, Barr E, Seltzer J *et al.* Cytostatic gene therapy for vascular proliferative disorders with a constitutively active form of the retinoblastoma gene product. *Science* 1995;**267**: 518–22.
296. von der Leyen H, Gibbons G, Morishita R *et al.* Gene therapy inhibiting neointimal vascular lesion: *in vivo* transfer of endothelial cell nitric oxide synthase gene. *Proc Natl Acad Sci* USA 1995;**92**:1137–41.
297. Nabel EG, Plautz G, Boyce FM, Stanley JC, Nabel GJ. Recombinant gene expression *in vivo* within endothelial cells on the arterial wall. *Science* 1989;**244**:1342–4.
298. Thompson MM, Budd JS, Eady SL *et al.* Endothelial cell seeding of damaged native vascular surfaces: prostacycline production. *Eur J Vasc Surg* 1992;**6**:487–93.
299. Thompson MM, Budd JS, Eady SL, James RFL, Bell PRF. A method to transluminal seed angioplasty sites with endothelial cells using a double balloon catheter. *Eur J Vasc Surg* 1993;**7**:113–21.
300. Baker JE, Nikolaychick V, Sahota H *et al.* Reconstruction of balloon injured artery with fibrin glue/endothelial cell matrix. *Circulation* 1994;**90**:1–492.
301. Ortu P, LaMuraglia GM, Roberts G, Flotte TJ, Hasan T. Photodynamic therapy of arteries. A novel approach for treatment of experimental intimal hyperplasia. *Circulation* 1992; **85**:1189–96.
302. Eton D, Borhani M, Spero K, Cvaa RA, Grossweiner L, Ahn SS. Photodynamic therapy. Cytotoxicity of aluminium phthalocyanin on intimal hyperplasia: acute and chronic. *J Vasc Surg* 1995;**19**:321–9.
303. Lamuraglia GM, Chandraekar NR, Flotte TJ, Abbott WM, Michaud N, Hasan T. Photodynamic therapy inhibition of experimental intimal hyperplasia: acute and chronic effects. *J Vasc Surg* 1994;**19**:321–9.
304. Tang G, Hyman S, Schneider JH, Giannotta SL. Application of photodynamic therapy to the treatment of atherosclerotic plaques. *Neurosurgery* 1993;**32**:438–43.
305. Mann GV, Spoerry A, Gray M, Jarashow D. Atherosclerosis in the Masai. *Am J Epidemiol* 1972;**95**:26–37.
306. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;**316**: 1371–5.
307. Schwartz RS, Topol EJ, Serruys PW, Sangiorgi G, Holmes DR. Artery size, neointima, and remodeling: time for some standards (Editorial). *J Am Coll Cardiol* 1998;**32**: 2087–94.
308. Kamiya A, Togawa T. Adaptative regulation of wall shear stress to flow change in the canine carotid artery. *Am J Physiol* 1980;**239**:H14–H21.
309. Zarins CK, Weisenberg E, Kolettis G, Stankunavicius R, Glagov S. Differential enlargement of artery segments in response to enlarging atherosclerosis plaques. *J Vasc Surg* 1988;**7**:386–94.

310.Langille BL, Bendeck MP, Keeley FW. Adaptations of carotid arteries of young and mature rabbits to reduced carotid blood flow. *Am J Physiol* 1989;**256**:H931–H9.
311.Langille BL. Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix. *J Cardiovasc Pharmacol* 1993;**21**:S11–S17.
312.Clarkson TB, Prichard RS, Morgan TM, Petrick GS, Klein KP. Remodeling of coronary arteries in human and nonhuman primates. *JAMA* 1994;**271**:289–94.
313.Zarins CK, Lu CT, Gewertz BL, Lyon RT, Rush DS, Glagov S. Arterial disruption and remodeling following balloon dilatation. *Surgery* 1982;**92**:1086–95.
314.Kakuta T, Currier JW, Haudenschild CC, Ryan TJ, Faxon DP. Differences in compensatory vessel enlargement, not intimal formation, account for restenosis after angioplasty in the hypercholesterolemic rabbit model. *Circulation* 1994;**89**:2809–15.
315.Kakuta T, Currier JW, Horten K, Faxon DP. Failure of compensatory enlargement, not neointimal formation, accounts for lumen narrowing after angioplasty in the atherosclerotic rabbit. *Circulation* 1993;**88**:I-619 (Abstract).
316.Pasterkamp G, Wensing PJW, Post MJ, Hillen B, Mali WPTM, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. *Circulation* 1995;**91**:1444–9.
317.Pasterkamp G, Borst C, Gussenhoven EJ *et al.* Remodeling of *de novo* atherosclerotic lesions in femoral arteries: impact on mechanism of balloon angioplasty. *J Am Coll Cardiol* 1995; **26**:422–8.
318.Kovach JA, Mintz GS, Kent KM *et al.* Serial intravascular ultrasound studies indicate that chronic recoil is an important mechanism of restenosis following transcatheter therapy. *J Am Coll Cardiol* 1993;**21**:484A (Abstract).
319.Mintz GS, Kenneth MK, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses: an intravascular ultrasound study. *Circulation* 1997;**95**:1791–8.
320.Kimura T, Kaburagi S, Tashima Y, Nobuyoshi M, Mintz GS, Popma J. Geometric remodeling and intimal regrowth as mechanisms of restenosis: observations from serial ultrasound analysis of restenosis (SURE) trial. *Circulation* 1995;**92**:I-76 (Abstract).
321.Libby P, Schwartz D, Brogi E, Tanaka H, Clinton SK. A cascade model for restenosis. A special case of atherosclerosis progression. *Circulation* 1992;**86**(Suppl. III):III-47–III-52.
322.Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. *N Engl J Med* 1994;**330**:1431–8.
323.Isner JM. Vascular remodeling: honey, I think I shrunk the artery. *Circulation* 1994;**89**:2937–41 (Editorial).
324.Mogford JE, Davies GE, Platts SH, Meininger GA. Vascular smooth muscle alpha(v)beta(3) integrin mediates arteriolar vasodilatation in response to RGD peptides. *Circ Res* 1996; **79**:821–6.
325.Lafont A, Guzman LA, Whitlow PL, Goormastic M, Cornhill JF, Chisolm GM. Restenosis after experimental angioplasty. Intimal, medial, and adventitial changes associated with constrictive remodeling. *Circ Res* 1995;**76**:996–1002.
326.Staab ME, Srivatsa SS, Lerman A *et al.* Arterial remodeling after percutaneous injury is highly dependent on adventitial injury histopathology. *Int J Cardiol* 1997;**58**:31–40.
327.Shi Y, Pieniek M, Fard A, O'Brien J, Mannion JD, Zalewski A. Adventitial remodeling after coronary arterial injury. *Circulation* 1996;**93**:340–8.
328.Sangiorgi G, Taylor AJ, Farb A *et al.* Histopathology of post-percutaneous transluminal coronary angioplasty remodeling in human coronary arteries. *Am Heart J* 1999;**138**:681–7.
329.Kuntz LL, Anderson PG, Schroff RW, Roubin GS. Sustained dilatation and inhibition of restenosis in pig femoral artery injury model. *Circulation* 1994;**90**:I-197 (Abstract).

Part IIIb

Specific cardiovascular disorders: Acute ischemic syndromes and acute myocardial infarction

John A Cairns and Bernard J Gersh, Editors

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

30 Acute non-ST-segment elevation coronary syndromes: unstable angina and non-ST-segment elevation myocardial infarction

Pierre Theroux, John A Cairns

Introduction and historical perspective

The definition of acute myocardial ischemic syndromes as well as their management has dramatically changed over the past two decades. Not long ago, clinical acute myocardial ischemia was classified as stable angina, Q and non-Q wave myocardial infarction, and unstable angina. The latter encompassed all the highly heterogeneous manifestations of ischemia intermediate between stable angina and myocardial infarction. Fowler proposed the terminology of unstable angina in 1971,[1] following half a century of retrospective observations on the premonitory symptoms of myocardial infarction and of prospective studies of the clinical outcomes. The importance of risk stratification became recognized, at that time focusing on ischemic chest pain patterns and on ST-T abnormalities. A variety of interventions were also attempted to interrupt the disease process and prevent death or myocardial infarction. One of these studies by Wood was prematurely interrupted because of the observation of a greater efficacy of oral anticoagulants versus no anticoagulants observed in a few patients.[2] The term "acute coronary syndromes" was introduced in 1985 by Fuster to highlight the specific pathophysiologic mechanisms that distinguish unstable angina and myocardial infarction from stable coronary artery disease.[3] Pathologic studies by Michael J Davies[4,5] and by Erling Falk[6,7] had then documented the presence of intracoronary thrombus on a ruptured plaque in 95% of patients with unstable angina suffering sudden cardiac death. Thrombi of various ages were described.[6] They could be at multiple sites, typically occurring on lesions of only moderate severity, and were often associated with platelet aggregates in small intramyocardial arteries and microscopic foci of necrosis.[4,5] DeWood documented that an occlusive thrombus was consistently present in angiograms obtained very early after the onset of myocardial infarction.[8] The analyses of angiograms in unstable angina then shifted from descriptions of the severity and extent of atherosclerosis, which could not distinguish unstable angina from stable angina, to morphologic descriptions of the culprit lesion. Complex plaques with fissures and ruptures and partially occlusive thrombi were identified and confirmed by angioscopic studies. The concept of the active vulnerable plaque was established, opening a new era of advances in cell biology and clinical investigation. The science was advanced and oriented by clinical trials that reached a level of unprecedented sophistication, providing the setting for the current evidence-based approach to clinical medicine.

New dimensions and definitions

Unstable angina has achieved the maturity of a syndrome with a well-defined spectrum of clinical manifestations, epidemiology and prognosis, pathophysiology, and options for effective treatment. Delineation of the syndrome has led to unique research opportunities for better understanding of atherosclerosis and mechanisms of plaque activation, and potential patient management. The definition has evolved to become practical by incorporating algorithms for rapid diagnosis, risk stratification, patient orientation, and therapy.

The diagnosis of an acute coronary syndrome implies recognition of a change in the pattern of ischemic chest pain – or equivalent symptoms – to more severe, in the absence of evidence of an extracoronary cause for the increased severity. Thus, the diagnosis of an acute coronary syndrome is first clinical. Current nomenclature has been developed to provide clinicians with a logical framework within which to categorize patients who present with a constellation of clinical symptoms that are compatible with acute myocardial ischemia, and to guide early diagnosis and management. The nomenclature is also helpful for ensuring consistency in clinical trials and in epidemiologic studies. Hence, the acute coronary syndromes are considered to encompass unstable angina, non-ST-segment elevation (non-Q wave) myocardial infarction (NSTEMI), and ST-segment elevation (Q wave)

myocardial infarction (STEMI). The designation of possible acute coronary syndrome (ACS) is useful when patients first present, at a point where there is uncertainty about the likelihood of the presence of myocardial ischemia. As ECGs are done and biochemical cardiac markers are assessed over the next few hours, the patient may eventually be characterized as having unstable angina, non-Q wave MI or Q wave MI. Unstable angina has been traditionally classified as new onset angina, increasing angina, rest angina, and recurrent ischemia after myocardial infarction (Table 30.1).[9] Braunwald classified unstable angina by severity of symptoms and clinical circumstances (Table 30.2).[10] Details of timing and duration of pain have been included in these classifications to optimize their specificity. Thus, classification as new onset angina and increasing angina requires a component of severity, and rest pain a component of duration.

Table 30.1 Clinical presentation of ACS

Rest angina	Angina occurring at rest and prolonged, usually >20 minutes
New onset angina	New onset angina of at least CCS class III severity
Increasing angina	Angina that has become distinctly more frequent, longer in duration, or lower in threshold (that is, increased by greater than or equal to 1 CCS class to at least CCS class III severity)
Early post-MI ischemia	Ischemic chest pain recurrent within 30 days after MI

Source: adapted from Braunwald *et al*[24]

The clinical management first requires a search for ST-segment elevation, the presence of which or a new left bundle branch block, mandates consideration for immediate reperfusion therapy.[10] In the absence of ST-segment elevation, the working diagnosis is non-ST-segment elevation acute coronary syndrome.[11] Table 30.1 summarizes the clinical manifestations, Table 30.2 the Braunwald classification, and Figure 30.1 an early and highly practical diagnostic scheme. Most ST-segment elevation will evolve to a Q wave myocardial infarction. Most non-ST-segment elevation ACS will eventually be diagnosed as unstable angina or non-ST-segment elevation MI according to the absence or presence of an elevation of the various markers of cell necrosis. Accordingly, all patients with suspect symptoms should be evaluated clinically and should have a 12-lead ECG as soon as possible – immediately if ischemic pain is present. The availability of troponin T and troponin I has increased the sensitivity of the diagnosis of myocardial infarction and has sharpened the distinction between unstable angina and myocardial infarction.[12] The troponins are highly sensitive and specific markers of cell damage and permit the diagnosis of cell necrosis and myocardial infarction in up to 30% of patients who would otherwise be diagnosed as having unstable angina based on normal CK-MB blood values.[13]

The new insights into disease have modified previous statistics on the incidence and prognosis of unstable angina versus myocardial infarction. Thus myocardial infarction is more frequently diagnosed with the use of the troponins. However, the non-ST-segment elevation MI is often small, does not affect ejection fraction, and is considered and managed more like unstable angina. Epidemiological data may include ST- and non-ST-segment elevation MI in a single category, whereas clinical data reflect on one hand STEMI and, on the other, unstable angina and NSTEMI.

Table 30.2 Braunwald classification of unstable angina

	Clinical circumstances		
Severity	A: Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary unstable angina)	B: Develops in absence of extracardiac condition (primary unstable angina)	C: Develops within 2 weeks after acute myocardial infarction (postinfarction unstable angina)
New onset of severe angina or accelerated angina: no rest pain	IA	IB	IC
Angina at rest within past month but not within preceding 48 h (angina at rest, subacute)	IIA	IIB	IIC
Angina at rest within 48 h (angina at rest, acute)	IIIA	IIIB	IIIC

Source: reproduced with permission from Braunwald[10]

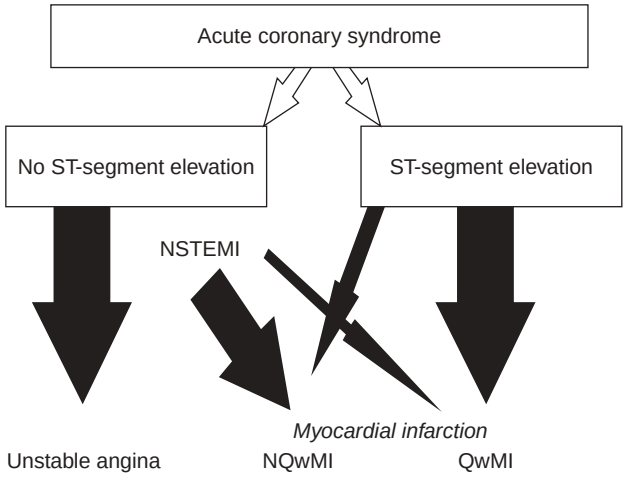


Figure 30.1 Nomenclature of acute coronary syndromes (ACS). The spectrum of clinical conditions that range from unstable angina to non-Q wave AMI and Q wave AMI is referred to as acute coronary syndrome. Patients with ischemic discomfort may present with or without ST-segment elevation on the ECG. Most patients who present with non-ST-segment elevation ACS will eventually be classified as having unstable angina or non-Q wave MI. The distinction between these two diagnoses is ultimately made based on the presence or absence of a cardiac marker detected in the blood. Only a minority of patients with non-ST-elevation MI will develop Q wave MI. Most patients with ST-segment elevation will evolve to develop Q wave MI. Adapted with permission from Antman and Braunwald.[11]

Incidence and prognosis

It is estimated that the number of consultations for chest pain in emergency departments in the USA approximates 5 500 000 yearly.[14] In the 1990s, hospital discharges for unstable angina exceeded 700 000 annually, about equal to those for MI, one third of which were of the non-Q wave type.[15,16] In 1996, a total of nearly 1 500 000 patients were hospitalized for unstable angina or NSTEMI, exceeding the number of hospitalizations for STEMI.

There is evidence that the incidence of acute coronary syndromes defined as unstable angina and non-ST-segment elevation has been increasing, whereas that of ST-segment elevation MI has been decreasing. Epidemiologic data using the WHO MONICA criteria for the diagnosis of Q wave myocardial infarction from Halifax county (Canada),[17] Turku (Finland), Oxfordshire (England),[18] Denmark,[19] the Netherlands,[20] France, and northern Italy showed that the mortality rates from Q wave MI have decreased by more than 30% between 1975 and 1995, two thirds of the decline being attributable to reduced incidence and one third to decreased hospital mortality. These decreases were observed in women as well as men.

On the other hand, the number of patients hospitalized for a non-ST-segment ACS exceeds that of ST-segment elevation MI and statistics suggest that the magnitude of the excess is increasing. In the ENACT registry of 3092 patients from 29 European countries performed in the mid-1990s, the admission diagnosis was unstable angina/NSTEMI in 46%, myocardial infarction in 39%, and a suspected ACS in 14% (ratio 1·2 : 1) and is similar across Europe.[21] The Global Registry of Acute Coronary Events (GRACE) extended the data collection to 10 693 patients recruited between 1999 and 2001 from North and South America, Australia, New Zealand, and Europe. Two thirds of admitted patients had unstable angina/non-ST-segment elevation ACS, and one third STEMI.[22]

A large epidemiologic study of 5 832 residents from metropolitan Worcester, Massachusetts has shown that the incidence of Q wave MI progressively decreased between 1975/78 (incidence rate = 171/100 000 population) and 1997 (101/100 000 population).[23] By contrast, the incidence of non-Q wave MI has progressively increased during the same period (62/100 000 population in 1975/78 and 131/100 000 population in 1997). While the hospital mortality of Q wave MI has progressively declined from 24% in 1975/78 to 14% in 1997, that of non-Q MI has remained constant at 12%. These trends persisted after adjusting for potentially confounding prognostic factors. Therefore, despite impressive declines in the incidence of Q wave MI and the inhospital and long-term mortality, the incidence of non-Q wave MI has been increasing with unchanged mortality rates compared to about 22 years ago.

The shifts in the clinical manifestations of acute coronary syndromes correspond to changes in patterns of practice and referral in accordance with the emphasis on primary and secondary prevention and earlier intervention. Public education programs may also favor early diagnosis, referral, and treatment. Figure 30.2 describes the distribution of admission diagnoses in the Coronary Care Unit of the Montreal Heart Institute, a referral center, over the past decade. There is a major shift in the distribution of admissions from STEMI to non-ST-segment elevation ACS, as well as an increase in the total number of admissions.

Natural history

Patients admitted for an ACS experience 10 times more events in the short term than patients with stable angina and several-fold more than individuals with high cholesterol values and no known coronary disease. The natural history of unstable angina/NSTEMI is determined by the severity and extent of coronary artery disease, the presence of comorbid conditions, age, and the ischemic pain pattern which may range from the simple onset of new angina, to profound and prolonged episodes of angina at rest,

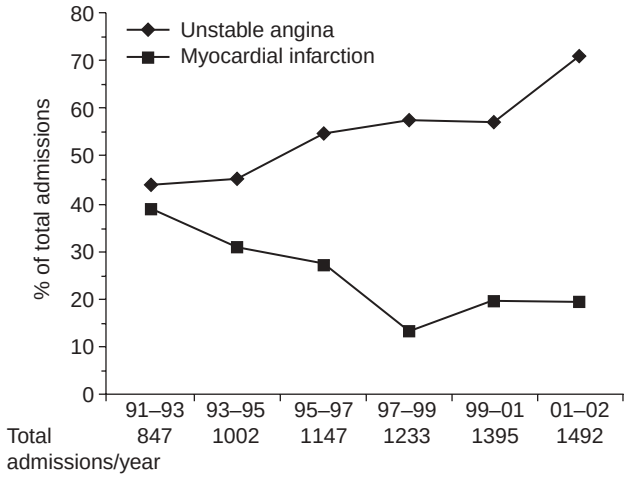


Figure 30.2 This figure describes the distribution of admission diagnosis in the Coronary Care Unit of the Montreal Heart Institute, a referral center, over the past decade. The total number of patients admitted through the past decade has nearly doubled. A major shift has occurred, however, in the distribution of ST-segment elevation versus non-ST-segment elevation ACS. Patients with a non-ST-segment elevation ACS now represent more than two thirds of patients admitted in the CCU, while the incidence of ST-segment elevation MI has decreased from 40% to 20% of admissions. This phenomenon is observed in most hospitals in industrialized countries.

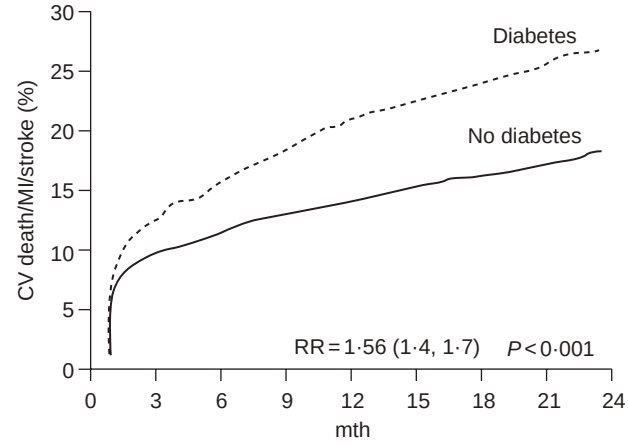


Figure 30.3 Kaplan-Meier event curves for diabetic and non-diabetic patients for total cardiovascular death, MI, stroke, and new onset of congestive heart failure for a 24 month follow up period after an episode of non-ST-segment elevation ACS. Data from the OASIS Registry study reproduced with permission from Malmberg *et al*.[25]

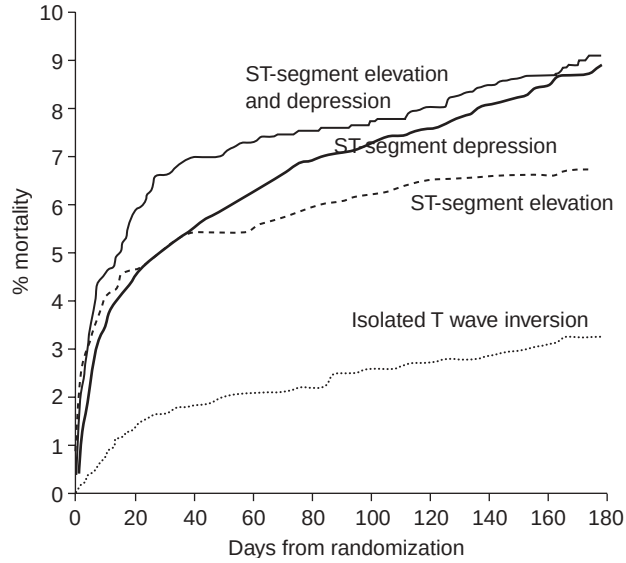
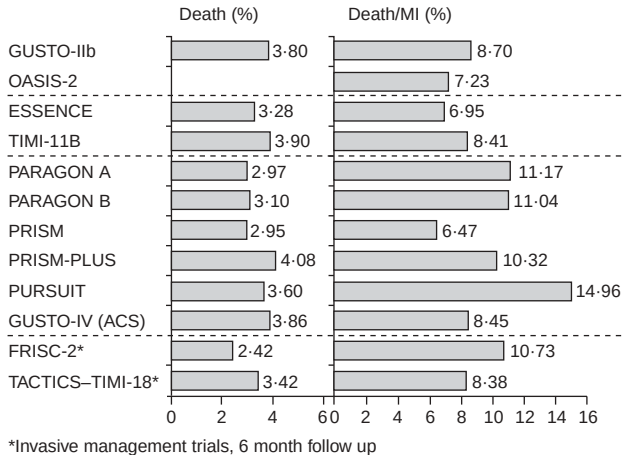


Figure 30.4 Kaplan-Meier estimates of probability of death at 6 months by ECG changes at admission. The event rate was highest inhospital in patients with ST-segment elevation MI. However, by 6 months, mortality in patients with ST depression exceeded that of patients with ST elevation. Data from the GUSTO-II study, reproduced with permission from Savonitto *et al*.[26]

accompanied by LV dysfunction and resistance to medical therapy.[24] The risk of the disease is highest in the first few days, decreases over the following weeks and months, and eventually becomes similar to the prognosis of patients with stable angina. The long-term prognosis is influenced by the severity of the underlying disease. In the OASIS registry, the incidence of events was 10% at one month and increased steadily in the following 2 years to reach more than 20% after 24 months (Figure 30.3), higher in diabetic patients and in patients with previously known coronary artery disease.[25] In the GUSTO-II study, the inhospital mortality rate was highest, as expected, in patients with STEMI; however, increasing mortality during follow up in patients with ST-segment depression eventually exceeded that of patients with ST elevation after 6 months, reaching 8·7% as against 6·8% (Figure 30.4).[26] The empirical concept that NSTEMI represents an unresolved acute coronary syndrome at risk of being completed by a recurrent MI may therefore be partially true in many patients, and is likely explained by an underlying disease process that remains active. This is supported by data showing that markers of inflammation and of activation of coagulation may remain elevated months past the acute phase of an episode of acute coronary syndrome.[27,28] It is difficult to evaluate the effect of advances in treatment on the natural history of unstable angina/NSTEMI, since the diagnostic criteria have evolved concurrently. Recent randomized trials have shown an impressive decrease in MI and death. Prior to the routine prescription of bed rest, nitrates and β blockers for unstable angina, the rate of MI after one month was in the range of 40% and of death, 25%.[29] By the 1970s these rates had fallen to about 10%

and 2%. In 1979–80, a study of all patients hospitalized with unstable angina in Hamilton, Canada over a period of one year noted inhospital and 1 year mortalities of 1·5% and 9·2% respectively.[30] By the time of the re-evaluation of heparin in the late 1980s, study inclusion criteria had shifted toward patients at somewhat higher risk, and some trials included patients with NSTEMI. In these trials, the rates of the composite outcome of death or non-fatal myocardial infarction by 5 days were about 10%.[31,32] These rates fell to the range of 4% with the addition of heparin to aspirin, and fell further with enoxaparin and the glycoprotein IIb/IIIa antagonists. The event rates at 30 days in recent trials with new antithrombotic therapies and an invasive management strategy are shown in Figure 30.5.[33–44]



*Invasive management trials, 6 month follow up

Figure 30.5 Rates of death and of death or myocardial infarction in contemporary trials that evaluated new antithrombotic drugs and routine invasive treatment strategy in patients with non-ST-segment ACS. Data are the average of events in the intervention and control groups. The interventions resulted in a reduction in rates of death ranging from −5% to 36% and in rates of death or myocardial infarction ranging from −8% to 27%.[33–44]

Risk stratification

A gradient in risk exists in ACS from relatively benign to severe; accordingly, patient management should be guided by clinical risk stratification. The high-risk features for death and ischemic events present at admission, or developing rapidly, have been identified in many registries and clinical trials. Registry studies look at a broad spectrum of patients with acute chest pain, while clinical trials enroll more selected populations predefined by entry criteria in a specific study. Recent registries have focused mainly on regional differences in application of drug therapy and interventional procedures,[21,22,25] whereas trials have evaluated specific predictors, biased by entry criteria of the trials. Nevertheless, important common determinants of risk have been identified by the two approaches. These include older age, presence of ST-segment shifts, elevation of the cardiac markers, and recurrent ischemia (Table 30.3). Ejection fraction is not available in the majority of patients but is known to be a potent predictor of prognosis in all manifestations of coronary artery disease. Cardiac risk factors are in general poor predictors of acute risk in patients with an ACS but are useful for the evaluation of the likelihood of coronary artery disease and its prognosis.[45] The rate of the progression of the severity of chest pain is clinically recognized as suggesting a more rapidly evolving coronary stenosis. There is a gradient in risk from new onset, to crescendo, to prolonged rest angina.[9] Women and the elderly are more likely to have atypical presentations. The prognosis for patients who have atypical symptoms at the time of their infarction can be worse than that of patients with more typical symptoms.[46] Women enrolled in clinical trials are in general older than men and have more risk factors such as diabetes and hypertension. The proportion of women with ST-segment elevation is less than in men but their prognosis is then worse. Women who present with a non-ST-segment elevation acute syndrome less often have an elevation of the cardiac markers and have a better prognosis. The odds for infarction and death in the GUSTO-IIb study in women compared to men was 0·65 (95% CI 0·49–0·87; $P = 0·003$),[47] and in the non-invasive strategy arm of the FRISC-II study 0·64 (95% CI 0·43–0·97; $P = 0·03$).[48] Coronary angiography in general revealed less severe coronary artery disease for women than for men.[48] Diabetes is present in 20–25% of patients

Table 30.3 Determinants of prognosis

Determinants of short-term prognosis	
Confirming the diagnosis of ACS	Clinical pattern of pain
	ST-T ischemic changes
	Troponin T or I elevation
	Hemodynamic or electrical instability
Other major determinants	Older age
	Left ventricular dysfunction
	Recent myocardial infarction
	Recurrent ischemia
	Diabetes
	Previous myocardial infarction
	Previous CABG
	Previous aspirin use
	Depression
Determinants of long-term prognosis	
	Left ventricular dysfunction
	Diabetes
	Extensive coronary artery disease
	Strongly positive provocative testing
	Elevated CRP levels
	Depression

enrolled in trials in ACS. Diabetes carries a major negative impact on morbidity and mortality in the setting of ACS and after percutaneous interventions and coronary artery bypass grafting. In the OASIS registry, diabetes was an important and independent predictor of 2 year mortality (RR 1·57; 95% CI 1·38–1·81; $P < 0·001$), as well as of cardiovascular death, new myocardial infarction, stroke, and new congestive heart failure.[25] The risk of death in diabetic women was significantly higher than the risk in diabetic men (RR 1·98 and 1·28 respectively). Diabetic patients without prior cardiovascular disease had the same event rates for all outcomes as non-diabetic patients with previous vascular disease (see Figure 30.3). The impact of depression on prognosis is more and more recognized. In a study of 430 patients with a non-ST-segment elevation ACS, depression predicted the end point of cardiac death or non-fatal MI, with an adjusted odds ratio of 6·73 (95% CI 2·43–18·64; $P < 0·001$) after controlling for other significant prognostic factors that included baseline ECG, left ventricular ejection fraction, and number of diseased coronary vessels.[49]

The 12-lead ECG and the troponin T or I blood levels have become powerful instruments for risk evaluation. They are now part of the entry criteria in clinical trials and of recommended treatment algorithms. Troponin elevation in the blood follows the ischemic insult by 6 hours, as does CK-MB. Myoglobin serum concentration rises earlier, within 2 hours after the onset of pain, and peaks within 4–6 hours. Myoglobin can be useful as an early and sensitive marker of necrosis, but it is non-specific, mandating confirmation of the cardiac origin with the CK-MB or troponin levels. Although failure to detect a rise of myoglobin after 2–4 hours rules out an infarction, the prognostic value with regard to recurrent coronary events in patients with non-ST-segment elevation ACS has been less well characterized.

The presence of ST-segment shifts and/or the elevation in troponin T or I levels confirm the working diagnosis of a non-ST-segment elevation ACS, identify the patient at high risk for an ischemic event, and are useful for immediate patient orientation and management by identifying those who will benefit most from the new treatment strategies that include enoxaparin, the Gp IIb/IIIa antagonists and revascularization procedures. The absence of such changes does not rule out the diagnosis, but places the patient in a more favorable risk category. Patients with an indefinite but possible diagnosis of an ACS need to be observed for the clinical evolution, changes on serial ECGs, and elevation of troponin levels after 8–12 hours.

Prognostic value of troponin levels

In contrast to CK-MB and myoglobin, cardiac troponins T and I are usually not detectable in the peripheral blood and, thus, provide a more distinct and sensitive marker of minute cardiomyocyte damage. The damage detected is usually of ischemic origin but may be due to non-ischemic myocardial injury, such as myocarditis, severe heart failure, pulmonary embolism, trauma or cardiotoxic agents. Multiple studies since the original publication by Hamm *et al* have validated the prognostic value of an elevation in the blood troponin levels.[50]

Figure 30.6 depicts the results of one trial of patients enrolled in a clinical trial[18] and of one study of patients consulting in the emergency department for acute chest pain;[18] the 30 day rate of death or myocardial infarction was highest in patients with elevated troponin T or troponin I levels, intermediate in patients with ST-segment depression, and lowest in patients with normal troponin levels. The higher the elevation in troponin levels,[51] the worse the prognosis, but even small elevations are associated with a significantly impaired prognosis.[52] In the FRISC study, among patients with a non-ST-segment elevation ACS, the risk of myocardial infarction or cardiac death at 6 months was respectively 4·3%, 10·5%, and 16·1% in patients within the first, second, and third tertile of maximal elevation of troponin during the first 24 hours.[53]

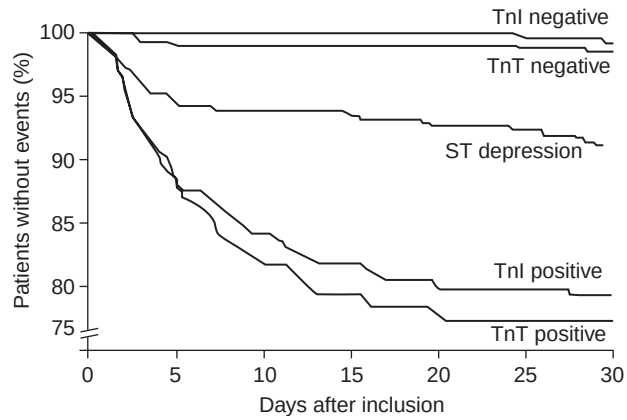


Figure 30.6 Risk of death or non-fatal myocardial infarction during 30 days of follow up by troponin T (TnT) and I (TnI) levels, elevation (positive) or no elevation (negative), and ST-segment depression on the ECG. The risk for myocardial infarction and death increases with increasing serum troponin concentrations and may be 20% in 30 days and 25% within 6 months in patients with the highest troponin levels. Reproduced with permission from Hamm *et al.*[13]

Three meta-analyses were performed and provided results in the same direction. The first, including 12 reports with troponin T and nine with troponin I of patients with unstable angina, demonstrated risk ratios for occurrence of myocardial infarction at 30 days of 4·2 (95% CI 2·7–6·4; $P < 0·001$) for troponin I and of 2·7 (95% CI 2·1–3·4; $P < 0·001$) for troponin T.[54] The second included 18 982 patients with unstable angina from 21 studies and showed odds of death or myocardial infarction at 30 days of 3·44

(95% CI 2·94–4·03; $P < 0·00001$) for the total population of troponin positive patients, 2·86 (95% CI 2·35–3·47; $P < 0·0001$) for patients with ST-segment elevation, 4·93 (95% CI 3·77–6·45; $P < 0·0001$) for patients with non-ST-segment elevation, and 9·39 (95% CI 6·46–13·67; $P < 0·0001$) for patients with unstable angina.[55] The third meta-analysis included seven clinical trials and 19 cohort studies. The odds of mortality among 11 963 patients with positive troponin T or I was 3·1 (5·2% *v* 1·6%). The discriminative value of elevated troponin levels was greater in cohort studies than in clinical trials, 8·4% *v* 0·7% (OR 8·5) for troponin I, and 11·6% *v* 1·7% (OR 5.1) for troponin T.[56]

Determination of troponin levels has many utilities. Beyond providing a highly sensitive and specific test for the diagnosis of myocardial infarction, any elevation provides important prognostic information in acute coronary syndromes. Patients with troponin elevation are also more likely to profit from therapy with a Gp IIb/IIIa antagonist,[57] from a low molecular weight heparin,[58] and from interventional procedures.[59] All evidence converges to relate the elevation of troponin to an ongoing intracoronary thrombotic process, associated with small foci of myocardial necrosis, likely related to distal embolization of thrombotic material originating from the culprit lesion.

Prognostic value of the 12-lead ECG

Current information on the prevalence of ECG abnormalities is difficult to obtain, in part because ECG criteria are often used to define eligibility for clinical studies and the use of heterogeneous inclusion criteria among trials. In a report by Langer *et al* on 135 patients hospitalized with unstable angina without evidence of acute myocardial infarction, ST-segment depression was found in 25% of patients, ST-segment elevation in 16%, both in 4%, and none in 55%.[60] In this study, ST-segment depression and the magnitude of depression were both associated with a higher prevalence of multivessel and left main disease.[60] In the TIMI-3 Registry of 1416 patients enrolled because of unstable angina or non-Q wave MI, ST-segment deviation ≥ 1 mm was present in 14·3% of patients, isolated T wave inversion in 21·9%, and left bundle branch block (LBBB) in 9·0%. By 1 year follow up, death or MI occurred in 11% of patients with ST-segment depression, 6·8% of patients with isolated T wave inversion, and in 8·2% of those with no ECG changes. ST-segment depression 0·5 mm or more and LBBB were significant predictors of death and MI, with rates of 16·3% and 22·9%, respectively.[61] The ECG is not infrequently confounded by LBBB, left ventricular hypertrophy, paced rhythm or other derangements. In the PARAGON-A study, these confounders were associated with near doubling in the 1 year mortality rates (12·6% *v* 6·5%).[62] Among the 12 142 patients enrolled in the GUSTO-II trial with symptoms at rest within 12 hours of admission and ischemic ECG changes, 22% had T wave inversion, 28% ST-segment elevation, 35% ST-segment depression, and 15% ST-segment elevation and depression.[26] The 30 day rates of death or myocardial re-infarction were 5·5%, 9·4%, 10·5%, and 12·4% respectively ($P < 0·001$). The cumulative rates of death in this study are shown in Figure 30.4.

There exists therefore a gradient of increasing risk of death or myocardial infarction in hospital and up to 1 year, from non-specific ECGs to T wave inversion to ST-segment depression including confounding ST-T changes. Such a gradient exists from ST-segment depression $>0·05$ mm, to >1 mm, to >2 mm, to ≥ 2 mm, and to depression in more than two contiguous leads.[62] The prognostic value of ST-segment depression extends to 4 years following hospital discharge.[63] Special attention is required for patients showing deep T wave inversions in leads V1 through V6 and in leads 1 and AVL on the admission or subsequent ECGs; the changes are quite specific for the presence of significant disease in the proximal left anterior coronary artery disease and are predictive of a high risk of progression to an infarction that can be massive.[64]

The importance of recording the 12-lead ECG during chest pain must be emphasized. The detection of ST-segment depression during pain has diagnostic and prognostic value.[65] Occasionally, transient ST-segment elevation will be detected associated with a critical dynamic coronary artery stenosis caused by spasm or thrombus formation. ST-segment shifts during pain occurring on medical management indicate refractory ischemia, an end point commonly used in clinical trials. Refractory ischemia predicts near tripling of adjusted 1 year mortality.[66]

Risk scores

Prognosis can be predicted by various clinical, ECG, and laboratory parameters. Accordingly, predictive models have been derived from various databases by applying multiple regression analyses to identify the independent predictors of prognosis. The results of such analyses are influenced by the characteristics of the test populations and by the baseline data collected. From the population of 9461 patients enrolled in the PURSUIT trial, more than 20 parameters were predictive of mortality and the composite end point of death or MI, the most important being age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure, and cardiac enzyme elevation.[67]

The TIMI risk score has gained popularity, since it can be readily and simply assessed at admission or shortly thereafter. It was derived from the control cohort of patients in the TIMI-11B study.[68] The seven independent predictors of death, myocardial infarction or recurrent ischemia that were identified are shown in Table 30.4. Their mathematical

Table 30.4 Components of the TIMI risk score

Age 65 yr
At least three risk factors for CAD
Significant coronary stenosis (for example, prior coronary stenosis 50%)
ST-segment deviation
Severe anginal symptoms (for example, two anginal events in last 24 h)
Use of aspirin in last 7 days
Elevated serum cardiac markers

Source: Antman *et al*[68]

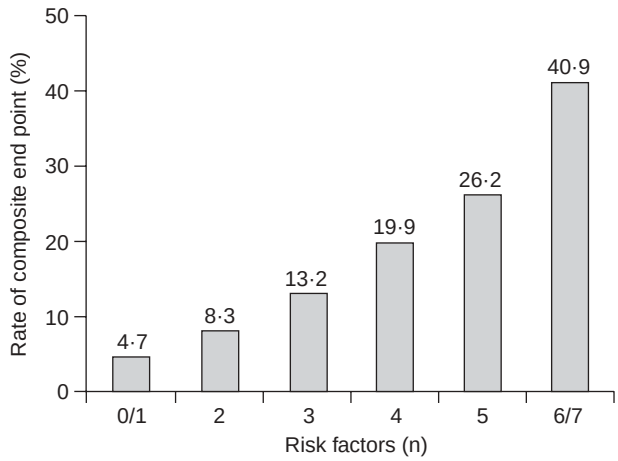


Figure 30.7 Original validation of the TIMI risk score. Rates of all-cause mortality, myocardial infarction, and severe recurrent ischemia prompting urgent revascularization through 14 days by TIMI risk score at admission. The score discriminates a gradient in risk from 5% to 40%. Reproduced with permission from Antman *et al*.[68]

addition provided a seven-point score that could discriminate a 10-fold difference in risk through 14 days (Figure 30.7). The score was subsequently validated in other populations including PRISM-PLUS[69] and TACTICS.[44] Greater treatment benefit was observed with enoxaparin treatment,[68] Gp IIb/IIIa antagonists[69] and reperfusion procedures[44] in patients with higher scores, ST-segment shifts, and elevated troponin levels.

Inflammation markers

Blood levels of numerous markers of inflammation are elevated in patients with an ACS, including acute phase proteins (C-reactive protein, serum amyloid A protein, fibrinogen), pro-inflammatory cytokines (interleukin-6, TNF-α, interleukin-18), soluble adhesion molecules (sVCAM-1, sICAM-1, E-selectin, P-selectin), and matrix metalloproteinases. C-reactive protein (CRP) is a non-specific but highly sensitive marker of an inflammatory state. Interleukin-6, which is induced by TNF-α, IL-1, IL-18, platelet derived growth factor, antigens, and endotoxins, is the main stimulus for the production of CRP by the liver. CRP has a half life of 19 hours and can be assessed in the blood by tests with high sensitivity. Many epidemiologic studies in individuals with or without known cardiovascular disease have consistently shown a 3- to 3·5-fold increase in the risk of cardiac events in the highest distribution quartile. The predictive value is additive to that of cholesterol levels.[70] CRP levels are elevated in myocardial infarction. The elevation preceded that of markers of myocardial necrosis in patients who had previous unstable angina, but not in patients who had no preceding angina.[71] Levels are elevated in 40–50% of patients with a non-ST-segment elevation acute coronary syndrome and remain high for months after the acute phase. These elevated levels are associated with high rates of late cardiac events, including death/MI/recurrent ischemia at 12 months,[72] death/MI at 6 months[73,74] and up to 2 years,[75] and death at 36 months.[76] The predictive value for occurrence of early events has been less consistent. In the TIMI-11A study of 630 patients with a non-ST-segment elevation ACS, the risk of death at 14 days was highest with elevated troponin T and CRP, intermediate when either marker was elevated, and lowest when both were normal (CRP $< 1{\cdot}55$ mg/l).[77] In the CAPTURE trial of 447 patients, CRP levels >10 mg/l did not predict mortality or myocardial infarction at 72 hours in contrast to elevated troponin T levels, but did predict death or MI at 6 months (18·9% compared to 9·5%), independently of the troponin status (Figure 30.8).[74]

The assessment of CRP levels is not currently part of the recommendations of various guidelines. The cut points that best predict early and late prognosis as well as the ideal timing for blood sampling at admission or hospital discharge remain to be better defined. Moreover, the impact on risk evaluation of treatment with statins, which reduce the CRP levels and the prognostic significance of elevated levels,[78] and of aspirin, which reduces the prognostic value,[79] need additional characterization. Of interest, PCI or CABG appear to have little effect on the 1 year excess of recurrent ischemic events in patients with a non-ST-segment elevation ACS and high CRP levels. Elevated CRP levels are associated with increased risk of restenosis and of acute complications after PCI,[80,81] and with an increased risk of new ischemic events up to 8 years after CABG.[82]

Pathophysiology

This section will focus on the mechanisms of acute coronary syndromes that are the most relevant with respect to management. Interested readers are referred to more exhaustive

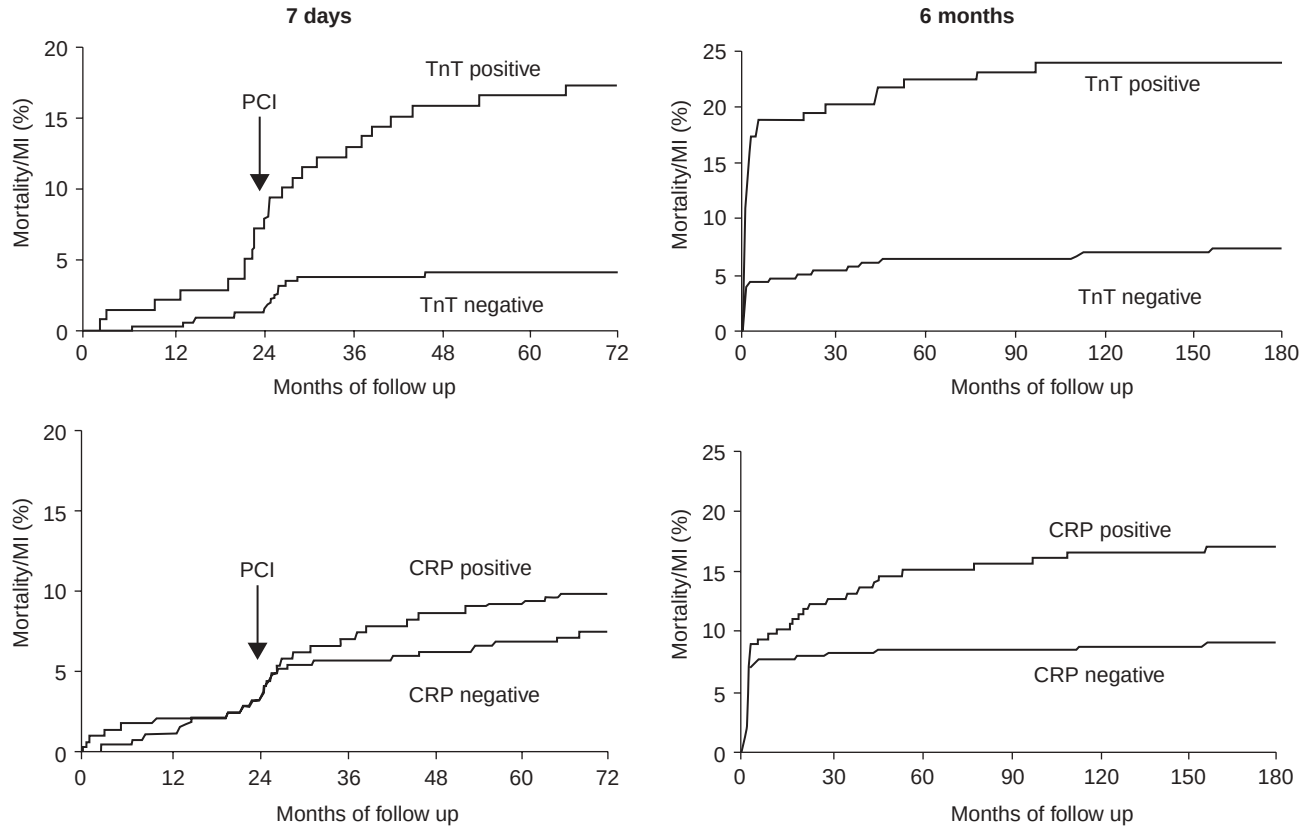


Figure 30.8 Rates of death or MI at 7 days (top left panel) and at 6 months (top right panel) by troponin T (TnT) status (top panels), and C-reactive protein (CRP) status (lower panels) at admission. PCI was performed in all patients 20–24 hours after admission. The risk of death or MI was especially high in TnT positive patients within the first 7 days and increased only slightly thereafter. The event rates were not statistically different for CRP negative patients and CRP positive patients after 7 days (including the coronary intervention) (10·3% *v* 8%; $P = 0{\cdot}41$). During the 6 month follow up period, however, the event rate curves for CRP positive and CRP negative patients continually diverged. There were significant differences both after 30 days (14·1% *v* 7·6%; $P = 0{\cdot}03$) and especially at 6 months (18·9% *v* 9·5%; $P = 0{\cdot}003$). The excess events in CRP-positive patients were related to higher incidence of MI (13·5% *v* 8·4%; $P = 0{\cdot}16$) and of mortality rate (5·4% *v* 1·1%; $P = 0{\cdot}005$). Reproduced with permission from Heeschen *et al.*[74]

reviews.[83–85] Figure 30.9 outlines the cascade of patho physiologic events that build up on an atherosclerotic plaque and eventually result in myocardial infarction and death. The culprit lesion becomes clinically manifest only with the development of an obstruction severe enough to impede coronary blood flow at rest, or when it is the site of a thrombotic occlusion shedding thromboembolic material into the distal circulation. Therefore, the active plaque is clinically detected only at an advanced stage of the underlying disease. Further, the concept of a single active plaque has been challenged. Pathologic studies have shown multiple rupture sites and thrombi at multiple sites often associated with platelet aggregates in small intramyocardial arteries and microscopic foci of necrosis.[7,86–88] An angiographic study in 253 patients with an acute myocardial infarction documented that complex and ruptured plaques could be found in 40% of patients and that these were associated with a 10-fold increase in the risk of a recurrent ACS.[89]

Atherosclerosis is the substrate for ACS. The severity of atherosclerosis in acute coronary syndromes is highly variable, ranging from absence of significant stenoses to the presence of left main disease in 5–10% of patients, and single, double or three vessel disease in respectively 20%, 30%, and 40%.[90] A severely obstructive lesion is most often identified, providing a rationale for coronary revascularization. On inspection and histologic analyses, the culprit lesion is clearly distinct from the stable plaque; it is most often of only moderate severity, with an inner core rich in cholesterol and cholesterol esters and a thin fibrous cap, poor in connective tissue and smooth muscle cells.[83] At microscopy, the culprit lesion is rich in monocyte-macrophages, mast cells, lymphocytes, and neutrophils. Biologically, it is extremely active, with an intense inflammatory reaction marked by heterotypic cell-to-cell interactions and activity of proinflammatory cytokines, matrix-degrading metalloproteinases, and growth factors.[84,85] This culprit lesion is the site of a rupture or

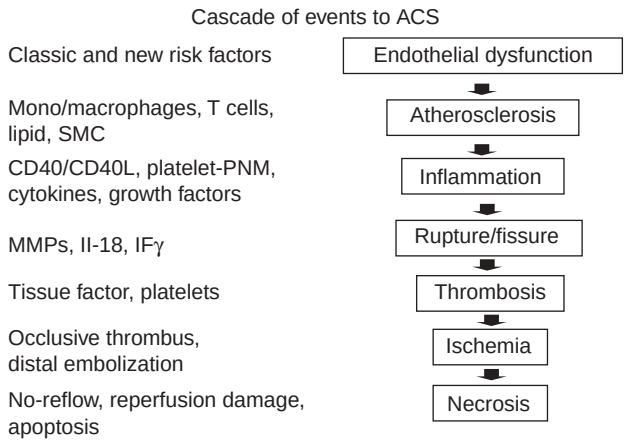


Figure 30.9 Cascade of events leading to ACS. There is a progression of events at the level of an atherosclerotic plaque to excessive inflammation, plaque degeneration, plaque rupture, and intravascular thrombus formation. These events become clinically manifest only when the thrombus becomes obstructive or sheds distal emboli to cause myocardial ischemia and eventually myocardial infarction and death. The cascade of events offers multiple possibilities for intervening at various levels to control and prevent ACS. Il-18, interleukin 18; IFγ, interferon γ.

fissure, occurring most often at the shoulder region of the plaque. The endothelial disruption is occupied by a thrombus extending variably within the lumen of the artery and the vessel wall.[83] The mainstay of immediate therapy in ACS is the control of the thrombotic activity to prevent its rapid progression to occlusion or distal microembolization of thrombotic material. The best results have been achieved with combinations of antiplatelet and anticoagulant therapy consistent with the contributions of both intravascular coagulation and platelet activation and aggregation to arterial thrombosis. Circulating platelets adhere within seconds to the damaged endothelium through receptor–ligand interactions. Gp Ib/IX recognizes von Willebrand factor present in large quantities in the subendothelium, and Gp Ia/IIa recognizes collagen. Platelet adhesion and other local agonists produce intracellular signaling that increases cytosolic Ca^{2+} content and induces shape change, release of potent vasoactive, proaggregant and procoagulant substances, and activation of the Gp IIb/IIIa receptor.[83] The activated Gp IIb/IIIa receptor recognizes and binds the RGD sequence of various moieties, particularly fibrinogen, resulting in platelet cross-bridging and platelet aggregation. The outside translocation of the inner anionic phospholipid layer of platelets early during activation provides a membrane surface well suited for the assembly of coagulation factors and thrombus formation and growth. Tissue factor, expressed by lipid laden macrophages in the core of the atherosclerotic plaque and the diseased endothelium, forms a complex with circulating factor VIIa to activate factors IX and X of the coagulation cascade. Factor IXa is part of the intrinsic tenase complex that activates factor X. Factor Xa converts prothrombin to thrombin within the prothrombinase complex. Thrombin has multiple pathophysiologic effects. It converts fibrinogen to fibrin, activates factor XIII which cross-links fibrin, amplifies its own generation by activation of factors V, VIII, and XI on the platelet surface, and is a potent platelet agonist. P-selectin expressed on the platelet membrane and on the endothelial cell attracts leukocytes, linking thrombosis and inflammation.

In addition to antithrombotic therapies, other strategies may be employed to control the acute coronary syndromes, as shown in Figure 30.9. The prevention of atherosclerosis is the ultimate goal. Realistic targets in the shorter term are plaque passivation to control the pathophysiologic triggers to plaque rupture and thrombus formation, and cell protection to prevent progression of ischemia to irreversible cell necrosis.[91]

Management

The goals of treatment in ACS are to decrease the substantial risk of myocardial infarction and death, relieve pain, and prevent recurrent ischemia. These objectives can be collectively regrouped under the term plaque passivation, implying the conversion of an unstable plaque into a plaque that will be stable and not prone to complications. During the acute phase, this is best achieved with prompt use of antithrombotic agents, and in selected patients reperfusion procedures. Anti-ischemic therapy is also used to control symptoms. Therapies to control the inflammatory processes within the plaque are effective in secondary prevention and their potential is now being investigated during the more acute phase.

Acute therapy

The therapeutic approaches include general measures, anti-ischemic therapies, antithrombotic therapies, and revascularization procedures. The intensity of treatment is guided by risk as estimated from the clinical presentation, the 12-lead ECG and the troponin levels, as discussed above. Additional patient characteristics associated with an enhanced risk must also be considered. These are listed in Table 30.3 above, along with other predictors of an impaired long-term prognosis. Risk stratification is an ongoing process that must be repeatedly updated during the clinical course and integrated with the results of the various tests performed.

General measures

The patient may present in a non-medical setting or by telephone, in the office, or in the hospital emergency room or ward. Those with the simple new onset of angina or mild exacerbation of previously stable angina, with no angina at rest, ECG changes, or hemodynamic abnormalities should be carefully assessed, initial treatment and educational materials provided, and medical follow up planned, but they

may generally be managed as outpatients with initial limitation of activities, providing that necessary investigations can be performed promptly. High-risk patients require admission to the CCU, generally to remain for about 24 hours following the last episode of rest pain. Patients at intermediate risk might go to the CCU, an intermediate care unit, or even to a regular ward depending on the availability of facilities and the specific level of risk.

Whatever the pathophysiology of the acute ischemia in a given patient, there is an imbalance of myocardial oxygen supply and demand, and restricted activities and rest in bed or a recliner chair will be helpful in reducing myocardial oxygen demand. Stool softeners are likely to be helpful. Emotional distress with its attendant increase in myocardial oxygen demand should be minimized by judicious control of environmental noise and light, supportive medical and nursing care, limitation and education of visitors, provision for restful sleep, and control of ischemic pain with intravenous narcotics and nitrates, and other specific anti-ischemic agents as appropriate. Special attention is indicated to detect depressive symptoms that carry an impaired prognosis independently of other predictors.[49] Routine oxygen administration is not recommended unless chest pain is ongoing or respiratory or left heart failure are present. **Grade C** Finger pulse oximetry is then recommended to monitor arterial oxygen saturation. **Grade B**

Anti-ischemic therapies

Nitroglycerin has been a mainstay in the therapy of unstable angina since the prognostic importance was first recognized, and as longer-acting nitrate preparations became available, these were incorporated into treatment regimens without rigorous comparisons to placebo. Studies of the use of IV nitroglycerin among patients with unstable angina have been relatively small, of sequential or case–control design, and the dose regimens have varied considerably.[92] At least partial relief of anginal episodes is usually achieved, occasionally relief is complete, and absence of benefit is an infrequent observation. However, the trials have been of brief duration, generally a few days only, and problems of nitrate tolerance and recurrence of ischemic events emphasize that nitrates are not definitive therapy for unstable angina beyond the acute phase. A trial comparing nitrate therapy and diltiazem[93] indicates that diltiazem is more effective in controlling angina and preventing ischemic events but these studies do not reflect clinical approaches that have employed long acting or intravenous nitroglycerin in combination with a β blocker or a rate limiting calcium antagonist. The widespread use of oral, topical, and IV nitrates in unstable angina is based upon reasonable extrapolation from pathophysiologic observations, case series, evidence of modest reduction of mortality in acute MI,[94–96] and extensive clinical experience using regimens developed in careful clinical studies.[96] **Grade B** Patients must be monitored for the potential adverse effect of marked arterial hypotension, which must be managed quickly to avoid exacerbating ischemia. The use of sildenafil (Viagra) within the preceding 24 hours is a contraindication to nitrate therapy.[97] **Grade B** Efforts should be made to minimize the development of nitrate tolerance by reducing IV dosage and intermittent dosing by non-IV routes when ischemic pain allows.

The β blockers were introduced in the 1960s and their effectiveness in the treatment of stable angina resulted in rapid acceptance for the management of unstable angina. There was remarkably little objective evidence for the efficacy of β blockers prior to their widespread use.[29] Subsequently, β blockers were evaluated in well-designed studies. In one study, a group of 126 patients hospitalized with unstable angina (characterized by progressive or rest ischemic pain plus ECG changes with pain and documented coronary artery disease) were randomly allocated to the addition to their regular therapy of either nifedipine or the combination of propranolol/isosorbide dinitrate, with appropriate placebos.[98] The principal outcome was absence of recurrent chest pain for at least 48 hours, and the period of evaluation was 14 days. There was no overall difference between the two treatment regimens. However, in a post-hoc analysis of the data amongst the 59 patients not receiving β blocker on admission, the propranolol/isosorbide was more effective than the nifedipine in producing pain relief ($P < 0{\cdot}001$). Conversely, among the 67% of patients already receiving a β blocker on admission, nifedipine was more effective than augmentation of β blocker accompanied by isosorbide ($P = 0{\cdot}026$).

The HINT study[99] examined metoprolol and nifedipine in patients hospitalized with prolonged rest pain. The 338 patients who were not receiving β blocker on admission were randomly allocated to nifedipine, metoprolol, both, or neither in a double-blind placebo-controlled fashion. The outcome of AMI or recurrent angina with ST change within 48 hours occurred with the following frequencies: placebo (37%), nifedipine (47%), metoprolol (28%), nifedipine plus metoprolol (30%). Metoprolol was significantly more effective than nifedipine ($P < 0{\cdot}05$). The 177 patients already on a β blocker on admission were randomly allocated in double-blind fashion to nifedipine or placebo and treatment failure occurred in 51% of placebo and 30% of nifedipine ($P < 0{\cdot}05$).

Gottlieb *et al.*[100] studied 81 patients hospitalized with at least 10 minutes of ischemic chest pain at rest. All patients were receiving "optimal" doses of nitrates and nifedipine and were therefore treatment failures on this regimen. They were randomly allocated to the addition of either propranolol or placebo. In the first 4 days, propranolol resulted in a statistically significant reduction of recurrent rest angina episodes, duration of angina, nitroglycerin requirement, and ECG abnormalities. Although recurrences of rest angina

remained less among the propranolol treated group over the next 4 weeks, the incidence of aortocoronary bypass, AMI, and sudden death was no different between the two groups.

In another study, patients hospitalized with prolonged pain accompanied by ECG abnormalities, and who had failed maximum treatment with propranolol and long-acting nitrates, were randomized to the addition of nifedipine or placebo;[101] the failure of medical treatment (sudden death, AMI, or bypass surgery) was less frequent with nifedipine than with placebo ($P = 0{\cdot}03$). The benefit was most marked among patients with ST-segment elevation.

These trials suggest that among patients not receiving a β blocker on hospitalization, the institution of β blockade and the institution or maintenance of nitrates is more effective treatment than the institution of nifedipine. **Grade A** Amongst patients whose pain persists with optimal doses of nitrates and nifedipine, the addition of a β blocker is efficacious in the initial few days, although the incidence of ischemic outcomes (bypass surgery, AMI, sudden death) is not reduced. **Grade A** On the other hand, in patients hospitalized and already receiving a β blocker, then the addition of nifedipine is more effective than simply augmenting the β blocker dose. **Grade B** Recent data suggesting potentially harmful effects of short-acting dihydropyridines[102] indicate that a more prudent choice for the addition to a β blocker would be a long-acting dose preparation or an agent with an intrinsically long half-life such as amlodipine, although rigorous studies have not been conducted. **Grade C**

Diltiazem was compared to propranolol in a randomized single-blind study of patients hospitalized for crescendo rest, or following MI angina accompanied by ECG abnormalities.[103] Chest pain frequency was significantly reduced by both regimens, and there was no difference in efficacy. The 5 month follow up was rather discouraging in both groups, with a high incidence of AMI, death, and bypass surgery, and few patients without bypass surgery were symptom free. In another study, patients with rest angina were randomized to diltiazem or propranolol in maximum tolerated doses.[104] The agents were equally effective in reducing the frequency of daily anginal episodes, but in the subgroup with angina only at rest, diltiazem was efficacious whereas propranolol was not.

There is little rigorous evidence for the value of verapamil in unstable angina. Small placebo-controlled trials[105,106] demonstrated statistically significant reductions in the frequency of ischemia. Long-term follow up in these small trials[107] showed that in general ischemic pain continued to be well controlled but there was a high incidence of AMI and death.

In addition to reducing ischemic episodes, a reduction in MI would be desirable. Yusuf *et al*[108] examined five trials involving about 4700 patients with threatened MI who were placed on intravenous β blocker followed by oral therapy for about a week. There was a modest 13% reduction in the risk of development of MI in this group. Meta-analysis of studies of calcium antagonists among patients with unstable angina shows no reduction of death or non-fatal MI.[108] Diltiazem and verapamil appear to be effective as initial single agents in the management of unstable angina, and diltiazem appears to be no different in efficacy from propranolol in one direct comparison. However, the meta-analytic data for benefit of β blocker but not calcium antagonists and the evidence for improved long-term outcomes with β blocker therapy among survivors of myocardial infarction,[108] and those with chronic ischemia, support β blockers over rate-limiting calcium antagonists as the first choice therapy in patients with unstable angina. **Grade A** Patients at high risk may have benefit from initial intravenous β blocker, followed by an oral regimen. **Grade C** Diltiazem or verapamil are suitable alternatives for patients with a contraindication to β blocker therapy. **Grade B** Nifedipine should not be the initial single agent for patients with unstable angina.[98] **Grade A** The new dihydropyridines have not been evaluated in patients with an acute coronary syndrome. Nicorandil, an ATP sensitive potassium (K^+) channel opener with arterial and venous vasodilator properties and cardioprotective potential by pharmacologic preconditioning, was shown in one small trial of 188 patients to reduce the number of transient ischemic episodes on continuous Holter monitoring.[109] Nicorandil is not approved for use in North America.

Among patients with variant angina, characterized by recurrent ischemic episodes occurring mainly at rest and in the early morning hours accompanied by transient ST-segment elevation, randomized placebo-controlled, double-blind trials of verapamil,[110–112] diltiazem,[113–116] and nifedipine[117–119] have demonstrated the efficacy of each of these agents in reduction of angina frequency. Several comparisons of calcium antagonists to β blockers have demonstrated greater efficacy with the calcium antagonists.[111,112,116] These agents are regarded along with nitrates as the therapy of choice for variant angina, although there is little direct comparative data with long-acting nitrates. **Grade A**

Antithrombotic therapy

Antithrombotic therapy is cornerstone therapy in ACS. It prevents death or myocardial infarction in patients managed medically and in patients undergoing a reperfusion procedure. Optimal benefit is obtained with combined inhibition of platelets and of the coagulation process. Thrombolytic therapy is beneficial in ST-segment elevation MI but contraindicated in non-ST-segment elevation MI.[120]

Antiplatelet therapy – Whereas aspirin has long been, and is still, the gold standard of antiplatelet therapy, a new armamentarium of agents acting on different platelet functions has

been developed. Physicians now have options in drug selection used in mono- or poly-therapy. Antiplatelet agents evaluated in ACS have been aspirin, dipyridamole, prostacyclin, sulfinpyrazone, inhibitors of thromboxane synthase and/or its receptor, ticlopidine, clopidogrel, and the intravenous and oral Gp IIb/IIIa antagonists. The various drugs can be classified first by their site of action on the main steps of platelet function from adhesion to activation and aggregation, and secondarily by their specific effects at each step (Figure 30.10). Adhesion can be inhibited by agents under development acting mainly on von Willebrand factor and its ligand, Gp 1b/IX. Activation can be inhibited by agents acting on intracellular calcium mobilization such as dypiridamole, which prevents catabolism of cAMP and nitric oxide, which promotes production of cGMP, and by agents inhibiting specific activation pathways. Aspirin blocks the thromboxane pathway and ADP-receptor antagonists block purinergic receptors on platelets. Gp IIb/IIIa antagonists occupy the receptor to prevent fibrinogen binding and platelet aggregation.

Aspirin – Four conclusive trials have shown consistent benefit with aspirin in patients with non-ST-segment elevation ACS, despite different study designs and different doses. The Veterans Administration Study, performed between 1974 and 1981, included 1338 men with unstable angina randomly allocated within 72 hours of admission to ASA 324 mg or placebo.[121] The rate of death or myocardial infarction was reduced from 10·1% to 5·0% (RR 49%, $P = 0{\cdot}0005$) over a 12 week treatment period.

In the Canadian Multicenter Trial conducted between 1979 and 1984, 555 patients (73% men) with unstable angina were randomized before hospital discharge to aspirin (325 mg four times daily), sulfinpyrazone (200 mg four times daily), placebo, or both drugs.[122] The outcome of death or myocardial infarction at 2 years was reduced from 17% to 8·6% (RR 49·2%; $P = 0{\cdot}008$) by efficacy analysis and by 30% ($P = 0{\cdot}072$) by intention-to-treat analysis, and the outcome of death was reduced by 71% ($P = 0{\cdot}004$) and 43·4% ($P = 0{\cdot}035$) respectively. Sulfinpyrazone had no

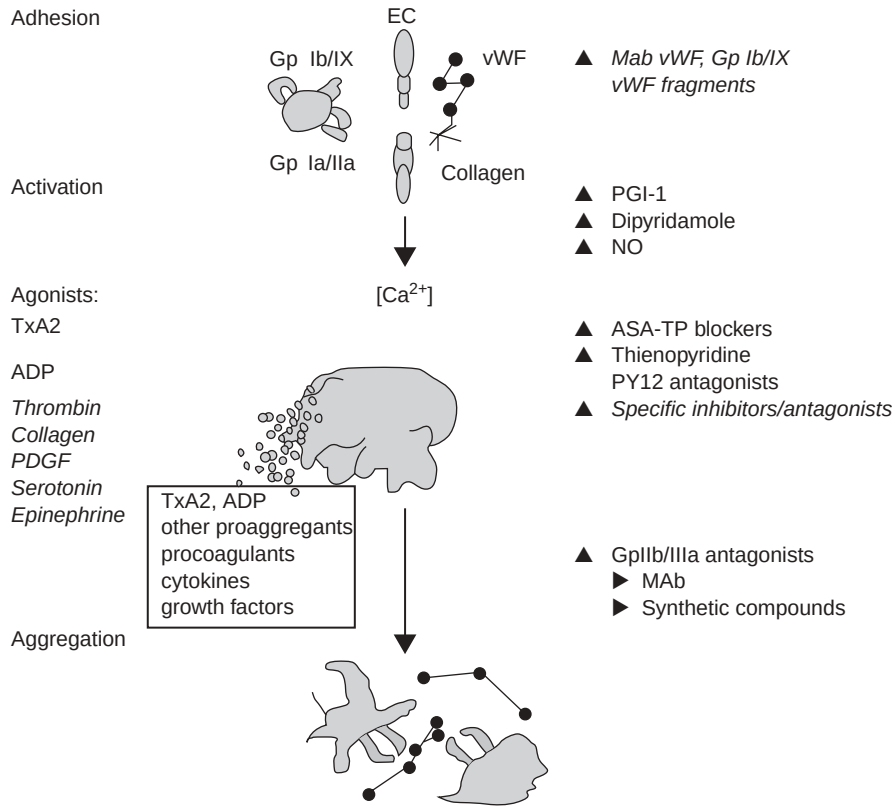


Figure 30.10 Mechanisms of platelet adhesion, secretion and aggregation, and sites of action of various antiplatelet drugs. The drugs approved for clinical use are in bold and the drugs under development in italics. Adhesion to the damaged endothelium and other agonists triggers intracellular signaling with an increase in cytosolic free calcium content (Ca^{2+}), shape change, and release of numerous proaggregants, procoagulants, growth factors, and inflammatory mediators. The GP IIb/IIIa receptors undergo conformational changes making them competent to cross-link fibrinogen to form platelet aggregates and the platelet thrombus. ADP, adenosine diphosphate; ASA, aspirin; Mab, monoclonal antibody; PDGF, platelet derived growth factor; PGI_1, prostacyclin; TP, thromboxane receptor; TxA2, thromboxane A2; vWF, von Willebrand factor. Reproduced with permission from Theroux P. Thrombosis in coronary artery disease: its pathophysiology and control. *Dialogues Cardiovas Med* 2002;**7**:3–18.

significant effect or interaction with aspirin. In the Montreal study, 479 patients were randomized during the acute phase of disease to aspirin (325 mg bid), heparin, both or neither in a 2×2 factorial design.[32] Aspirin reduced the risk of death or myocardial infarction at 6 days from 6·3% to 2·6%, a 63% risk reduction ($P = 0{\cdot}04$). The RISC study randomized 945 patients to aspirin (80 mg daily), intravenous heparin, both or placebos.[31] End points were assessed in 796 patients meeting the entry criteria. Aspirin, compared to no aspirin, reduced the rate of death or MI at 5 days from 5·8% to 2·6% ($P = 0{\cdot}033$), at 7 days from 13·4% to 4·3% ($P = 0{\cdot}0001$), and at 30 days from 17·1% to 6·5% ($P = 0{\cdot}0001$).

The Antiplatelet Trialists' Collaboration updated their initial meta-analysis by including 287 studies involving 135 000 patients administered antiplatelet therapy versus control and 77 000 patients randomized to different antiplatelet regimens.[123] Overall, among high-risk patients, allocation to antiplatelet therapy reduced the outcome of any serious vascular event by 25%, non-fatal MI by 33%, non-fatal stroke by 25%, and vascular mortality by 16%. Aspirin was the most widely studied antiplatelet drug. The absolute benefit of aspirin increases with the inherent risk of the condition for which it is prescribed, and is substantial in patients with a non-ST-segment elevation ACS, as illustrated in Figure 30.11.[124] Aspirin has numerous physiologic effects on platelets and the inflammatory process, many of which are only partly characterized. The mechanism accounting for the benefit in ACS is believed to be the irreversible inhibition of cyclo-oxygenase-1 (COX-1) in platelets, blocking formation of thromboxane A2; the doses of 75–160 mg daily that have been shown to be at least as clinically effective as higher doses are quite specific for this effect.[123] This inhibition is dose-related, cumulative and irreversible. A loading dose of 160–365 mg is recommended followed by doses of 80–160 mg daily. **Grade A** Higher doses have anti-inflammatory effects and inhibit cyclo-oxygenase-2 (COX-2). COX-2 is not constitutive and is expressed in endothelial cells and white cells in response to an inflammatory stimulus. It is inhibited selectively by the coxibs and less selectively by the non-steroidal anti-inflammatory drugs (NSAIDs). The term aspirin resistance is increasingly used to describe failure of aspirin to prevent events in some patients. Laboratory data suggest that there is a non-optimal biologic response in about 30% of patients.[125,126] Practical reasons for the failure of aspirin are non-compliance to therapy and intake of NSAIDs prior to aspirin. NSAIDS, and typically ibuprofen, flurbiprofen, indomethacin, and suprofen, bind COX-1 on the same serine residue as aspirin to mask the active site; the biologic actions of aspirin are therefore prevented when these NSAIDS are present in blood, an effect that is favored by the short plasma half life of aspirin.[127] Other reasons for aspirin failure could be individual variations in metabolism

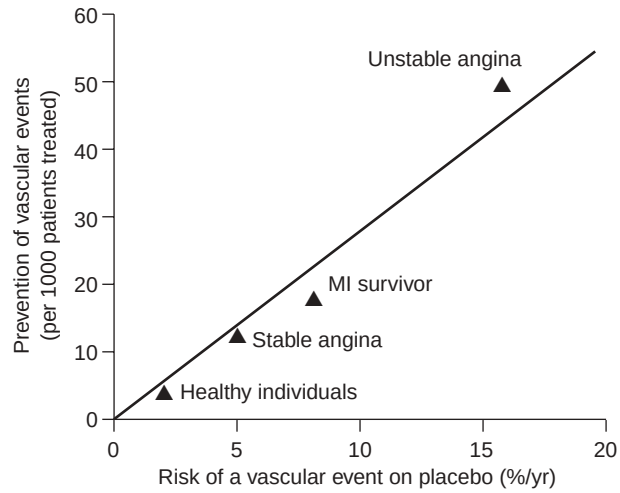


Figure 30.11 Benefits of aspirin by risk groups. The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arms of the trials. The absolute benefit of antiplatelet treatment is reported on the ordinate axis as the number of subjects in whom an important vascular event (that is, non-fatal MI, non-fatal stroke, or vascular death) is actually prevented by treating 1000 subjects with aspirin for 1 year. Reproduced with permission from Patrono *et al.*[124]

of low doses of aspirin possibly influenced by genetic polymorphism, thromboxane A2 independent pathways of thrombus formation, generation of thromboxane A2 by COX-2, and agonists of thromboxane receptors other than thromboxane A2, such as the isoprostanes which are non-enzymatically derived products of arachidonic acid.[128] The diagnosis of aspirin resistance is based on clinical suspicion as no single test has so far been prospectively and reproducibly validated. Since an alternative therapy to aspirin exists with drugs that have been shown to be at least as useful as aspirin, aspirin monotherapy should be questioned in patients clinically suspected of aspirin resistance because of recurrent ischemic events occurring on aspirin therapy. **Grade B**

Other agents acting on the cyclo-oxygenase pathway – The inhibition of prostacyclin (PGI_2) generation by aspirin does not appear to limit its protective effects significantly. Nevertheless, it was shown that an infusion of prostacyclin in unstable angina patients resulted in no benefit.[129] Analogs of PGI_1 that are more stable and that have less hemodynamic effects are now being investigated in various situations. The thromboxane synthase inhibitors and/or receptor antagonists investigated so far were not shown to be superior or

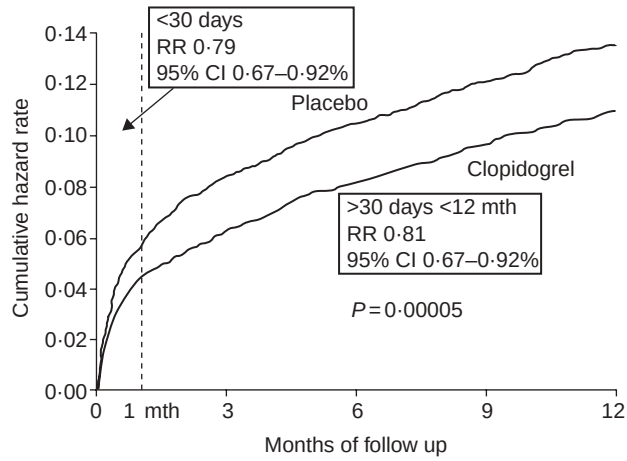
inferior to aspirin. S18886 is a new agent under clinical investigation, which blocks the thromboxane (TP) receptor and has favorable pharmacokinetic and pharmacodynamic profiles. Experimental data have suggested that the drug could be protective against progression of atherosclerosis.[130]

ADP receptor antagonists

The thienopyridines ticlopidine and clopidogrel are the two ADP receptor antagonists currently approved. Clopidogrel has replaced ticlopidine as it is devoid of the serious life-threatening adverse effects of leukopenia and thrombocytopenia found with ticlopidine. Clopidogrel is also more potent than ticlopidine and can be safely administered in loading doses to achieve full drug effects approximately 2 hours after the administration of a bolus dose of 300 mg. Clopidogrel effects are dose-related, cumulative, and irreversible, as are those of aspirin. Placebo-controlled trials with ticlopidine in unstable angina and in the secondary prevention of stroke have documented risk reductions in the range of those observed with aspirin.[131] One direct comparison trial has shown superiority of ticlopidine over aspirin in the secondary prevention of stroke.[132] Many trials in coronary stenting have confirmed the greater efficacy and safety of clopidogrel.[133]

Clopidogrel was evaluated in two large trials, in one as single therapy,[134] and in the other as combined therapy with aspirin versus aspirin alone.[135] In the CAPRIE trial, a total of 19 185 patients with atherosclerotic vascular disease manifested as recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral vascular disease were randomized to aspirin, 325 mg/day, or clopidogrel, 75 mg/day.[134] The annual risk of ischemic stroke, myocardial infarction, or vascular death during a follow up of 1–3 years was reduced by 8·7% from 5·83% to 5·32% by clopidogrel ($P = 0{\cdot}043$). The risk reductions (RR) were, however, heterogeneous among the entry groups: 23·8% ($P = 0{\cdot}00028$) in patients enrolled because of peripheral vascular disease, 7·3% in patients enrolled because of stroke, and an excess of 5·03% ($P = 0{\cdot}66$) in patients enrolled because of a myocardial infarction.

In the CURE trial, 12 562 patients were randomized within 24 hours after the onset of a non-ST-segment elevation ACS to receive clopidogrel (300 mg bolus, 75 mg daily) or placebo in addition to aspirin 160–360 mg daily for 3–12 months. The primary composite outcome of cardiovascular death, non-fatal MI, or stroke occurred in 9·3% of patients in the clopidogrel group and 11·4% of patients in the placebo group (RR 0·80; 95% CI 0·72–0·90; $P < 0{\cdot}001$) (Figure 30.12).[136] Clopidogrel further reduced the rates of inhospital severe ischemia and of revascularization, the need for thrombolytic therapy or intravenous Gp IIb/IIIa-receptor antagonists, and the occurrence of heart failure. The benefits became apparent within a few hours of treatment initiation and increased throughout the follow up period to one year. These benefits were homogeneous among all secondary end points, subgroup analyses, and patients at low, medium, and high risk, enhancing the clinical relevance of the trial. Thus even patients with no ST-segment depression and patients with no elevation of cardiac markers benefit, contrasting with the benefits of enoxaparin and the Gp IIb/IIIa antagonists which are apparent only in high-risk patients. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3·7% *v* 2·7%; RR 1·38; $P = 0{\cdot}001$), but there was no excess in life-threatening bleeding (2·2% *v* 1·8%; $P = 0{\cdot}13$) or hemorrhagic stroke (0·1% *v* 0·1%). The risk of major bleeding was particularly increased in patients undergoing CABG surgery within the first 5 days of stopping clopidogrel (9·6% *v* 6·3%, RR 1·53; $P = 0{\cdot}06$) but not when CABG was performed after 5 days (4·4% *v* 5·3% with placebo). The CURE trial was mainly aimed at medical management, although revascularization was performed during the initial admission in 23% of the patients, among whom there was a benefit of clopidogrel. A benefit of clopidogrel was also noted in patients who received thrombolytic therapy or a Gp IIb/IIIa antagonist, but these drugs were administered in only 1·1% and 5·9% of patients respectively.



Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

Figure 30.12 Cumulative hazard rates for the outcome of cardiovascular death, non-fatal myocardial infarction, or stroke during the 12 months of the CURE study with the use of clopidogrel versus placebo on a background of aspirin in all patients. The results demonstrate sustained benefit of clopidogrel from the time of randomization through to the end of the study. Reproduced with permission from The CURE Investigators.[136]

Gp IIb/IIIA-receptor blockers – Three Gp IIb/IIIa antagonists are approved for clinical use: abciximab, eptifibatide,

and tirofiban. Clinical trials failed to show a benefit of lamifiban, a synthetic Gp IIb/IIIa antagonist with properties similar to those of eptifibatide and tirofiban.[37,137] Abciximab is a Fab fragment of a chimeric monoclonal antibody that binds the RGD and dodecapeptide recognition sequences of the receptor. The plasma half life of the drug is approximately 10 minutes but the biologic half life extends to 6–12 hours. Abciximab has strong affinity for the receptor and receptor occupancy persists weeks after drug exposure, although platelet aggregation progressively returns to normal within 12–24 hours. Abciximab is not specific for the Gp IIb/IIIa integrin, also inhibiting the vitronectin receptor ($\alpha v\beta 3$) on the endothelium and smooth muscle cell and the MAC-1 ($\alpha m\beta 2$) integrin on neutrophils and monocytes. The clinical relevance of occupancy of these receptors involved in cell proliferation and leukocyte activation respectively remains ill defined. Eptifibatide is a cyclic heptapeptide derived from the structure of barbourin in the venom of the pigmy rattlesnake possessing a KGD sequence recognized by the receptor. Tirofiban is a non-peptide mimetic of the RGD sequence. The half life of the two small molecules is approximately 2 hours. After drug discontinuation, there is 50% recovery of receptor occupancy and platelet aggregation within 4 hours and nearly 100% within 8 hours. These drugs have no special affinity for the receptor and receptor occupancy parallels blood levels. Many trials have documented the efficacy of abciximab in reducing periprocedural MI and the need for urgent revascularization when it is administered in the cardiac catheterization laboratory before a revascularization procedure and continued for 12 hours thereafter.[138,139] In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory angina (CAPTURE)[140] trial involving 1265 patients with refractory unstable angina, abciximab was administered after a first angiogram identifying a culprit lesion suitable for coronary angioplasty. The procedures were performed 20–24 hours later and abciximab was continued for one hour after the procedure.[140] Abciximab, compared with placebo, reduced the rate of death and myocardial infarction by 30 days from 15·9% to 11·3% ($P = 0{\cdot}012$). In a comparison trial, abciximab was shown to be significantly superior to tirofiban in preventing complications associated with urgent or elective stent placement.[141] The doses of tirofiban used in this study had previously been shown to be ineffective.[142] Contrasting with the benefits observed in percutaneous intervention and in stent implantation trials, the GUSTO-IV trial failed to show a benefit of abciximab in the medical management of patients with a non-ST-segment elevation ACS. In this trial, 7800 patients with chest pain and either ST-segment depression or raised troponin T or I concentrations were randomly assigned placebo, an abciximab bolus and 24 h infusion, or an abciximab bolus and 48 h infusion.[42] The primary outcome of death or myocardial infarction 30 days after randomization occurred in 8·0% of patients on placebo, 8·2% of patients on 24 h abciximab, and 9·1% of patients on 48 h abciximab (OR 1·0 between placebo and 24 h abciximab, and 1·1 (95% CI 0·94–1·39) for difference between placebo and 48 h abciximab). The lack of benefit with abciximab was consistent in most subgroups investigated including, remarkably, patients with elevated troponin T or I, although they were at a high risk of subsequent events.

Tirofiban was investigated in two ACS trials. In one, tirofiban alone with placebo heparin versus heparin with placebo tirofiban was associated with an early benefit at 72 hours, a benefit that was not, however, sustained after 30 days.[35] The second trial compared the combination of tirofiban with heparin to heparin alone. The combination reduced the occurrence of the primary end point of death, myocardial infarction, or refractory ischemia at 7 days by 32% ($P = 0{\cdot}004$) and of death or myocardial infarction by 43% ($P = 0{\cdot}006$).[36] The gain appeared early and was sustained after 6 months.

Many trials were performed with eptifibatide. In the PURSUIT trial, 9461 patients with a non-ST-segment elevation ACS were randomized to eptifibatide or placebo; the rate of death or myocardial infarction after 30 days was reduced by 10% with eptifibatide (14·2% *v* 15·7%, $P = 0{\cdot}042$).[39] In the placebo-controlled ESPRIT trial, eptifibatide used at higher doses and with a double bolus injection significantly reduced the event rate associated with coronary stenting to an extent similar to that observed with abciximab.[143]

Altogether, these trials show efficacy of abciximab and eptifibatide in reducing event rates in percutaneous coronary interventions and of tirofiban and eptifibatide in non-ST-segment elevation ACS. The benefits were additive to those of aspirin and of heparin. **Grade A**

Several meta-analyses demonstrated a benefit of intravenous Gp IIb/IIIa antagonist therapy in patients with an ACS. One meta-analysis published in 1999, before the confounding results of GUSTO-IV were known and including the data from the CAPTURE, PURSUIT, and PRISM-PLUS trials, showed event rates of 2·5% with treatment and 3·8% with placebo during the period of medical management and of 4·9% and 8·0% respectively in the 48 hours that followed PCI in the subgroups of patients who underwent a procedure (RR reduction 34%, $P < 0{\cdot}001$). An early benefit of Gp IIb/IIIa inhibitors during medical treatment was documented, and a larger benefit when PCI was performed on drug therapy.[144] A second meta-analysis with data on individual patients included trials, which enrolled at least 1000 patients and did not recommend early coronary revascularization (this criterion did not apply in PRISM-PLUS).[36,145] Among 31 402 patients from six trials, including GUSTO-IV, the Gp IIb/IIIa antagonists reduced the odds of death or MI at 30 days by 9% (10·8% *v* 11·8%; OR 0·91; 95% CI 0·84–0·98; $P = 0{\cdot}015$). The relative treatment benefit was largest in high-risk patients. Benefit was present in both males and females when the baseline troponin levels were elevated but only in males when normal.

A third meta-analysis examined more specifically the 6458 diabetic patients enrolled in the six trials. In these patients,

the Gp IIb/IIIa inhibitors reduced the mortality at 30 days from 6·2% to 4·6% (OR 0·74; 95% CI 0·59–0·92; $P < 0·007$) with a statistically significant interaction between treatment and diabetic status ($P = 0·036$). Mortality at 30 days among the 1279 who underwent PCI was reduced from 4·0% to 1·2% (OR 0·30; 95% CI 0·14–0·69; $P < 0·002$).[146]

Puzzling observations with the use of Gp IIb/IIIa antagonists include the absence of benefit in patients with prolonged use of abciximab not referred for invasive management, the failure of lamifiban to show a significant benefit, and, as will be seen below, the excess mortality observed with the prolonged use of orally active agents.

Oral Gp IIb/IIIa antagonists – In an attempt to extend the benefit of intravenous Gp IIb/IIIa antagonists to the subacute and chronic phases of the disease, orally active inhibitors were developed. Four different agents – xemilofiban, orbofiban, sibrafiban and latrofiban – were investigated in five large trials. These agents have rapid on and off binding to the receptor. No single trial showed a benefit in reducing ischemic events and two were prematurely interrupted because of excess mortality. A meta-analysis of four of these trials totaling 33 326 patients showed a statistically significant increase in mortality with therapy (OR 1·37; $P = 0·001$) and trends to more MI. There was a twofold increase in the rate of major bleeding and a high rate of less severe bleeding leading to study drug discontinuation.[147]

Anticoagulants

Anticoagulants evaluated during the acute phase of non-ST-segment elevation ACS have been unfractionated heparin, direct thrombin inhibitors including recombinant hirudin and small molecules, and the low molecular weight heparins. New and promising agents such as r-tissue factor pathway inhibitor, r-protein C, and pentasaccharide and other specific inhibitors of factor Xa are under investigation (Figure 30.13). Documentation of reactivation of the disease

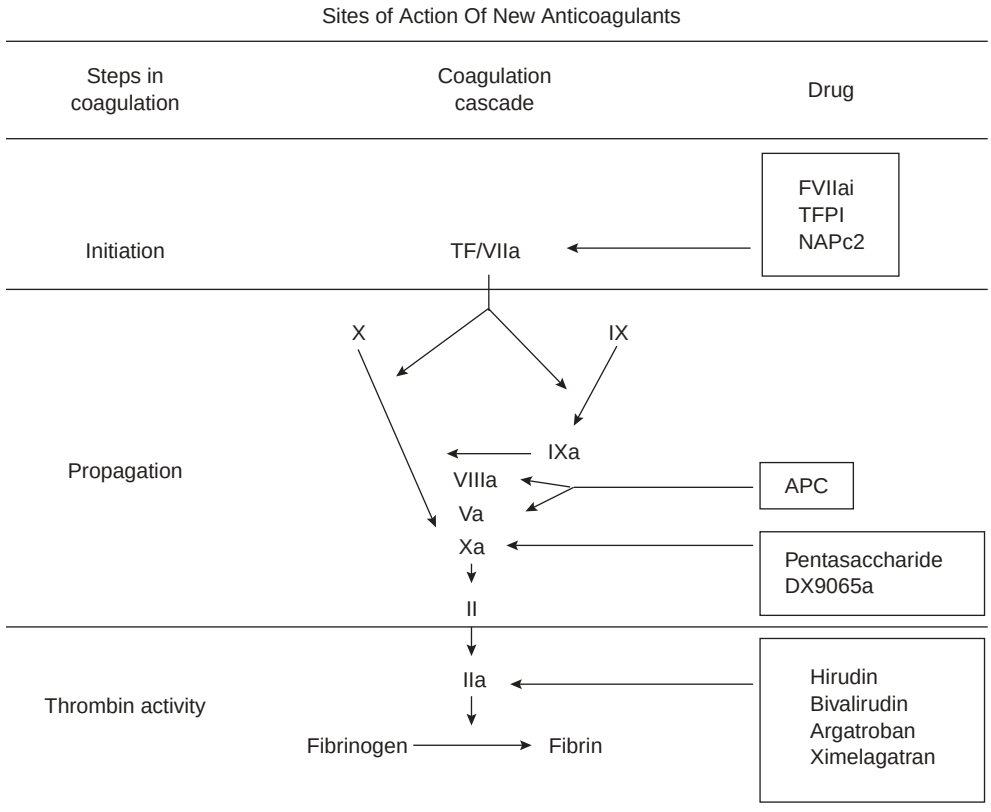


Figure 30.13 The coagulation cascade and sites of action of new anticoagulants. Initiation of coagulation is triggered by the tissue factor/factor VIIa complex (TF/VIIa), which activates factor IX (IX) and factor X (X). Activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (VIIIa) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. Active site-blocked VIIa (VIIai) competes with VIIa for TF, whereas tissue factor pathway inhibitor (TFPI) and nematode anticoagulant peptide (NAPc2) target VIIa bound to TF. Synthetic pentasaccharide and DX-9065a inactivate Xa, activated protein C (APC) inactivates Va and VIIIa, and hirudin, bivalirudin, argatroban, and ximelagatran target thrombin. Reproduced with permission from Weitz and Buller.[154]

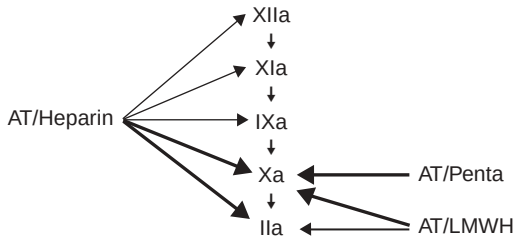


Figure 30.14 Antithrombin (AT)-mediated inhibition of coagulation factors. The complex heparin/AT inhibits especially factor Xa and thrombin (IIa) and also factor XIIa, factor XIa, and factor IXa. The shorter saccharide chains contained in the low molecular weight heparins (LMWH) allow more selective inhibition of factor Xa than factor IIa. The unique pentasaccharide chain of fondaparinux allows highly specific inhibition of factor Xa. Adapted with permission from Hirsh *et al*.[149]

following the discontinuation of heparin[148] and persisting prothrombotic activity past the acute phase have led to the evaluation of long-term therapy with coumadin and the low molecular weight heparins.

Unfractionated and low molecular weight heparins – Unfractionated heparin, low molecular weight heparins, and the heparin pentasaccharide inhibit coagulation factors by greatly enhancing the physiologic properties of circulating antithrombin, with differential effects on factor Xa and thrombin related to the molecular weight of the various heparins (Figure 30.14).[149] In the study by Theroux *et al* of 479 patients, the incidence of fatal and non-fatal myocardial infarction was reduced from 7·5% to 1·2% (RR 85%; $P = 0{\cdot}007$) with unfractionated heparin compared with placebo, and of recurrent refractory ischemia from 19·7% to 9·6% (RR 51%; $P = 0{\cdot}02$).[32] In the RISC study, which enrolled 945 men, the combination of aspirin and heparin resulted in a significant risk reduction in death and myocardial infarction at 5 days.[31] In the FRISC study, 1506 patients were randomized to subcutaneous dalteparin twice daily for 6 days followed by once a day for 35–45 days or placebo.[150] During the first 6 days the rate of death or MI was reduced with dalteparin (1·8% *v* 4·8%; RR = 0·37; 95% CI 0·20–0·68). Survival analysis showed a risk of reactivation and re-infarction when the dose was decreased; the benefit persisted at 40 days but not at 4–5 months.[150] A meta-analysis of 12 trials that compared unfractionated heparin or a low molecular weight heparin to placebo in a total of 17 157 patients showed an odds ratio for myocardial infarction or death during the short term (up to 7 days) of 0·53 (95% CI 0·38–0·73; $P = 0{\cdot}0001$) in favor of the anticoagulant. These results validate the use of unfractionated heparin or of a low molecular weight heparin in combination with aspirin in patients with a non-ST-segment elevation ACS. **Grade A**

Low molecular weight heparins present distinct advantages over unfractionated heparin. They can be administered subcutaneously once or twice a day. They bind plasma proteins and endothelial cells less avidly than unfractionated heparin resulting in more predictable anticoagulation, with no need for monitoring. The ratio of inhibition factor Xa/thrombin is greater. Low molecular weight heparins also stimulate platelets less and are less often associated with heparin-induced thrombocytopenia.

Four trials have directly compared a low molecular weight heparin with unfractionated heparin. No advantages were observed with dalteparin in a trial involving 1482 patients[151] and with nadroparin in a trial of 3468 patients.[152] Enoxaparin was shown to be superior to unfractionated heparin in the two trials that evaluated the drug. In the ESSENCE trial, enoxaparin, 1 mg/kg administered twice daily for 48 hours to 8 days (median 2·6 days) in 3171 patients, reduced the composite outcome of death, MI or recurrent angina by 16·2% at 14 days (16·6% *v* 19·8%; $P = 0{\cdot}019$), and by 19% at 30 days (19·8% *v* 23·3%; $P = 0{\cdot}017$) compared to unfractionated heparin. The rate of death was unaffected, but the rate of myocardial infarction was reduced by 29% (3·2% *v* 4·5%; $P = 0{\cdot}06$) at 14 days, and by 26% (3·9% *v* 5·2%) at 30 days ($P = 0{\cdot}08$).[34] The TIMI-11B trial showed in 3910 patients a reduction in the composite outcome of death, myocardial infarction or refractory ischemia requiring an urgent revascularization from 16·6% to 14·2% at 14 days ($P = 0{\cdot}04$) and from 19·6% to 17·3% at 43 days ($P = 0{\cdot}06$).[41] A meta-analysis of trials that directly compared any low molecular weight heparin to unfractionated heparin showed no statistically significant difference in the odds of death or MI (OR 0·88; 95% CI 0·69–1·12; $P = 0{\cdot}34$). On the other hand, a combined analysis of the data from ESSENCE and TIMI-11B showed a statistically significant reduction in the rate of death or myocardial infarction in favor of enoxaparin.[153]

The pentasaccharide binds antithrombin to inhibit factor Xa with high specificity. It does not produce thrombocytopenia. The drug is now approved for the prevention of deep vein thrombosis in orthopedic surgery and is under investigation in ST-segment elevation and non-ST-segment elevation acute coronary syndromes.

Direct thrombin inhibitors – These drugs are potent anticoagulants that specifically inhibit thrombin (Figure 30.13); they require a cofactor for their effects and have a highly predictable response. Hirudin, now produced by recombinant technology, is the prototype of these agents. Various other inhibitors have been synthesized with different binding properties to the active site and substrate-binding site of thrombin that affect their relative potency and bleeding risk.[154]

Hirudin tightly binds the active and substrate-binding sites of thrombin. The drug has been investigated in four major trials. The dose regimen of 0·6 mg/kg bolus followed

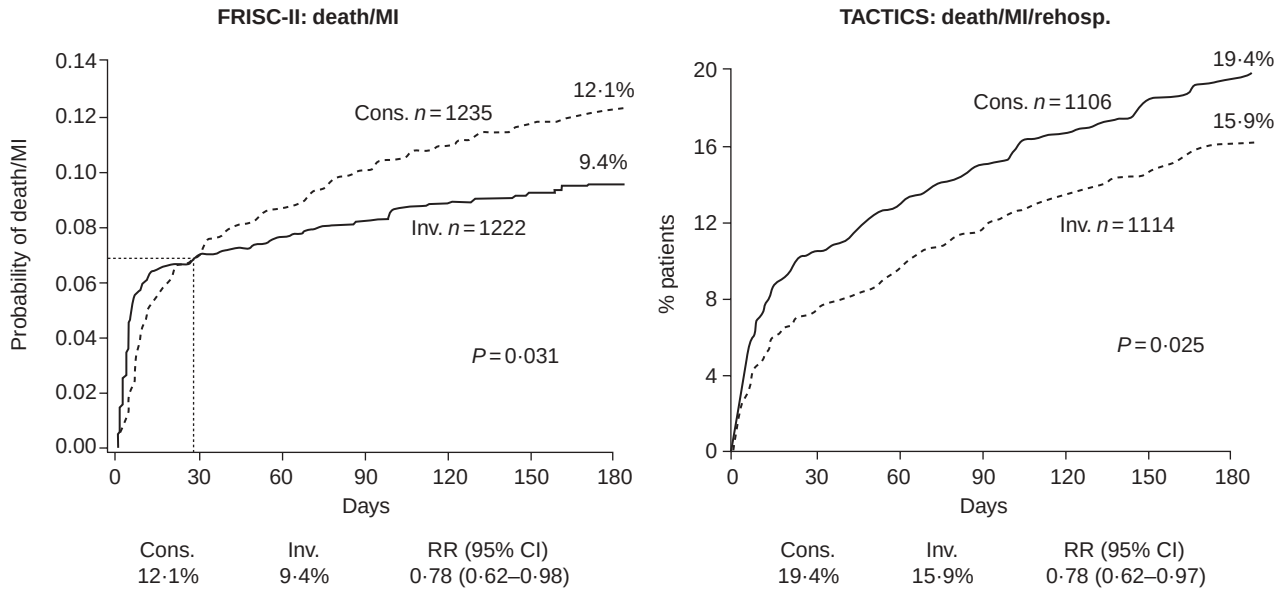


Figure 30.15 Invasive versus non-invasive management of non-ST-segment elevation ACS. Results of the two most recent trials that have compared an early routine invasive management strategy to an early routine medical management strategy. The intervention was performed relatively late in the FRISC-II study after a course of treatment with aspirin and dalteparin and relatively early after a median of 22 hours in TACTICS on treatment with aspirin, heparin, and tirofiban. The two trials show a definitive gain with the early invasive approach in patients with high-risk features as documented by ST-segment shifts and/or an elevation of cardiac markers. Adapted with permission from the FRISC-II Investigators[43] and Cannon *et al.*[44]

by 0·2 mg/kg/hour infusion initially evaluated had to be dropped because of excess bleeding.[155] A dose of 0·2 mg/kg bolus with infusion of 0·1 mg/kg/hour was used in the GUSTO-IIb, which enrolled 12 142 patients, two thirds of them with a non-ST-segment elevation ACS and one third with ST-segment elevation MI,[33] and in the TIMI-9B trial, which enrolled 3002 patients with ST-segment elevation MI.[156] Among patients with no ST-segment elevation in GUSTO-IIb, the composite end point of death or MI at 30 days occurred in 8·3% of the patients on hirudin and in 9·1% of patients on heparin (OR 0·90; 95% CI 0·78–1·06; $P = 0·22$); at 24 h, the risk of death or MI was significantly lower in the patients who received hirudin (2·1% *v* 1·3%; $P = 0·001$). The OASIS pilot study suggested a greater benefit with an intermediate dose of 0·4 mg/kg bolus and 0·15 mg/kg/hour infusion.[157] This dose was used in the large OASIS-2 trial, which randomized 10 141 patients to UFH (5000 IU bolus plus 15 U/kg/h) or recombinant hirudin for 72 h.[40] The primary end point of cardiovascular death or new MI at 7 days was reduced with hirudin from 4·2% to 3·6% ($P = 0·064$); there was an excess of major bleeds requiring transfusions (1·2% *v* 0·7%; $P = 0·014$). A meta-analysis of the GUSTO-IIb, TIMI-9B, OASIS pilot and OASIS-2 showed that the risk of death or MI at 35 days was significantly reduced with hirudin compared with heparin (RR 0·90; $P = 0·015$).[40]

Bivalirudin, argatroban, efegatran, and inogatran have been evaluated in smaller trials in acute coronary syndromes and in coronary angioplasty. A meta-analysis of 35 970 patients in 11 trials, including the hirudin trials, showed an overall reduction in the risk of death or MI at the end of the treatment period with the direct antithrombin (4·3% *v* 5·1%; OR 0·85; 95% CI 0·77–0·94; $P = 0·001$) and after 30 days (7·4% *v* 8·2%; OR 0·91; 95% CI 0·84–0·99; $P = 0·02$).[158] The benefit was, however, restricted to hirudin and bivalirudin, the two agents inhibiting the two active sites of thrombin, and was not present with agents inhibiting only the catalytic or exosite binding site of thrombin. Hirudin increased the risk of major bleeding compared with heparin but bivalirudin reduced it.[158] Hirudin, bivalirudin, and argatroban are approved for use in patients with heparin-induced thrombocytopenia. Hirudin is also approved for the prevention of deep vein thrombosis in patients undergoing orthopedic surgery and bivalirudin for use in percutaneous interventions.

Long-term anticoagulation – Prolonged administration of low molecular weight heparins and of warfarin has been evaluated to prolong the benefit of anticoagulants past the acute phase and prevent reactivation of the disease. In the ATACS trial, 214 patients were randomized to ASA alone or the combination of ASA plus UFH followed by warfarin. At 14 days, there was a reduction in the composite outcome of death, MI, and recurrent ischemia with the combination therapy (27·0% *v* 10·5%; $P = 0·004$). In a small randomized pilot study of 57 patients allocated to warfarin or placebo in

addition to ASA, there was less progression and more regression in the severity of the culprit lesion after a few weeks of treatment with warfarin. The OASIS pilot study[157] compared a fixed dosage of 3 mg of warfarin with a moderate dose titrated to an international normalized ratio (INR) of 2 to 2·5 administered for 7 months. Low-intensity warfarin had no benefit, whereas the moderate-intensity regimen reduced the risk of death, MI, or refractory angina by 58% and the need for rehospitalization for unstable angina by 58%. These results were not reproduced in the larger OASIS-2 trial[40] which randomized 3712 patients to the moderate-intensity regimen. The rate of cardiovascular death, MI, or stroke after 5 months was 7·65% with the anticoagulant and 8·4% without ($P = 0·37$). The authors suggested that poor compliance with treatment in some countries could have explained the negative results. A meta-analysis of 30 randomized studies published between 1960 and July 1999 among patients with CAD showed that high-intensity and moderate-intensity anticoagulation were effective in reducing MI and stroke but increased the risk of bleeding. In the presence of aspirin, low-intensity anticoagulation was not superior to aspirin alone, while moderate- to high-intensity anticoagulation and aspirin versus aspirin alone appeared promising with a modest increase in bleeding risk.[159]

A meta-analysis of prolonged use of low molecular weight heparin for up to 3 months after hospital discharge showed no consistent benefit (OR 0·98; 95% CI 0·81–1·17; $P = 0·80$) but an excess risk of major bleeding (OR 2·26; 95% CI 1·63–3·14; $P < 0·0001$).[160] In FRISC-II, dalteparin was administrated double-blind for 3 months following 5 days of open label administration. A significant reduction in rates of death, MI, and revascularization was observed after 30 days (3·1% *v* 5·9%; RR 0·53; $P = 0·02$) and 3 months (29·1% *v* 33·4%; $P = 0·03$), which was not sustained at 6 months.[161]

Coronary reperfusion procedures

Reperfusion therapy is increasingly successful as expertise, adjunctive pharmacotherapies, and technology are improving. It is a common clinical experience that reperfusion is the only effective means to control the unstable patient. It has also been long recognized that interventions are associated with a higher risk of complications when performed early during an unstable coronary condition and which are attenuated when interventions can be delayed past a period of medical stabilization. This early hazard can now be minimized with the use of coronary stenting and of ticlopidine or clopidogrel, and of the Gp IIb/IIIa antagonists. Modern trials are comparing treatment strategies randomizing patients to an early invasive or an early conservative management strategy. In the early invasive approach, coronary angiography is routinely performed followed by revascularization with either PCI or CABG; the choice of procedures is governed by expert judgment. In the early non-invasive approach, coronary angiography is performed only when there is evidence of recurrent spontaneous ischemia or when the ischemia can be induced by a provocative test, the criteria for evaluation being more or less stringent. Earlier trials that had compared CABG to medical therapy failed to show a difference in mortality with the two treatment strategies but succeeded in identifying subgroups of patients with depressed ejection fraction and with three vessel disease that benefitted significantly from surgery. Short- and long-term quality of life was also generally improved with reperfusion, and crossovers from medical therapy to CABG were frequent.[162–164]

The results of four major recent trials and of a few smaller trials comparing early invasive management to early conservative management were reported. The TIMI-3b randomized 1473 patients. The primary outcome of death, MI or an unsatisfactory symptom-limited exercise stress test performed at 6 weeks occurred in 18·1% of patients assigned to the early conservative strategy and 16·2% of patients assigned to the early invasive strategy (NS). The average length of initial hospitalization, the incidence of rehospitalization within 6 weeks, and days of rehospitalization were all decreased in the early invasive group.[165]

In the VANQWISH trial, 920 patients with a NSTEMI on the basis of CK-MB elevation were randomized within 72 hours of admission. More patients in the early invasive group experienced inhospital death (21 *v* 6; $P = 0·007$) or a composite of death or MI (36 *v* 15; $P = 0·004$); statistically significant differences persisted at 1 year and a trend towards higher mortality was still observed at 2 years.[166] The results of this study were questioned on the basis of the high mortality associated with CABG; no mortality was seen with PCI.

The MATE trial assigned 201 ACS patients ineligible for thrombolytic therapy to triage angiography within 24 hours, or early conservative strategy. Follow up at a median of 21 months showed no significant difference in the cumulative incidence of death, MI, rehospitalization, or revascularization between the two groups.[167] In the VINO study, 131 patients were randomized to first day angiography/angioplasty or conservative strategy. Death by 6 months occurred in 3·1% of invasive patients versus 13·4% of conservative patients ($P < 0·03$) and non-fatal MI in 3·1% and 14·9% ($P < 0·02$) respectively.[168]

More recently, the FRISC-II study enrolled 2457 patients with chest pain within the previous 48 hours and ST or T wave changes or elevated troponin T or CK-MB.[43] All patients received dalteparin in addition to aspirin in the first 5 days and were thereafter randomized to placebo or continued dalteparin administration for 3 months. Coronary angiography was done within the first 7 days in 96% of patients in the invasive arm and in 10% in the non-invasive arm, and revascularization was performed within the first

10 days in 71% and 9% of patients respectively. After 6 months there was a decrease in the composite end point of death or MI in the invasive group (9·4% *v* 12·1%; RR 0·78; 95% CI 0·62–0·98; $P < 0·031$) (Figure 30.15). At 1 year the mortality rate in the invasive strategy group was 2·2% compared with 3·9% in the non-invasive strategy group ($P = 0·016$).[169] There was a heterogeneous effect of the invasive strategies, which provided greater advantages at older age, in men, and with longer duration of angina, chest pain at rest, and ST-segment depression or Troponin-T elevation. The frequencies of symptomatic angina and readmission were halved by the invasive strategy. It was concluded that patients who first received an average of 6 days of treatment with LMWH, ASA, nitrates, and β blockers have a better outcome at 6 months.

The TACTICS trial enrolled 2220 patients with non-ST-segment elevation ACS characterized by ST-T changes suggestive of ischemia or elevated levels of cardiac markers or a history of coronary artery disease.[44] All patients received aspirin, heparin, and tirofiban. In the invasive arm, routine coronary angiography was performed within 4 to 48 hours and revascularization as appropriate. The primary outcome of death, non-fatal MI, or rehospitalization for an acute coronary syndrome at 6 months was 15·9% with use of the early invasive strategy and 19·4% with use of the conservative strategy (OR 0·78; 95% CI 0·62–0·97; $P = 0·025$). The rate of death or non-fatal MI at 6 months was similarly reduced (7·3% *v* 9·5%; OR 0·74; 95% CI 0·54–1·00; $P < 0·05$) (Figure 30.15). As in the FRISC-II trial, the patients who benefitted were those at medium or high risk, as defined by an elevation of TnT greater than 0·01 ng/ml, the presence of ST-segment deviation, or a TIMI risk score of greater than 3. In the absence of these high-risk features, outcomes in patients assigned to the two strategies were similar. Women in the FRISC-II trial derived no benefit from invasive management.[48] They were older, yet had less severe CAD and a better prognosis compared with men. Such a gender difference was not present in the TACTICS trial,[48] suggesting that the differences were related to baseline risk. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy.

Thus, the two most recent trials comparing invasive versus conservative strategies in patients with non-ST-segment elevation ACS showed a benefit in patients assigned to the invasive strategy using state-of-the-art pharmacologic therapy and stenting in the majority of cases. In FRISC-II, the invasive strategy involved treatment for an average of 6 days in the hospital with ASA and dalteparin. In TACTICS–TIMI-18, treatment included ASA, unfractionated heparin, and tirofiban and interventions were performed earlier (mean 22 h). A routine invasive management strategy is therefore recommended in patients with a non-ST-segment elevation ACS with high-risk features characterized by elevation of troponin levels, ST-segment ischemic changes or a high risk score determined by the global clinical evaluation. **Grade A** These patients also require aggressive antithrombotic therapy. **Grade A** Drugs that have been shown to be useful in randomized placebo-controlled studies include aspirin, clopidogrel, heparin, dalteparin, bivaluridin, and the Gp IIb/IIa antagonists eptifibatide and tirofiban in medical management and abciximab and eptifibatide in patients undergoing percutaneous intervention. **Grade A** Direct comparisons of the various drugs have shown superiority of enoxaparin over unfractionated heparin,[34,44] and over tinzaparin,[170] and of abciximab over tirofiban when administered in the cardiac catheterization laboratory before procedures. The combination of enoxaparin with eptifibatide[171] and with tirofiban[172] has been shown to be at least as effective and safe as the combination with unfractionated heparin. No direct comparisons, however, have been conducted between the various regimens that have been shown to be useful in non-ST-segment elevation ACS. Thus, the relative benefits of the combination of aspirin and clopidogrel (CURE regimen) versus the combination of aspirin and a Gp IIb/IIa antagonist (PURSUIT and PRISM-PLUS regimen), versus the combination of enoxaparin and ASA (ESSENCE regimen), are unknown. Further, the potential benefits of various drug combinations, such as for example ASA and enoxaparin with clopidogrel or with a Gp IIb/IIIa antagonist, have not been studied. Also, uncertainties exist as to the optimal timing for performing interventions. FRISC-II employed a delayed intervention strategy and TACTICS an accelerated strategy. Many centers used an immediate intervention strategy. On the other hand, no early routine invasive procedure was used in the CURE trial. The PCI–CURE study was designed to characterize prospectively the event rates in patients who underwent PCI in the trial. A total of 1313 patients, 21·2% of the total population, had such an intervention a median of 10 days after randomization; in 65% of patients, it was performed during the initial hospitalization, a median of 6 days after randomization. Open labeled ticlopidine or clopidogrel was administered during PCI and for 4 weeks thereafter. The primary end point of cardiovascular death, MI, or urgent target vessel revascularization within 30 days of PCI occurred in 4·5% of patients in the clopidogrel group compared with 6·4% in the placebo group (RR 0·70; 95% CI 0·50–0·97; $P = 0·03$). There was also less use of Gp IIb/IIIa inhibitor in the clopidogrel group ($P = 0·001$).[173] These results may suggest that more prolonged administration of clopidogrel before percutaneous interventions could amplify the benefit, possibly by more complete plaque passivation. Thus, much evidence remains to be acquired to define the optimal modalities for medical and invasive management of patients with non-ST-segment elevation ACS. In the mean time, the best current evidence dictates the use of a combination of ASA and clopidogrel, **Grade A** plus unfractionated heparin or low

molecular weight heparin, **Grade A** plus a Gp IIb/IIIa antagonist in the patients remaining unstable and referred for an interventional procedure. **Grade A** An early invasive management approach is recommended for patients with ST-segment shifts or an elevation of troponin T or I. **Grade A** Enoxaparin is preferred over unfractionated heparin when the primary emphasis is placed on medical management with no immediate intervention planned, **Grade A** and caution is advised in the use of clopidogrel in patients with immediate PCI and a possibility of rapid CABG. **Grade A** In the low-risk patients with no ischemic changes, no troponin elevation and no recurrent ischemia, risk stratification with a treadmill or another provocative test is recommended. **Grade A**

Case series support the use of the intra-aortic balloon pump as a bridge to PCI or CABG to stabilize hemodynamically unstable patients and patients with severe recurrent ischemia on treatment. **Grade B**

Cell protection

Cell necrosis is a significant problem in patients with a non-ST-segment elevation acute coronary syndrome, as close to 50% of patients have some degree of necrosis at admission and 5–15% develop a new myocardial infarction within a few weeks (Figure 30.5). Reperfusion procedures are frequently associated with myocardial infarction and there is a correlation between subsequent mortality and elevation of blood markers of necrosis, even within the range of only one and three times normal.[174] Measures that could prevent or halt the progression of myocardial cell ischemia to necrosis could therefore optimize the benefit of current treatment strategies (see Figure 30.9).[91] These have been investigated mainly in evolving ST-segment elevation MI, with the goal of reducing infarct size. A number of interventions have been shown to be protective in experimental models of ischemia reperfusion. None of these interventions, however, have translated into relevant benefit in humans. Beta blockers were shown in a meta-analysis to be of moderate benefit to prevent myocardial infarction in patients with threatened myocardial infarction.[108] A recent trial with cariporide, an inhibitor of the Na^+/H^+ exchanger that prevents the accumulation of anions within the ischemic cell, failed to prevent myocardial infarction in patients with a non-ST-segment elevation ACS and in patients undergoing high-risk percutaneous interventions.[175] Pilot studies with antibodies against leukocyte integrins and against the cytokine tissue necrosis factor α (TNF-α) suggested no reductions of infarct size.[176]

Plaque passivation

An attractive treatment strategy for acute coronary syndromes is control of inflammatory processes associated with plaque degradation that result in plaque rupture and thrombus formation (see Figure 30·9). In principle, these therapies could be applied before, during or after the rupture. Since there are no means to easily and reliably identify vulnerable plaques, administration of these therapies before the clinical manifestations of acute coronary syndromes is not practicable. On the other hand, secondary preventive measures applied past the very acute phase, as will be discussed in the next section, are rewarding, particularly statin therapy and control of risk factors. Percutaneous interventions including stent implantation are very effective during the acute process, possibly by interrupting some of the processes implicated in the disease. A 48 hour course of methylprednisone in a small pilot study in patients with unstable angina was ineffective to prevent ischemic events and even accelerated their manifestations.[177] Statins and ACE inhibitors can promote plaque stabilization by their anti-inflammatory, antioxidant, anti-cell proliferative and anticoagulant properties.[178]

Many trials and registries have shown that statins started 2–10 days after an ACS are well tolerated and associated with reductions in total and low density lipoprotein cholesterol. In pooled observational data of 20 809 ACS patients enrolled in clinical trials, the presence of lipid lowering therapy at hospital discharge was associated with a 56% reduction in risk of mortality at 1 month ($P = 0{\cdot}001$).[179] A Swedish registry of 5528 AMI survivors reported a 1 year mortality of 9·3% in the 14 071 patients who had no statin at hospital discharge and of 4·0% in the 5528 patients with a statin.[180]

In a small randomized trial, the initiation of pravastatin 6 days after the acute phase was associated with a significant reduction in the incidence of major cardiovascular events at 2 years ($P < 0{\cdot}03$).[181] The MIRACL study was the first large-scale clinical trial to investigate early treatment with a statin in patients with an ACS.[182] A total of 3086 patients with no interventions anticipated were randomized within 24–96 hours of hospital admission to high-dose atorvastatin or placebo. The primary outcome of death, non-fatal MI, resuscitated cardiac arrest or worsening angina requiring urgent rehospitalization occurred at 16 weeks in 14·8% of treated patients and 17·4% of placebo patients (RR 0·84; $P = 0{\cdot}048$). The benefit was limited to the reduction of the outcome of worsening angina and there were no significant differences in the risk of death, non-fatal MI, or cardiac arrest. The survival curves diverged after a few weeks. The MIRACL trial showed no definitive evidence of an early benefit for statins. Nevertheless, until the results of ongoing trials are known, it is recommended to initiate statin therapy in hospital, before hospital discharge. **Grade B** This approach increases the likelihood that patients will continue to comply with statin therapy and results in a greater percentage of patients using a statin after one year.[183] Numerous large-scale trials have documented marked benefits of statins used in primary and secondary prevention.

Subacute therapy

Those patients who respond quickly to optimal medical therapy in hospital, and who are found to be at relatively low risk based upon a variety of prognostic factors and non-invasive testing, require long-term follow up. Once they have stabilized for about 24–48 hours in hospital, with no ischemic pain recurrence, intravenous nitrate therapy is generally tapered with the substitution of oral or topical nitrates. The early efficacy of β blockers, and evidence for long-term benefits in patients following MI[184] and with stable ischemia, suggest that the therapy should be continued indefinitely. Similar analogies appear reasonable if a rate-limiting calcium antagonist was chosen because of contraindications to a β blocker, although there is no good evidence for long-term benefit in terms of major cardiovascular outcomes. If large doses of β blocker or calcium antagonists, or combined therapy, were required for control of the ischemic episodes, judicious decrements of intensity are likely to be appropriate once the patient is fully mobilized and non-invasive testing has indicated that revascularization is not obligatory. **Grade A**

The evidence from the initial trials of aspirin for unstable angina[121] demonstrated ongoing benefit for up to 2 years, consistent with evidence in survivors of MI and patients with stable angina.[123] Accordingly, aspirin should be continued indefinitely. Clopidogrel, 75 mg daily should be started on admission, and continued for at least 9–12 months, in conjunction with aspirin. **Grade A1b** For those patients intolerant of aspirin, clopidogrel alone is likely to be efficacious. **Grade A** Heparin should be sustained for at least 48 hours following the resolution of acute ischemic episodes.[148] Low molecular weight heparins appear to be at least as efficacious as unfractionated heparin and may be preferable in terms of ease of use and cost–benefit considerations. They have generally been used in clinical trials for longer periods of time than unfractionated heparin and can therefore be administered until hospital discharge. **Grade C** Clinical trials of oral Gp IIb/IIIa receptor antagonists have demonstrated no benefit and potential harm from these agents. **Grade A**

Early attention to optimal management of coronary risk factors is mandatory as their control is definitively of benefit. **Grade A** It is recommended to initiate a statin in hospital. **Grade A1c** The HPS study showed benefit independently of initial cholesterol levels.[185]

Recent evidence indicates that tight control of glucose in patients with type 2 diabetes reduces the risk of death following MI and among patients with newly detected type 2 diabetes.[186–188] The recurrence of an unstable phase of coronary artery disease or poor symptomatic control in patients being managed on medical therapy generally mandates reconsideration of the option of revascularization **Grade A** and, if not feasible, alternative medical therapy and the consideration of possible aspirin failure. **Grade B** Risk factor management is of great importance in those patients who have undergone revascularization and is focused on limiting progression of disease in non-revascularized vessels and in areas of percutaneous intervention and bypass conduits. The long-term use of an ACE inhibitor is likely to be beneficial in all but the lowest-risk patients who have experienced non-ST-segment elevation acute coronary syndromes.[189] **Grade A**

References

1. Fowler NO. "Preinfarctional" angina: a need for an objective definition and for a controlled clinical trial of its management. *Circulation* 1971;**44**:755–8.
2. Wood P. Therapeutic application of anticoagulants. *Trans Med Soc Lond* 1948;**66**:80.
3. Fuster V, Steele PM, Chesebro JH. Role of platelets and thrombosis in coronary atherosclerotic disease and sudden death. *J Am Coll Cardiol* 1985;**5**:175B–184B.
4. Davies MJ and Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984;**310**:1137–40.
5. Davies M, Thomas A, Knapman P, Hangartner R. Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischaemic cardiac death. *Circulation* 1986; **73**:418–27.
6. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total coronary occlusion. *Circulation* 1985;**71**:699–708.
7. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaque underlying fatal occlusive thrombi. *Br Heart J* 1983;**50**:127–34.
8. DeWood MA, Spores J, Notske R *et al.* Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.
9. Braunwald E, Antman EM, Beasley JW *et al.* ACC/AHA guidelines for the management of patients with unstable angina-non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). 2002. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf
10. Braunwald E. Unstable angina. A classification. *Circulation* 1989;**80**:410–14.
11. Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 2001.
12. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the

redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959–69.
13. Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;**102**:118–22.
14. Nourjah P. National Hospital Ambulatory Medical Care Survey: 1997 emergency department summary. Advance data from Vital and Health Statistics. Hyattsville, MD: National Center for Health Statistics, 1999:**304**.
15. National Center for Health Statistics. Detailed diagnoses and procedures. National Hospital Discharge Survey, 1996.
16. Data from Vital and Health Statistics. Hyattsville, MD: National Center for Health Statistics, 1998:**13**.
17. Bata IR, Gregor RD, Eastwood BJ, Wolf HK. Trends in the incidence of acute myocardial infarction between 1984 and 1993 – The Halifax County MONICA Project. *Can J Cardiol* 2000;**16**:589–95.
18. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998;**80**:40–4.
19. Madsen M, Rasmussen S, Juel K. [Acute myocardial infarction in Denmark. Incidence development and prognosis during a 20-year period]. *Ugeskr Laeger* 2000;**162**:5918–23.
20. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978–1994. *Eur Heart J* 1998;**19**:429–34.
21. Fox KA, Cokkinos DV, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J* 2000;**21**:1440–9.
22. Goldberg RJ, Steg PG, Sadiq I *et al.* Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (the GRACE registry). *Am J Cardiol* 2002;**89**:791–6.
23. Furman MI, Dauerman HL, Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi- hospital, community-wide perspective. *J Am Coll Cardiol* 2001; **37**:1571–80.
24. Braunwald E, Mark DB, Jones RH *et al.* Unstable angina: diagnosis and management. Clinical practice guideline, no. 10 (Agency for Health Care Policy and Research Publications No. 94: 6–2). Rockville, MD: US Department of Health and Human Services, 1994.
25. Malmberg K, Yusuf S, Gerstein HC *et al.* Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;**102**:1014–19.
26. Savonitto S, Ardissino D, Granger CB *et al.* Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;**281**:707–13.
27. Bogaty P, Poirier P, Simard S, Boyer L, Solymoss S, Dagenais GR. Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. *Circulation* 2001;**103**:3062–8.
28. Bahit MC, Granger CB, Wallentin L. Persistence of the prothrombotic state after acute coronary syndromes: implications for treatment. *Am Heart J* 2002;**143**:205–16.
29. Cairns JA, Fantus IG, Klassen GA. Unstable angina pectoris. *Am Heart J* 1976;**92**:373–86.
30. Cairns J, Singer J, Gent M *et al.* One-year mortality outcomes of all coronary and intensive care units with acute myocardial infarction, unstable angina or other chest pain in Hamilton, Canada, a city of 375 000 people. *Can J Cardiol* 1989;**5**: 239–46.
31. The RISC Group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;**226**:827–30.
32. Theroux P, Waters D, Qiu S *et al.* Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993;**88**:2045–8.
33. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775–82.
34. Cohen M, Demers C, Gurfinkel EP *et al.* A comparison of low molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;**337**:447–52.
35. Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM) Study Investigators. A comparison of aspirin plus tirofiban versus aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498–505.
36. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488–97.
37. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network. *Circulation* 1998;**97**:2386–95.
38. Mahaffey KW, Roe MT, Dyke CK *et al.* Misreporting of myocardial infarction end points: results of adjudication by a central clinical events committee in the PARAGON-B trial. Second Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network Trial. *Am Heart J* 2002;**143**:242–8.
39. PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436–43.
40. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomized trial. *Lancet* 1999;**353**:429–38.

41.Antman EM, McCabe CH, Gurfinkel EP *et al.* Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;**100**:1593–601.
42.The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomized trial. *Lancet* 2001;**357**:1915–24.
43.FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomized multicenter study. *Lancet* 1999; **354**:708–15.
44.Cannon CP, Weintraub WS, Demopoulos LA *et al.* Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001; **344**: 1879–87.
45.Jayes RL Jr, Beshansky JR, D'Agostino RB, Selker HP. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992;**45**:621–6.
46.Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. *Ann Intern Med* 2001;**135**:801–11.
47.Hochman JS, Tamis JE, Thompson TD *et al.* Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med* 1999;**341**:226–32.
48.Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol* 2001;**38**:41–8.
49.Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000;**160**:1354–60.
50.Hamm CW, Ravkilde J, Gerhardt W *et al.* The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;**327**:146–50.
51.Antman EM, Tanasijevic MJ, Thompson B *et al.* Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;**335**:1342–9.
52.Lindahl B, Venge P, Armstrong P *et al.* Troponin-T 0·03 μg/l is the most appropriate cut-off level between high and low risk acute coronary syndrome patients: prospective verification in a large cohort of placebo patients from the GUSTO-IV ACS study. *J Am Coll Cardiol* 2001;**37**(Suppl. A):326A.
53.Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996; **93**:1651–7.
54.Olatidoye AG, Wu AH, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. *Am J Cardiol* 1998;**81**:1405–10.
55.Ottani F, Galvani M, Nicolini FA *et al.* Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J* 2000;**140**: 917–27.
56.Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol* 2001;**38**:478–85.
57.Hamm CW, Heeschen C, Goldmann B *et al.* Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999;**340**:1623–9.
58.Morrow DA, Antman EM, Tanasijevic M *et al.* Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. *J Am Coll Cardiol* 2000;**36**:1812–17.
59.Morrow DA, Cannon CP, Rifai N *et al.* The TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA* 2001;**286**: 2405–12.
60.Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. *J Am Coll Cardiol* 1989;**13**:1495–502.
61.Cannon CP, McCabe CH, Stone PH *et al.* The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol* 1997;**30**:133–40.
62.Kaul P, Fu Y, Chang WC *et al.* Prognostic value of ST-segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. *J Am Coll Cardiol* 2001; **38**:64–71.
63.Hyde TA, French JK, Wong CK *et al.* Four-year survival of patients with acute coronary syndromes without ST segment elevation and prognostic significance of 0·5-mm ST segment depression. *Am J Cardiol* 1999;**84**:379–85.
64.de Zwaan C, Bär FW, Janssen JHA *et al.* Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989;**117**:657–65.
65.Cohen M, Hawkins L, Greenberg S, Fuster V. Usefulness of ST-segment changes in >2 leads on the emergency room electrocardiogram in either unstable angina pectoris or non-Q-wave myocardial infarction in predicting outcome. *Am J Cardiol* 1991;**67**:1368–73.
66.Armstrong PW, Fu Y, Chang WC *et al.* Acute coronary syndromes in the GUSTO-IIb trial. Prognostic insights and impact of recurrent ischemia. *Circulation* 1998;**98**:1860–8.
67.Boersma E, Pieper KS, Steyerberg EW *et al.* Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–67.
68.Antman EM, Cohen M, Bernink PJ *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision-making. *JAMA* 2000; **284**:835–42.
69.Morrow DA, Antman EM, Snapinn S *et al.* An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI

risk score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J* 2002;**23**:223–9.
70. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;**97**:2007–11.
71. Liuzzo G, Biasucci LM, Gallimore JR *et al.* Enhanced inflammatory response in patients with pre-infarction unstable angina. *J Am Coll Cardiol* 1999;**34**:1696–703.
72. Biasucci LM, Liuzzo G, Grillo RL *et al.* Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation* 1999;**99**: 855–60.
73. Toss H, Lindahl B, Siegbahn A *et al.* Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *Circulation* 1997; **96**:4204–10.
74. Heeschen C, Hamm CW, Bruemmer J *et al.* Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. *J Am Coll Cardiol* 2000;**35**:1535–42.
75. Haverkate F, Thompson SG, Pyke SD *et al.* Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997;**349**:462–6.
76. Lindahl B, Toss H, Siegbahn A *et al.* Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000;**343**:1139–47.
77. Morrow DA, Rifai N, Antman EM *et al.* C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol* 1998;**31**:1460–5.
78. Ridker PM, Rifai N, Clearfield M *et al.* Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;**344**:1959–65.
79. Ridker PM, Cushman M, Stampfer MJ *et al.* Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;**336**:973–9.
80. Buffon A, Liuzzo G, Biasucci LM *et al.* Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. *J Am Coll Cardiol* 1999;**34**:1512–21.
81. Chew DP, Bhatt DL, Robbins MA *et al.* Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. *Circulation* 2001;**104**:992–7.
82. Milazzo D, Biasucci LM, Luciani N *et al.* Elevated levels of C-reactive protein before coronary artery bypass grafting predict recurrence of ischemic events. *Am J Cardiol* 1999;**84**:459–61.
83. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998;**97**:1195–206.
84. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135–43.
85. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001;**104**:365–72.
86. Arbustini E, Bello BD, Morbini P *et al.* Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 1999;**82**:269–72.
87. Frink RJ. Chronic ulcerated plaques: new insights into the pathogenesis of acute coronary disease. *J Invas Cardiol* 1994;**6**:173–85.
88. Tracy RE, Devaney K, Kissling G. Characteristics of the plaque under a coronary thrombus. *Virchows Arch A Pathol Anat Histopathol* 1985;**405**:411–27.
89. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000; **343**:915–22.
90. The TIMI IIIA Investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients with ischemic cardiac pain at rest. Results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. *Circulation* 1993;**87**:38–52.
91. Theroux P. Myocardial cell protection: a challenging time for action and a challenging time for clinical research. *Circulation* 2000;**101**:2874–6.
92. Orlander R. Use of nitrates in the treatment of unstable and variant angina. *Drugs* 1987;**33**:131–9.
93. Gobel EJAM, Hautvast RWH, van Gilst WH *et al.* Randomized, double-blind trial of intravenous diltiazem versus glyceral tinitrate for unstable angina pectoris. *Lancet* 1995;**346**:1653–7.
94. Jugdutt BL, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarction size, expansions and complications. Effective timing, dosage and infarct location. *Circulation* 1988;**78**:906–20.
95. ISIS-4. A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected myocardial infarction. *Lancet* 1995;**345**:669–85.
96. Gruppo Italiano per lo Studio della Sopravvivenze nell'Infarto Miocardico. GISSI-3: effects of lisinopril and trandermal glyceryl trinitrate single and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;**343**:1115–22.
97. Cheitlin MD, Hutter AMJ, Brindis RG *et al.* ACC/AHA expert consensus document use of sildenafil (Viagra) in patients with cardiovascular disease: American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 1999;**33**:273–82.
98. Muller JE, Turi ZG, Pearle DL *et al.* Nifedipine and conventional therapy for unstable angina pectoris: a randomized, double-blind comparison. *Circulation* 1984;**69**:728–39.
99. The Netherlands Interuniversity Nifedipine/Metropolol Trial (HINT) Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double-blind, placebo controlled comparison of recurrent ischemia in patients treated with nifedipine or metropolol or both. *Br Heart J* 1986;**73**:331–7.
100. Gottlieb So, Weisfeldt M, Ouyang P *et al.* Effect of the addition of propranolol to therapy with nifedipine for unstable

angina pectoris. A randomized, double-blind, placebo-controlled trial. *Circulation* 1986;**73**:331–7.
101. Gerstenblith G, Ouyang P, Achuff SC *et al.* Nifedipine in unstable angina: a double-blind, randomized trial. *N Engl J Med* 1982;**306**:885–9.
102. Furberg CD, Psaty BM, Meye JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;**92**:1326–31.
103. Theroux P, Taeymans Y, Morrissette D, Bosch Y, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;**5**:717–22.
104. Andre-Fouet X, Usdin JP, Gayet CH *et al.* Comparison of short-term efficacy of diltiazem and propranolol in unstable angina at rest. A randomized trial in 70 patients. *Eur Heart J* 1983;**4**:691–8.
105. Parodi O, Maseri A, Simonetti I. Management of unstable angina by verapamil. A double-blind crossover study in CCU. *Br Heart J* 1979;**41**:167–74.
106. Mehta J, Pepine CJ, Day M, Guerrero JR, Conti CR. Short-term efficacy of oral verapamil in rest angina. A double-blind controlled trial in CCU patients. *Am J Med* 1981;**71**: 977–82.
107. Scheidt S, Frishman WH, Packer M, Parodi O, Subramanian VB. Long-term effectiveness of verapamil in stable and unstable angina pectoris. One-year follow-up of patients treated in placebo-controlled double-blind randomized clinical trials. *Am J Cardiol* 1982;**50**:1185–90.
108. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;**260**:2259–63.
109. Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the K(ATP) channel in unstable angina. Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil. CESAR 2 investigation. Clinical European studies in angina and revascularization. *Eur Heart J* 1999;**20**:51–7.
110. Johnson SM, Mauritson DR, Willerson JT, Hillis LD. A controlled trial of verapamil for Prinzmetal's variant angina. *N Engl J Med* 1981;**304**:862–66.
111. Capucci A, Bracchetti D, Carini GC, DiCio G, Maresta A, Magnani B. Propranolol versus verapamil in patients with unstable angina. In: Zanchetti A, Krikler DM, eds. *Calcium antagonism in cardiovascular therapy. Experience with verapamil.* Amsterdam: Excerpta Medica, 1981.
112. Parodi O, Simoneti I, Michelassi C *et al.* Comparison of verapamil and propranolol therapy for angina pectoris at rest. A randomized, multiple-crossover, controlled trial in the coronary care unit. *Am J Cardiol* 1986;**57**:899–906.
113. Rosenthal SJ, Ginsburg R, Lamb IH, Baim DS, Schroeder JS. Efficiacy of diltiazem for control of symptoms of coronary artery spasm. *Am J Cardiol* 1980;**46**:1027–32.
114. Pepine CJ, Feldman RL, Whittle J, Curry RC, Conti GR. Effect of diltiazem in patients with variant angina. A randomized double-blind trial. *Am Heart J* 1981;**101**:719–25.
115. Schroeder JS, Feldman RL, Giles TD *et al.* Multiclinic controlled trial of diltiazem for Prinzmetal's variant angina. *JAMA* 1982;**72**:227–32.
116. Tilmant PY, LaBlanche JM, Thieuleux FA, Dupuis BA, Bertrand ME. Detrimental effect of propranolol in patients with coronary arterial spasm countered by combination with diltiazem. *Am J Cardiol* 1983;**52**:230–3.
117. Previtali M, Salerno J, Tavazzi L *et al.* Treatment of angina at rest with nifedipine: a short-term controlled study. *Am J Cardiol* 1980;**45**:825–30.
118. Ginsburg R, Lab IH, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J* 1982;**103**:44–8.
119. Hill JA, Feldman RI, Pepine CJ, Conti CR. Randomized double-blind comparison of nifedipine and isosorbide dinitrate in patients with coronary arterial spasm. *Am J Cardiol* 1982; **49**:431–8.
120. Rizik DG, Healy S, Margulis A *et al.* A new clinical classification for hospital prognosis of unstable angina pectoris. *Am J Cardiol* 1995;**75**:993–7.
121. Lewis HD, Davis JW, Archibald DG *et al.* Protective effects of aspirin against myocardial infarction and death in men with unstable angina. *N Engl J Med* 1983;**313**:396–403.
122. Cairns JA, Gent M, Singer J *et al.* Aspirin, sulfinpyrazone, or both in unstable angina. *N Engl J Med* 1985;**313**: 1369–75.
123. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002;**324**: 71–86.
124. Patrono C, Coller B, Dalen JE *et al.* Platelet-active drugs. The relationships among dose, effectiveness, and side effects. *Chest* 2001;**119**:39S–63S.
125. Gum PA, Kottke-Marchant K, Poggio ED *et al.* Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 2001;**88**:230–5.
126. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;**105**:1650–5.
127. Catella-Lawson F, Reilly MP, Kapoor SC *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;**345**:1809–17.
128. Cipollone F, Ciabattoni G, Patrignani P *et al.* Oxidant stress and aspirin-insensitive thromboxane biosynthesis in severe unstable angina. *Circulation* 2000;**102**:1007–13.
129. Theroux P, Latour JG, Diodati J *et al.* Hemodynamic, platelet, and clinical response to prostacycline in unstable angina pectoris. *Am J Cardiol* 1990;**65**:1084–9.
130. Cayatte AJ, Du Y, Oliver-Krasinski J, Lavielle G, Verbeuren TJ, Cohen RA. The thromboxane receptor antagonist S18886 but not aspirin inhibits atherogenesis in apo E-deficient mice. Evidence that eicosanoids other than thromboxane contribute to atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000; **20**:1724–8.
131. Balsano F, Rizzon P, Violi F *et al.* Antiplatelet treatment with ticlopidine in unstable angina. *Circulation* 1990;**82**: 17–26.
132. Gent M, Blakely JA, Easton JD *et al.* The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;**1**:1215–20.

133.Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:363–8.
134.CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
135.Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
136.The CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.
137.The Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-B Investigators. Randomized, placebo- controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation* 2002;**105**:316–21.
138.EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1997;**336**: 1689–96.
139.The EPISTENT Investigators. Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
140.The CAPTURE Investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE trial. *Lancet* 1997;**349**:1429–35.
141.Topol EJ, Moliterno DJ, Herrmann HC *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;**344**:1888–94.
142.The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;**96**:1445–53.
143.O'Shea JC, Hafley GE, Greenberg S *et al.* Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. *JAMA* 2001;**285**:2468–73.
144.Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;**100**:2045–8.
145.Boersma E, Harrington RA, Moliterno DJ *et al.* Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomized clinical trials. *Lancet* 2002;**359**:189–98.
146.Roffi M, Chew DP, Mukherjee D *et al.* Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001;**104**:2767–71.
147.Chew DP, Bhatt DL, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists. A meta-analysis of phase III multicenter randomized trials. *Circulation* 2001;**103**:201–6.
148.Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin [see comments]. *N Engl J Med* 1992;**327**: 141–5.
149.Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy. Heparin: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;**103**: 2994–3018.
150.Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**: 561–8.
151.Klein W, Buchwald A, Hillis SE *et al.* Fragmin in unstable coronary artery disease study: comparison of low- molecular weight- heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. *Circulation* 1997;**96**:61–8.
152.The FRAXIS Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAXIS (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;**20**:1553–62.
153.Antman EM, Cohen M, Radley D *et al.* Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;**100**:1602–8.
154.Weitz JI, Buller HR. Direct thrombin inhibitors in acute coronary syndromes. Present and future. *Circulation* 2002;**105**: 1004–11.
155.The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;**90**:1631–7.
156.Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996;**94**:911–21.
157.Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. *Circulation* 1997;**96**:769–77.
158.The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;**359**:294–302.
159.Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999; **282**: 2058–67.
160.Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low- molecular weight-heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;**355**:1936–42.
161.Fragmin and Revascularization during InStability in Coronary artery disease (FRISC II) Investigators. *Lancet* 1999;**353**: 701–7.

162. Luchi RJ, Scott SM, Deupree RH *et al.* Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1987;**316**:977–84.
163. Parisi AF, Khuri S, Deupree RH, Sharma GV, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina: 5-year mortality and morbidity in the Veterans Administration Study. *Circulation* 1989;**80**: 1176–89.
164. Booth DC, Deupree RH, Hultgren HN *et al.* Quality of life after bypass surgery for unstable angina. *Circulation* 1991;**83**: 87–95.
165. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994;**89**:1545–56.
166. Boden WE, O'Rourke RA, Crawford MH *et al.* Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;**338**:1785–92.
167. McCullough PA, O'Neill WW, Graham M *et al.* A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;**32**: 596–605.
168. Spacek R, Straka SE, Polasek JD *et al.* Value of first day angiography/angioplasty in evolving non-ST-segment elevation myocardial infarction: an open multicenter trial. The VINO Study. *Eur Heart J* 2002;**23**: 230–8.
169. Wallentin L, Lagerqvist B, Husted S *et al.* Outcome at one year after an invasive compared with a non-invasive strategy in unstable coronary artery disease: the FRISC II invasive randomized trial. *Lancet* 2000;**356**:9–16.
170. Michalis LK, Papamichail N, Katsouras C *et al.* Enoxaparin versus tinzaparin in the management of unstable coronary artery disease (EVET Study) (Abstract). *J Am Coll Cardiol* 2001;**37**:365a.
171. Goodman S. The INTERACT trial. Presented at the ACC Scientific Sessions, Atlanta, GA, March 2002.
172. Cohen M, Theroux P, Frey MJ *et al.* Anti-thrombotic combination using tirofiban and enoxaparin: the ACUTE II Study (Abstract). *Circulation* 2000;**102**(Suppl. II):II-826.
173. Mehta SR, Yusuf S, Peters RJ *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–33.
174. Tardiff BE, Califf RM, Tcheng JE *et al.* Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. IMPACT-II Investigators. Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II. *J Am Coll Cardiol* 1999; **33**:88–96.
175. Theroux P, Chaitman BR, Danchin N *et al.* Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations. Main results of the GUARDIAN trial. Guard During Ischemia Against Necrosis (GUARDIAN) Investigators. *Circulation* 2000;**102**:3032–8.
176. Baran KW, Nguyen M, McKendall GR *et al.* Double-blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction: limitation of myocardial infarction following thrombolysis in acute myocardial infarction (LIMIT AMI) study. *Circulation* 2001;**104**: 2778–83.
177. Azar RR, Rinfret S, Theroux P *et al.* A randomized placebo-controlled trial to assess the efficacy of anti-inflammatory therapy with methylprednisolone in unstable angina (MUNA trial). *Eur Heart J* 2000;**21**:2026–32.
178. Davignon J, Mabile L. Mechanisms of action of statins and their pleiotropic effects. *Ann Endocrinol (Paris)* 2001; **62**: 101–12.
179. Aronow HD, Topol EJ, Roe MT *et al.* Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet* 2001;**357**:1063–8.
180. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;**285**:430–6.
181. Arntz HR, Wunderlich W, Schnitzer L. The decisive importance of cholesterol lowering therapy for coronary lesions and clinical course immediately after an acute coronary event: short and long-term results of a controlled study. *Circulation* 1998;**98**(Suppl. 1):I-45.
182. Schwartz GG, Olsson AG, Ezekowitz MD *et al.* Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–18.
183. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol* 2001;**87**:819–22.
184. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Progr Cardiovasc Dis* 1985;**27**:335–71.
185. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20/536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
186. Malmberg K, Ryden L, Efendic S *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGA-MI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57–65.
187. American Diabetes Association. Standards of medical care for patients with diabetes mellitus (position statement). *Diabetes Care* 1999;**22**(Suppl. 1):S32–41.
188. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**: 703–13.
189. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.

31 Fibrinolytic therapy

James S Zebrack, Jeffrey L Anderson

Impact, pathophysiology, and rationale

Over 5 million people visit US emergency departments each year for evaluation of chest pain and related symptoms, and almost 1·5 million are hospitalized for an acute coronary syndrome.[1–3] Acute myocardial infarction (AMI) is the primary discharge diagnosis in the US in 750 000 annually,[4,5] and over 225 000 deaths are attributed to AMI each year.[4] At least one half of AMI-related deaths occur within one hour of onset of symptoms and before reaching a hospital emergency department.[6] In addition, the majority of sudden cardiac deaths (300 000 annually in the US) are believed to have an ischemic basis.[7–9]

Acute reperfusion (achieved by fibrinolysis or coronary angioplasty) represents the greatest of global conceptual and practical advance for therapy ST-segment elevation (STE) AMI.[10] STE-AMI currently represents approximately one third of AMI presentations.[5,11] With broad application of reperfusion therapy, 30 day mortality rates from STE-AMI have progressively declined (from 20–30% to 5–10%).[11–14]

Herrick in the US and Obraztsov in Russia postulated almost a century ago that thrombosis-related coronary occlusion precipitates AMI.[15,16] However, controversy about the role of thrombosis continued[17–19] until 1980 when DeWood *et al*[20] demonstrated coronary occlusion in 87% of STE-AMI patients studied within 4 hours of symptom onset. The occlusion was proved to be thrombotic by observations during emergent bypass surgery or intracoronary fibrinolysis. Renewed focus on acute coronary thrombosis and reperfusion therapy ensued.

Erosion or sudden rupture of an atherosclerotic cap, weakened by internal metalloproteinase activity, has been determined to be the precipitant of coronary thrombosis.[21] Exposure of blood to collagen, other matrix elements, and the lipid core with its macrophage-derived tissue factor stimulates platelet adhesion, activation, and aggregation; thrombin generation; and fibrin formation. Vasospasm and initiation of a platelet-rich clot ensue. When these processes lead to reduction or interruption of coronary blood flow, myocardial infarction may occur. In canine models,[22,23] myocardial cell death begins within 15 minutes of coronary occlusion and proceeds rapidly in a wavefront from endocardium to epicardium. Timely reperfusion (within about 3 hours) achieves partial myocardial salvage. The rate and extent of necrosis (and salvage) is modified by metabolic demands and collateral blood supply.

The benefits of therapy depend on the rate and extent to which myocardial perfusion is effectively achieved.[24–26] Reperfusion is scored by the Thrombolysis In Myocardial Infarction (TIMI) visual[24] or frame-counts[27] supplemented, recently, by a TIMI myocardial perfusion (TMP) score.[28] Restoration of TIMI grade 3 (normal) epicardial flow is associated with lower mortality rates than TIMI grades 0–2 (3·7% *v* 7·0%).[25,28] Among those with TIMI 3 flow, lower mortality is associated with TMP grade 3 (0·7%) than with TMP grades 2 (2·9%) or 0–1 (5·4%).[28] The factors differentiating epicardial and myocardial reperfusion are incompletely understood. Platelet and platelet-leukocyte aggregates and secreted vasoactive and thrombogenic factors have received recent attention, and combinations of fibrinolytic therapy with potent platelet inhibitors to further improve myocardial perfusion are being actively studied.[29]

Early observational and controlled studies

In 1933, Tillet and Garner published their discovery of a streptococcal fibrinolysin.[30,31] Clinical application of streptokinase to AMI was first reported in 1958.[32] From then until 1979, at least 17 studies were published, but AMI pathophysiology was not well understood, and results were inconclusive and poorly accepted.[33–35] With the establishment of the thrombotic nature of coronary occlusion[20] several groups demonstrated the feasibility of clinical fibrinolysis to achieve early reperfusion under angiographic monitoring (≅75% success with intracoronary [IC] SK) in the period 1976–83.[36–39]

Randomized studies in AMI followed. Anderson *et al.* reported in 1983[40] a benefit of early (<4 h) IC SK on clinical, ECG, enzymatic, and imaging end points. Later therapy (at >6 hours) relieved ischemic pain but did not benefit regional myocardial function in another study.[41] The potential for mortality benefit of IC SK was suggested by subsequent Western Washington and Dutch studies in a few hundred patients.[42–44] The logistic difficulties with intracoronary administration stimulated the re-evaluation of IV SK (Schröder *et al*[45]). By the mid-1980s, favorable comparisons with IC SK[46–48] and a larger outcomes study of

IV SK (ISAM)[49] established the intravenous route for subsequent clinical trials.

Fibrinolytic agents

General mechanisms of action and pharmacological properties

Fibrinolysis is mediated by plasmin, a non-specific serine protease that degrades clot-associated fibrin and fibrinogen, disrupting a forming thrombus, facilitating reperfusion. The fibrinolytic (or "thrombolytic") agents are all plasminogen activators, directly or indirectly converting the proenzyme plasminogen to plasmin by cleaving the arginine 560–valine 561 bond (Figure 31.1). Plasmin degrades several proteins, including fibrin, fibrinogen, prothrombin, and factors V and VII. The fibrinolytic agents differ in several properties, as summarized in the text and Table 31.1.

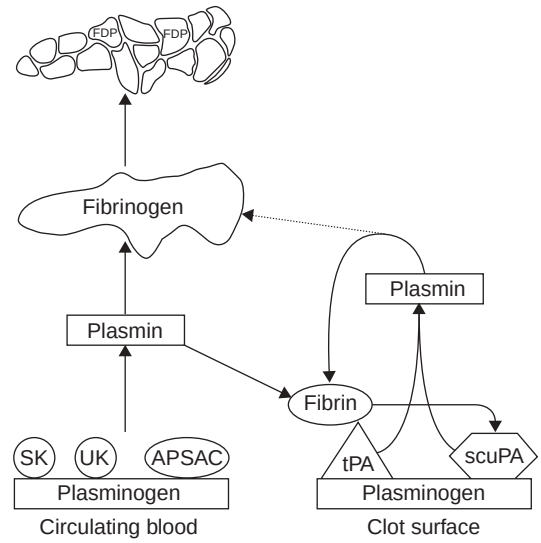


Figure 31.1 Schematic representation of the action of fibrinolytic enzymes. Streptokinase (SK), urokinase (UK), and anisoylated plasminogen streptokinase activator complex (APSAC) work predominantly on circulating plasminogen, whereas tissue type plasminogen activator (tPA) and single chain urokinase-type plasminogen activator (scuPA) are relatively clot-selective. (From Topol EJ. Clinical use of streptokinase and urokinase to treat acute myocardial infarction. *Heart Lung* 1987;**16**:760.)

Approved fibrinolytic agents

Streptokinase

Streptokinase (SK) is a 415 amino acid bacterial protein sharing homology with serine proteases.[35,53] Upon

Table 31.1 Comparison of fibrinolytic agents approved by the US FDA for intravenous use

	SK (Streptokinase)	APSAC (anistreplase)	tPA (alteplase)	rPA (reteplase)	TNK (tenecteplase)
Dose	1·5 million units (MU) in 30–60 min	30 U in 5 min	100 mg in 90 min[a]	10 U + 10 U, 30 min apart	30–50 mg[b] over 5 seconds
Circulating half life (min)	≅20	≅100	≅6	≅18	≅20
Antigenic	Yes	Yes	No	No	No
Allergic reactions	Yes	Yes	No	No	No
Systemic fibrinogen depletion	Severe	Severe	Mild–moderate	Moderate	Minimal
Intracerebral hemorrhage	≅0·4%	≅0·6%	≅0·7%	≅0·8%	≅0·7%
Patency (TIMI-2/3) rate, 90 min[c]	≅51%	≅70%	≅73–84%	≅83%	≅77–88%
Lives saved per 100 treated	≅3[c]	≅3[d]	≅4[e]	≅4	≅4
Cost per dose (approx US dollars)	290	1700	2750	2750	2750

[a] Accelerated tPA given as follows: 15 mg bolus, then 0·75 mg/kg over 30 min (maximum, 50 mg), then 0·50 mg/kg over 60 min (maximum 35 mg).
[b] TNK is dosed by weight (supplied in 5 mg/ml vials): <60 kg = 6 ml; 61–70 kg = 7 ml; 71–80 kg = 8 ml; 81–90 kg = 9 ml; >90 kg = 10 ml.
[c] Based on Granger *et al*[50] and Bode *et al*[51]
[d] Patients with ST elevation or BBB, treated in <6 h.
[e] Based on the finding from the GUSTO trial[52] that tPA saves 1 more additional life per 100 treated than does SK.

injection, SK forms a 1:1 stoichiometric complex with plasminogen or plasmin, activating a catalytic site that cleaves plasminogen to plasmin. The half life of the SK complex is about 23 minutes. SK is antigenic, has little fibrin specificity, and causes substantial systemic lytic effects in clinical doses. Least expensive of fibrinolytics and still widely used globally, SK is administered by short-term ($\leq$1 h) infusions.

Urokinase

Urokinase (UK) is a native, 2-polypeptide protein derived from human urine or renal cell cultures.[54] UK directly converts plasminogen to plasmin. It is non-antigenic and is cleared from the circulation predominantly by the liver with a half life of 16 minutes. Clinically used doses produce moderately extensive systemic fibrinolysis. Its principal use in North America has been for intra-arterial (including intracoronary) fibrinolysis. It has not been approved for and currently is not available for IV use in AMI.

Anistreplase

Anisoylated plasminogen streptokinase activator complex (APSAC or anistreplase) was the first "designer" fibrinolytic, synthesized by complexing streptokinase with lysplasminogen and reversibly inactivating it by reacting it with the anisoyl group of a special reversible acylating agent.[55] It was tailored to allow simple injection ("bolus") delivery, more rapid onset and prolonged duration of action than SK (half life 90–105 min), with improved plasma stability and fibrin binding compared with SK. Like SK, it is antigenic and produces extensive systemic fibrinolysis. Its greater expense and bleeding risk than SK, coupled with little evidence for added benefit, has limited its clinical acceptance.

Tissue-type plasminogen activator (tPA)

Tissue-type plasminogen activator (tPA), a 526 amino acid single polypeptide chain, is the major intrinsic (physiological) plasminogen activator.[56] The marketed form (alteplase) is manufactured by recombinant DNA technology (rtPA). tPA is converted by plasmin to a double-chain form with equivalent fibrinolytic activity.[57] tPA has greater activity in the locale of the thrombus and causes less systemic plasminemia, fibrinogenolysis, and proteolysis than SK. tPA is non-antigenic, is inhibited by a circulating plasminogen activator inhibitor (PAI-1), and is rapidly cleared (half life about 5 minutes). This short half life has necessitated bolus/infusion regimens (over 1–3 hours); bolus-only tPA regimens have been tested but abandoned in favor of longer-acting mutant forms of tPA (see below).

Reteplase

Reteplase (rPA) was the first variant (mutant) of tPA to be developed and marketed.[58] It is a non-glycosylated, single-chain deletion variant consisting only of the kringle 2 and proteinase (plasmin cleavage site) domains of human tPA. Fibrin specificity is lower and half life longer (14–18 minutes) than tPA, allowing more convenient, double-bolus administration.

Tenecteplase

Tenecteplase (TNK-tPA) is a triple-site substitution variant of tPA: at amino acid 103, threonine (T) is replaced by asparagine, adding a glycosylation site; at site 117, asparagine (N) is replaced by glutamine, removing a glycosylation site; at a third site, four amino acids (lysine [K], histidine, arginine and arginine) are replaced by four alanines.[59] The first two changes decrease clearance rate (half life 20 minutes), allowing for single bolus dosing. The third change confers greater fibrin specificity and resistance to PAI-1.

Selected investigational fibrinolytics

Prourokinase or single chain urokinase-type plasminogen activator (scuPA)

In the early 1980s, a glycosylated, single chain form of urokinase (scuPA) was isolated from human urine and cell culture media and characterized biochemically as a proenzyme form of the active two-chain urokinase (tcuPA).[10] Prourokinase was of interest in part because it appeared to be more fibrin-specific than urokinase. This effect is believed to be mediated by the preferential conversion of scuPA to active tcuPA at the fibrin surface. The circulating half life of natural and recombinant scuPA is 4 and 8 minutes respectively, with predominant hepatic clearance.[60] A Phase II study of glycosylated prourokinase produced in mouse hybridoma cells suggested promising coronary patency rates,[61] but further development for AMI has not been undertaken.

Saruplase

Saruplase is a recombinant non-glycosylated form of human prourokinase which has less fibrin specificity and stability than glycosylated prourokinase.[10] Elimination is biphasic, with an initial half life of 6–9 minutes. Administration has been by bolus (20 mg) plus infusion (60 mg/60 min). Saruplase has undergone comparative clinical studies with SK and tPA.[62–64] Saruplase achieves early (60–90 minute) coronary patency rates greater than SK and similar to 3 hour tPA infusions. Mortality rates were at least equivalent to SK, but intracranial hemorrhage rates were greater.

An application for clinical use was rejected by the European Medical Evaluation Agency (EMEA).

Lanoteplase

Lanoteplase (nPA) is a tPA mutant with deletions of the epidermal growth factor, the fibronectin finger domain, and the amino acid 117-glycosylation site.[10] The result is slower clearance (half life 37 minutes), allowing for bolus injection, but decreased fibrin specificity. In comparative studies with tPA, nPA achieved equivalent patency rates[65] and similar 30 day mortality rates,[66] but an increase in intracranial hemorrhage was seen (1·13% *v* 0·62%). It is believed that the dosing strategy of both nPA and heparin may have contributed, but further development of nPA is uncertain.

Staphylokinase

Staphylokinase (SAK) is a single chain, 136 amino acid protein secreted by strains of *Staphylococcus aureus* and manufactured for clinical use by recombinant DNA technology.[67,68] The SAK-plasmin complex is fibrin selective, efficiently activating plasminogen while bound to fibrin at the thrombus surface. SAK has shown at least equivalent reperfusion potential and greater fibrin-specificity than accelerated-dose tPA in Phase II studies. Staphylokinase is antigenic, inducing neutralizing antibodies within 1 week. A pegylated form has been generated to increase half life and allow for bolus dosing.

Efficacy of intravenous fibrinolytic therapy

Effects on coronary arterial patency

Because myocardial reperfusion is the postulated mechanism of benefit of fibrinolysis for AMI, many angiographic studies have been undertaken to assess patency profiles of the infarct-related coronary artery after fibrinolytic therapy.[24] Granger *et al* summarized 14 124 angiographic observations from 58 studies (Figure 31.2).[50] Because the extent of myocardial salvage is time-dependent, early (60–90 min) patency has generally formed the primary end point in these studies. Without fibrinolytic therapy, spontaneous perfusion early after ST elevation AMI occurs in only 15% and 21% at 60 and 90 minutes after study entry, respectively, remains unchanged at 1 day, then gradually increases to about 60% by 3 weeks. All fibrinolytic regimens improve early patency rates. At 60 and 90 minutes, streptokinase had the lowest rates (48%, 51%), APSAC and standard (3 hour) tPA infusions intermediate rates (about 60%, 70%), and accelerated (90 minute) tPA infusions the highest rates (74%, 84%). However, patency rates at ≥3 hours were similar for all regimens, and reocclusion rates were higher after tPA than non-fibrin-specific (systemically active) agents (13% *v* 8%) ($P = 0{\cdot}002$). The GUSTO angiographic study,[69] embedded within a larger comparative mortality study,[52] directly demonstrated that early but not late patency rates accurately predict mortality differences among AMI therapies (see below), providing direct support for the open artery hypothesis of fibrinolytic benefit.

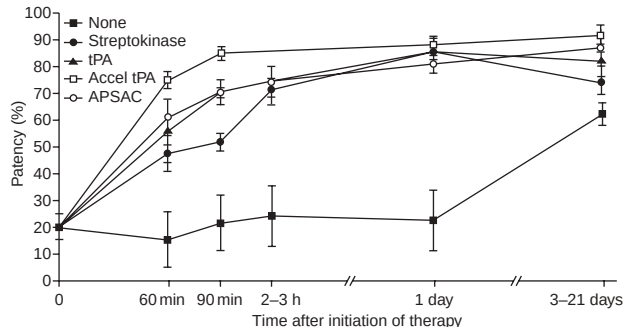


Figure 31.2 Pooled angiographic patency rates with 95% confidence intervals over time after no fibrinolytic agent, streptokinase, conventional dose tPA, accelerated dose tPA, and APSAC from 14124 angiographic observations. (From Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. *Am J Cardiol* 1994;**74**:1220–8[50].)

Effects on mortality

Selected randomized trials with non-fibrinolysis controls

By the late 1980s, accumulating clinical trials data provided support for a survival benefit of IV fibrinolysis.[70–72] The most important survival trials, comparing fibrinolysis to placebo or standard non-fibrinolytic care, are summarized in Figure 31.3.

Agent	Trial name	Deaths/patients		Odds ratio (& 95% CI)	Odds reduction (±SD)
		Active	Control		
Streptokinase	GISSI	495/4865	623/4878		23% ± 6
	ISAM	50/842	61/868		16% ± 18
	ISIS-2	471/5350	468/5360		30% ± 5
APSAC	AIMS	32/502	61/502		50% ± 16
tPA	ASSET	182/2516	245/2495		28% ± 9
Overall: any fibrinolytic		1230/14 075	1638/14 103		27% ± 3

Figure 31.3 Reduction in the odds of early death among ST elevation AMI patients treated within 6 hours; overview from five largest randomized control trials of fibrinolytic therapy versus placebo. (From Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction. *Drugs* 1992;**44**:293.)

The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) – This study[73] was the first "definitive" mortality trial. Eleven thousand eight hundred and six AMI patients with ST elevation were randomized to receive 1·5 million units (MU) of IV SK over 1 hour or standard therapy. Aspirin was not routinely given. Inhospital mortality was 10·7% in the SK group and 13·0% in the control group, a 17·6% risk reduction ($P = 0{\cdot}0002$; RR [relative risk]; 0·81). Survival differences remained at 1–2 years.[74] Benefit was time-dependent and particularly large for treatment within 1 hour of symptom onset (47% mortality reduction, RR 0·49) but was not significant after 6 hours.

The second International Study of Infarct Survival (ISIS-2) – This study[75] randomized 17 187 patients with *suspected* AMI within 24 hours to IV SK (1·5 MU), aspirin (162·5 mg), both, or neither (placebos) in a 2×2 factorial design. The 35 day vascular mortality rate (13·2% for the double placebo group) was reduced 23% by aspirin alone, 25% by SK alone, and 42% by combined aspirin and SK (all $P < 0{\cdot}00001$). When both were given early (within 4 hours of symptom onset), a 53% odds reduction was achieved.

The APSAC Intervention Mortality Study (AIMS) – This[76,77] was a randomized, double-blind, placebo-controlled trial of APSAC (30 U) in 1258 AMI patients under age 70 with ST elevation and symptoms of <6 hours' duration. Adjunctive therapy included heparin, begun 6 hours after APSAC, followed by warfarin for at least 3 months. APSAC reduced 30 day mortality from 12·2% to 6·4% (odds reduction (OR) 51%, $P = 0{\cdot}0006$) and 1 year mortality from 17·8% to 11·1% (OR 43%, $P = 0{\cdot}0007$). Virtually all patient subgroups benefitted.

The Anglo-Scandinavian Study of Early Thrombolysis (ASSET) – This Study[78] evaluated tPA (alteplase) with heparin versus heparin alone within a randomized, double-blind, placebo-controlled design. ASSET enrolled 5013 patients within 5 hours of *suspected* AMI. Therapies were IV tPA (100 mg over 3 hours) plus heparin (5000 U IV bolus, then 1000 U/h), or placebo plus heparin. The 30 day mortality was lower in the tPA than the placebo group (7·2% *v* 9·8%, $P = 0{\cdot}0011$). Hemorrhagic risk was acceptable.

The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group – This group[79] pooled data from nine controlled trials that randomized 1000 or more patients with suspected AMI. The database consisted of 58 600 patients of whom 6177 (10·7%) died, 564 (1·0%) had strokes, and 436 had major non-cerebral bleeds. The 45 000 patients who presented with ST elevation or bundle branch block (BBB) had an absolute mortality reduction of 30 per 1000 for treatment within the first 6 hours, 20 per 1000 for hours 7–12, and a statistically uncertain reduction of 13 per 1000 beyond 12 hours.

Given its large size, FTT also performed subgroup analysis. Analysis by presenting electrocardiogram (ECG) (Figure 31.4) showed mortality reductions for those with ST elevation (21%, $P < 0{\cdot}000001$) and bundle branch block (BBB) (25%, $P < 0{\cdot}01$). Benefit was greater for those with anterior (37 lives saved per 1000 treated) compared with inferior (8 per 1000) or other (27 per 1000) AMI sites. The absolute benefit was greater in those with greater risk, for example, BBB (49 lives saved per 1000 treated) and anterior ST elevation (37 per 1000). Those with normal ECGs or with ST depression alone showed no benefit and adverse trends (7 and 14 more deaths per 1000, respectively).

The FTT study[79] suggested that proportional mortality reduction was little influenced by systolic blood pressure or heart rate. Benefits also were confirmed for other high-risk groups, including those with prior MI and diabetes.

Benefits of very early (<1 hour) therapy

The magnitude of mortality reductions in FTT was dependent on time to therapy from symptom onset. For those with ST elevation or BBB, the absolute benefit was 39 (at 0–1 h), 30 (>1–3 h), 27(>3–6 h), 21 (>6–12 h), and 7 (>12–24 h) lives saved per 1000 treated (Figure 31.5).

Others also studied the benefits of therapy within 1 hour.[80,81] Boersma *et al*[81] reappraised very early therapy

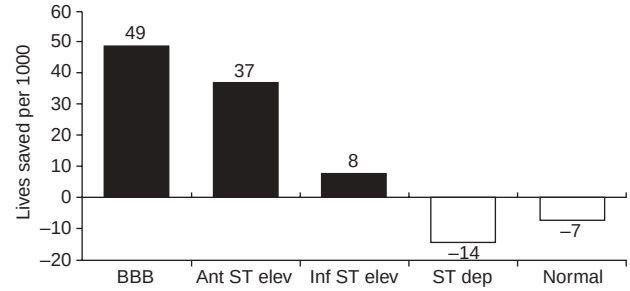


Figure 31.4 The effect of fibrinolytic therapy on mortality (lives saved per 1000 treated) in various patient subsets classified according to admission ECG. Patients presenting with bundle branch block and anterior ST segment elevations derived most benefit from fibrinolytic therapy. Patients with inferior ST segment elevation derived much less benefit, while those with ST depression or normal ECG did not benefit. (Based on data from FTT Collaborative Group[79]). The FTT found that for elderly patients (over age 75), proportional mortality reduction was less and the trend to benefit was not significant. Absolute mortality reduction was interpreted to be still worthwhile (Figure 31.5). Fibrinolytic therapy in the very elderly continues to be debated (see later).

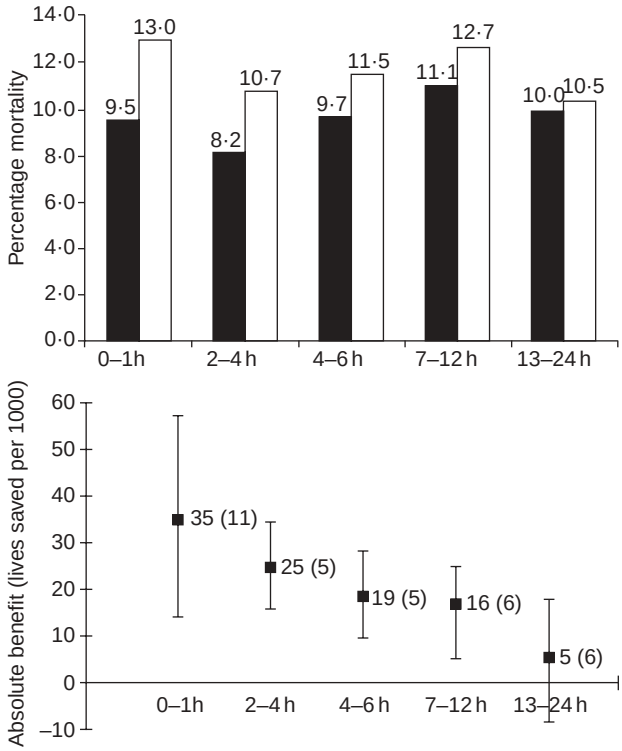


Figure 31.5 The effect of fibrinolytic therapy on mortality in various patient subsets classified according to duration of symptoms before treatment: (*above*) mortality in each subgroup of fibrinolytic treated (black bars) versus placebo treated (white bars) patients; (*below*) absolute benefit (lives saved per 1000 treated, standard deviation in parentheses) with confidence intervals. (Based on data from FTT Collaborative Group.[79])

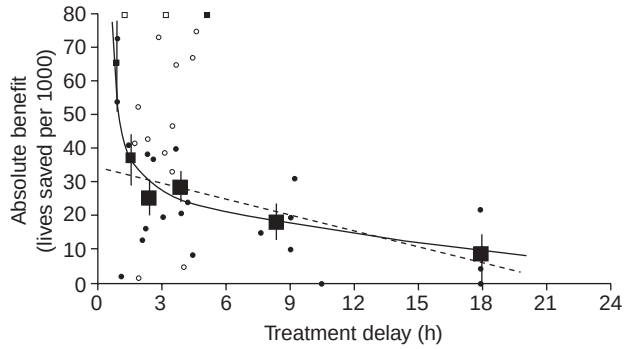


Figure 31.6 Absolute 35 day mortality reduction *v* treatment delay: small closed dots, information from trials included in FTT analysis; open dots, information from additional trials; small squares, data beyond scale of X/Y cross. The linear ($34{\cdot}7-1{\cdot}6X$) and non-linear ($19{\cdot}4-0{\cdot}6X+29{\cdot}3X^{-1}$) closed regression lines are fitted within these data, weighted by the inverse of the variance of the absolute benefit at each data point. The black squares denote the average effects in six time-to-treatment groups (areas of squares inversely proportional to the variance of absolute benefits described). (From Boersma E, Maas ACP, Deckers JW *et al.* Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**:771–5.[81])

based on a larger database (50 246 patients, derived from all randomized trials of ≥100 patients). The absolute mortality reduction for treatment within 1 hour of symptom onset was 65 per 1000. The delay/benefit relation (Figure 31.6) was non-linear.

Benefit of delayed (≥6 hour) therapy

In contrast to earlier therapy, the benefit of fibrinolysis after 6 hours is less certain. The Late Assessment of Thrombolytic Efficacy (LATE) study[82] enrolled 5711 patients with evidence of AMI between 6 and 24 hours from symptom onset and randomized them to tPA (100 mg over 3 h) or placebo. A 26% relative mortality reduction (8·9% *v* 11·9%, $P=0{\cdot}02$) was observed for those treated within 12 hours. The 12–24 hour subgroup showed a non-significant trend to benefit (8·7% *v* 9·2% mortality rate). The South American EMERAS collaborative group[83] treated 4534 patients with IV SK or placebo within 24 hours after onset of suspected AMI and found a non-significant trend towards a mortality benefit between hours 7 and 12 (SK 11·7%, placebo 13·2%). These with other late treatment trials[79] have provided the rationale for recommending fibrinolysis for hours 7–12 after the onset of AMI in patients with persistent symptoms and ECG changes.[5]

Risks of thrombolytic therapy

Bleeding

Bleeding is the primary risk of fibrinolytic therapy. Intracranial (or intracerebral) hemorrhage (ICH) is the most important bleeding risk, occurring in about 0·5–1·0%, with substantial risk of fatality (44–75%) or disability.[84–88] Non-cerebral but not cerebral bleeding risk has benefitted by increased fibrin selectivity. The absolute and relative contraindications to fibrinolytic therapy are summarized in Box 31.1 (after[5]).

Box 31.1 Absolute and relative contraindications to fibrinolytic therapy

Contraindications, absolute
- Active bleeding; bleeding diathesis
- Prior hemorrhagic stroke; intracranial pathology
- Aortic dissection

Contraindications, relative
- Severe, uncontrolled hypertension (>180/110 mmHg)
- Oral anticoagulation with INR >1·5
- Major recent trauma/surgery
- Pregnancy
- Recent non-hemorrhagic stroke

Box 31.1 Continued
Non-compressible recent vascular punctures
Recent retinal laser therapy
Cardiogenic shock when revascularization available

The risk of ICH varies with patient characteristics, the fibrinolytic agent, and adjunctive antithrombotic therapy.[84–88] Simoons *et al*[87] identified four independent predictors of increased ICH risk: age > 65 years (OR 2·2; 95% CI 1·4–3·5), weight <70 kg (OR 2·1; 95% CI 1·3–3·2), hypertension on admission (OR 2·0; 95% CI 1·2–3·2), and use of tPA (alteplase) (OR 1·6; 95% CI 1·0–2·5) versus SK. The GUSTO-1 group[88] identified seven predictors of ICH: advanced age, lower weight, history of cerebrovascular disease, history of hypertension, higher systolic or diastolic pressure on presentation, and randomization to tPA (*v* SK). In contrast, the incidence of non-cerebral bleeding is higher with SK.[89]

The safety of bolus compared with infusion administration of fibrinolysis for ICH was questioned by a meta-analysis of several different agents.[90] However, problems with the meta-analysis have been raised,[91,92] and large, well-controlled trials of the two bolus agents in general use, rPA[93] and TNK-PA,[94] have not shown excess ICH rates compared with front-loaded rt-PA.

The critical importance of dose and adjunctive therapies to ICH risk is now realized. Excessive ICH was observed with tPA doses >100 mg.[24] Excessive adjunctive therapy (for example, heparin, hirudin, glycoprotein IIb/IIIa receptor inhibition) with fibrinolytics also has resulted in unacceptable rates of bleeding including ICH.[95–97] In the GUSTO-I trial, the risk of ICH increased with aPTT levels beyond 70 seconds.[98] Three concurrent trials[95–97] were stopped prematurely and reconfigured because of excessive hemorrhage. With lower doses of antithrombins, hemorrhage rates subsequently decreased. Recommendations for adjuvant heparin therapy have been adjusted downward to 60 U/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units), adjusted after 3 hours to maintain aPTT at 50–70 seconds for 48 hours.[5] Further reductions in heparin dosing have been required with combined fibrinolytic and glycoprotein IIb/IIIa receptor inhibitor therapy (see below).

Previously, prolonged cardiopulmonary resuscitation (CPR) has been considered a contraindication to fibrinolytic therapy. Recently, Bottiger *et al* observed 90 patients with AMI who had out-of-hospital cardiac arrest.[99] Patients treated with heparin and tPA more frequently had return of spontaneous circulation (68% *v* 44%, $P < 0.03$), admission to the ICU ($P < 0.01$), and survival to discharge (15% *v* 8%). Bleeding complications were not problematic.

Allergy, hypotension, and fever

SK and APSAC are antigenic and may be allergenic although serious anaphylaxis or bronchoconstriction are rare (<0·2–0·5%).[75] In ISIS-3,[86] any allergic-type reaction was reported after SK in 3·6%, APSAC in 5·1%, and tPA (duteplase) in 0·8%; only 0·3%, 0·5%, and 0·1%, respectively, required treatment. Angioneurotic and periorbital edema, hypersensitivity vasculitis, serum sickness or renal failure due to interstitial nephritis, and purpuric rashes have been rarely reported, especially after repeat administration.[35,75,77,86]

SK and APSAC may acutely release bradykinin, a vasodilator. The incidence of clinical hypotension was similar after SK (11·8%) and APSAC (12·5%) but lower after tPA (7·1%);[86] only half of episodes required treatment.

Fever occurs in 5–30% of SK and 5–10% of APSAC treated patients. Delayed-type hypersensitivity may provoke fever and may respond to acetaminophen. The role of fibrinolytics in reports of splenic rupture, aortic dissection, and cholesterol embolization is uncertain.

Comparative fibrinolytic trials

After establishing the general utility of fibrinolysis in STE-AMI, clinical trials focused on comparisons with new drug regimens. Salient features of major early comparative outcomes trials are presented in Table 31.2; bolus fibrinolytic trials are summarized in Table 31.3; and recent combination therapy trials are shown in Table 31.4.

The GISSI-2/International Study Group trial[100,101] randomized 20 891 patients with STE-AMI <6 h old to tPA (alteplase, 100 mg/3 h) or SK (1·5 MU/1 h) and to subcutaneous (SC) heparin (12 500 U twice daily) beginning 12 hours later or no heparin. Aspirin and atenolol were given as standard therapies. Inhospital mortality was: SK 8·5% and tPA 8·9% (P = NS). ICH rates were 0·5% and 0·8%, respectively; other major bleeds were most frequent with SK plus heparin. At 35 days, death or severe left ventricular dysfunction did not differ by fibrinolytic. Delayed, SC heparin added little benefit (RR 0·95; 95% CI 0·86–1·04).

The third ISIS study *(ISIS-3)*[86] randomized 41 299 patients with suspected AMI <24 h old to receive SK (1·5 MU/1 h), tPA (duteplase 0·6 MU/kg/4 h) or APSAC (30 U/3 min) and to SC heparin (12 500 U, 4 hours after beginning thrombolytics and bid) or no heparin. Aspirin (162 mg/day) was given to all patients. The median time to treatment was 4 hours; 88% presented within 6 hours and had ST elevation. Mortality rates at 35 days were: SK 10·6%, APSAC 10·5%, and tPA 10·3% overall, and 10·0%, 9·9%, and 9·6%, respectively, in those with clear indications (P = NS). Similar outcomes also were observed after 6 months. SC heparin tended to improve 1 week mortality (7·4% *v* 7·9%, $P = 0.06$) at the expense of increased bleeding, but mortality rates at 35 days were similar (10·3% *v* 10·6%, P = NS).

In comparing fibrinolytic regimens, GISSI-2 and ISIS-3 were limited by the suboptimal use of heparin for short-acting,

Table 31.2 Clinical end points in early comparative fibrinolytic outcomes trials

End points	GISSI-2/ International[100]		ISIS-3[86]			GUSTO-1[69]		
	SK (10 396)	tPA (10 372)	SK (13 607)	tPA (13 569)	APSAC (13 599)	SK (20 173)	tPA[a] (10 344)	SK+tPA (10 328)
Death (%)	8·5	8·9	10·6	10·3	10·5	7·3	6·3[b]	7·0
Re-infarction (%)	3·0	2·6	3·5	2·9[b]	3·6	3·7	4·0	4·0
Any stroke (%)	0·9	1·3[b]	1·0	1·4[b]	1·3	1·3	1·6	1·7
Hemorrhagic stroke (%)	0·3	0·4	0·2	0·7[b]	0·6	0·5	0·7[b]	0·9
Non-CNS bleeds (%)	0·9	0·6[b]	4·5	5·2[b]	5·4	6·0	5·4[b]	6·1

[a] Accelerated dose tPA.
[b] Statistically significant; statistical comparisons are only listed for SK *v* tPA.

Table 31.3 Comparative trials of bolus agents with accelerated tPA

End points	ASSENT-II[94]		GUSTO-III[93]		In-TIME-II[66]	
	tPA ($n = 8488$)	TNK (8461)	tPA (4921)	rPA (10 138)	tPA (5022)	nPA (10 038)
Death (%) at 30 days	6·15	6·18	7·24	7·47	6·61	6·75
Re-infarction (%)	3·8	4·1	4·2	4·2	5·5	5·0
Any stroke (%)	1·66	1·78	1·79	1·64	1·53	1·87
Hemorrhagic stroke (%)	0·94	0·93	0·87	0·91	0·64*	1·12*
Major bleed (%)	5·94*	4·66*	1·2	0·95	0·6	0·5

* $P < 0·001$ for comparisons.

Table 31.4 Comparative outcomes trials with combined fibrinolytic and GP IIb/IIIa inhibitor therapy

End points	GUSTO-V AMI1[25]		ASSENT-3[14]		
	rPA ($n = 8260$)	1/2 rPA + abciximab (8328)	TNK-tPA with heparin (2038)	TNK-tPA with enoxaparin (2040)	1/2 dose TNK-tPA + abciximab (2017)
30 day death (%)	6·2	5·9	6·0	5·4	6·6
Re-infarction (%)	3·5	2·3*	4·2[d]	2·7[d]	2·2[d]
Combined death, Re-AMI, UA (or urgent revasc) (%)	20·6	16·2*	15·4[e]	11·4[e]	11·1[e]
Any stroke (%)	0·9	1·0	1·52	1·62	1·49
ICH (%)	0·6[a]	0·6[b]	0·93	0·88	0·94
Major bleed (%)	2·3[c]	4·6[c]	2·2[f]	3·0[f]	4·3[f]

[a] ICH rates for patients >75 = 1·1%.
[b] ICH rates for patients >75 = 2·1%.
[c] Severe and moderate bleeding combined.
[d] Inhospital events, $P = 0·0009$ among groups.
[e] $P < 0·0001$ among groups for 30 day death, inhospital re-infarction, or inhospital refractory ischemia.
[f] Major inhospital bleeding (other than ICH), $P = 0·0005$ among groups.
* $P < 0·0001$ between groups.

fibrin-selective tPA (SC dosing after a delay of 4–12 hours), treatment was relatively late (mean times >4 hours) and did not require ST elevation (ISIS-3), and tPA was not front-loaded.[102–104]

These concerns led to the Global Use of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) study.[52] GUSTO randomized 41 021 patients with STE-AMI <6 h old to:

1. SK 1·5 MU/1 h with SC heparin 12 500 U every 12 h starting 4 h after SK;
2. IV SK with IV heparin, 5000 U bolus then 1000 U/h, titrating aPTT to 60–85 seconds;
3. front-loaded tPA (15 mg bolus, 0·75 mg/kg – maximum 50 mg – over 30 minutes, then 0·50 mg/kg – maximum 35 mg – over 60 minutes, for a maximum of 100 mg over 90 minutes) and IV heparin as per the SK regimen;
4. a combination of tPA 1·0 mg/kg and SK 1·0 MU, administered concurrently over 60 minutes, plus IV heparin.

The primary end point, 30 day mortality, was lowest with accelerated tPA with IV heparin (6·3%), representing a 14% risk reduction ($P = 0·001$) compared to the two SK strategies (7·3%), which did not differ. Combined tPA and SK gave an intermediate outcome. The risk of hemorrhagic stroke was higher with tPA (0·7%) than SK (0·5%), but the combined end point of death or disabling stroke favored tPA (6·9% *v* 7·8%, $P = 0·006$). Implications of GUSTO for selection of fibrinolytic regimens have been debated.

Three additional angiographic studies compared APSAC and tPA.[105–107] Early patency profiles, convalescent ejection fraction, and unsatisfactory clinical outcomes end points tended to favor tPA.

Comparative trials with bolus fibrinolytics

INJECT (The International Joint Efficacy Comparison of Thrombolytics)[58] compared reteplase (rPA) and SK in a 6010 patient double-blind, randomized trial. Mortality rates at 35 days were: rPA 9·0% and SK 9·5% (0·5% absolute reduction; 95% CI 1·9–0·96). On this basis "equivalence" (non-inferiority) of rPA to standard, SK therapy, was established and rPA approved. Outcomes trials of bolus agents subsequent to INJECT used accelerated tPA as comparator (Table 31.3).

Reteplase

Reteplase was next favorably compared to tPA in an angiographic study, leading to a large mortality study. In RAPID 2 (Reteplase *v* Alteplase Patency Investigation During acute myocardial infarction)[51] 90 minute TIMI grade 2 or 3 patency rates among 324 patients were 83% *v* 73% (rPA *v* tPA, $P = 0·03$), with TIMI-3 flow rates of 60% *v* 45%, $P = 0·01$. On this basis, a comparative mortality trial, GUSTO-3,[93] was undertaken and randomized 15 059 patients 2:1 to rPA (two 10 mg IV injections 30 minutes apart), or accelerated tPA (alteplase). A postulated survival advantage for rPA was not demonstrated (30 day mortality: rPA 7·5%, tPA 7·2%).

Lanoteplase

Lanoteplase (nPA), a longer-acting tPA variant, was studied in doses of 15–120 kU/kg in the Phase II angiographic trial Intravenous n-PA for Treating Infarcting Myocardium Early (InTIME).[65] A dose response in 60 minute TIMI-3 patency was observed over the 3 lowest doses but not between 60 and 120 kU/kg, and neither of these doses was superior to rt-PA. A subsequent double-blind mortality equivalence trial, InTIME-2[66] selected the 120 kU/kg dose and randomized 15 078 STE-AMI patients within 6 hours to nPA or tPA (2 : 1). Although 30 day mortality rates were similar (nPA = 6·77%, tPA = 6·60%), a significantly higher ICH rate occurred in the nPA group (1·13% *v* 0·62%). As concerns developed about excessive ICH rates during InTIME-2, heparin down-titration was undertaken earlier (at 3 hours) if PTT exceeded 70 seconds. Reductions in ICH with both nPA and tPA ensued. In an extension study (InTIME-2b, $n = 1491$), the heparin bolus was omitted and heparin initiated with an infusion of 15 U/kg/h (1000 U/h maximum). ICH rates declined further for nPA to 0·87%. These observations have impacted heparin recommendations generally (see below).

Tenecteplase

Tenecteplase (TNK-tPA), a fibrin-selective, single bolus fibrinolytic, was evaluated in the TIMI 10 dose finding trials.[108,109] In Phase II studies, a clear dose-response was observed[109] both for coronary patency and hemorrhage (including ICH for the 50 mg dose). With limitation and weight-adjustment of TNK-tPA dose and reduction and earlier down-titration of heparin dosing, satisfactory bleeding rates and comparable TIMI-3 patency rates were demonstrated at 90 minutes compared to accelerated rt-PA.[110] The double-blind Phase III Assessment of the Safety and Efficacy of a New Thrombolytic-2 (ASSENT-2) mortality equivalence trial[94] compared weight adjusted TNK (as a 30–50 mg bolus over 5–10 seconds) and accelerated rt-PA. All patients received aspirin and heparin. Thirty day mortality rates were virtually identical for TNK-tPA (6·18%) and rt-PA (6·15%) and met statistical criteria for equivalence. ICH rates also were identical (at 0·93% and 0·94%, respectively). However, major non-cerebral bleeding was lower with the more fibrin-selective TNK (4·66% *v* 5·94%, $P = 0·0002$) as was need for blood transfusion (4·25% *v* 5·49%, $P = 0·0002$). A lower mortality rate with TNK-tPA was observed among patients presenting >4 hours after symptom onset (7·0% *v* 9·2%), which may be due to either

greater activity of the more fibrin-specific TNK-tPA against older, fibrin-rich clots or chance.

Thus, none of the newer fibrinolytic regimens has surpassed accelerated tPA. However, the ease of administration of TNK-tPA, together with its reduced transfusion requirements, is likely to lead to rapid acceptance of its clinical use. Lower rates of dosing errors with bolus fibrinolytics such as TNK-tPA also may contribute to superior clinical outcomes.[111]

Combinations of fibrinolytic therapy and glycoprotein IIb/IIIa receptor inhibitors or low molecular weight heparins

With the failure of new fibrinolytic monotherapies to improve early coronary patency and clinical outcomes compared to rt-PA, interest has shifted toward combination pharmacotherapies. A strong theoretical argument can be made for combined fibrinolytic and augmented antiplatelet therapy.[29] The platelet membrane glycoprotein (GP) IIb/IIIa receptor, a specific fibrinogen receptor, is the final common pathway in platelet activation and an attractive therapeutic target. Antibodies, peptides, and small molecules have been developed that block the platelet GP IIb/IIIa receptor. These have potent platelet anti-aggregatory effects and have demonstrated efficacy in the setting of non-STE acute coronary syndromes and coronary angioplasty.[112–115] In STE-AMI, their utility as adjunctive therapy for patients undergoing direct PTCA with stenting has been recently shown.[116] Given the critical role of platelets in coronary arterial thrombosis, the combination of fibrinolytic with GPIIb/IIIa inhibitor (GPI) therapy has substantial appeal as an approach to improving pharmacologic reperfusion.

Abciximab, a monoclonal chimeric antibody against GP IIb/IIIa, was tested as conjunctive therapy with lower doses of tPA in the TIMI-14 dose-ranging angiographic trial.[117] The combination of half dose rt-PA and full dose abciximab (with reduced doses of heparin) produced impressive increments in TIMI-3 flow rates at 60 minutes (72% *v* 43%, $P < 0{\cdot}001$) and 90 minutes (77% *v* 62%, $P = 0{\cdot}02$) with acceptable bleeding rates.

Another angiographic study, Strategies for Patency Enhancement in the Emergency Department (SPEED)[118] tested reteplase with abciximab (versus rPA alone) in two phases. The best combination in phase A (half dose reteplase –5 U + 5 U 30 minutes apart – with full dose abciximab) was re-evaluated in phase B with two heparin bolus doses (40 or 60 U/kg). Improved TIMI-3 flow rates were observed with combination therapy, 54% *v* 47%, although differences were not significant. Higher rates of bleeding (9·8% *v* 3·7%) were observed with combination therapy. SPEED piloted the GUSTO-V AMI outcomes trial (Table 31.4).

An argument also has been made for substituting an antithrombin more effective than heparin in combination with a fibrinolytic. Low molecular weight heparins (LMWHs) have theoretical advantages over unfractionated heparin. Unlike unfractionated heparin, LMWHs do not bind extensively to plasma proteins, do not activate platelets, have more predictable kinetics, are effective inhibitors of thrombin activity (anti factor Xa activity) as well as thrombin activity (anti-IIa activity), and are given in fixed doses without the requirement for monitoring.[119] LMWHs are effective in the non-STE acute coronary syndromes,[120] and some LMWH trials also have shown clinical superiority to unfractionated heparin.[121,122] Combinations of fibrinolytics with LMWH have been less extensively tested but have shown promise, with improved late patency and reduced re-infarction/reocclusion compared to intravenous heparin.[123,124]

GUSTO-V AMI[125] was an unblinded mortality study in 16 588 patients with STE-AMI enrolled within 6 hours and randomized to standard rPA (10 U + 10 U) or half dose rPA (5 U + 5 U) plus full dose abciximab. The primary hypothesis, that 30 day mortality rates with combination therapy would be less than with standard fibrinolytic therapy, was disproved (5·6% *v* 5·9%, respectively, $P = 0{\cdot}43$) although the criterion for non-inferiority was reached. However, of 16 prespecified inhospital adverse AMI-related outcomes, 14 occurred less frequently with combination therapy. Combined death or non-fatal re-infarction (relative risk, 0·83, $P = 0{\cdot}001$), non-fatal MI alone ($P < 0{\cdot}0001$), recurrent ischemia ($P = 0{\cdot}004$), urgent coronary intervention (relative risk, 0·64, $P < 0{\cdot}0001$), ventricular tachycardia or fibrillation, and high-grade AV block, and total complications (28·5% *v* 31·7%, $P < 0{\cdot}0001$) were significantly reduced. On the other hand, spontaneous bleeding rates and transfusion requirements were increased up to twofold with combination therapy ($P < 0{\cdot}0001$). Moreover, there was a significant ($P = 0{\cdot}03$) adverse treatment interaction by age for ICH: 2·1% *v* 1·1% for combined versus standard therapy for age >75; ICH 0·4% *v* 0·5%, respectively, for age ≤75. GUSTO-V AMI was interpreted as validating an alternative reperfusion strategy for patients ≤75 years old, although the lack of incremental mortality benefit and the increased bleeding risks were disappointing. Younger patients at higher AMI risk (anterior AMI) arguably now might be considered for the GUSTO-V AMI combination regimen although ASSENT-3 suggests another alternative (below).

ASSENT-3[14] was a randomized but unblinded trial in 6095 patients with STE-AMI enrolled within 6 hours of symptom onset and assigned to one of three regimens:

- TNK-tPA and unfractionated heparin (both weight adjusted)
- TNK-tPA with the low molecular weight heparin enoxaparin
- half dose TNK-tPA with heparin and full dose abciximab.

Enoxaparin was given as a 30 mg IV bolus and 1 mg/kg SC repeated every 12 hours until hospital discharge or for

7 days except that the first two SC doses could not exceed 100 mg. Unfractionated heparin was dosed according to recent ACC/AHA guidelines: 60 U/kg bolus (maximum, 4000 U) and 12 U/kg per hour initial infusion (maximum, 1000 U/h), adjusted after 3 hours to an aPTT of 50–70 sec. With abciximab co-therapy, the heparin dose was further reduced to 40 mg/kg bolus (maximum 3000 U) followed by 7 U/kg per h initial infusion (maximum, 800 U/h).

The primary efficacy end point of ASSENT-3 was the composite of 30 day mortality and inhospital re-infarction or refractory ischemia. The primary efficacy plus safety end point was the efficacy end point plus inhospital ICH or other major bleeding. The efficacy end point was significantly lower in both the enoxaparin (11·4%, $P = 0{\cdot}0002$) and the abciximab co-therapy groups (11·1%, $P < 0{\cdot}0001$) than the TNK-tPA/heparin group (15·4%). The efficacy plus safety end point also was significantly lower with adjunctive enoxaparin (13·7%, $P < 0{\cdot}004$) and conjunctive abciximab (14·2%, $P = 0{\cdot}014$) than with unfractionated heparin (17·0%) (Figure 31.7). A lesser need for urgent coronary interventions was observed with the two experimental therapies. Despite the positive overall results with combination abciximab, there was no mortality benefit (6·6%, *v* 6·0% for TNK-tPA/heparin control). Moreover, a significant adverse interaction of treatment with age (RR 1·30 for >75 years *v* 0·74 for ≤75, $P = 0{\cdot}001$) (Figure 31.7) and diabetes (RR = 1·35 with *v* 0·74 without diabetes, $P = 0{\cdot}0007$) was observed for the efficacy plus safety end point. More major bleeding complications, transfusions, and thrombocytopenia occurred in the abciximab group (all $P < 0{\cdot}001$), and the rates were three times higher in those older than 75 years. Bleeding was only slightly increased with enoxaparin and

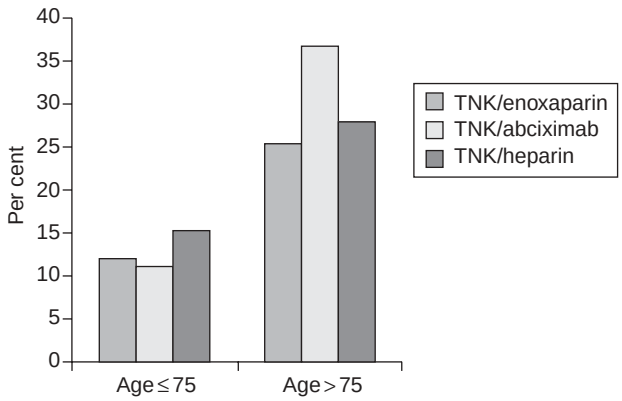


Figure 31.7 Efficacy plus Safety End point (death at 30 days, inhospital re-infarction, refractory ischemia, ICH or major bleeding) from ASSENT-3 trial, by age and treatment group. Patients over age 75 years had poorer outcomes with abciximab, those 75 or younger had poorer outcomes with heparin as adjunc-tive therapy ($P = 0{\cdot}0010$ for interaction or age, therapy). TNK, TNK-tPA.

no treatment interactions were seen. Taking into account efficacy and safety, TNK-tPA with adjunctive enoxaparin therapy emerged as the best overall therapy. Ease of administration and lack of need for monitoring advantaged enoxaparin over heparin, and greater safety in the elderly and diabetics distinguished it from the abciximab combination.

A combination of half dose fibrinolytic, GP IIb/IIIa inhibition and enoxaparin was studied in ENTIRE-TIMI 23 (Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy in ST Elevation MI), and results were recently presented.[126] A total of 461 patients were enrolled. Patients tended to have higher rates of ST segment resolution with enoxaparin versus heparin and with combination therapy versus TNK-tPA alone. Rates of major hemorrhage were higher with TNK-tPA combinations, as expected. However, bleeding rates tended to be lower if enoxaparin was used instead of heparin (5·6% *v* 7·8%). Although the study was not powered to detect efficacy, the 30 day rates of death or MI were reduced in the enoxaparin groups (15·9% with TNK-tPA/heparin *v* 4·4% with TNK-tPA/enoxaparin, and 6·5% with half TNK-tPA/abciximab/heparin *v* 5.5% with half TNK-tPA/abciximab/enoxaparin).

Based on these two recent trials (Table 31.4), combined enoxaparin and TNK-tPA appears to be the most attractive current alternative pharmacological reperfusion strategy and deserves further study. The role of combined GP IIb/IIIa and fibrinolytic therapy, in contrast, is less certain after GUSTO-V and ASSENT-3. Further studies should be limited to younger patients at lower risk of bleed and high risk of AMI-related complications and might include those likely to undergo early percutaneous coronary interventions or include combination therapy with enoxaparin. Whether shorter-acting GPI's (such as eptifibatide or tirofiban) or further changes in adjunctive heparin dosing can improve the benefit/risk ratio of combination regimens with fibrinolytics must await ongoing and future studies.

Combinations of fibrinolytic therapy and direct antithrombins

Initial testing of antithrombins as adjuncts to fibrinolytics was complicated by excessive bleeding.[95–97] Recently, the results of HERO-2, which used adjusted doses, were reported.[127] HERO-2 randomized 17 073 AMI patients to unfractionated heparin or bivalirudin, given 3 minutes before streptokinase administration. All patients received aspirin. Thirty day mortality, the primary end point, did not differ between the bivalirudin and heparin groups (10·8% *v* 10·9%). However, adjudicated 30 day re-infarction was reduced (2·8% *v* 3·6%, $P = 0{\cdot}004$) at the expense of increased moderate to severe bleeding (2·1% *v* 1·5%, $P < 0{\cdot}05$) and increased ICH (0·55% *v* 0·37%, $P = 0{\cdot}09$). Thus, bivalirudin could lead to 8 fewer AMI's at a cost of 3 more transfusions for every

1000 patients treated. The value of hirudin analogs as adjuncts to fibrinolytics, instead of heparin, continues to be uncertain.

Indications for fibrinolytic therapy in AMI

In the 1999 guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA),[5] fibrinolytic therapy is strongly recommended **Grade A1a** within 12 hours of the onset of suggestive clinical features (ischemic chest discomfort or equivalent) and ST elevation (>0·1 mV, ≥2 contiguous ECG leads) or BBB (obscuring ST segment analysis), and age ≤75 years. Fibrinolytic therapy also is generally recommended **Grade A1c** for these same features and age >75 years (in the absence of contraindications). Therapy is considered possibly effective – that is, consider selected use **Grade B/C** for these ECG findings but time 12–24 hours or blood pressure on presentation >180 mmHg systolic and/or >110 mmHg diastolic and associated with a high risk AMI. Fibrinolysis is not indicated for those with ST elevation (or BBB) but time to therapy >24 hours and ischemic pain resolved and those with ST depression (at any time). These recent ACC/AHA guidelines are summarized in Table 31.5.

Fibrinolysis in the elderly

The appropriate use of fibrinolytics in the elderly continues to be debated. In a recent analysis of over 37 000 Medicare patients with AMI age 65 or older who were eligible for fibrinolytic therapy,[128] 38% received fibrinolytic therapy and 4·2% received primary angioplasty. After multivariate adjustments, fibrinolytic therapy was not associated with improved 30 day survival (OR 1·01; 95% CI [0·94–1·09]), whereas primary angioplasty was (OR 0·79; 95% CI [0·66–0·94]). However, at 1 year, both fibrinolytic therapy (OR 0·84 ; 95% CI [0·79–0·89]) and primary angioplasty (OR 0·71 ; 95% CI [0·61–0·83]) were associated with lower

Table 31.5 ACC/AHA guidelines for management of acute myocardial infarction (1999)

Prerequisites for considering fibrinolytic therapy	Choice/time of fibrinolytic agent	Adjuvant therapy
Class I: **Grade A1a**	No specific recommendations	Aspirin 162–325 mg/d
1. ST elevation, time to therapy less than 12 h and age <75 years	In patients with large area of infarction, early after symptom onset, and at low risk for ICH may consider the use of tPA.	β Blockers unless contraindicated or CHF
2. BBB with history suggestive of MI	In smaller infants with smaller potential of survival benefit and if a greater risk of ICH exists, SK may be the choice	ACE inhibitors for anterior MI, CHF or ejection fraction <40% (alternatively: all patients, reassess need for continued therapy at 6 weeks).
Class IIa: **Grade A1c**		IV heparin with tPA, rPA, TNK-tPA, and non-STE-AMI
1. Age >75 years with ST elevation or BBB, suggestive history, time <12 hours		SC heparin with SK or APSAC unless at high risk for thromboembolism, when IV heparin is preferred
Class IIb: **Grade B/C**	Door to needle time less than 30 min	
1. ST elevation, time to therapy 12–24 h 2. Systolic BP >180 mmHg, or diastolic BP >110 mmHg with high-risk MI		
No evidence for benefit, possibly harmful **Grade A1a** against therapy		
1. ST elevation, time to therapy >24 h, pain resolved 2. ST segment depression		

mortality rates. Another Medicare analysis[129] suggested that fibrinolytic therapy even might be harmful in those over 75 years. In contrast, a large Swedish registry found a 12% risk reduction in the composite end point of cerebral bleeding and 1 year mortality.[130] Similarly, the Fibrinolytic Therapy Trialists' overview of randomized trials data in patients over 75 years reported 35 day mortality to be reduced (trend) from 29·4% to 26·0% with fibrinolytic therapy.[79] Analyses restricted to elderly patients with clear indications for fibrinolytic therapy, suggested similar greater *absolute* benefit from fibrinolytic therapy than in younger patients. Fibrinolytic regimens should be chosen to minimize the risk of ICH, which increases in the elderly. Weight adjusting treatment regimens and avoidance of excessive heparin and other adjunctive antithrombotics (for example GP IIb/IIIa inhibitors) is important. When safety concerns predominate, SK, which carries a lower risk of ICH, or primary angioplasty should be considered as preferred reperfusion strategies in the elderly.

LBBB and fibrinolysis

In patients with left BBB *not known to be new*, diagnosis of AMI may be obscured and fibrinolytics withheld. In order to define a prediction rule for evaluating left BBB, the GUSTO-1 investigators[131] found three ECG criteria to have independent value in the diagnosis of AMI:

- ST elevation of 1 mm or more in leads with a positive QRS complex
- ST depression of 1 mm or more in leads V1, V2 or V3
- ST elevation of 5 mm or more with a negative QRS complex. Using an index score, a sensitivity of 36% and a specificity of 96% for AMI were found in a validation group.

Current use of fibrinolytics

The National Registry of Myocardial Infarction (NRMI) tracks the use of reperfusion therapies in the United States, which is accomplished through surveys of 1432 hospitals. Over three phases, from 1990 to 1999, information on 1 514 292 patients with AMI were accumulated.[11] During this decade, the percentage of AMIs eligible for fibrinolytic therapy (ST elevation or LBBB presenting within 12 hours) fell from 36% to 27%, but the percentage of eligible patients who received reperfusion therapy remained constant (69% *v* 70%). Among patients eligible for reperfusion therapy, the relative use of fibrinolytic therapy fell, from 59% to 48%, whereas use of primary coronary angioplasty increased, from 12% to 24%. Of those receiving fibrinolytic therapy, the mean time from hospital arrival to drug delivery decreased, from 62 minutes to 38 minutes.

Selection of a fibrinolytic regimen

The selection of a fibrinolytic regimen is based on the risk of the AMI, a benefit versus risk analysis of therapy, and consideration of economic constraints. Using these factors, tPA-related fibrinolytics have become dominant in the United States, whereas in Europe and elsewhere, less costly SK is still widely used. These same factors undoubtedly will influence the rate of incorporation of new fibrinolytics and adjunctive therapies into practice. A number of algorithms for selecting the reperfusion regimen (that is, a specific fibrinolytic or primary PTCA) have been proposed,[132,133] but none has been prospectively validated and universally accepted.

The authors view primary percutaneous coronary intervention (PCI) as preferred therapy when readily available (time to PCI $<90\pm30$ min).[5] In other circumstances, fibrinolytic therapy is standard of care. TNK-tPA, accelerated dose rt-PA, or rPA may be recommended for high risk patients who have the potential for a large therapeutic benefit, for example, anterior AMI, BBB-related AMI, or poor-prognosis inferior AMI (that is, with right ventricular involvement, anterior reciprocal ST depression, or lateral and posterior extension), time <6 hours, and age <75 years. (Older patients have greater mortality risk but also greater bleeding risk and derive less proportionate benefit.) TNK-tPA offers the advantage of single bolus dosing and lower transfusion requirement, yet maintains efficacy equivalent to rt-PA. For other patients, efficacy advantages are less clear, and physician preference, patient safety, cost issues, and availability can guide choice. SK is preferred when the risk of ICH is high (for example, the elderly) and when cost is an important consideration. A non-immunogenic fibrinolytic is preferred in patients with a history of prior SK or APSAC use (neutralizing antibodies may persist for several years).

Despite two large outcomes trials,[14,125] the role of combination therapies with GP IIb/IIIa inhibitors remains unclear and recommendations on use cannot be given. Clearly, the combinations tested in GUSTO-V and ASSENT-3 should be avoided in the elderly (>75 years old).

Adjunctive therapy with the LMWH enoxaparin presents another co-therapy option. Based on ASSENT-3,[14] enoxaparin appears to be an attractive alternative to unfractionated heparin as an adjunctive antithrombin with standard dose TNK-tPA. Further testing and assimilation of enoxaparin into official guidelines is anticipated in the near future.

Adjunctive therapy

Adjunctive medical and antithrombotic therapy will be covered more completely in related chapters. Current guidelines strongly recommend **Grade A1a** aspirin on admission in a dose of 162–325 mg, preferably chewed. Aspirin is then continued in the same dose, once daily,

indefinitely (enteric coated forms are popular).[5] For aspirin allergy, clopidogrel (preferred) or ticlopidine may be used.

Intravenous heparin is recommended **Grade A1c** with tPA-related fibrinolytics,[5] beginning concurrently and given for 48 hours, with a target aPTT at ≥12 hours after thrombolytics of 50–70 seconds (1·5 to 2 times control).[98] Currently recommended dosing includes a 60 U/kg bolus (maximum 4000 U) followed initially with a 12 U/kg per hour infusion (maximum 1000 U/hour) with adjustment after *3* hours based on aPTT.[5]

IV heparin is not routinely recommended with systemically active (non-fibrin-selective) agents such as SK and APSAC, especially within 6 hours of fibrinolysis. **Grade A1c**[5] Rather, subcutaneous heparin (7500–12 500 U twice daily until ambulatory) or low molecular weight heparin may be given. IV heparin is "probably effective" after 6 hours in patients at high risk for further thrombosis or thromboembolism (for example, those with large or anterior MI, atrial fibrillation, previous embolus, or known left ventricular thrombus) **Grade B**.[5]

It is likely that the LMWH enoxaparin may be included as an antithrombin option or preference in future guidelines, based on ASSENT-3 **Grade A1d**. Direct antithrombins (hirudin derivatives) also have been tested as adjunctive therapies (for example, HERO-2), but their role has not yet been clearly established.

References

1. Braunwald E, Antman EM, Beasley JW *et al.* ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000;**36**:970–1062.
2. Nourjah P. National Hospital Ambulatory Medical Care Survey: 1997 emergency department summary. *National Center for Health Statistics; advance data from vital and health statistics*. Hyattsville, MD: National Institutes of Health, 1999.
3. Statistics NCfH. *Detailed diagnoses and procedures: National Hospital Discharge Survey, 1996*. Hyattsville, MD: National Center for Health Statistics, 1998.
4. National Heart Lung, and Blood Institute. *Morbidity and mortality: 1996 chartbook on cardiovascular, lung, and blood diseases*. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1996.
5. Ryan TJ, Antman EM, Brooks NH *et al.* 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999;**34**:890–911.
6. Herlitz J, Blohm M, Hartford M, Hjalmarsson A, Holmberg S, Karlson BW. Delay time in suspected acute myocardial infarction and the importance of its modification. *Clin Cardiol* 1989; **12**:370–4.
7. Priori SG, Aliot E, Blomstrom-Lundqvist C *et al.* Task force on sudden cardiac death of the European Society of Cardiology. *Eur Heart J* 2001;**22**:1374–450.
8. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992;**85**(Suppl. 1):I2–10.
9. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995;**92**:1701–9.
10. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction: current status and new horizons for pharmacological reperfusion, part 1. *Circulation* 2001;**103**:2862–6.
11. Rogers WJ, Canto JG, Lambrew CT, *et al.* Temporal trends in the treatment of over 1·5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol* 2000;**36**:2056–63.
12. Hunink MG, Goldman L, Tosteson AN *et al.* The recent decline in mortality from coronary heart disease, 1980–1990. The effect of secular trends in risk factors and treatment. *JAMA* 1997;**277**:535–42.
13. Rogers WJ, Canto JG, Barron HV, Boscarino JA, Shoultz DA, Every NR. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. Investigators in the National Registry of Myocardial Infarction. *J Am Coll Cardiol* 2000;**35**:371–9.
14. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;**358**:605–13.
15. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *JAMA* 1912;**59**:220–8.
16. Obraztsov VP, Strazhesko ND. On the symptomatology and diagnosis of coronary thrombosis. In: Vorobeva VA, Konchalovski MP, eds. *Works of the First Congress of Russian Therapists*: Comradeship typography of A E Mamontov, 1910.
17. Blumgart HL, Schlesinger MJ, Davis D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings with particular reference to the significance of the collateral circulation. *Am Heart J* 1940;**19**:1–91.
18. Roberts WC. Coronary arteries in fatal acute myocardial infarction. *Circulation* 1972;**45**:215–30.
19. Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. *Br Heart J* 1976;**38**:659–64.
20. DeWood MA, Spores J, Notske R *et al.* Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.
21. Shah PK, Falk E, Badimon JJ *et al.* Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Potential role of matrix-degrading metalloproteinases and implications for plaque rupture. *Circulation* 1995;**92**:1565–9.
22. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct

size vs duration of coronary occlusion in dogs. *Circulation* 1977;**56**:786–94.
23. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; **40**:633–44.
24. Chesebro JH, Knatterud G, Roberts R *et al.* Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–54.
25. Anderson JL, Karagounis LA, Califf RM. Meta-analysis of five reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. *Am J Cardiol* 1996;**78**:1–8.
26. Ito H, Okamura A, Iwakura K *et al.* Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996;**93**:1993–9.
27. Gibson CM, Murphy SA, Rizzo MJ *et al.* Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation* 1999;**99**:1945–50.
28. Gibson CM, Cannon CP, Murphy SA *et al.* Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;**101**:125–30.
29. Topol EJ. Toward a new frontier in myocardial reperfusion therapy: emerging platelet preeminence. *Circulation* 1998; **97**:211–18.
30. Tillet WS, Garner RL. The fibrinolytic activity of hemolytic streptococci. *J Exp Med* 1933;**58**:485–502.
31. Sherry S. The origin of thrombolytic therapy. *J Am Coll Cardiol* 1989;**14**:1085–92.
32. Fletcher AP, Alkjaersig N, Smyrniotis FE *et al.* Treatment of patients suffering from early acute myocardial infarction with massive and prolonged streptokinase therapy. *Trans Assoc Am Phys* 1958;**71**:287–97.
33. Streptokinase in acute myocardial infarction. European Cooperative Study Group for Streptokinase Treatment in Acute Myocardial Infarction. *N Engl J Med* 1979;**301**:797–802.
34. Sharma GV, Cella G, Parisi AF, Sasahara AA. Thrombolytic therapy. *N Engl J Med* 1982;**306**:1268–76.
35. Anderson JL, Smith BR. Streptokinase in acute myocardial infarction. In: Anderson JL, ed. *Modern management of acute myocardial infarction in the community hospital.* New York: Marcel Dekker, 1991.
36. Chazov EI, Matveeva LS, Mazaev AV *et al.* Intracoronary administration of fibrinolysin in acute myocardial infarction (in Russian). *Ter Arkh* 1976;**48**:8–19.
37. Rentrop KP, Blanke H, Karsch KR *et al.* Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol* 1979;**2**:354–63.
38. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 1981; **63**:307–17.
39. Ganz W, Ninomiya K, Hashida J *et al.* Intracoronary thrombolysis in acute myocardial infarction: experimental background and clinical experience. *Am Heart J* 1981; **102**:1145–9.
40. Anderson JL, Marshall HW, Bray BE *et al.* A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983;**308**:1312–18.
41. Khaja F, Walton JA, Jr., Brymer JF, *et al.* Intracoronary fibrinolytic therapy in acute myocardial infarction. Report of a prospective randomized trial. *N Engl J Med* 1983;**308**:1305–11.
42. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1983;**309**: 1477–82.
43. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK. The western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. A 12-month follow-up report. *N Engl J Med* 1985;**312**:1073–8.
44. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J *et al.* Improved survival after early thrombolysis in acute myocardial infarction. A randomized trial by the Interuniversity Cardiology Institute in The Netherlands. *Lancet* 1985; **2**:578–82.
45. Schröder R, Biamino G, von Leitner ER *et al.* Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation* 1983;**67**:536–48.
46. Rogers WJ, Mantle JA, Hood WP, Jr. *et al.* Prospective randomized trial of intravenous and intracoronary streptokinase in acute myocardial infarction. *Circulation* 1983;**68**:1051–61.
47. Anderson JL, Marshall HW, Askins JC *et al.* A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation* 1984;**70**:606–18.
48. Alderman EL, Jutzy KR, Berte LE *et al.* Randomized comparison of intravenous versus intracoronary streptokinase for myocardial infarction. *Am J Cardiol* 1984;**54**:14–9.
49. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). Mortality, morbidity, and infarct size at 21 days. The I.S.A.M. Study Group. *N Engl J Med* 1986;**314**:1465–71.
50. Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. *Am J Cardiol* 1994;**74**:1220–8.
51. Bode C, Smalling RW, Berg G *et al.* Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. *Circulation* 1996;**94**:891–8.
52. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;**329**:673–82.
53. Sherry S, Marder MJ. Streptokinase. In: Messerli FH, ed. *Cardiovascular drug therapy, 2nd edn.* Philadelphia: W B Saunders, 1996.
54. Rutherford RB, Comerota AJ. Urokinase. In: Messerli FH, ed. *Cardiovascular Drug Therapy, 2nd edn.* Philadelphia: W B Saunders, 1990.
55. Anderson JL, Califf RM. Anisoylated plasminogen-streptokinase activator complex (APSAC). In: Messerli FH, ed. *Cardiovascular drug therapy.* Philadelphia: W B Saunders, 1996.

56. Tiefenbrunn AJ. Tissue-type plasminogen activator. In: Messerli FH, ed. *Cardiovascular drug therapy*. Philadelphia: W B Saunders, 1996.
57. Rijken DC, Hoylaerts M, Collen D. Fibrinolytic properties of one-chain and two-chain human extrinsic (tissue-type) plasminogen activator. *J Biol Chem* 1982;**257**:2920–5.
58. Randomized, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. International Joint Efficacy Comparison of Thrombolytics. *Lancet* 1995;**346**:329–36.
59. Keyt BA, Paoni NF, Refino CJ *et al.* A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci USA* 1994;**91**:3670–4.
60. Van de Werf F, Vanhaecke J, de Geest H, Verstraete M, Collen D. Coronary thrombolysis with recombinant single-chain urokinase-type plasminogen activator in patients with acute myocardial infarction. *Circulation* 1986;**74**:1066–70.
61. Weaver WD, Hartmann JR, Anderson JL, Reddy PS, Sobolski JC, Sasahara AA. New recombinant glycosylated prourokinase for treatment of patients with acute myocardial infarction. Prourokinase Study Group. *J Am Coll Cardiol* 1994;**24**:1242–8.
62. Randomized double-blind trial of recombinant pro-urokinase against streptokinase in acute myocardial infarction. PRIMI Trial Study Group. *Lancet* 1989;**1**:863–8.
63. Bar FW, Meyer J, Vermeer F *et al.* Comparison of saruplase and alteplase in acute myocardial infarction. SESAM Study Group. The Study in Europe with Saruplase and Alteplase in Myocardial Infarction. *Am J Cardiol* 1997;**79**:727–32.
64. Tebbe U, Michels R, Adgey J *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS Equivalence Trial. Comparison Trial of Saruplase and Streptokinase (COMASS) Investigators. *J Am Coll Cardiol* 1998;**31**:487–93.
65. den Heijer P, Vermeer F, Ambrosioni E *et al.* Evaluation of a weight-adjusted single-bolus plasminogen activator in patients with myocardial infarction: a double-blind, randomized angiographic trial of lanoteplase versus alteplase. *Circulation* 1998;**98**:2117–25.
66. Intravenous NPA for the treatment of infarcting myocardium early; InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000;**21**:2005–13.
67. Collen D, Lijnen HR. Staphylokinase, a fibrin-specific plasminogen activator with therapeutic potential? *Blood* 1994; **84**:680–6.
68. Vanderschueren S, Barrios L, Kerdsinchai P *et al.* A randomized trial of recombinant staphylokinase versus alteplase for coronary artery patency in acute myocardial infarction. The STAR Trial Group. *Circulation* 1995;**92**:2044–9.
69. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *N Engl J Med* 1993;**329**: 1615–22.
70. Yusuf S, Collins R, Peto R *et al.* Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, re-infarction and side-effects from 33 randomized controlled trials. *Eur Heart J* 1985;**6**: 556–85.
71. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;**260**:2088–93.
72. Yusuf S, Sleight P, Held P, McMahon S. Routine medical management of acute myocardial infarction. Lessons from overviews of recent randomized controlled trials. *Circulation* 1990;**82**:II117–34.
73. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986;**1**:397–402.
74. Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1987;**2**:871–4.
75. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;**2**:349–60.
76. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. AIMS Trial Study Group. *Lancet* 1988;**1**:545–9.
77. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. AIMS Trial Study Group. *Lancet* 1990;**335**:427–31.
78. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 1988;**2**:525–30.
79. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994;**343**:311–22.
80. Gersh BJ, Anderson JL. Thrombolysis and myocardial salvage. Results of clinical trials and the animal paradigm–paradoxic or predictable? *Circulation* 1993;**88**:296–306.
81. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**:771–5.
82. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993;**342**:759–66.
83. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. *Lancet* 1993;**342**:767–72.
84. Anderson JL, Karagounis L, Allen A, Bradford MJ, Menlove RL, Pryor TA. Older age and elevated blood pressure are risk factors for intracerebral hemorrhage after thrombolysis. *Am J Cardiol* 1991;**68**:166–70.
85. Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic

treatment. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II (GISSI-2), and The International Study Group. *N Engl J Med* 1992;**327**:1–6.
86. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. *Lancet* 1992;**339**:753–70.
87. Simoons ML, Maggioni AP, Knatterud G, *et al.* Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993;**342**:1523–8.
88. Gore JM, Granger CB, Simoons ML *et al.* Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995;**92**:2811–18.
89. Berkowitz SD, Granger CB, Pieper KS *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. The Global Utilization of Streptokinase and Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) I Investigators. *Circulation* 1997; **95**:2508–16.
90. Mehta SR, Eikelboom JW, Yusuf S. Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000;**356**:449–54.
91. Armstrong PW, Granger C, Van de Werf F. Bolus fibrinolysis: risk, benefit, and opportunities. *Circulation* 2001;**103**:1171–3.
92. Anderson JL. Bolus thrombolytic treatment is associated with an increased risk of intracranial hemorrhage in patients with ST segment elevation infarction. A Commentary. *Evidence-based Cardiovasc Med* 2000;**4**:110–111.
93. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med* 1997;**337**:1118–23.
94. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. *Lancet* 1999;**354**:716–22.
95. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. *Circulation* 1994;**90**:1631–7.
96. Antman EM. Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. *Circulation* 1994; **90**:1624–30.
97. Neuhaus KL, von Essen R, Tebbe U *et al.* Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study. A study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte (ALKK). *Circulation* 1994;**90**:1638–42.
98. Granger CB, Hirsch J, Califf RM *et al.* Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;**93**:870–8.
99. Bottiger BW, Bode C, Kern S *et al.* Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. *Lancet* 2001;**357**:1583–5.
100. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12490 patients with acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1990;**336**:65–71.
101. In-hospital mortality and clinical course of 20891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. The International Study Group. *Lancet* 1990;**336**:71–5.
102. de Bono DP, Simoons ML, Tijssen J *et al.* Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992;**67**:122–8.
103. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med* 1990;**323**:1433–7.
104. Anderson JL, Karagounis LA. Does intravenous heparin or time-to-treatment/reperfusion explain differences between GUSTO and ISIS-3 results? *Am J Cardiol* 1994;**74**:1057–60.
105. Anderson JL, Becker LC, Sorensen SG *et al.* Anistreplase versus alteplase in acute myocardial infarction: comparative effects on left ventricular function, morbidity and 1-day coronary artery patency. The TEAM-3 Investigators. *J Am Coll Cardiol* 1992;**20**:753–66.
106. Neuhaus KL, von Essen R, Tebbe U *et al.* Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC patency study (TAPS). *J Am Coll Cardiol* 1992;**19**:885–91.
107. Cannon CP, McCabe CH, Diver DJ *et al.* Comparison of front-loaded recombinant tissue-type plasminogen activator, anistreplase and combination thrombolytic therapy for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. *J Am Coll Cardiol* 1994;**24**:1602–10.
108. Cannon CP, McCabe CH, Gibson CM *et al.* TNK-tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 10A dose-ranging trial. *Circulation* 1997;**95**:351–6.
109. Cannon CP, Gibson CM, McCabe CH *et al.* TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. *Circulation* 1998;**98**:2805–14.
110. Van de Werf F, Cannon CP, Luyten A *et al.* Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. The ASSENT-1 Investigators. *Am Heart J* 1999; **137**:786–91.
111. Cannon CP. Thrombolysis medication errors: benefits of bolus thrombolytic agents. *Am J Cardiol* 2000;**85**:17C–22C.
112. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;**349**:1429–35.
113. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable

Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436–43.
114. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;**338**:1488–97.
115. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomized, placebo-controlled trial. *Lancet* 2000;**356**:2037–44.
116. Montalescot G, Barragan P, Wittenberg O *et al.* Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895–903.
117. Antman EM, Giugliano RP, Gibson CM *et al.* Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999;**99**:2720–32.
118. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. *Circulation* 2000;**101**:2788–94.
119. Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: Heparin : a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;**103**:2994–3018.
120. Turpie AG, Antman EM. Low molecular weight heparins in the treatment of acute coronary syndromes. *Arch Intern Med* 2001;**161**:1484–90.
121. Cohen M, Blaber R, Demers C *et al.* The Essence Trial: Efficacy and Safety of Subcutaneous Enoxaparin in unstable angina and non-Q-wave MI: a double-blind, randomized, parallel-group, multicenter study comparing enoxaparin and intravenous unfractionated heparin: methods and design. *J Thromb Thrombolysis* 1997;**4**:271–4.
122. Antman EM, Cohen M, Radley D *et al.* Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;**100**:1602–8.
123. Ross AM, Molhoek P, Lundergan C *et al.* Randomized comparison of enoxaparin, a low molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation* 2001;**104**:648–52.
124. Wallentin L, Dellborg DM, Lindahl B *et al.* The low molecular weight heparin dalteparin as adjuvant therapy in acute myocardial infarction: the ASSENT Plus study. *Clin Cardiol* 2001;**24**:I12–14.
125. Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001;**357**:1905–14.
126. Antman EM, Louwerenburg HW, Baars HF *et al.* Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation* 2002;**105**:1642–9. (Erratum in *Circulation* 2002;**105**:2799).
127. White H and the The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001;**358**:1855–63.
128. Berger AK, Radford MJ, Wang Y, Krumholz HM. Thrombolytic therapy in older patients. *J Am Coll Cardiol* 2000;**36**:366–74.
129. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 2000;**101**:2239–46.
130. Stenestrand U, Wallentin L. Thrombolysis is beneficial in elderly acute myocardial infarctin patients. *J Am Coll Cardiol* 2002:in press.
131. Sgarbossa EB, Pinski SL, Barbagelata A *et al.* Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996;**334**:481–7.
132. Simoons ML, Arnold AE. Tailored thrombolytic therapy. A perspective. *Circulation* 1993;**88**:2556–64.
133. Cairns JA, Fuster V, Gore J, Kennedy JW. Coronary thrombolysis. *Chest* 1995;**108**:401S–23S.

32 Mechanical reperfusion strategies in patients presenting with acute myocardial infarction

Sanjaya Khanal, W Douglas Weaver

Introduction

Mechanical reperfusion of the coronary artery is well established as an effective modality of treatment in patients presenting with an acute myocardial infarction. As the pathophysiology of an acute myocardial infarction most commonly involves thrombosis in an area of coronary artery with atherosclerotic narrowing with plaque rupture, advances in treating the thrombus and the underlying stenosis have significantly improved the therapy of this group of patients. Most patients with non-ST-segment elevation myocardial infarction (NSTEMI) have a non-occlusive or partially occlusive thrombus in an atherosclerotic coronary artery with the exception of true posterior myocardial infarction. The pathophysiology and the initial 30 day course of the group of patients with NSTEMI is similar to those who have unstable angina. These patients are initially managed with anticoagulants and antiplatelet agents and then risk stratified. Recently it has been shown that invasive risk stratification and appropriate revascularization in these patients improve outcomes compared to continued medical management.[1] **Grade A**

Patients with ST-segment elevation MI (STEMI) usually have a total thrombotic occlusion of the infarct artery and therefore it is critical to re-establish flow to the distal myocardium as rapidly as possible to reduce the ongoing damage to the cardiac tissue. Antiplatelet and fibrinolytic therapy has been shown to improve outcome and reduce mortality in multiple randomized studies in these patients.[2–4] **Grade A** At the same time, catheter-based percutaneous coronary interventions (PCI) have also been shown to re-establish flow in the infarct artery quite effectively, improving outcome in these patients.[5] **Grade A** Surgical revascularization is required only in a very small percentage of patients with acute STEMI. As the technology has advanced, besides balloon angioplasty, current mechanical reperfusion strategies involve stenting, various thrombectomy devices, distal protection devices, and adjunctive medications. Therefore the terminology percutaneous coronary interventions (PCI) is more appropriate than balloon angioplasty. The focus of this chapter is to explore therapies for STEMI.

Patients who present with STEMI should be treated with either fibrinolytics or percutaneous coronary intervention (PCI) as the initial modality of reperfusion if they are otherwise eligible and have potential to benefit from therapy. **Grade A** The clear advantage of fibrinolytic therapy remains its rapidity and ease of use. It can be used in medical facilities without dedicated cardiac catheterization laboratories and the outcome does not depend on the volume of patients treated by the institution as opposed to PCI. Despite multiple randomized studies showing improved outcome with fibrinolytic therapy as compared to placebo, it is still underused in appropriate patients, most often due to perceived risk of bleeding or cerebral complications. Appropriate contraindications are infrequent. Even with the newer fibrinolytic agents, a small but significant risk (<1%) of intracranial hemorrhage remains and results in death or disability in two thirds of these patients.[7,8,25] **Grade A** The fibrinolytics establish normal TIMI grade 3 flow in only 50–60% of the patients (Figure 32.1).[9,10] **Grade A** Only a third of treated patients have complete resolution of ST-segment elevation and only about 50% have >70% resolution of ST-segment elevation 24–36 hours after fibrinolytic administration – a marker of lower mortality.[11] Since there are no absolutely reliable clinical symptoms or signs that indicate success of fibrinolytic therapy, it is difficult to evaluate whether the infarct artery is open with the treatment in

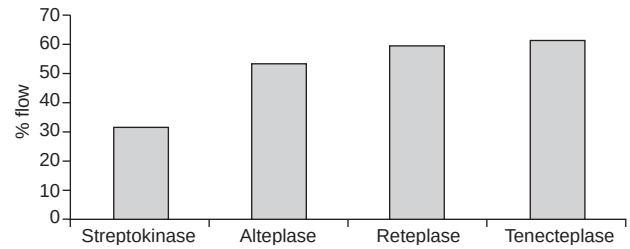


Figure 32.1 Percent TIMI-3 flow at 90 minutes with different fibrinolytic agents

an individual patient. Even in those patients who have successful fibrinolysis, many go on to have reocclusion and re-infarction due to the ongoing vulnerability of the underlying atherosclerotic plaque (Figure 32.2).[9,12,13] **Grade A**

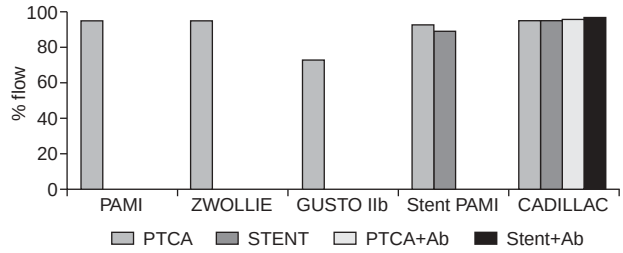


Figure 32.2 Percent TIMI-3 flow in the infarct artery after direct PCI. (Ab, abciximab; PTCA, balloon angioplasty.)

Mechanical reperfusion can overcome many of these limitations. Direct (or primary) PCI, intervention of the infarct artery without prior fibrinolysis, can be done in many patients with contraindications for fibrinolytic therapy. The overall risk of intracranial bleeding is significantly lower with direct PCI.[5] **Grade A** With the strategy of direct PCI, there is an opportunity to evaluate coronary anatomy, ventricular function, and intracardiac pressures essentially at the time of admission and possibly to detect anatomic features or mechanical complications that would require earlier treatment with surgery. The cardiac catheterization laboratory also gives an opportunity to observe directly the effects of medications and mechanical devices like intraaortic balloon counterpulsation. The other benefit of direct PCI is the availability of highly trained staff in the cardiac catheterization laboratory if circulatory resuscitation is needed. In most randomized studies of direct PCI, the success rate is quite high and the rate of TIMI-3 flow in the infarct artery is substantially higher than is achieved with fibrinolytic therapy (Figure 32.3).[5,14,15] **Grade A** Rapid assessment and treatment also results in shorter lengths of hospital stay for patients, potentially reducing the cost of care.[16] **Grade B** The primary limitation of direct PCI in acute MI is logistical. Access to a tertiary care center with a cardiac catheterization laboratory facility and highly trained personnel is required. The majority of the patients with acute MI present to hospitals with neither of these. Even in facilities able to do PCI, the time to treatment is usually longer compared to administering fibrinolytic therapy. Transfer to these tertiary centers is often impractical because it would further delay therapy.[17] One study has suggested that the initial advantage of primary PCI over fibrinolytics is lost when the delay in doing primary PCI is more than 90 minutes from the time of presentation.[17] **Grade B** Despite these limitations, direct PCI for STEMI and elective PCI for NSTEMI are done in a significant proportion of patients with acute MI. Better understanding of the cardiovascular hemodynamics, advances in catheter technology and stents, and use of adjunctive pharmacologic therapies in the cardiac catheterization laboratory have improved results and outcomes in patients with acute MI. This has resulted from improvement in procedure safety, procedural success, and decreased need for repeat revascularization.

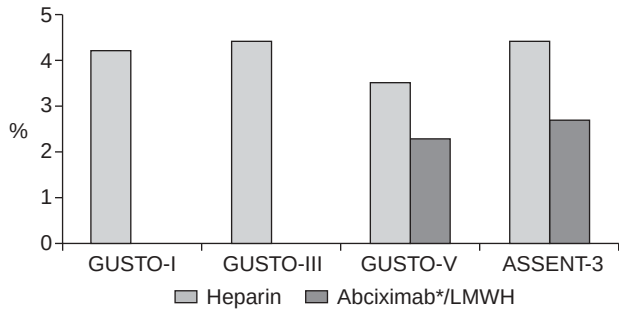


Figure 32.3 Re-infarction rates (per cent) after successful fibrinolytic therapy. (*GUSTO-V: half dose reteplase and abciximab; †ASSENT-3: half dose tenecteplase and enoxaparin; LMWH, low molecular weight heparin.)

Randomized controlled trials: direct PTCA *v* fibrinolytic therapy

Randomized controlled trials have compared various regimens of fibrinolytic therapy with balloon angioplasty (Table 32.1). **Grade A** These studies were small in size compared to the studies of fibrinolytics versus placebo and the results may not be as generalizable. The studies are limited in that third generation fibrinolytics such as tenecteplase and reteplase along with modern regimens of heparin were not used; nor do they include the use of stents and glycoprotein (Gp) IIb/IIIa receptor inhibitors in those patients treated by direct PCI. Overall, direct balloon angioplasty seems to result in better outcomes than fibrinolysis in certain settings (Table 32.2). **Grade A** The first reported studies to compare the strategies in a randomized setting used 3 hour infusion of tPA and 1·5 MU of streptokinase.[14,15] These were done in specialized centers dedicated to direct PCI. Grines *et al* reported a trend towards improved hospital mortality and a significant decrease in the end point of death and re-infarction in patients treated with direct balloon angioplasty (OR 0·40; 95% CI 0·16–0·89). Zijlstra *et al* also reported significant mortality benefit for direct angioplasty (OR 0·25; 95% CI 0·04–0·99). **Grade A** Among the three other smaller randomized studies comparing streptokinase to direct angioplasty, two of them favored angioplasty and one streptokinase.[15,18,19] Among the smaller studies using 3–4 hour tPA regimens there were no differences in survival.[20,21] Two small studies and one large study compared the optimum accelerated tPA regimen with direct angioplasty.[22–24] The smaller studies showed a trend

Table 32.1 Trials comparing direct balloon angioplasty and fibrinolytics

Study (first author)	Lytic agent	Patient population description	Duration of symptoms (h)	Primary follow up period	Patients PTCA (*n*)	Patients FTX (*n*)	Time to Rx (min)	
							PTCA	FTx
DeWood[21]	Duteplase 4 h	ST ↑ <76 yr	<12	30 days	46	44	294	258
Grines[14]	tPA 3 h	ST ↑	<12	Discharge	195	200	60	32
Zijlstra[15]	1·5 mU SK ×1 h	ST ↑ <76 yr	<6	Discharge	152	149	62	30
Gibbons[20]	Duteplase 4 h	ST ↑ <80 yr	<12	Discharge	47	56	45	20
Ribeiro[18]	1·2 mU SK ×1 h	ST ↑ <75 yr	<6	Discharge	50	50	238	179
Zijlstra[15]	1·5 mU SK ×1 h	ST ↑ Low risk	<6	30 days	45	50	68	30
Ribichini[22]	tPA 90 min	Inf. MI Ant. ST ↓ <80 yr	<6	Discharge	41	42	40[a]	33[a]
Grinfeld[19]	1·5 mU SK ×1 h	ST ↑	<12	30 days	54	58	63[a]	18[a]
GUSTO-II[24]	tPA 90 min	ST ↑ LBBB	<12	30 days	565	573	72[a]	114[a]
Garcia[23]	tPA 90 min	Ant. MI	5	30 days	95	94	69	84
Total					1290	1316		

[a] From randomization.
Arrow indicates ST-segment elevated or depressed; FTx, fibrinolysis; LBBB, left bundle branch block; PTCA, percutaneous transluminal coronary angioplasty

Table 32.2 Mortality at end of study period: direct PTCA *v* fibrinolysis

Study	PTCA	Fibrinolysis	Odds ratio (95% CI)
Zijlstra[15]	3/152 (2·0%)	11/149 (7·4%)	0·25 (0·04–0·99)
Ribeiro[18]	3/50 (6·0%)	1/50 (2·0%)	3·13 (0·24–1·67)
Grinfeld[19]	5/54 (9·3%)	6/58 (10·3%)	0·88 (0·20–3·73)
Zijlstra[15]	1/45 (2·2%)	0/50 (0·0%)	
DeWood[21a]	3/46 (6·5%)	2/44 (4·6%)	1·47 (0·16–18·3)
Grines[14]	5/195 (2·6%)	13/200 (6·5%)	0·38 (0·11–1·16)
Gibbons[20a]	2/47 (4·3%)	2/56 (3·6%)	1·20 (0·08–17·1)
Ribichini[22]	0/41 (0%)	1/42 (2·4%)	0·00 (0·0–19·6)
Garcia[23]	3/95 (3·2%)	10/94 (10·6%)	0·27 (0·04–1·12)
GUSTO-II[24]	32/565 (5·7%)	40/573 (7·0%)	0·80 (0·48–1·32)
Total	57/1290(4·4%)[b]	86/1316 (6·5%)[b]	0·66 (0·46–0·94)

[a] Duteplase.
[b] Percentages are pooled results and odds ratio calculated by exact method using all trials.

that favored angioplasty, but the difference was not statistically significant. **Grade A**

The largest study to date that compared accelerated tPA and direct angioplasty is the GUSTO-IIb.[24] This was a multicenter study that was a substudy of the larger GUSTO-II study comparing hirudin and heparin in the treatment of acute MI. It represented more of community practice for treating MI, with 57 hospitals participating rather than a few specialized centers. In this study, the incidence of the primary end point (death, non-fatal re-infarction and stroke at 30 days) was 9·6% in the angioplasty group and 13·7% in the tPA group ($P = 0{\cdot}03$). However, there was no difference in the incidence of the composite end point (14·1% *v* 16·1% P = NS) at 6 months. **Grade A** Of note, this study reported only 73% of patients undergoing direct angioplasty achieved TIMI-3 flow when analyzed by a core laboratory. Most of other direct PCI studies have reported achieving TIMI-3 flow rates of over 90%. Subgroup analysis of the GUSTO-IIb study seems to suggest more benefit of direct angioplasty in elderly patients and patients who present after 4 hours of symptoms. **Grade B** When the results of GUSTO-IIb are combined with all others, it appears that there is a significant reduction in the composite mortality and re-infarction (approximately 70% net reduction at 30 days that is maintained to at least 6 months).

A meta-analysis of the studies described above by Weaver *et al* found that patients treated with direct angioplasty had 30 day or less mortality of 4·4% compared with 6·5% in patients treated with fibrinolytic therapy (OR 0·66; 95% CI 0·46–0·94).[5] The rates of death or non-fatal re-infarction were 7·2% for angioplasty and 11·9% for fibrinolytics (OR 0·58; 95% CI 0·44–0·76). Furthermore, the risk of stroke was also significantly reduced (0·7% *v* 2·0%; $P = 0·007$). **Grade A** Intracranial hemorrhage is a significant limitation of intravenous fibrinolytic therapy. Major fibrinolytic studies have consistently reported a small but significant risk of intracranial hemorrhage.[9,25] **Grade A** This risk is lower with direct angioplasty compared to fibrinolytics in the randomized trials.[5] Patients at higher risk of intracranial bleeding (for example, age >75 years or systemic hypertension) may derive more benefit from direct PCI as opposed to fibrinolytic therapy.[24] **Grade A** The risk of bleeding increases with more aggressive fibrinolytic therapy. Pilot studies suggested better TIMI-3 flow rates in the infarct artery when a reduced dose fibrinolytic was combined with a GP IIb/IIIa inhibitor.[26–28] However, there was no mortality benefit seen with the use of half-dose fibrinolytic therapy plus a GP IIb/IIIa inhibitor compared to full-dose fibrinolytic in the GUSTO-V study.[29] There was a reduction in re-infarction rate but a higher bleeding rate with the combination therapy. **Grade A** In the ASSENT-3 study, the combination of low molecular weight heparin had greater efficacy (30 day mortality, re-infarction or refractory ischemia) and safety (intracranial hemorrhage or major bleeding) than tenecteplase plus unfractionated heparin or half-dose tenecteplase plus abciximab.[30] **Grade A** Therefore, it appears that adjusting fibrinolytic dose or combining it with IIb/IIIa inhibitors has not reduced overall mortality in AMI without compromising safety.

Observational studies: direct angioplasty *v* fibrinolytic therapy

Randomized controlled trials have demonstrated that direct angioplasty results in superior outcomes if done in a controlled setting. Whether this superiority is maintained in the community is not clear. Observational studies of large registries provide insight into this.[31,32] Randomized trials of direct angioplasty are usually carried out in tertiary hospitals with the facility and personnel dedicated to PCI. Therefore, a community hospital may not be able to replicate the results of the randomized trial for various reasons. The Myocardial Infarction Triage and Intervention Investigation registry compared mortality in 1050 patients undergoing direct angioplasty with 2095 patients treated with fibrinolytics for AMI.[32] The primary angioplasty patients were treated in three high volume and seven low volume centers, reflecting community practice. There was no difference of inhospital mortality or long-term mortality between the groups (5·6% *v* 5·5%, $P = 0·93$; long-term adjusted hazard ratio 0·95; 95% CI 0·8–1·2) (Figure 32.4). **Grade B** Procedure use and costs were lower in patients in the fibrinolytic group by the time of hospital discharge and at 3 years (33% fewer coronary angiograms, 20% fewer PCIs, and 14% lower costs). **Grade B** However, this study did not include the use of stents, which have been shown to significantly reduce target vessel revascularization. Currently, 40–60% of patients who are treated with fibrinolytics undergo further revascularization, and it is now likely that cost–benefit analysis will favor PCI. **Grade B/C**

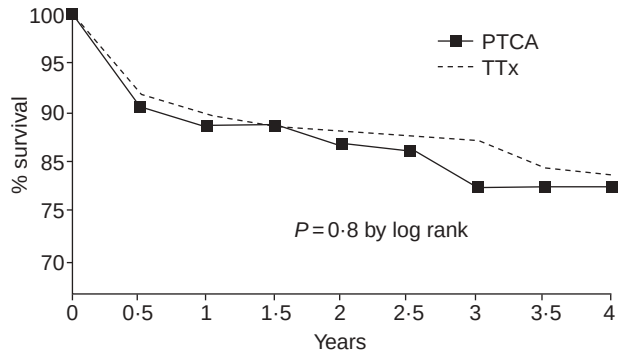


Figure 32.4 Cumulative survival among 1050 patients in the primary-angioplasty group and 2095 patients in the fibrinolytic group

Tierfenbrunn *et al* reported a similar comparison between 4939 patients undergoing direct angioplasty and 24 705 patients undergoing fibrinolysis for AMI.[33] The time to treatment with fibrinolytic was shorter than direct angioplasty (42 min *v* 111 min, $P < 0·0001$). Inhospital mortality in the two groups was the same (5·2% *v* 5·4%). The stroke rate was higher in the fibrinolytic group (1·6% *v* 0·7%, $P < 0·001$). The inhospital mortality was higher in patients with shock treated with fibrinolytics than direct angioplasty (52% *v* 32%). The results were maintained after adjustments for baseline risk by multivariate analysis. **Grade B**

Observational studies therefore suggest that the mortality advantage of direct PCI may not be maintained in the community setting, although the results are probably no worse than with fibrinolytic therapy. There are various explanations for this, but the delay in doing direct PCI as compared to administering fibrinolytic in the community setting is likely a major factor. Since the experience of the institution and the operator doing the PCI influences outcome, results of direct PCI in the community may not be as good as those from specialized tertiary centers.[34] **Grade B** Cannon *et al*, using a retrospective analysis, have demonstrated that an increase in the door-to-balloon time increases mortality significantly in patients undergoing direct angioplasty for AMI (121–150 min, OR 1·41; 151–180 min OR 1·62; > 180 min, OR 1·61).[17] **Grade B** Canto *et al*., reporting from

the same registry, noted that inhospital mortality was 28% lower among patients who underwent direct angioplasty in hospitals with the highest volume compared with those who were treated at hospitals with the lowest volume (adjusted RR 0·72; 95% CI 0·60–0·87).[31] At the same time there was no significant relation between inhospital mortality and volume of patients when fibrinolytic therapy was used. **Grade B** Another possible factor explaining this finding may be the bias of treating sicker patients with direct angioplasty in a non-randomized setting. Although baseline risk adjustments were done to exclude this, it is possible that the risk adjustments may have been incomplete.

There has been continuous improvement in the outcomes following both fibrinolytic therapy and direct angioplasty over time. However, direct angioplasty may have had more incremental improvement than fibrinolytic therapy over time. Rogers *et al* reported that the temporal trend in 1·5 million patients with MI in the USA from 1990 through 1999 revealed that patients are being administered fibrinolysis more rapidly, there is increasing use of direct PCI, and more frequent use of adjunctive therapies.[35] **Grade B** These factors may be contributing to shorter hospital stays (median duration from 8·3 days *v* 4·3 days) and lower inhospital mortality (11·2% *v* 9·4%). Zahn *et al* reported data from two large German registries of 10 118 fibrinolytic eligible patients.[36] There were 1385 patients treated with direct angioplasty and 8733 who received fibrinolysis. The proportion of an inhospital delay of more than 90 minutes significantly decreased inpatients treated with direct angioplasty between 1994 and 1998 (multivariate OR 0·84; 95% CI 0·73–0·96) but did not change significantly for patients treated with fibrinolysis. Hospital mortality decreased significantly in the direct angioplasty group (multivariate OR 0·73; 95% CI 0·58–0·93), but there was no significant improvement in mortality over time in patients treated with fibrinolysis. **Grade B**

Fibrinolytic therapy *v* stenting

Use of stents in elective percutaneous coronary interventions has been shown to have superior results in the form of lower restenosis and better target vessel revascularization rates in many coronary lesion subsets. **Grade A** Stent implantation in the setting of MI has been studied in comparison to fibrinolytic therapy and balloon angioplasty alone with and without concomitant Gp IIb/IIIa inhibitor therapy. Schomig *et al* randomized 140 AMI patients to receive either accelerated intravenous tPA or direct coronary stenting plus abciximab.[37] The median size of the infarct as measured by Tc^{99m} sestamibi scan was smaller in the stent plus abciximab group compared to the tPA group (14·3% *v* 19·4%, $P = 0·002$). The combined end point of death, re-infarction, or stroke was also lower in the stent plus abciximab group (8·5% *v* 23·2%, $P = 0·02$). **Grade A** Le May *et al*, in a smaller study of 123 AMI patients, reported that compared to accelerated tPA, stenting reduced the combined end point of death, re-infarction, stroke or repeat target vessel revascularization in a 6 month follow up (24·2% *v* 55·7%, $P < 0·001$).[38] The median length of hospital stay was significantly reduced in the stented patients (4 days *v* 7 days, $P < 0·001$). **Grade A** Kastrati *et al* compared the administration of alteplase plus abciximab with stenting plus abciximab in 162 AMI patients.[39] Stenting was associated with greater myocardial salvage than alteplase (median 13·6% *v* 8·0%, $P = 0·007$). Stenting therefore results in superior outcome to fibrinolytic therapy if done in appropriate settings. **Grade A**

Fibrinolytics, transport or direct PCI without on-site cardiac surgery

One major limitation of direct PCI is the excessive time it takes to mobilize the patient and do the procedure. The advantage of direct PCI is decreased in the community setting primarily because of major difference in treatment times as compared to randomized studies.[32,33] Ideally, if door-to-balloon time could be substantially reduced, direct PCI would probably have a significant advantage over fibrinolytic therapy. The Air PAMI study randomized patients to on-site fibrinolysis versus transfer to tertiary facility for direct PCI.[40] There was a non-statistically significant 38% reduction in the end point of death, re-infarction or disabling stroke (8·4% *v* 13·6%) in patients treated with direct PCI. **Grade A** Widimsky *et al* have shown that patients transported from presenting hospitals to tertiary hospitals for direct PCI have lower incidence of the combined end point of death, re-infarction, and stroke at 30 days than patients treated with fibrinolytic therapy in the community hospital or fibrinolytic therapy during transportation to PCI (8% *v* 23% *v* 15%, $P < 0·02$).[41] **Grade A** Anderson *et al* presented data in a randomized study reporting that patients treated with direct PCI with or without transfer had a lower incidence of the combined end point of death, re-infarction or disabling stroke at 30 days than patients treated with fibrinolytic therapy (9·8% *v* 13·7%, $P = 0·0003$).[42] **Grade A** The delay in door-to-balloon time with the transport in both these studies averaged only 10 minutes, which is hard to achieve in most settings.

The other limitation of direct PCI is the accessibility of patients to centers that can perform the procedure safely. Whether direct PCI can or should be done in facilities without surgical backup has been debated. Aversano *et al* compared fibrinolytic therapy versus primary PCI in patients presenting to hospitals without on-site cardiac surgery.[43] After extensive formal PCI programs were developed at the treating facilities, 451 patients were randomly assigned to

either direct PCI or fibrinolytic therapy with accelerated tPA. The composite end point of death, re-infarction or stroke was reduced in patients treated with direct PCI at 6 weeks (10·7% *v* 17·7%, $P = 0·03$) and 6 months (12·4% *v* 19·9%, $P = 0·03$). The median length of hospital stay was also reduced in the PCI group (4·5 days *v* 6·0 days, $P = 0·02$). **Grade A**

Therefore, the choice of whether to treat AMI patients with direct PCI or fibrinolytic therapy should be made depending on each institution's preparedness to do direct PCI and its success rate. If conditions close to those in the randomized studies prevail the choice should clearly be direct PCI. In less optimal conditions, the choice depends on the likelihood of good outcomes in individual and groups of patients. **Grade A** Finally, as advances in pharmacologic therapy and PCI continue, there may be a role in doing both approaches in the form of facilitated PCI. **Grade B/C**

Balloon angioplasty *v* stenting

Grines *et al* compared balloon angioplasty to implantation of a heparin coated stent in a randomized study of 900 patients with AMI undergoing direct PCI.[44] The combined primary end point of death, re-infarction, disabling stroke or target vessel revascularization was lower in the stent group (12·6% *v* 20·1%, $P < 0·001$). The benefit resulted primarily from a reduction in target vessel revascularization, with a larger minimal luminal diameter achieved after stenting ($2·56 + 0·44$ mm *v* $2·12 + 0·45$ mm, $P < 0·001$) resulting in a lower restenosis rate (20·3% *v* 33·5%, $P < 0·001$) than the angioplasty group. **Grade A** This study was done without significant use of Gp IIb/IIIa inhibitors and reported a marginally higher death rate in the stent group than the angioplasty group (3·5% *v* 1·8%, $P = 0·15$). Although this was not statistically significant, there was a question as to whether the lower TIMI-3 flow rate achieved with stenting in this study (89·4% *v* 92·7%, $P = 0·10$) contributed to this. Subsequent studies have not reproduced this. Maillard *et al* reported a study which randomized 211 AMI patients to direct angioplasty versus stenting and found that the primary end point of restenosis at 6 months was lower in the stent group (25% *v* 40%, $P = 0·04$).[45] There was no acute difference in angiographic success rates between the two groups (86% for stent and 82% for angioplasty, $P =$ NS). **Grade A** Stone *et al* demonstrated that implantation of stents to treat lesions causing an acute MI had the best overall results when compared to balloon angioplasty with or without the Gp IIb/IIIa inhibitor abciximab.[46] In this study 2082 patients with acute MI undergoing direct PCI were randomly assigned four different treatment groups: angioplasty alone, angioplasty with abciximab, stent alone, and stent with abciximab. The stent group had the lowest incidence of major cardiovascular events at 6 months (20·0% PTCA, 16·5% PTCA plus abciximab, 11·5% stenting and 10·2% stenting plus abciximab, $P < 0·001$). **Grade A** This benefit was primarily driven by target vessel revascularization. There was no deterioration of flow or possible early hazard seen with the stent in this study. It therefore appears safe and desirable in patient undergoing direct PCI in the setting of an acute MI to treat the coronary lesions with stents if feasible. **Grade A**

PCI with or without Gp IIb/IIIa inhibitors

There are several studies evaluating the use of Gp IIb/IIIa inhibitors during direct PCI for AMI. Brener *et al* randomized 483 patients to receive abciximab or placebo during direct AMI angioplasty. When the results were analyzed by intention to treat, there was no difference in the incidence of the combined end point of death, re-infarction, and target vessel revascularization (TVR) at 6 months (28·1% *v* 28·2%, $P = 0·97$).[45] There was a trend toward a lower rate of death or re-infarction with abciximab in an actual treatment analysis (6·9% *v* 12·0%, $P = 0·07$) but this was achieved with more frequent major bleeding in the abciximab group (16·6% *v* 9·5%, $P = 0·02$). **Grade A** Montalescot *et al* randomly assigned 300 patients to abciximab and stenting or placebo and stenting. The composite end point of death, re-infarction or urgent TVR was lower in the abciximab group at 30 days (6·0% *v* 14·6%, $P = 0·01$) and at 6 months (7·4% *v* 15·9%, $P = 0·02$).[48] The TIMI-3 flow was better in the abciximab group immediately prior to the procedure (16·8% *v* 5·4%, $P = 0·01$), immediately after the stenting procedure (95·1% *v* 86·7%, $P = 0·04$) and at 6 month angiographic follow up (94·3% *v* 82·8%, $P = 0·04$). There was significantly more minor bleeding (12·1% *v* 3·3%, $P = 0·004$) but only one major bleed was reported in the abciximab group. The better results with abciximab in this study may be influenced by the better TIMI-3 flow rate achieved prior to PCI in the patients who received abciximab well ahead of the PCI. **Grade A** In the 2082 patient randomized study reported by Stone *et al*, patients treated with abciximab and stent did not have statistically significantly better outcome than those treated with stent alone.[46] In this study, the abciximab was used after angiography and randomization with no difference in the TIMI-3 flow between the groups treated with stent alone or stent plus abciximab either before (21·3% *v* 24%) or after (94·5% *v* 96·9%) the PCI. The combined end point of death, re-infarction, disabling stroke or TVR was also not statistically different between the groups (11·5% *v* 10·2%). **Grade A** We have to therefore conclude that use of the Gp IIb/IIIa inhibitor abciximab during direct PCI has either marginal or no advantage over stenting alone. There are no randomized data with the other Gp IIb/IIIa inhibitors in this setting.

Facilitated PCI

Earlier achievement of normal perfusion of the infarct artery results in better myocardial salvage and clinical outcome.[49] **Grade A** Facilitated PCI is the term used to designate the use of pharmacologic therapy to aid reperfusion of the infarct artery while preparing for direct PCI. This may be achieved with either full-dose fibrinolytics or reduced dose fibrinolytics combined with platelet inhibitors. Earlier studies showed that routinely undertaking PCI after full-dose fibrinolytic administration results in worse outcomes and therefore is not recommended unless there is clinical evidence of failure of fibrinolytic therapy.[50,51] **Grade A** However, with advancements in catheter technology, better hemostatic techniques, and safer pharmacologic regimens, it may be feasible to combine various doses of fibrinolytics and direct PCI. Since fibrinolytics can be administered much more quickly than PCI can be performed, whether this approach results in better patient outcome needs to be studied. The potential advantage of this approach would be that more patients would have open infarct arteries prior to doing PCI resulting in better myocardial salvage. Ross *et al.* reported a pilot study of 606 AMI patients randomly assigned to half-dose rtPA or placebo before undergoing angiography.[52] PCI was carried out only if there was less than TIMI-3 flow in the infarct artery. More patients with half-dose rtPA had TIMI-3 flow at first angiography (33% *v* 15%, $P < 0{\cdot}001$) but there was no difference in bleeding rates, stroke or 30 day mortality between the groups. **Grade B** Herrman *et al* reported the result of a subanalysis of the GUSTO-IV Pilot in which 323 patients underwent PCI at the time of initial angiography.[53] In this analysis PCI was done safely and efficaciously in patients receiving half-dose rtPA and full-dose abciximab. **Grade B**

Facilitated PCI may also address the delay in reperfusion in patients undergoing direct PCI. If PCI in patients who have received a combination of reduced dose fibrinolytic and platelet inhibitors can be demonstrated to be safe, this strategy may reduce time to reperfusion and maintain the benefit of direct PCI. **Grade B/C** Whether transferring patients after administration of combination therapy from community medical centers to tertiary centers to perform facilitated PCI results in better outcome requires further study.

The other potential advantage of facilitated PCI may be the opportunity to improve distal myocardial perfusion. Distal myocardial perfusion is normal only in the one third of patients who undergo direct PCI and achieve TIMI-3 flow in the culprit artery. Poor distal myocardial perfusion in spite of TIMI-3 flow in the epicardial artery predicts a worse outcome in patients with AMI.[54] **Grade B** Thrombectomy devices or distal protection devices may decrease the chance of worsening distal myocardial flow during PCI. **Grade B/C** Systemic or intracoronary administration of agents such as Gp IIb/IIIa inhibitors and adenosine may improve distal myocardial perfusion.[53,55] **Grade A/B** A variety of other pharmacologic agents is being tested in combination with fibrinolysis or PCI to see if infarct size can be reduced. Invasive assessments of the coronaries and myocardium currently allow accurate assessment. Facilitated PCI is in its early stages of investigation and no definite recommendations can be made with the current evidence.

Resource use and cost effectiveness of direct PCI

As clinical outcomes vary between randomized trials and observational studies of direct PCI and fibrinolysis, so too does cost analysis between individual randomized studies and observational studies. In general, randomized studies report cost advantages of direct angioplasty because of reduced length of stay, repeat hospitalizations, and need for subsequent revascularization. **Grade A** Whether these factors overcome the higher upfront costs of an invasive procedure requires systematic analysis. Zijlstra *et al* have reported a 5 year follow up of 395 patients randomly treated with intravenous streptokinase or direct angioplasty.[56] The direct angioplasty group had higher survival (mortality 13% *v* 24%, RR 0·54; 95% CI 0·15–0·52%) less non-fatal re-infarctions, and fewer readmissions for heart failure and ischemia. The total medical charges were also lower in the angioplasty group ($16 090 *v* 16 813, $P = 0{\cdot}05$). **Grade A** In the randomized PAMI study, Stone *et al* reported direct angioplasty achieved better clinical outcomes with no significant difference in cost ($27 653 for angioplasty *v* $30 227 for fibrinolysis, $P = 0{\cdot}21$).[57] **Grade A**

Analysis of the MITI registry, however, shows that patients treated with angioplasty for AMI were more likely to undergo further catheterization and revascularization procedures and incurred 13% higher costs than patients treated with fibrinolysis.[32] **Grade B** This is in contrast with the results of most of the randomized studies of direct PCI and fibrinolysis. When patients are randomly assigned in a carefully conducted study, the physician preference or bias is controlled. But in an observational study, it may be that sicker patients are referred for direct PCI and the additional invasive assessment after the primary PCI may be driven by the physician preference for invasive assessment.

Therefore the cost of direct PCI probably is lower or equal to the cost of fibrinolysis in the long term if it is done in centers practicing methods used in the randomized control trials, but the comparison of the costs in the community setting is not as favorable. Estimates of cost effectiveness using randomized data and assuming a large (40–50%) mortality benefit from direct PCI favor direct PCI.[58] But if the more modest reduction in events noted in the GUSTO-IIb or the observational studies are used, the estimate of benefit may be much less.[24,32] **Grade B** Because therapeutic strategies

for both fibrinolysis and direct PCI are evolving, it is hard to compare the cost or calculate the cost effectiveness of either therapy.[59] Upfront costs of direct PCI have increased with the more frequent use of Gp IIb/IIIa inhibitors and stents during the procedures, but the shorter hospital stay and improving clinical outcomes may offset the initial costs. Grines *et al* have demonstrated that omission of intensive care and discharge at day 3 of hospital stay after direct PCI for AMI is safe in some lower-risk patients and has the potential for cost savings.[16] **Grade B** The cost of fibrinolysis is in flux, with newer agents, adjunctive therapies, and increasing use of invasive risk stratification after fibrinolytic administration. Because of this, and the wide variation of cost of procedures in patients with AMI, formal cost effective analysis is difficult and inaccurate to extrapolate to all settings.

The use of bypass surgery in the setting of AMI

With the advent of stents for acute vessel closures, the percentage of patients requiring emergency bypass surgery for acute myocardial infarction has fallen below 1% in contemporary randomized studies of direct PCI.[37,44] **Grade A** However, earlier studies of direct PCI and observational registries reported this rate as 4–6%.[14,15,60] **Grade B** Bypass surgery may be required owing to anatomical considerations, such as left main disease or coronary disease not suitable for immediate PCI, or mechanical complications from the MI such as acute severe mitral regurgitation, ventricular septal defect or a failed PCI. Observational studies report that stable patients with acute MI can undergo bypass surgery with good results. But, the complexity of performing cardiac surgery in patients with acute MI and potentially other manifestations like failed PCI or cardiogenic shock is definitely greater. Randomized studies comparing surgery to medical therapy or PCI in this situation are lacking.

When bypass surgery was the only available therapy for acute coronary reperfusion in the 1970s, there were some studies that reported surprisingly good results. DeWood *et al* reported on their experience with 187 patients treated with early coronary bypass surgery.[61] In this observational study, all patients under 65 years of age who presented with ST-segment elevation underwent cardiac catheterization. After exclusion of 28 patients (comorbidity, diffuse or no coronary disease), 187 patients were treated with bypass surgery and 200 were treated medically. Although treatment was not randomly assigned, the groups were well balanced in terms of age, prior history, and presenting signs and symptoms. Hospital and long-term mortality was lower in the bypass patients (5·8% *v* 11·5%, $P = 0{\cdot}08$ in hospital; 11·7% *v* 20·5%, $P < 0{\cdot}03$ at 56 months). In surgical patients placed on cardiopulmonary bypass within 6 hours of symptoms, hospital mortality was 2%. **Grade B** Similar results have been reported in 261 patients treated with acute bypass surgery at the lowa Heart Center (hospital mortality 5·7%).[62] **Grade B** These findings, however, are limited by the fact that the comparisons between surgical and medical therapy were not randomized. Patients were excluded from the surgical cohort due to coronary anatomy, comorbidity or shock. Thus, these excellent results are probably not generalizable to the larger population of acute infarct patients.

In the PAMI-2 study of AMI patients treated with direct angioplasty, 10·9% underwent cardiac surgery before hospital discharge, 57% of whom underwent the surgery urgently.[55] The inhospital mortality was 6·4% in those who underwent surgery urgently versus 2·0% in the elective surgery group. **Grade B** The mortality associated with bypass surgery after AMI increases with the instability of the patient. Lee *et al* reported on 316 patients undergoing bypass surgery after AMI, among whom the mortality was 1·2% in stable patients and 26% in patients with cardiogenic shock.[63] Hochman *et al* reported the results a randomized study comparing medical therapy versus revasularization therapy in 304 patients with acute MI and cardiogenic shock.[64] In the revascularization group 64% were treated with angioplasty and 36% by surgery. At 30 days the mortality was 46·7% in the revascularization group versus 56% in the medical therapy group ($P = 0{\cdot}11$) but at 6 months the mortality was statistically lower in the revascularization group (50·3% *v* 63·1%, $P = 0{\cdot}027$). There was no difference in mortality between the angioplasty group (45·3%) and the surgery group (42%). Although patients have a high mortality when they present with acute MI and cardiogenic shock, revascularization strategy may improve the outcome in selected patients. **Grade A** As a subgroup, patients ≥75 years of age had higher mortality with the revascularization strategy (RR 1·41; 95% CI 0·97–2·03) than medical therapy. **Grade B** Therefore, it is unclear at this time whether elderly patients in cardiogenic shock should undergo revascularization therapy in the setting of an acute MI.

The American College of Cardiology/American Heart Association practice guidelines for the treatment of AMI recommend acute bypass surgery only in the case where catheter-based intervention has failed or is not feasible.[65] Class I recommendations for urgent/emergent bypass in the setting of AMI include those patients with failed PTCA with persistent pain or hemodynamic instability, persistent or recurrent ischemia refractory to medical therapy in candidates not eligible/suitable for catheter-based intervention, or in the setting of a surgical repair for ventricular septal defect or mitral valve insufficiency. Class II indications include cardiogenic shock or failed angioplasty in patients with a small amount of myocardium at risk.

Conclusions and recommendations

Although a small subset of patients will require emergent surgery, in the current environment, mechanical reperfusion in the setting of an acute MI is mostly limited to percutaneous coronary intervention. The majority of patients with STEMI present to hospitals without dedicated PCI facilities or personnel and will be treated pharmacologically with fibrinolytics, antithrombotics, and platelet inhibitors. In centers with dedicated PCI facilities, the choice of therapy should be direct PCI in all patients presenting with STEMI unless contraindicated. **Grade A** This is especially so if it can be done in an expeditious manner, by an experienced operator in a high volume center. **Grade B** Although there are no randomized study data to substantiate the numbers associated with the time to therapy, operator volume or institution PCI volume, the American College of Cardiology and American Heart Association recommends a door-to-balloon time of <90 minutes, operator PCI volume of >75 per year, and institution volume of >200 per year.[65] Whether surgical backup is necessary to do direct AMI PCI is debatable, but a small number of patients continue to require emergency surgical therapy because of coronary anatomy or failed PCI, and surgical backup close at hand is recommended. **Grade B** Younger patients (<75 years) with cardiogenic shock, patients with contraindications to fibrinolytic therapy with high risk of bleeding, and patients who have failed fibrinolytic therapy should also be considered for PCI.[64] **Grade A**

Myocardial salvage and therefore prognosis depends on the time delay to opening the blocked infarct artery. Everything possible should be done to expedite the re-establishment of flow into the distal myocardium. **Grade A** Whether the benefit of direct PCI by transferring patients from community hospitals to tertiary centers outweighs the additional myocardial damage brought on by the delay needs to be studied further. **Grade B** Facilitated PCI by using full or reduced dose fibrinolytics with or without IIb/IIIa inhibitors during the time delay to the catheterization laboratory also shows promise, but again needs further study. **Grade C**

During the actual PCI, there are no clear guidelines about procedural approaches. Many operators minimize the time to open the infarct artery by forgoing the right heart catheterization or the left ventriculography in the majority of patients and using a guiding catheter to do culprit vessel angiography. **Grade C** Gp IIb/IIIa inhibitors, especially abciximab, have been shown to improve periprocedural outcome in some randomized studies if started well in advance to achieve better TIMI-3 flow prior to the PCI.[48] **Grade A** Implantation of a stent to treat the culprit stenosis also reduces combined event rates, especially target vessel revascularization. **Grade A** The possible early hazard observed in the PAMI stent study was not seen in other studies using different stents with or without a GP IIb/IIIa inhibitor.[44,46] Elective use of intra-aortic balloon counterpulsation in stable patients after successful PCI is not beneficial. **Grade B** Distal protection and thrombectomy devices have potential for reducing distal embolization but need systematic study.[66] **Grade B/C**

Although a large majority of patients achieve TIMI-3 flow in the culprit artery after PCI, distal myocardial perfusion is completely normal in only a minority of these patients. The status of myocardial perfusion also directly influences prognosis, with the best outcomes observed in patients with normal myocardial perfusion. Some studies found that vasodilators like adenosine seem to improve the distal myocardial perfusion.[53,54,67] **Grade A/C** Whether these agents and other newer anti-inflammatory agents will result in improved outcomes by improving distal myocardial perfusion needs to be studied further. Other strategies to reduce myocardial damage, such as lowering body temperature and infusing supersaturated oxygen, also need further study.[68,69] **Grade C**

References

1. Cannon CP, Weintraub W, Demopoulos LA *et al.* Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–87.
2. Second International Study of Infarct Survival (ISIS-2) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither in 17 187 cases of suspected acute myocardial infarction. *Lancet* 1988;**ii**:349–60.
3. Fibrinolytic Therapy Trialists (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
4. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–82.
5. Weaver WD, Simes J, Betriu A *et al.* Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction. *JAMA* 1997;**278**:2093–8.
6. Magid DJ, Calonge BN, Rumsfeld JS *et al.* Relation between hospital primary angioplasty volume and mortality for patients treated with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* 2000;**284**:3131–8.
7. Gore JM, Granger CB, Simoons ML *et al.* Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995;**92**:2811–18.
8. The GUSTO-III Investigators. An international, multicenter, randomized comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;**337**;1118–23.
9. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;**329**:1615–22.

10.TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase 1 findings. *N Engl J Med* 1985; **312**:932–7.
11.Fu Y, Goodman S, Chang WC, Van De Werf F, Granger CB, Armstrong PW. Time to treatment influences the impact of ST-segment resolution on one year prognosis: insights from the assessment of the safety and efficacy of a new thrombolytic (ASSENT-2) trial. *Circulation* 2001;**104**:2653–9.
12.Hudson MP, Granger CB, Topol EJ *et al.* Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO-I) and global use of strategies to open occluded arteries (GUSTO-III) trials. *Circulation* 2001;**104**:1229–35.
13.Gibson CM, Cannon CP, Piana RN *et al.* Angiographic predictors of reocclusion after thrombolysis: results from the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. *J Am Coll Cardiol* 1995;**25**:582–9.
14.Grines CL, Browne KF, Marco J *et al.* A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;**328**:673–9.
15.Zijlstra F, de Boer MJ, Hoornje JC *et al.* A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680–4.
16.Grines CL, Marsalese DL, Brodie B *et al.* Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. *J Am Coll Cardiol* 1998;**31**:967–72.
17.Cannon CP, Gibson CM, Lambrew CT *et al.* Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;**283**:2941–7.
18.Ribeiro EE, Silva LA, Carneiro R *et al.* Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1993;**22**:376–80.
19.Grinfeld L, Berrocal D, Belardi J *et al.* Fibrinolytics vs primary angioplasty in acute myocardial infarction (FAP): a randomized trial in a community hospital in Argentina. *J Am Coll Cardiol* 1996;**27**:222A (Abstract).
20.Gibbons RJ, Holmes DR, Reeder GS *et al.*, for the Mayo Coronary Care Unit and Catheterization Laboratory Groups. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med* 1993;**328**:685–91.
21.DeWood MA. Direct PTCA vs intravenous t-PA in acute myocardial infarction: results from a prospective randomized trial. Thrombolysis and interventional therapy in acute myocardial infarction. George Washington University, VI Symposium, 1990, pp 28–9.
22.Ribichini F, Steffenino G, Dellavalle A *et al.* Primary angioplasty versus thrombolysis in inferior acute myocardial infarction with anterior ST-segment depression: a single-center randomized study. *J Am Coll Cardiol* 1996;**27**:221A (Abstract).
23.Garcia E, Elizaga J, Soriano J *et al.* Hospital Gregorio Maranon, Madrid Spain. Primary angioplasty versus thrombolysis with t-PA in the anterior myocardial infarction: results from a single center trial. *J Am Coll Cardiol* 1997;**389**(Suppl. A) (Abstract).
24.GUSTO-IIb. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621–8.
25.ASSENT-2 (Assessment of the Safety and Efficacy of a New Thrombolytic) Investigators. The ASSENT-2 double-blind randomized trial. *Lancet* 1999;**354**;716–22.
26.Antman EM, Guigliano RP, Gibson CM *et al.* Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction-14 (TIMI-14) trial. *Circulation* 1999;**99**:2720–32.
27.SPEED Group. Trial of Abciximab with and without low dose reteplase for acute myocardial infarction. *Circulation* 2000; **101**:2788–94.
28.Brener SJ, Zeymer U, Adgey AA *et al.* Eptifibatide and low-dose tissue plasminaogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002;**39**:377–86.
29.GUSTO-V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO-V randomized trial. *Lancet* 2001; **357**:1905–14.
30.The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. *Lancet* 2001;**358**:605–13.
31.Canto JG, Every NR, Magid DJ *et al.* The volume of primary angioplasty procedures and survival after acute myocardial infarction. *N Engl J Med* 2000;**342**:1573–80.
32.Every NR, Parson LS, Hlatky M *et al.*, for the MITI Investigators. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1996;**335**:1253–60.
33.Tierfenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary PTCA compared with alteplase (rtPA) in patients with acute myocardial infarction. A report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol* 1998;**31**:1240–5.
34.Ritchie J, Phillips D, Luft H. Coronary angioplasty. Statewide experience in California. *Circulation* 1993;**88**:2735–43.
35.Rogers WJ, Canto JG, Lambrew CT *et al.* Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol* 2000;**36**;2056–63.
36.Zahn R, Schiele R, Schneider S *et al.* Decreasing hospital mortality between 1994 and 1998 in patients with acute myocardial infarction treated with primary angioplasty but not in patients treated with intravenous thrombolysis. Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) registry and the Myocardial Infarction Registry (MIR). *J Am Coll Cardiol* 2000;**36**: 2064–71.
37.Schomig A, Kastrati A, Dirschinger J *et al.* Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 2000;**343**:385–91.

38. Le May MR, Labinaz M, Davies RF *et al.* Stenting versus thrombolysis in acute myocardial infarction trial (STAT). *J Am Coll Cardiol* 2001;**37**:985–91.
39. Kastrati A, Mehilli J, Dirshinger J *et al.* Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomized trial. *Lancet* 2002;**359**:920–5.
40. Grines CL, Westerhausen DR, Grines LL *et al.* A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in high-risk myocardial infarction (Air PAMI study). *J Am Coll Cardiol* 2002;**39**:1713–19.
41. Widimsky P, Groch L, Zeliko M, Aschermann M, Bednar F, Suryapranata H. Multicenter randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J* 2000;**21**:823–31.
42. Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) Investigators. The Danish multicenter randomized trial on thrombolytic therapy versus acute coronary angioplasty in acute myocardial infarction. Oral presentation ACC 3/20/2002.
43. Aversano T, Aversano LT, Passamani E *et al.*, for the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT). Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery. A randomized controlled trial. *JAMA* 2002;**287**:1943–51.
44. Grines CL, Cox DA, Stone GW *et al.* Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med* 1999;**341**:1949–56.
45. Maillard L, Hamon M, Khalife K *et al.*, for the STENTIM-2 Investigators. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardila infarction. *J Am Coll Cardiol* 2000;**35**:1729–36.
46. Stone GW, Grines CL, Cox DA *et al.*, for the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**:957–66.
47. Brener SJ, Barr LA, Burchenal JE *et al.* Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and primary PTCA organization and randomization trial (RAPPORT) investigators. *Circulation* 1998;**98**:734–41.
48. Montalescot G, Barragan P, Wittenberg O *et al.* Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895–903.
49. Gibson CM, Cannon CP, Murphy SA *et al.* Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2002;**101**:125–30.
50. The TIMI Research Group. Immediate vs delayed catheterization and PCI following thrombolytic therapy for acute myocardial infarction: TIMI II A results. *JAMA* 1988;**260**:2849–58.
51. Topol EJ, Califf RM, George BS *et al.* The Thrombolysis and Angioplasty in Myocardial Infarction Study Group. A randomized trial of immediate versus delayed elective PCI after intravenous tissue plasmiogen activator in acute myocardial infarction. *N Engl J Med* 1987;**317**:581–8.
52. Ross AM, Coyne KS, Reiner JA *et al.* A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. *J Am Coll Cardiol* 1999;**34**:1954–62.
53. Herrmann HC, Moliterno DJ, Ohman EM *et al.* Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-IV Pilot) trial. *J Am Coll Cardiol* 2000;**36**:1497–9.
54. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol* 2002;**39**:591–7.
55. Stone GW, Brodie BR, Griffin JJ *et al.* Role of cardiac surgery in the hospital phase management of patients treated with primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2000;**85**:1292–6.
56. Zijlstra F, Hoorntje JCA, De Boer M *et al.* Long term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**:1413–19.
57. Stone GW, Grines CL, Rothbaum D *et al.* Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. *J Am Coll Cardiol* 1997; **29**:901–7.
58. Parmley WW. Cost-effectiveness of reperfusion strategies. *Am Heart J* 1999;**138**:142–52.
59. Cohen DJ, Taira DA, Berezin R *et al.* Cost-effectiveness of coronary stenting in acute myocardial infarction: results form the Stent Primary Angioplasty in Myocardial Infarction (Stent-PAMI) Trial. *Circulation* 2001;**104**:3039–345.
60. Grassman ED, Johnson SA, Krone RJ. Predictors of success and major complications for primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. An analysis of the 1990 to 1994 Society for Cardiac Angiography and Interventions registries. *J Am Coll Cardiol* 1997;**30**:201–8.
61. DeWood MA, Spores J, Notske RN *et al.* Medical and surgical management of acute myocardial infarction. *Am J Cardiol* 1979;**44**:1356–64.
62. Phillips SJ, Zeff RH, Skinner JR *et al.* Reperfusion protocol and results in 738 patients with evolving myocardial infarction. *Ann Thorac Surg* 1986;**41**:119–25.
63. Lee JH, Murrell HK, Strony J *et al.* Risk analysis of coronary bypass surgery after acute myocardial infarction. *Surgery* 1997;**122**:675–80.
64. Hochman JS, Sleeper LA, Webb JG *et al.* Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999;**341**:625–34.
65. Ryan TJ, Anderson JL, Antman EM *et al.* ACC/AHA guidelines for the management of patients with acute myocardial infarction: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;**28**:1328–428.
66. Silva JA, Ramee SR, Cohen DJ *et al.* Rheolytic thrombectomy during percutaneous revascularization for acute myocardial infarction: experience with the Angiojet catheter. *Am Heart J* 2001;**141**:353–9.

67. Marzilli, M, Orsini E, Marraccini P, Roberto T. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000; **101**:2154–9.
68. Dixon SR, Bartorelli AL, Marcovitz PA *et al.* Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction: results of a pilot study utilizing intracoronary aqueous oxygen therapy. *J Am Coll Cardiol* 2002;**39**:387–92.
69. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;**346**:549–56.

33 Adjunctive antithrombotic therapy for ST-elevation acute myocardial infarction

John K French, Harvey D White

Introduction

In reperfusion-eligible patients[1] with acute myocardial infarction (MI), the aim of treatment is to restore normal (Thrombolysis in Myocardial Infarction [TIMI] grade 3)[2] epicardial blood flow in the infarct-related coronary artery and microvascular blood flow to the affected myocardium as soon as possible,[3,4] in order to preserve left ventricular function[5] and improve early survival rates.[6] Sustained patency of the infarct artery is associated with enhanced late survival.[7] In reperfusion-eligible patients, high rates of both early and sustained TIMI-3 flow may be achieved by using a combination of fibrinolytic, antiplatelet, and antithrombin agents and/or percutaneous coronary intervention (PCI). Although TIMI-3 flow has been shown to correlate with improved survival,[4] bleeding and intracranial hemorrhage are major adverse effects of the current fibrinolytic regimens, and the balance of benefit and risk needs to be assessed in appropriately designed large clinical trials. This chapter will examine the evidence for the use of adjunctive antithrombin therapies in patients with ST-segment elevation acute MI treated with or without reperfusion therapies.

Indirect antithrombins

Unfractionated heparin

Mechanism of action of heparin

Unfractionated heparin, the clinical prototypical antithrombin agent, is a heterogeneous glycoprotein with a molecular mass that varies between 5000 and 30 000 kilodaltons (mean 15 000 kDa). Upon binding to antithrombin III, heparin forms a complex that inhibits the actions of thrombin (Figure 33.1) and factors IXa, Xa, and XIa. The varying molecular masses of commercial heparin preparations result in only partial (approximately one third) stoichiometric binding to antithrombin III, with unpredictable pharmacokinetics and pharmacodynamics and hence an unpredictable anticoagulant effect.[8] Low molecular weight heparins have lower mean molecular masses than unfractionated heparin, and lack the 18 saccharide moieties required for simultaneous binding of thrombin and antithrombin III, thus they effectively inhibit factor Xa without concurrent binding to thrombin and antithrombin. At a heparin concentration that prolongs the activated partial thromboplastin time (APTT) to twice normal, there is only 20–40% inhibition of clot-bound thrombin activity.[9] The heparin–antithrombin III complex is inhibited by fibrin monomer II and is relatively inaccessible to factor Xa in the prothrombinase complex. Heparin binds to several other plasma proteins including platelet factor 4, vitronectin, fibronectin and von Willebrand factor, which inhibits platelet function.

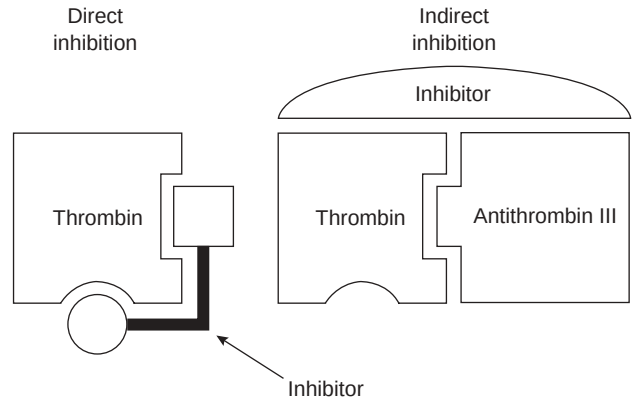


Figure 33.1 Direct thrombin inhibitors such as bivalirudin and hirudin bind to both the catalytic and antithrombin III binding sites of thrombin, directly inhibiting each function. Indirect thrombin inhibitors affect the activation of thrombin indirectly by binding at different sites.

The procoagulant state after administration of fibrinolytic therapy

Administration of fibrinolytic therapy results in a procoagulant state. Plasmin activates platelets either by activating the

thrombin receptor[10] or by triggering thrombin generation through activation of factor V (Figure 33.2).[11] The amount of thrombin activity induced by fibrinolytic agents is directly related to the extent of free plasmin activity (Figure 33.3).[12] Administration of streptokinase results in the breakdown of circulating fibrinogen and an increase in fibrin degradation products, which have anticoagulant effects. However, because streptokinase induces extensive plasmin activity, it may be associated with more marked procoagulant effects than fibrin-specific agents such as alteplase, reteplase or tenecteplase, which activate plasminogen to a lesser degree.[12] The exposure of clot-bound thrombin acts as a nidus for further thrombosis, and provides the rationale for adjunctive use of antithrombotic therapies.

Effect on infarct artery patency of unfractionated heparin alone

The effect of a large single bolus of intravenous unfractionated heparin on infarct artery patency in patients not given fibrinolytic therapy was examined in the Heparin in Early Patency (HEAP) trial after the HEAP pilot study showed that a single intravenous heparin bolus of 300 IU/kg produced TIMI-3 flow in 31% of patients.[13] The HEAP trial,[14] which randomized 584 patients, found that 13% of patients given weight adjusted high-dose heparin (20 000–30 000 IU) had TIMI-3 flow at a mean of 79 minutes, compared with 9% of patients given either no heparin or weight adjusted low-dose heparin (0–5000 IU). These rates of TIMI-3 flow are similar to those seen prior to primary angioplasty,[13] and show that heparin on its own does not enhance early infarct artery patency.

Effect on infarct artery patency of adjunctive unfractionated heparin with fibrinolytic therapy

Early angiographic studies evaluated the use of heparin versus aspirin (but not heparin with aspirin) after fibrinolytic therapy. In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-3 study,[15] patients receiving a 3 hour infusion of alteplase were randomized to receive either a 10 000 IU bolus of heparin or a placebo. There was no difference in the rates of TIMI-3 flow at 90 minutes (54% in the heparin group versus 53% in the placebo group). However, three other studies that performed angiography at means of 18,[16] 57,[17] and 81 hours[18] after administering alteplase concluded that heparin did improve patency; in the third study all patients also received 80 mg of aspirin. No trials have found that heparin improved 90 minute patency rates when an aspirin dose of >100 mg was used in conjunction with alteplase.

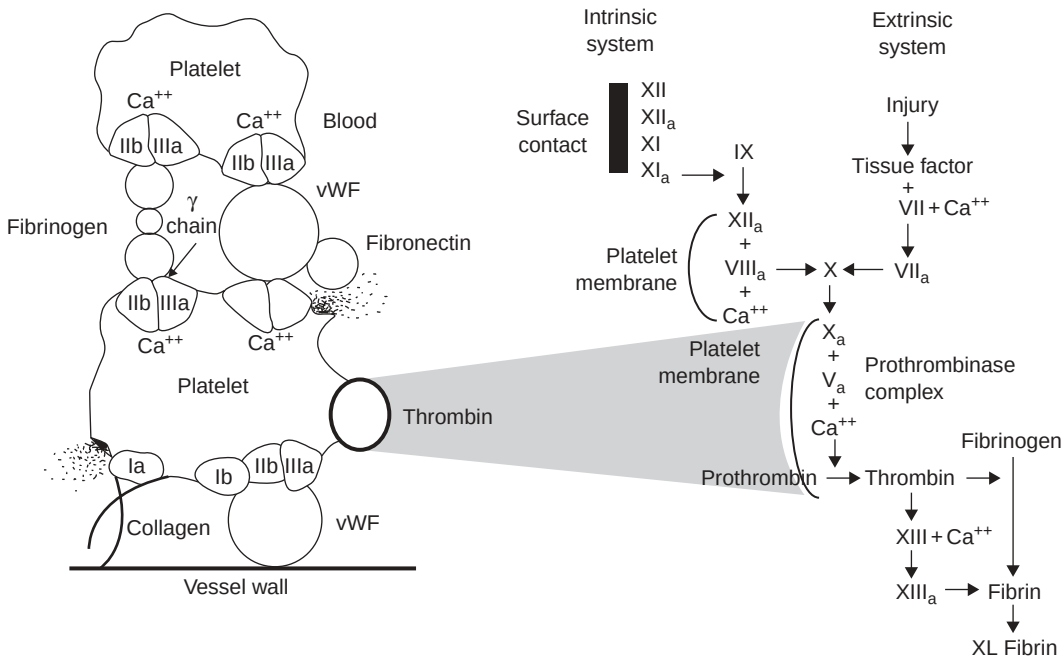


Figure 33.2 Interactions between platelets and thrombotic, coagulation, and fibrinolytic pathways, showing the biochemical interactions between platelet membrane receptors, vessel walls, and adhesive macromolecules during platelet adhesion and aggregation (*left*). Also depicted are the intrinsic and extrinsic systems of the coagulation cascade and their interaction with the platelet membrane (*right*), such as via the prothrombinase complex, which is the activator complex for thrombin. Coronary thrombosis is associated with both platelet and coagulation processes. Ca^{++}, calcium; Ia, glycoprotein Ia; Ib, glycoprotein Ib; IIb/IIIa, glycoprotein IIb/IIIa; vWF, von Willebrand factor; XL, cross-linked. (Modified with permission from Stein B, Fuster V, Halperin JL, Chesebro JH. Antithrombotic therapy in cardiac disease: an emerging approach based on pathogenesis and risk. *Circulation* 1989;**80**:1501–13.)

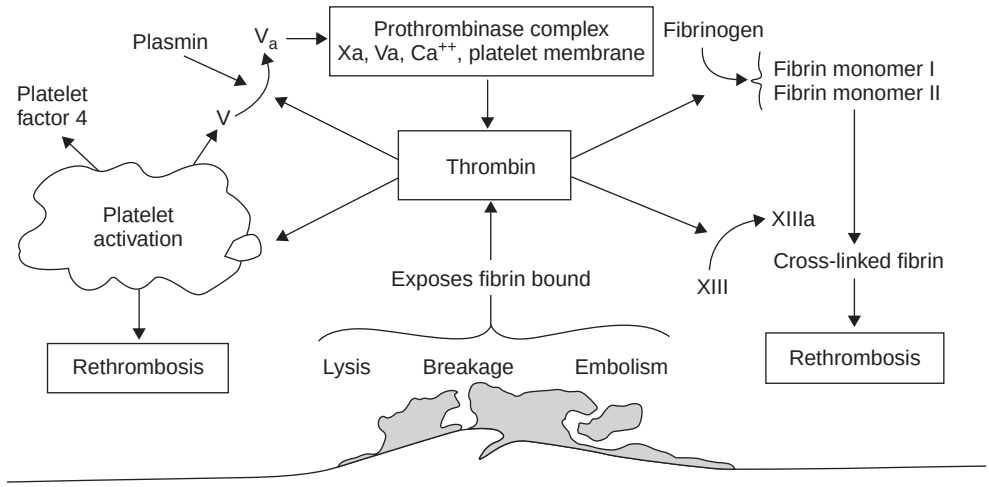


Figure 33.3 Clot lysis and thrombin generation. Disturbance of thrombus by lysis (endogenous or exogenous), mechanical breakage (including PCI), or spontaneous embolism exposes thrombin bound to fibrin. Thrombin activates platelets, activates factor V to Va (which leads to generation of more thrombin via the prothrombinase complex), converts fibrinogen to fibrin I and fibrin II, and activates factor XIII to XIIIa (which cross-links fibrin). These processes combine to produce rethrombosis. Heparin may only partially prevent rethrombosis because factor Xa within the prothrombinase complex is protected from heparin–antithrombin III, platelet factor 4 neutralizes heparin, and fibrin monomer II inhibits heparin–antithrombin III. (Modified with permission from Webster MWI, Chesebro JH, Fuster V. Antithrombotic therapy in acute myocardial infarction: enhancement of thrombolysis, reduction of reocclusion, and prevention of thromboembolism. In: Gersh BJ, Rahimtoola SH, eds. *Current topics in cardiology – acute myocardial infarction*. New York: Elsevier Science, 1990.)

Adjunctive subcutaneous heparin

Subcutaneous heparin is usually administered at either 4 or 12 hours after the start of fibrinolytic therapy. This route of administration results in variable absorption and can take up to 24 hours to achieve significant prolongation of the APTT, hence it may not prevent early reocclusion prior to that time.[19]

In the Studio sulla Calciparina nell-Angina e nella Trombosi Ventricolare nell'Infarto (SCATI) trial,[20] 433 patients were given streptokinase without routine aspirin and randomized to receive either control treatment or a 2000 IU heparin bolus followed 9 hours later by 12 500 IU given subcutaneously twice daily. The inhospital mortality rates were 8·8% in the control group and 4·6% in the heparin group ($P = 0{\cdot}05$).

Several large trials have tested subcutaneous heparin regimens in conjunction with aspirin and fibrinolytic therapy.[21–23] The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) study[21] randomized 20 891 patients to receive either control treatment or subcutaneous heparin (12 500 IU twice daily throughout hospitalization starting 12 hours after the initiation of either streptokinase or alteplase). The patients also received 160–325 mg of aspirin. Heparin was found to reduce the inhospital mortality rate from 6·0% to 5·4% ($P < 0{\cdot}05$).

In the Third International Study of Infarct Survival (ISIS-3),[22] 41 299 patients were given 162 mg of crushed enteric coated aspirin and randomized to receive either streptokinase, duteplase or anisoylated plasminogen streptokinase activator complex (APSAC). Four hours after the start of fibrinolytic therapy the patients were randomized to receive either control treatment or 12 500 IU of subcutaneous heparin twice daily. During the scheduled heparin treatment period there was a trend towards a mortality reduction in the patients randomized to receive heparin (7·4% *v* 7·9% in the control group, $P = 0{\cdot}06$), which may represent a benefit of 5 lives saved per 1000 patients treated. However, because 12% of the patients randomized to receive heparin were given none and 25% of those randomized to receive no heparin were given intravenous heparin (14%) or high-dose subcutaneous heparin (11%), the true benefit of subcutaneous heparin is estimated to have been nearer 7 lives saved per 1000 patients treated.[22] A meta-analysis of the GISSI-2 and ISIS-3 studies showed that the groups randomized to receive subcutaneous heparin had 2 fewer deaths and 2 fewer non-fatal re-infarctions per 1000 patients treated, at a cost of 3 more transfusions and 0·3 more non-fatal disabling strokes (Table 33.1).[24]

Comparison of intravenous heparin with control treatment

Four trials[18,25–27] have randomized patients treated with aspirin to receive either intravenous heparin or control treatment after fibrinolysis (Table 33.2). There were no significant

differences in mortality or re-infarction rates, but these trials lacked the statistical power to evaluate these outcomes, and would have needed to randomize at least five times as many patients in order to detect clinically meaningful differences of 15% in either end point.[28]

Attempts to evaluate the potential benefit of intravenous heparin after fibrinolysis have been confounded in clinical trials because a significant proportion of patients in the control or placebo treatment arms were given intravenous heparin electively by the treating physicians. It is appropriate to conclude that there is a paucity of information comparing intravenous heparin with placebo in patients receiving streptokinase or alteplase.

Meta-analyses of heparin trials

In a meta-analysis of trials that randomized a total of 5459 patients to receive either heparin or no antithrombotic therapy in the absence of routine aspirin therapy (although 14% received fibrinolytic therapy), heparin was found to reduce mortality by 25% (95% CI 10–37) from 14·9% to 11·4% at a mean of 10 days ($P = 0{\cdot}002$). The re-infarction rate was not significantly reduced (6·8% *v* 8·3%, $P = 0{\cdot}1$), but the rate of stroke was reduced from 2·1% to 1·1% ($P = 0{\cdot}01$) and the rate of pulmonary embolism was reduced from 3·8% to 2·0% ($P \leq 0{\cdot}001$).[29] In patients with contraindications for aspirin, the use of intravenous heparin is recommended. Although there is no supporting clinical trial evidence, the use of clopidogrel may be appropriate in these circumstances. **Grade A1c**

A total of 68 000 patients treated with aspirin (93% of whom also received fibrinolytic therapy) have been randomized in trials examining various heparin regimens.[24] In patients randomized to receive heparin, 35 day mortality was reduced from 9·1% to 8·6% (95% CI 0–10, $P = 0{\cdot}03$), inhospital re-infarction from 3·3% to 3·0% ($P = 0{\cdot}04$), and inhospital pulmonary embolism from 0·4% to 0·3% ($P = 0{\cdot}01$). There was no significant difference in the rate of stroke (1·2% with heparin *v* 1·4% with control treatment, $P =$ NS), but major bleeding was more common in patients randomized to receive heparin (1·0% *v* 0·7%, $P = 0{\cdot}001$).

Table 33.1 Benefits and risks associated with adjunctive delayed subcutaneous heparin in patients receiving streptokinase in the ISIS-3[22] and GISSI-2[21] studies

	Events per 1000 patients treated		
	ISIS-3	GISSI-2	Combined
Benefit			
Reduction in mortality	2·8	1·0	2·2[a]
Reduction in non-fatal MI	1·8	1·9	1·8
Risk			
Transfusions	2·6	4·5	3·2
Non-fatal strokes	0·5	0·6	0·6[b]

[a] Figures do not sum up because of rounding.
[b] Half of the patients had fully recovered by the time of discharge.

Intravenous versus *subcutaneous heparin*

In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-I trial, 20 173 patients were randomized to receive streptokinase and either subcutaneous or intravenous heparin.[30] However, 36% of the patients randomized to receive subcutaneous heparin were electively given intravenous heparin (not counting the use of intravenous heparin for cardiac catheterization, which occurred in 54% of patients), and this reduced the power of the study to detect a difference between these two treatment randomizations to 71%. In effect, the heparin comparison in GUSTO-I was actually between intravenous heparin and the ISIS-3 regimen[22] of subcutaneous heparin delayed 4 hours after fibrinolytic therapy with a substantial crossover of patients to intravenous heparin. A "no heparin" strategy was not tested. It is perhaps not surprising, therefore, that there was no difference in

Table 33.2 Effect of adjunctive intravenous heparin in patients treated with aspirin and fibrinolytic therapy

	Death (%)		Re-infarction (%)		Bleeding (%)	
	Control	Heparin	Control	Heparin	Control	Heparin
ISIS-2 Pilot ($n = 626$)[25]	6	8	5	1	1	0
ECSG ($n = 1296$)[18]	3	2	10	10	NA	NA
OSIRIS ($n = 256$)[26]	11	9	1	2	4	6
DUCCS ($n = 250$)[27]	9	12	4	9	8	15

Abbreviations: DUCCS, Duke University Clinical Cardiology Study; ECSG, European Cooperative Study Group; NA, not available; OSIRIS, Optimization Study of Infarct Reperfusion Investigated by ST Monitoring

clinical end points. However, at 5–7 days, 84% of patients randomized to receive streptokinase and intravenous heparin had TIMI-2 or -3 (that is, slow or normal) flow (the same percentage as in the alteplase group), compared with 72% of those randomized to receive streptokinase and subcutaneous heparin ($P < 0{\cdot}05$). Given the importance of long-term patency of the infarct-related artery, this may partly explain why those randomized to streptokinase and intravenous heparin had a 5 year survival rate equal to that of those randomized to alteplase, and a 1% higher absolute survival rate than those randomized to streptokinase and subcutaneous heparin.[31] Furthermore, in patients with cardiogenic shock, those randomized to streptokinase and intravenous heparin had the lowest mortality rate (54% *v* 58% in those randomized to streptokinase and subcutaneous heparin, and 63% in those randomized to alteplase and intravenous heparin).[32]

Recent dose adjustments in adjunctive intravenous heparin regimens

Because of concern about the high bleeding rates (including intracranial hemorrhage) seen with alteplase and with modified fibrinolytic regimens including alteplase or other genetically modified plasminogen activators, the dose of adjunctive unfractionated heparin used in conjunction with fibrinolytic therapy has been reduced in recent trials.[33] The current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[34] recommend an APTT of 1·5–2·0 times control (50–70 seconds) at 12 hours, as this was associated with the lowest mortality rates in GUSTO-I irrespective of the fibrinolytic agent used.[35] In GUSTO-I, heparin was initially administered as a 5000 IU bolus and 1000 IU/hour infusion, but after approximately 10 000 patients had been enrolled the infusion dose was changed to 1200 IU/hour in patients weighing >80 kg. It was observed that the overall rates of moderate bleeding, severe bleeding, and intracranial hemorrhage increased in a linear manner in patients with APTTs above 60–70 seconds at both 12 and 24 hours. The risk factors for these complications included older age, lower body weight, female gender, and African ethnicity. In the GUSTO-I hemostasis substudy, these regimens (which showed good correlation between heparin levels and APTTs) were associated with attenuation of increases in the levels of fibrinopeptide A, but not thrombin generation as measured by prothrombin fragment 1·2.[30]

Unfractionated heparin was compared with hirudin in the TIMI-9A trial[36] and the GUSTO-IIA trial.[37] Both trials were stopped early because of increased rates of intracranial bleeding in both the heparin and the hirudin treatment groups. In patients with ST-segment elevation acute coronary syndromes, the overall intracranial hemorrhage rates were 1·3% in those randomized to receive heparin (a 5000 IU bolus and 1000 IU/hour infusion or a 1300 IU/hour infusion in those weighing >80 kg) and 2·1% in those randomized to receive hirudin (a 0·6 mg/kg bolus and 0·2 mg/kg infusion for 96 hours). TIMI-9 and GUSTO-II were recommenced using lower doses of hirudin (a 0·1 mg bolus and 0·1 mg/kg/hour infusion) and heparin (a 5000 IU bolus and 1000 IU/hour infusion), with the APTT adjusted to 55–85 seconds in TIMI-9B[38] and 60–85 seconds in GUSTO-IIB.[39] These adjustments resulted in lower bleeding rates. The results are discussed below in the section on meta-analysis of direct thrombin inhibitors.

In the TIMI-10B[40] and Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-1[41] trials, the doses of unfractionated heparin used in conjunction with alteplase or tenecteplase were reduced and weight adjusted (a 5000 IU bolus and 1000 IU/hour infusion in patients weighing >67 kg, and a 4000 IU bolus and 800 IU/hour infusion in those weighing <67 kg). The infusion rates were modified according to the APTT at 6 hours, with a target APTT of 50–70 seconds.

The unfractionated heparin dose was also reduced in the TIMI-14 trial[42] and in the Strategies for Patency Enhancement in the Emergency Department (SPEED) trial,[43] which tested the effect on TIMI flow grades of abciximab used in conjunction with reduced doses of alteplase or reteplase. In both trials the patients receiving a full-dose fibrinolytic were given a 70 IU/kg bolus of unfractionated heparin, while those receiving a reduced-dose fibrinolytic were given either a 30 IU/kg bolus of unfractionated heparin plus abciximab or a 60 IU/kg bolus of unfractionated heparin without abciximab. In TIMI-14 the heparin bolus was followed by an infusion of either 7 IU/kg/hour or 4 IU/kg/hour. In SPEED the heparin infusion was adjusted to maintain an APTT of 50–70 seconds if early sheath removal (recommended in the protocol) did not occur. With the reduced heparin regimens, the point estimates for TIMI-3 flow at 60 minutes were 4% lower in the TIMI-14 trial and 10% lower in the SPEED trial, but the confidence intervals were wide (Figure 33.4).

In the ASSENT-2 trial[44] comparing alteplase with tenecteplase and the Intravenous NPA for Treatment of Infarcting Myocardium Early (InTIME)-II study[45] comparing alteplase with lanoteplase (also known as NPA), unfractionated heparin was administered as a 70 IU/kg bolus (maximum 4000 IU) and a 15 IU/kg/hour infusion (maximum 1000 IU/hour). In the ASSENT-3 trial[46] (where patients received either half-dose tenecteplase plus low-dose unfractionated heparin plus abciximab, full-dose tenecteplase plus unfractionated heparin, or full-dose tenecteplase plus enoxaparin), the unfractionated heparin regimen in patients not receiving abciximab was reduced to a 60 IU/kg bolus (maximum 4000 IU) and a 12 IU/kg/hour infusion (maximum 1000 IU/hour). The first adjustment of the heparin infusion took place after measurement of

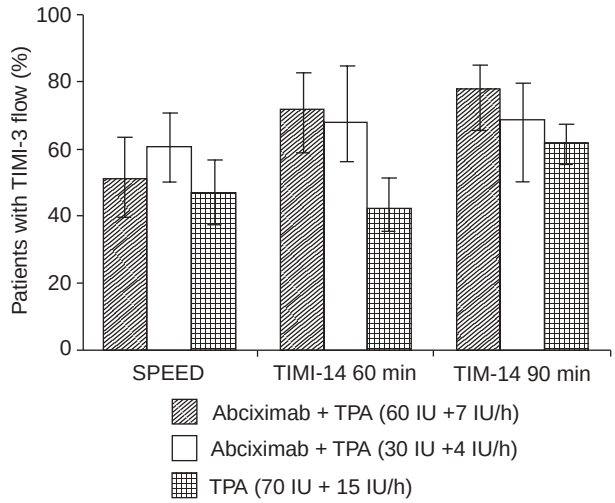


Figure 33.4 TIMI-3 flow rates with different unfractionated heparin regimens in the SPEED[43] and TIMI-14[42] trials

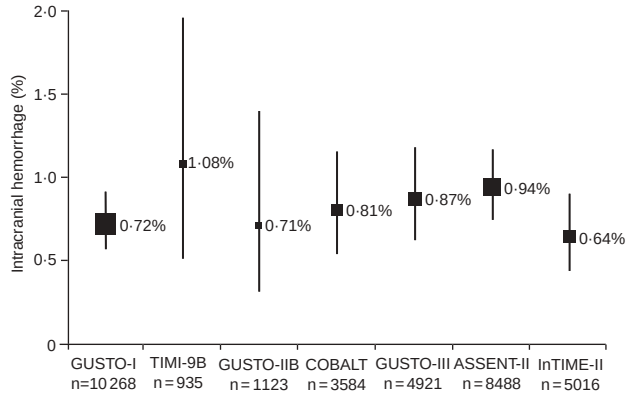


Figure 33.5 Rates of intracranial hemorrhage in the GUSTO-I,[23] TIMI-9B,[38] GUSTO-IIB,[39] COBALT,[94] GUSTO-III,[95] ASSENT-2,[44] and InTIME-II[45] trials using accelerated alteplase and intravenous unfractionated heparin. COBALT, Continuous Infusion Versus Double-Bolus Administration of Alteplase. (Modified with permission from Giugliano RP, McCabe CH, Antman EM *et al.* Lower dose heparin with fibrinolysis is associated with lower rates of intracranial haemorrhage. *Am Heart J* 2001;**141**:742–50.)

the APTT at 3 hours. In the initial phase of InTIME-II, the heparin dose was adjusted according to the APTT at 6 hours, but in the latter part of the trial this was done at 3 hours. Compared with previous trials, these trials had stricter entry criteria for patients at increased risk of intracranial hemorrhage, and excluded those with a documented blood pressure of >180/110 mmHg at any time. Despite these precautions, intracranial hemorrhage occurred in 0·88% of all patients in ASSENT-2 and 0·92% of all patients in ASSENT-3. By comparison, the intracranial hemorrhage rate in patients randomized to receive accelerated alteplase and intravenous heparin in GUSTO-I was 0·72%.[23] The intracranial hemorrhage rates in alteplase-treated patients were 0·94% in ASSENT-2, 0·74% in the initial phase of InTIME-II, and 0·51% in the latter phase of In-TIME-II. The confidence intervals of the point estimates for intracranial hemorrhage in the alteplase groups in these trials overlap (Figure 33.5). The intracranial hemorrhage rate in lanoteplase-treated patients fell from 1·22% to 1·00% when the APTT measurement was brought forward from 6 hours to 3 hours in InTIME-II, and dropped further to 0·50% when the heparin bolus was omitted in InTIME-IIB (χ^2 trend $P = 0{\cdot}021$).

Comparison of patients with similar baseline characteristics who received tenecteplase in ASSENT-2 and ASSENT-3 showed that the heparin dose reduction and use of the 3 hour APTT measurement in ASSENT-3 was associated with lower rates of major bleeding (2·16 *v* 4·66%) and transfusion (2·31 *v* 4·25%), although the rates of intracranial hemorrhage were the same (0·93%). Randomized trials with clinical end points are required to determine whether lower heparin doses really do improve safety without compromising efficacy.

Table 33.3 and Figure 33.6 show the rates of major, moderate, and minor bleeding, transfusion, stroke, and intracranial hemorrhage in the ASSENT-3 trial,[46] the GUSTO-V trial,[47] which tested abciximab in patients receiving reteplase and unfractionated heparin, and the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial,[48] which compared bivalirudin with unfractionated heparin in patients receiving streptokinase.

Low molecular weight heparins

Low molecular weight heparins, which block ongoing thrombin generation by inhibiting factor Xa (see Figure 33.1), have recently been evaluated as adjuncts to fibrinolytic therapy. Factor Xa inhibition is dose-dependent, and significant inhibition occurs at a comparatively lower dose of low molecular weight heparin than unfractionated heparin. The ratio of inhibition of factor Xa:thrombin varies from one low molecular weight heparin to another, and is approximately 2:1 with dalteparin and 3:1 with enoxaparin, the two agents most commonly evaluated in clinical trials. Low molecular weight heparins are not inactivated by platelet factor 4, and stimulate the release of tissue factor pathway inhibitor from endothelium.

Dalteparin

Two randomized placebo-controlled trials have compared twice-daily subcutaneous dalteparin with a placebo in patients treated with aspirin and streptokinase. In the Fragmin in Acute Myocardial Infarction (FRAMI) study,[49]

Table 33.3 Bleeding and stroke rates in the ASSENT-3,[46] GUSTO-V[47] and HERO-2[48] trials

	ASSENT-3			GUSTO-V		HERO-2	
	Tenecteplase + UF heparin	Tenecteplase + enoxaparin	Half-dose tenecteplase + UF Heparin + abciximab	Full-dose reteplase	Half-dose reteplase + abciximab	Streptokinase + UF heparin	Streptokinase + bivalirudin
Bleeding							
Severe (%)	2·16	3·04	4·31[a]	0·51	1·08[b]	0·47	0·68
Moderate (%)	–	–	–	1·79	3·47[b]	1·05	1·39[c]
Minor (%)	18·7	22·6	35·3[b]	11·4	20·01[b]	9·0	12·8[b]
Transfusions (%)	2·31	3·43[d]	4·16[b]	3·98	5·71[b]	1·11	1·39
Strokes							
All strokes (%)	1·52	1·62	1·49	0·88	0·97	0·90	1·24
Non-fatal disabling stroke	–	–	–	0·3	0·2	0·3	0·2
Intracranial (%) hemorrhages	0·93	0·88	0·94	0·59	0·62	0·39	0·55

[a] $P = 0·003$.
[b] $P < 0·0001$.
[c] $P = 0·05$.
[d] $P = 0·03$.
Abbreviations: LMW, low molecular weight; UF, unfractionated

which randomized 776 patients, dalteparin (150 IU/kg twice daily during hospitalization) reduced the incidence of left ventricular thrombus or embolism within 9 days from 21·9% to 14·2% ($P = 0·03$). The only significant difference in clinical end points was in the rate of major hemorrhage, which occurred in 2·9% of the dalteparin group versus 0·3% of the placebo group ($P = 0·006$). In the Biochemical Markers in Acute Coronary Syndromes (BIOMACS)-II study of 101 patients,[50] TIMI-3 flow was observed at 20–28 hours in 68% of patients given dalteparin (100 IU/kg initially and 120 IU/kg at 12 hours) versus 51% of those given a placebo ($P = 0·10$). Dalteparin reduced the incidence of recurrent ischemic episodes (recorded by continuous electrocardiography) from 38% to 16% ($P = 0·037$). There were no differences in major bleeding or clinical events.

In the ASSENT PLUS trial,[51] patients were given alteplase ($n = 439$) and randomized to receive either subcutaneous dalteparin (120 IU/kg every 12 hours) for 4–7 days or an intravenous infusion of unfractionated heparin for 48 hours. TIMI-3 flow was achieved in similar proportions of the dalteparin and heparin treatment groups (69·3% *v* 62·5%, $P = 0·16$), but patients in the dalteparin group were less likely to have TIMI-0 or -1 flow (13·4% *v* 24·4%, $P = 0·006$) or intraluminal thrombus with or without TIMI 0-1 flow (27·9% *v* 42·0%, $P = 0·003$). Although there were fewer re-infarctions within 7 days in the dalteparin group (1·4% *v* 5·4%, $P = 0·01$), there was no significant difference in the re-infarction rates at 30 days (6·5% *v* 7·0%, $P =$ NS), and no difference in the combined end point of death/re-infarction at 30 days. Intracranial hemorrhage occurred in 0·9% of the dalteparin group versus 1·9% of the unfractionated heparin group ($P = 0·43$), major bleeding in 7·2% *v* 9·5% respectively ($P = 0·37$), and minor bleeding in 24·1% *v* 20% respectively ($P = 0·30$) (Table 33.4).

Enoxaparin

In the Acute Myocardial Infarction–Streptokinase (AMI–SK) trial,[52] 496 patients with MI were given aspirin and streptokinase and randomized to receive either enoxaparin or a placebo for 3–8 days. The primary end point was TIMI-3 flow at 5–10 days, which was observed in 70% of the enoxaparin group and 58% of the placebo group ($P = 0·01$). Major bleeding occurred in 2·5% *v* 4·8% respectively ($P = 0·13$). ST recovery of ≥70% was more common in the enoxaparin group than in the placebo group ($P = 0·012$ at 90 minutes and $P = 0·004$ at 180 minutes).

In the Heparin and Aspirin Reperfusion Therapy (HART)-II trial,[54] 400 patients were given aspirin and alteplase and randomized to receive either unfractionated heparin or enoxaparin (30 mg intravenously and 1 mg/kg subcutaneously every 12 hours) for at least 3 days. The primary aim of the trial was to show that enoxaparin was not inferior to adjunctive unfractionated heparin for the end point of TIMI-2 or -3 flow at 90 minutes, which was achieved in 80% of the enoxaparin group versus 75% of the unfractionated heparin group ($P =$ NS), while TIMI-3 flow was achieved in 53% *v* 48% respectively ($P =$ NS). By 5–7 days, reocclusion

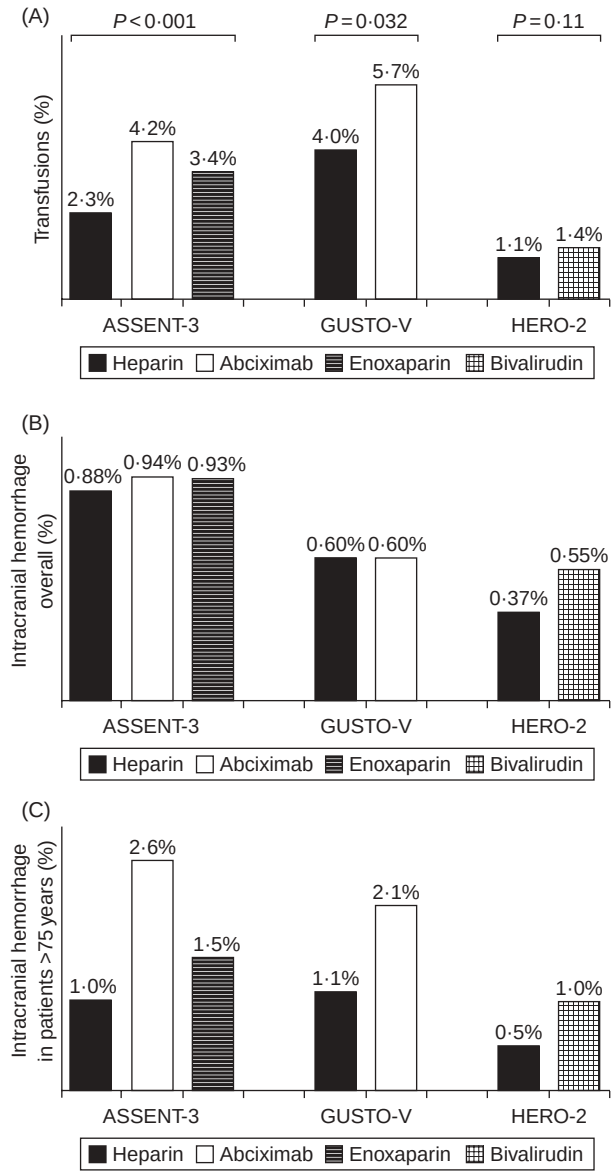


Figure 33.6 Transfusion and intracranial hemorrhage in the ASSENT-3,[46] GUSTO-V,[47] and HERO-2[48] trials: (A) transfusion; (B) intracranial hemorrhage; (C) intracranial hemorrhage in patients >75 years

(TIMI-0 or -1 flow) had occurred in 9·8% of enoxaparin patients and 9·1% of heparin patients who had initially had TIMI-3 flow, and in 5·9% of enoxaparin patients and 3·1% of heparin patients who had initially had TIMI-2 or -3 flow ($P = 0·26$). The rates of major bleeding were similar in both treatment groups (see Table 33.4), and intracranial hemorrhage occurred in 1% of each group.

In the ASSENT-3 trial, 6095 patients were randomized to receive either full-dose tenecteplase plus enoxaparin for a maximum of 7 days, half-dose tenecteplase plus weight adjusted low-dose unfractionated heparin for 48 hours and a 12 hour infusion of abciximab, or full-dose tenecteplase plus weight-adjusted unfractionated heparin for 48 hours.[46] The trial did not have a prespecified primary hypothesis. The combined rates of 30 day mortality/inhospital investigator-reported re-infarction/inhospital refractory ischemia were significantly lower in the enoxaparin group (11·4%; RR 0·74; 95% CI 0·63–0·87; $P = 0·0002$) and in the abciximab group (11·1%; RR 0·72; 95% CI 0·61–0·84; $P < 0·0001$) than in the unfractionated heparin group (15·4%). The combined rates of 30 day mortality/inhospital investigator-reported re-infarction/inhospital refractory ischemia/inhospital intracranial hemorrhage/inhospital major bleeding were 13·7% in the enoxaparin group (RR 0·81; 95% CI 0·70–0·93; $P = 0·0037$), 14·2% in the abciximab group (RR 0·84; 95% CI 0·72–0·96; $P = 0·014$) and 17·0% in the unfractionated heparin group. In patients with anterior MI, the lowest rates of 30 day mortality/inhospital investigator-reported re-infarction/inhospital refractory ischemia were seen in the abciximab group (13·6% *v* 14·6% in the enoxaparin group and 19·4% in the unfractionated heparin group). Overall, intracranial hemorrhage occurred in 0·88% of the enoxaparin group, 0·94% of the abciximab group and 0·93% of the unfractionated heparin group. Transfusions were less common in the unfractionated heparin group (2·3%) than in the enoxaparin (3·4%) and abciximab groups (4·2%, $P = 0·003$ for the three-way comparison, and $P = 0·03$ for the comparison between unfractionated heparin and enoxaparin) (Figure 33.6 and Table 33.3). In patients over 75 years of age, intracranial hemorrhage occurred in 1·0% of those given unfractionated heparin and 1·5% of those given enoxaparin ($P = 0·72$).

Given the increased transfusion rates with enoxaparin versus unfractionated heparin in ASSENT-3, and the need to define the bleeding risks in high-risk subgroups such as the elderly, women, patients with low body weights and patients with renal dysfunction, further trials will be needed to evaluate low molecular weight heparins in conjunction with new fibrinolytic regimens. The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT-TIMI-25) trial is currently randomizing 20 000 patients to receive either enoxaparin or unfractionated heparin in a double-blind manner, together with a fibrinolytic agent chosen by the treating physician. The composite primary end point of the trial is death/re-infarction within 30 days. Low molecular weight heparins will also need to be tested with regimens combining modified-dose fibrinolytics and glycoprotein IIb/IIIa inhibitors, and in patients undergoing primary or facilitated PCI. The high rates of bleeding (including intracranial hemorrhage) in patients aged >75 years suggest that specific studies are needed to examine the efficacy and safety of low molecular weight heparins in elderly patients.

Low molecular weight heparin is recommended as an acceptable alternative to intravenous unfractionated heparin for adjunctive use with tenecteplase. **Grade A1c**

Table 33.4 Bleeding rates in angiographic fibrinolytic trials comparing adjunctive low molecular weight heparin with unfractionated heparin

		LMW heparin	UF heparin or placebo*	*P* value
Dalteparin				
FRAMI[49]	Major bleeding (%)	2·9	0·3*	0·006
	Minor bleeding (%)	13·4	2·1*	<0·001
BIOMACS-II[50]	Major bleeding (%)	3·7	0*	0·50
	Minor bleeding (%)	5·5	2.0*	0·62
ASSENT PLUS[51]	Major bleeding (%)	7·4	9·5	0·39
	Minor bleeding (%)	24.0	20.0	0·35
Enoxaparin				
AMI–SK[52]	Major bleeding (%)	4·8	2·5*	0·23
	Major bleeding defined according to TIMI bleeding criteria[53] (%)	1·6	0·8*	–
	Transfusion of ≥2 units (%)	0·8	1·3*	0·68
HART-II[54]	Major bleeding defined according to TIMI bleeding criteria[53] (%)	3·6	3·0	0·79
	Transfusion of ≥2 units (%)	5·6	7·1	0·68
ENTIRE-TIMI-23[55]	Major bleeding with full-dose tenecteplase (%)	2·5	2·5	–
	Major bleeding with half-dose tenecteplase + abciximab (%)	8·5	5·2	–

Abbreviations: LMW, low molecular weight; UF, unfractionated

Direct thrombin inhibitors

A number of direct antithrombins have been shown in animal models to accelerate lysis of platelet-rich thrombi and to limit the size of the infarct.[56–59] The prototypical agent is hirudin, which is a leech-derived protein containing 65 amino acids. Because it is excreted renally, blood levels may be increased in patients with renal impairment. Bivalirudin (previously known as hirulog) is a synthetic 20-amino-acid peptide that directly inhibits free and clot-bound thrombin, and is 20% renally excreted. The univalent direct thrombin inhibitors, argatroban, inogatran and efegatran, are synthetic thrombin inhibitors. The evidence for the adjunctive use of direct thrombin inhibitors has recently been strengthened by the publication of a meta-analysis of direct thrombin inhibitor trials[60] and the 17 073-patient HERO-2 trial.[48]

Hirudin

The TIMI-5 trial[61] randomized patients to receive either adjunctive intravenous heparin or escalating doses of hirudin prior to alteplase. Although there was no significant difference in the proportion of patients achieving TIMI-3 flow by 90 minutes (57% in the heparin group *v* 65% in the hirudin group, *P* = NS), there was a trend towards less reocclusion at 18–36 hours in the hirudin group (1·6% *v* 6·7%, *P* = 0·07) and a lower combined rate of death/re-infarction (6·8% *v* 16·7%, *P* = 0·02). The highest incidence of TIMI-3 flow (73%) was seen with the same dose of hirudin (a 0·1 mg/ kg bolus and 0·1 mg/kg/hour infusion for 3–5 days to maintain an APTT of 60–85 seconds) that was subsequently tested in the TIMI-9B and GUSTO-IIb trials, where it was given after the start of fibrinolytic therapy. When the data from these two trials were combined, there was no reduction in mortality with hirudin, but the incidence of re-infarction was 14% lower (*P* = 0·024).[62]

In the Hirudin for the Improvement of Thrombolysis (HIT)-4 study,[63] 1200 patients were given streptokinase and randomized to receive either intravenous heparin or intravenous hirudin (a 0·2 mg/kg bolus followed by 0·5 mg/kg subcutaneously twice daily). At 30 days there was no difference in the combined incidence of death/re-infarction/stroke/rescue angioplasty/refractory angina (22·7% with hirudin *v* 24·3% with heparin, *P* = NS). In an angiographic substudy of 447 patients,[64] TIMI-3 flow was achieved by 90 minutes in 41% of the hirudin group versus 33% of the heparin group (*P* = 0·08). The rates of intracranial hemorrhage (0·2% with hirudin *v* 0·3% with heparin) and major bleeding (3·3% *v* 3·5%) were similar in both treatment groups, and there were no clinical or electrocardiographic differences between the groups.

Bivalirudin

Bivalirudin has a half life of approximately 25 minutes compared with 2–3 hours for hirudin. When used in appropriate regimens as an adjunctive agent with fibrinolytic therapy,

bivalirudin may prevent clot formation and extension and facilitate clot lysis.

In the HERO-1 trial,[65] 412 patients presenting within 12 hours of symptom onset were given aspirin and streptokinase (administered over 30–60 minutes) and randomized to receive either heparin, low-dose bivalirudin (a 0·125 mg/kg bolus and 0·25 mg/kg/hour infusion for 12 hours, then 0·125 mg/kg/hour) or high-dose bivalirudin (a 0·25 mg/kg bolus and 0·5 mg/kg/hour infusion for 12 hours, then 0·25 mg/kg/hour). TIMI-3 flow at 90–120 minutes was achieved in 35% of the heparin group, 46% of the low-dose bivalirudin group and 48% of the high-dose bivalirudin group ($P = 0·024$).[65] Continuous ST-segment monitoring showed that the patients given bivalirudin achieved stable ST recovery earlier than those given heparin.[66]

In the HERO-2 trial,[48] 17 073 patients presenting within 6 hours of symptom onset were randomized to receive a bolus and 48 hour infusion of either bivalirudin or heparin immediately prior to beginning streptokinase. By 30 days, 10·8% of the bivalirudin group and 10·9% of the heparin group had died (OR 0·99; 95% CI 0·90–1·09). After adjustment for a gender imbalance (as more women had been randomized to receive bivalirudin than heparin) and for the factors identified in the GUSTO risk model,[67] the mortality rates were 10·5% in the bivalirudin group and 10·9% in the heparin group (OR 0·96; 95% CI 0·86–1·07) (Figure 33.7). At 96 hours the rates of re-infarction (adjudicated by an independent blinded committee) were 1·6% in the bivalirudin group versus 2·3% in the heparin group (OR 0·70; 95% CI 0·56–0·88; $P = 0·001$). Analysis of investigator-reported re-infarctions (as was done in the ASSENT-3 and GUSTO-V trials) showed that the combined rate of death/re-infarction was lower in the bivalirudin group than in the heparin group (12·9% *v* 14·2%, OR 0·90; 95% CI 0·82–0·99; $P = 0·023$). The overall rates of intracranial bleeding (0·5%) and transfusion (1·2%) were lower than those reported by the ASSENT-3 and GUSTO-V trials (see Figure 33.6), even though the HERO-2 population had greater baseline risk factors for bleeding. The rates of non-fatal disabling stroke, intracerebral bleeding, and severe bleeding were low and similar in both treatment groups, but moderate and minor bleeding were more common with bivalirudin than with heparin (see Table 33.3). This may be partially explained by the fact that the bivalirudin group had more prolonged APTTs at 12 and 24 hours than the heparin group. Statistical adjustment for this factor did not affect the reduction in re-infarction seen with bivalirudin, but did explain 50–100% of the increase in bleeding. In a non-prespecified analysis, the adjusted rates of the composite end point of death/re-infarction/non-fatal disabling stroke were 12·7% in the bivalirudin group versus 13·8% in the heparin group ($P = 0·049$) (Figure 33.7). Based on these data, bivalirudin should be used instead of intravenous heparin as adjunctive therapy with streptokinase to reduce the risk of re-infarction. **Grade A1a**

Univalent direct thrombin inhibitors

The univalent direct thrombin inhibitors include argatroban, inogatran, efegatran, and D-Phe-Pro-Arg-CH_2Cl. These anticoagulants inhibit early stages of the coagulation pathway and have been shown experimentally to be effective adjuncts to fibrinolytic therapy.[68–70]

In the Antithrombin-Argatroban in Acute Myocardial Infarction (ARGAMI-2) study,[71] 1001 patients were given either streptokinase or alteplase and randomized to receive

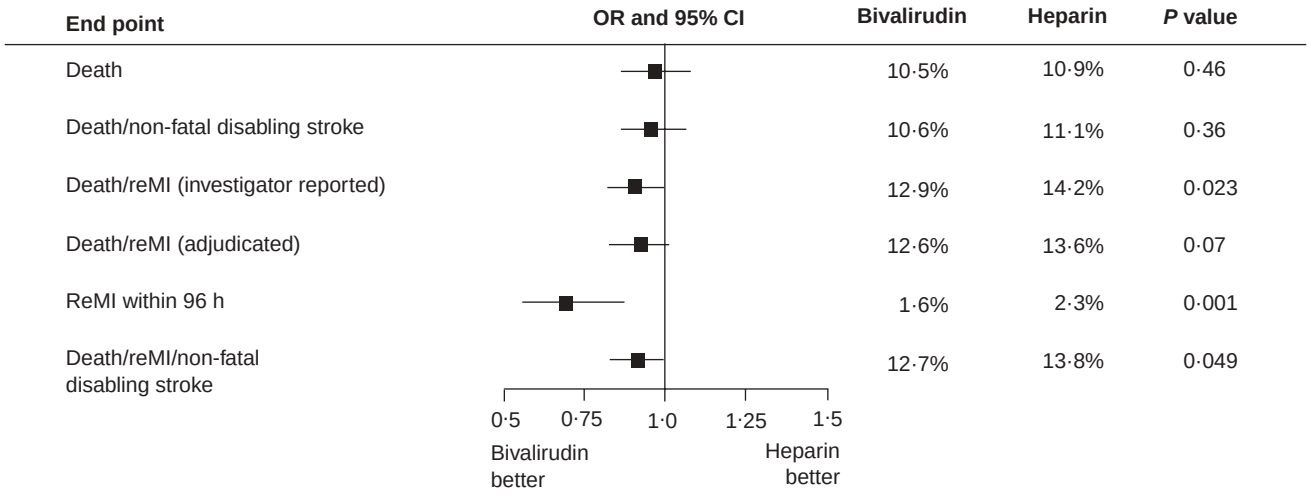


Figure 33.7 Forrest plot of clinical outcomes in the HERO-2[48] trial

either heparin or argatroban (a 120 micrograms bolus and 4 micrograms/kg/minute infusion for 72 hours). A third treatment arm in which patients received half this argatroban regimen was terminated due to lack of efficacy after 609 patients had been enrolled. By 30 days, 5·5% of the argatroban group and 5·7% of the heparin group had died (P = NS). There was a trend towards less bleeding in patients randomized to receive argatroban, but there was no difference in other clinical event rates.

Meta-analysis of direct thrombin inhibitor trials

The Direct Thrombin Inhibitor Trialists' Collaborative Group recently published a meta-analysis of 11 randomized trials in which direct thrombin inhibitors (hirudin, bivalirudin, argatroban, efegatran or inogatran) were compared with unfractionated heparin in a total of 35 970 patients with ST-segment elevation or non-ST-segment elevation acute coronary syndromes.[60] There were no significant differences in mortality between the patients given direct thrombin inhibitors and those given unfractionated heparin: 1·9% *v* 2·0% respectively at the cessation of therapy (OR 0·97; 95% CI 0·83–1·13, P = 0·69), 2·2% *v* 2·3% at 7 days (OR 1·00; 95% CI 0·87–1·16; P = 0·95), and 3·6% *v* 3·7% at 30 days (OR 1·01; 95% CI 0·90–1·12; P = 0·90). Likewise, direct thrombin inhibitors did not reduce mortality at 6 months (OR 1·00; 95% CI 0·91–1·09; P = 0·92). However, they did reduce the incidence of MI compared with heparin: 2·8% *v* 3·5% at the cessation of therapy (OR 0·80; 95% CI 0·71–0·90; P < 0·001), 3·2% *v* 3·9% at 7 days (OR 0·81; 95% CI 0·72–0·91; P < 0·001) and 4·7% *v* 5·3% at 30 days (OR 0·87; 95% CI 0·79–0·95; P = 0·004). The absolute risk reduction of 7 MIs prevented per 1000 patients treated with direct thrombin inhibitors remained constant at the cessation of therapy, at 7 days and at 30 days. Direct thrombin inhibitors were also shown to reduce the combined incidence of death/MI at the cessation of therapy (4·3% *v* 5·1% with heparin, OR 0·85; 95% CI 0·77–0·94; P = 0·001), at 7 days (5·0% *v* 5·8%, OR 0·88; 95% CI 0·80–0·96; P = 0·006) and at 30 days (7·4% *v* 8·2%, OR 0·91; 95% CI 0·84–0·99; P = 0·02). The 0·8% absolute risk reduction in death/MI remained constant at the cessation of therapy, at 7 days and at 30 days.

Five trials in this meta-analysis[38,39,63,65,71] (not including HERO-2) involved patients with ST-elevation MI. When the HERO-2 data[48] are combined with the data from these five trials (Figure 33.8), the results show that direct thrombin inhibitors have no effect on mortality alone, but do reduce the combined risk of death/re-infarction by 5% at 30 days compared with unfractionated heparin. This is due primarily to a 20% reduction in the rate of re-infarction. When compared with intravenous heparin, direct thrombin inhibitors reduce the risk of re-infarction after fibrinolytic therapy without altering the rates of ischemic stroke, intracranial hemorrhage or major bleeding. **Grade A1a**

Factor X inhibitors

The newer antithrombotic drugs, vasoflux and pentasaccharide (which also has other effects as detailed below), have been recently evaluated as adjuncts to fibrinolytic therapy in patients with acute MI. These agents inhibit factor Xa, and offer potential advantages over unfractionated and low molecular weight heparin in that they do not interact with platelets or bind to platelet factor 4.

Vasoflux is a derivative of low molecular weight heparin that catalyzes fibrin-bound thrombin inactivation by heparin cofactor II, and inhibits factor IXa activation of factor X independently of antithrombin and heparin cofactor II. In the Vasoflux International Trial for Acute Myocardial Infarction Lysis (VITAL),[72] patients presenting within 6 hours of the onset of acute ST-elevation MI were given aspirin and streptokinase and randomized to receive either intravenous heparin or one of four intravenous doses of vasoflux (1 mg/kg, 4 mg/kg, 8 mg/kg or 16 mg/kg) in a dose-escalating phase II study. The incidence of TIMI-3 flow was similar in all treatment groups (35–42% with the various vasoflux doses *v* 41% with heparin), but major bleeding was more common with the higher doses of vasoflux (13% with 8 mg/kg of vasoflux (P = 0·05) and 28% with 16 mg/kg of vasoflux (P = 0·01) versus 8% with heparin). The development of this drug has been abandoned.

The Synthetic Pentasaccharide as an Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction (PENTALYSE) study investigated the efficacy of pentasaccharide (a selective factor Xa inhibitor with a half life of 15–18 hours) in 316 patients presenting within 6 hours of the onset of ST-elevation MI.[73] The patients were given aspirin and alteplase and randomized to receive either unfractionated heparin or weight adjusted low-dose (4–6 mg), medium-dose (6–10 mg) or high-dose (10–12 mg) pentasaccharide administered once daily for 5–7 days. The first dose was given intravenously prior to alteplase, and the subsequent doses were given subcutaneously. The incidence of TIMI-3 flow at 90 minutes was similar in all treatment groups (68% with unfractionated heparin *v* 64% with all three pentasaccharide doses). While there was a trend towards less reocclusion (measured on day 6±1) with pentasaccharide among patients who had achieved TIMI-3 flow by 90 minutes (0·9% *v* 7% with unfractionated heparin, P = 0·065), there was no difference in the rate of re-infarction within 30 days (3·8% with pentasaccharide *v* 3·6% with unfractionated heparin, P = 1·00). One patient randomized to receive 4 mg of pentasaccharide suffered an intracranial hemorrhage. Transfusions (excluding those related to bypass surgery)

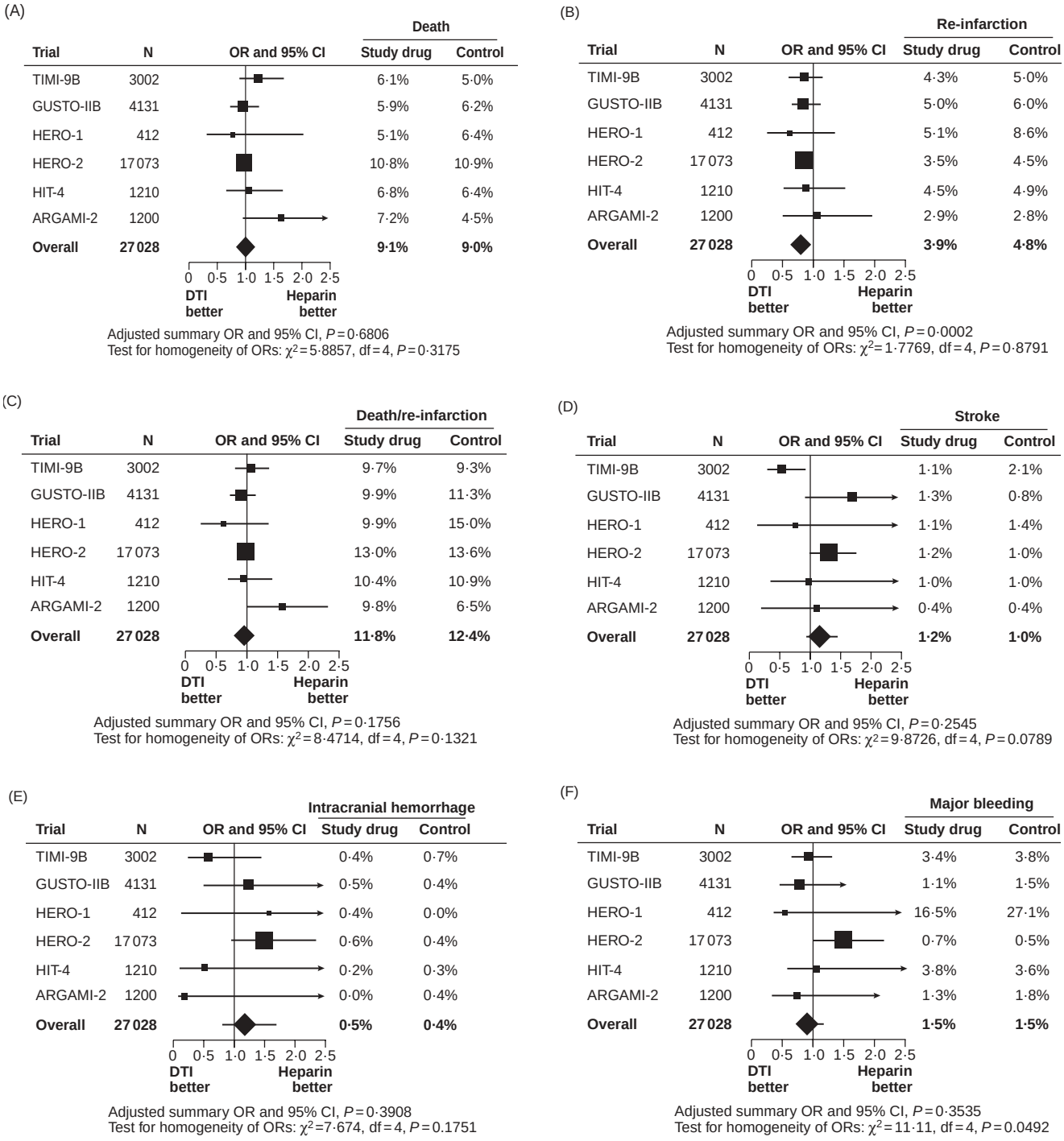


Figure 33.8 30 day event rates in patients with ST-elevation MI randomized to receive direct thrombin inhibitors (DTI) or unfractionated heparin in the HERO-1,[65] HERO-2,[48] TIMI-9B,[38] GUSTO-IIB,[39] HIT-4,[63] and ARGAMI-2[71] trials: (A) death; (B) re-infarction; (C) death/re-infarction; (D) stroke; (E) intracranial hemorrhage; (F) major bleeding. HIT = Hirudin for Improvement of Thrombolysis

were given to 3·3% of the pentasaccharide patients and 7·1% of the unfractionated heparin patients ($P = 0·21$).

Antiplatelet agents

Aspirin

Aspirin inhibits the cyclo-oxygenase-1 pathway of platelet activation (Figure 33.9).[74] The major support for its use in conjunction with fibrinolytic therapy comes from the ISIS-2 study, which was designed as a double-blind placebo-controlled 2×2 factorial trial.[75] Over 17 000 patients presenting within 24 hours of the onset of suspected acute MI were randomized to receive either streptokinase (1·5 million IU over 1 hour) or aspirin (162·5 mg daily for 1 month), or both, or neither. Aspirin on its own was found to reduce vascular mortality by 23% at 1 month, and when combined with streptokinase the reduction in this end point was 42%. The rates of non-fatal re-infarction (OR 0·51) and non-fatal stroke (OR 0·49) were also reduced by aspirin.

Aspirin should be given to all patients with ST-elevation MI and without contraindications in a dose of ⩾150 mg. **Grade A1a**

The results of a 1992 meta-analysis suggested that aspirin reduced reocclusion in the first 2 weeks after MI,[76] but there has been no convincing evidence that aspirin prevents late reocclusion.[77,78]

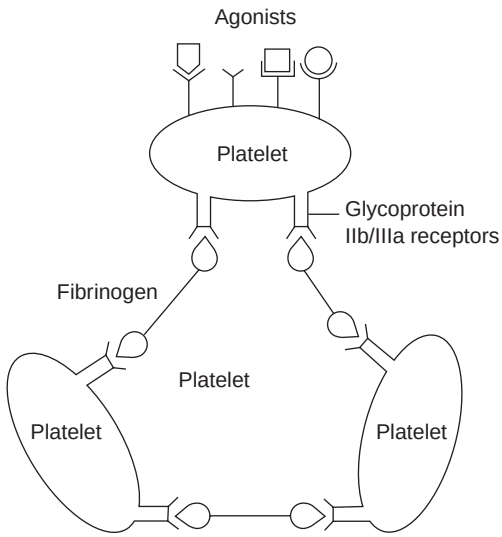


Figure 33.9 Glycoprotein IIb/IIIa receptors and platelet aggregation. Platelets are activated to aggregate by several mechanisms including high shear stress. The most common mechanism is the binding of an agonist to an external receptor, which activates signal transduction pathways. This causes the glycoprotein IIb/IIIa receptor to bind to fibrinogen, which binds to other platelets.

Glycoprotein IIb/IIIa inhibitors

Inhibition of the glycoprotein IIb/IIIa receptor blocks the final common site of several signal transduction pathways that lead to platelet aggregation (see Figure 33.9). There are two main types of drug in this class: (1) abciximab, which is a composite (human–murine) monoclonal antibody to the IIb/IIIa receptor; and (2) "small molecule" non-competitive IIb/IIIa inhibitors.

Abciximab used alone

Abciximab has been shown to enhance the likelihood of achieving TIMI-3 flow, but its effect is time-dependent. Figure 33.10 shows the percentages of patients achieving TIMI-2 and TIMI-3 flow after ST-elevation MI in five studies[45,79–82] where abciximab was administered prior to angiography.

Abciximab with percutaneous coronary interventions (PCI)

In the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up (ADMIRAL) study, 300 patients with acute MI were randomized in a double-blind manner to receive either abciximab or a placebo prior to primary angioplasty with stenting.[81] Some patients received the study drugs in the ambulance en route to hospital. Death/re-infarction/urgent target vessel revascularization occurred in 6·0% of the abciximab group versus 14·6% of the placebo group within 30 days ($P = 0·01$), and in 7·4% versus 15·9% respectively

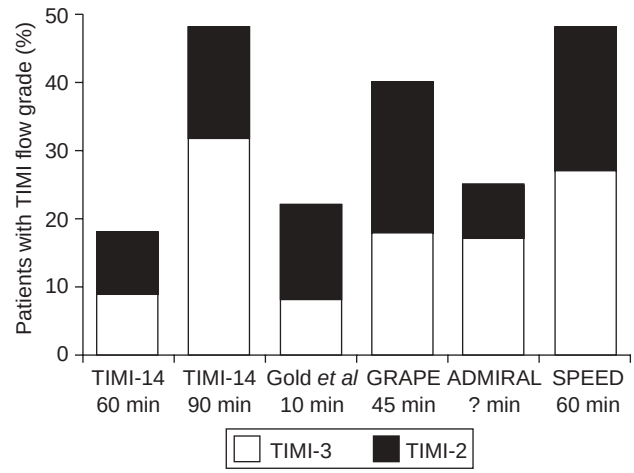


Figure 33.10 TIMI-2 and -3 flow rates in patients with acute MI treated with abciximab prior to angiography in the TIMI-14,[42] Gold *et al*,[79] GRAPE,[80] ADMIRAL,[81] and SPEED[82] trials. The time intervals between administration of the abciximab bolus and angiography are shown. GRAPE, Glycoprotein Receptor Antagonist Patency Evaluation.

within 6 months ($P = 0{\cdot}02$). Patients in the abciximab group had a higher incidence of TIMI-3 flow prior to the procedure (16·8% *v* 5·4%; $P = 0{\cdot}01$), immediately afterwards (95·1% *v* 86·7%; $P = 0{\cdot}04$) and at 6 months (94·3% *v* 82·8%; $P = 0{\cdot}04$). There was one major bleeding event in the abciximab group (0·7%) and none in the placebo group.

In the larger Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial,[83] 2082 patients presenting within 12 hours of the onset of ST elevation MI without cardiogenic shock were randomized in a 2×2 manner to receive either abciximab or a placebo, and either stenting or balloon angioplasty. Abciximab was not administered prior to angiography. TIMI-3 flow was achieved in 94·5% of the angioplasty group, 96·1% of the angioplasty plus abciximab group, 92·9% of the stenting group, and 96·4% of the stenting plus abciximab group. The mortality rates at 6 months were 5·3%, 2·9%, 3·2%, and 5·0% respectively, and reocclusion occurred in 12·9%, 9·7%, 5·4%, and 6·9% respectively. At 12 months the incidence of major adverse cardiac events was reduced (mainly due to a reduction in target vessel revascularization) from 15·9% in both balloon angioplasty groups to 9·3% and 6·6% in the stenting and stenting plus abciximab groups respectively ($P < 0{\cdot}01$ for the four-way comparison between the groups).

The Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI)-1 and -2 trials evaluated the effects of abciximab in conjunction with stenting or alteplase on myocardial salvage indices, measured by technetium-99 m sestamibi on paired scintigrams at presentation (area at risk) and at 10 days (final infarct size). In the STOPAMI-1 trial,[84] 140 patients were randomized to receive either stenting plus abciximab, or alteplase. The salvage indices were 0·57 (interquartile range (IQR) 0·35–0·69) in the stenting plus abciximab group versus 0·26 (IQR 0·09–0·61; $P < 0{\cdot}001$) in the alteplase group. In the STOPAMI-2 trial,[85] 162 patients were randomized to receive either half-dose alteplase plus abciximab or stenting plus abciximab. The salvage indices were 0·41 (IQR 0·13–0·58) in the alteplase plus abciximab group versus 0·60 (IQR 0·37–0·82) in the stenting plus abciximab group ($P = 0{\cdot}001$). At 6 months 5% of the stenting plus abciximab group versus 9% of the alteplase plus abciximab group had died (RR 0·56; 95% CI 0·17–1·88; $P = 0{\cdot}35$), while 0% *v* 4·9% respectively had suffered reinfarction ($P = 0{\cdot}12$). There were no differences in the rates of stroke (1·2% in both groups) or major bleeding (also 1·2% in both groups).

Glycoprotein IIb/IIIa inhibitors and full-dose fibrinolytics

In the Combined Accelerated Tissue-Plasminogen Activator and Platelet Glycoprotein IIb/IIIa Integrin Receptor Blockade With Integrilin in Acute Myocardial Infarction (IMPACT-AMI) dose-escalation study, 180 patients were given alteplase, aspirin, intravenous unfractionated heparin, and either a placebo or one of six doses of eptifibatide (previously known as integrilin).[86] TIMI-3 flow was achieved in 66% of patients given the highest dose of eptifibatide (a 180 micrograms/kg bolus and 0·75 micrograms/kg/minute infusion) versus 39% of those not given eptifibatide ($P = 0{\cdot}007$). The major bleeding rates in these two groups were 3·9% and 5·4% respectively. However, this study involved small patient numbers, and so the results need to be confirmed in a larger study.

A pilot study[87] tested three doses of eptifibatide in conjunction with full-dose streptokinase in 181 patients who were randomized to receive a 180 micrograms/kg bolus of eptifibatide (or a placebo) followed by an infusion of 0·75, 1·33 or 2 micrograms/kg/minute. TIMI-3 flow at 90 minutes was achieved in 44–53% of patients in the various eptifibatide groups versus 38% of the group given streptokinase alone ($P =$ NS). Bleeding requiring transfusion (mainly angiography-related) occurred in 17% of patients given the highest dose of eptifibatide, 11% of those given the two lower doses, and none of those given the placebo ($P = 0{\cdot}007$).

Glycoprotein IIb/IIIa inhibitors and modified-dose fibrinolytics

A number of angiographic and clinical trials have tested full-dose IIb/IIIa inhibitors in conjunction with reduced doses of fibrinolytic agents.

Angiographic studies

In the TIMI-14 trial,[42] patients were randomized to one of four treatment strategies: accelerated alteplase (a 100 mg infusion); full-dose abciximab with 20, 35 or 50 mg of alteplase; full-dose abciximab with 0·5, 0·75 or 1·25 million IU of streptokinase; or full-dose abciximab alone. All patients received a bolus of either 40 IU/kg or 60 IU/kg of unfractionated heparin. The highest incidence of TIMI-3 flow (77% at 90 minutes) was achieved with 50 mg of alteplase plus full-dose abciximab and 40 IU/kg of heparin. Overall, 3 of the 181 patients (1·7%) who received abciximab suffered intracranial hemorrhage. A high bleeding rate led to discontinuation of the treatment limbs that included streptokinase.

The SPEED trial[82] randomized patients to receive either abciximab alone (a 0·25 microgram/kg bolus and 0·125 microgram/kg/minute infusion for 12 hours), reteplase alone (two 10 mg boluses), or abciximab plus one of six double-bolus doses of reteplase (2·5–15 mg). Abciximab alone achieved TIMI-3 flow in 23% of patients by 60 minutes, while the highest incidence of TIMI-3 flow (62%) was achieved with 60 IU/kg of heparin plus two 5 mg

boluses of reteplase and full-dose abciximab. Major bleeding occurred in 9·8% of the patients who received two 5 mg boluses of reteplase plus abciximab versus 3·7% of those who received reteplase alone ($P = 0·11$).

In the dose-finding phase of the Integrilin and Low-Dose Thrombolytics in Acute Myocardial Infarction (INTRO AMI) study,[88] eptifibatide was administered as a single 180 micrograms/kg bolus or as double boluses (30 minutes apart) of 180+90 micrograms/kg or 180+180 micrograms/kg, followed by an infusion of 1·33 or 2·0 micrograms/kg/minute for 72 hours after 25 or 50 mg of alteplase. In the dose-confirmation phase, the highest rates of TIMI-3 flow (65% at 60 minutes and 78% at 90 minutes) were achieved with 50 mg of alteplase plus a 180+90 micrograms/kg double bolus and 1·33 micrograms/kg/minute infusion of eptifibatide. The 180+90 micrograms/kg double bolus (given 10 minutes apart) and 2·0 micrograms/kg/minute infusion of eptifibatide achieved TIMI-3 flow in 54% of patients by 60 minutes, but major bleeding occurred in 11%, intracranial hemorrhage in 3%, and death in 5% of patients treated with this dose. For reasons that are not fully understood, the rates of intracranial hemorrhage have been higher in angiographic studies than in large clinical trials.

Glycoprotein IIb/IIIa inhibitors and low molecular weight heparin

In the Enoxaparin and TNK-t-PA With or Without Glycoprotein IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation Myocardial Infarction (ENTIRE-TIMI-23) trial,[55] patients were randomized to one of three treatment regimens: tenecteplase (0·53 mg/kg) plus either enoxaparin or unfractionated heparin, or half this dose of tenecteplase plus abciximab. The TIMI-3 flow rates at 60 minutes ranged from 47% to 58% with the various treatment regimens, but did not differ significantly between the groups. Major bleeding was less common with enoxaparin than with unfractionated heparin (1·9% *v* 2·4%, $P < 0·05$).

In the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trial,[89] patients received either tenecteplase alone (0·375 mg) or reduced-dose tenecteplase (0·25 mg) plus eptifibatide (two boluses of 180 and 90 mg/kg given 10 minutes apart followed by a 2 mg/kg infusion). TIMI-3 flow was achieved by 60 minutes in 49% of patients receiving tenecteplase alone versus 59% of those receiving tenecteplase and eptifibatide (P = NS).

The Fibrinolytic and Aggrastat ST-Elevation Resolution (FASTER) trial[90] tested various bolus doses of tirofiban (between 10 and 15 micrograms/kg followed by 0·15 micrograms/kg/minute for 24 hours) in combination with half or two thirds doses of tenecteplase (0.27 or 0.36 mg/kg, respectively). A control group received full-dose tenecteplase alone (0.53 mg/kg). The patients receiving the half and two thirds doses of tenecteplase were given a 40 IU/kg heparin bolus (maximum 3000 IU) and a 7 IU/kg/hour infusion (maximum 800 IU/hour) to maintain an APTT of 50–70 seconds, while those receiving full-dose tenecteplase (the control group) were given a 60 IU/kg heparin bolus (maximum 4000 IU) and a 12 IU/kg/hour infusion (maximum 1000 IU). The end points of the trial were TIMI-3 flow in the infarct artery at 60 minutes, the corrected TIMI frame count at 60 minutes and ST-segment resolution at 60 and 180 minutes. TIMI-3 flow was achieved by 60 minutes in 59% of the tirofiban groups overall versus 58% of the control group, and there were no differences in their corrected TIMI frame counts. Complete ST-segment resolution was achieved by 60 minutes in 41% of the tirofiban groups overall versus 29% of the control group ($P = 0.07$), and by 180 minutes in 76 versus 65%, respectively ($P = 0.10$). TIMI major bleeding[53] occurred within the first 48 hours in 2.3% of the tirofiban groups overall versus 4·7% of the control group. There were no episodes of intracranial hemorrhage (personal communication from Dr EM Ohman).

Trials with clinical end points

The ASSENT-3 trial[46] randomized patients to receive either full-dose tenecteplase plus enoxaparin (30 mg intravenously plus 1 mg/kg subcutaneously every 12 hours) for a maximum of 7 days, half-dose tenecteplase plus weight adjusted low-dose unfractionated heparin and a 12 hour infusion of abciximab, or full-dose tenecteplase plus weight adjusted unfractionated heparin for 48 hours. A summary of the clinical outcomes, including a reduction in investigator-reported re-infarction, is shown in Figure 33.11.

In the GUSTO-V trial,[47] 16 588 patients presenting within 6 hours of the onset of acute ST-segment elevation MI were randomized to receive either half-dose reteplase plus a modified dose of heparin and abciximab, or full-dose reteplase and heparin without abciximab. By 30 days, 5·6% of the abciximab group versus 5·9% of the no-abciximab group had died (OR 0·95; 95% CI 0·83–1·08; $P = 0·43$). The abciximab group had a lower rate of investigator-reported re-infarction (Figure 33.11), but higher rates of severe bleeding (1·1% *v* 0·5%; OR 2·14; 95% CI 1·48–3·09; $P < 0·001$) and transfusion (5·7% *v* 4·0%; OR 1·46; 95% CI 1·26–1·69; $P < 0·001$). Intracranial hemorrhage occurred in 0·6% of both groups. In a prespecified analysis, the regimen including abciximab was shown not to be inferior to the regimen excluding abciximab. Subgroup analysis showed that the abciximab group had a lower point estimate for mortality in patients presenting after 4 hours (7·1% *v* 8·1%; $P = 0·33$) and in patients with anterior MI (7·6% *v* 8·5%, $P = 0·17$).

In ASSENT-3[46] and GUSTO-V[47] the risk of bleeding in patients aged >75 years (including intracranial hemorrhage) (see Figure 33.6) was higher with regimens involving half-dose fibrinolytic therapy plus full-dose abciximab than in those involving full-dose fibrinolytic therapy without abciximab.

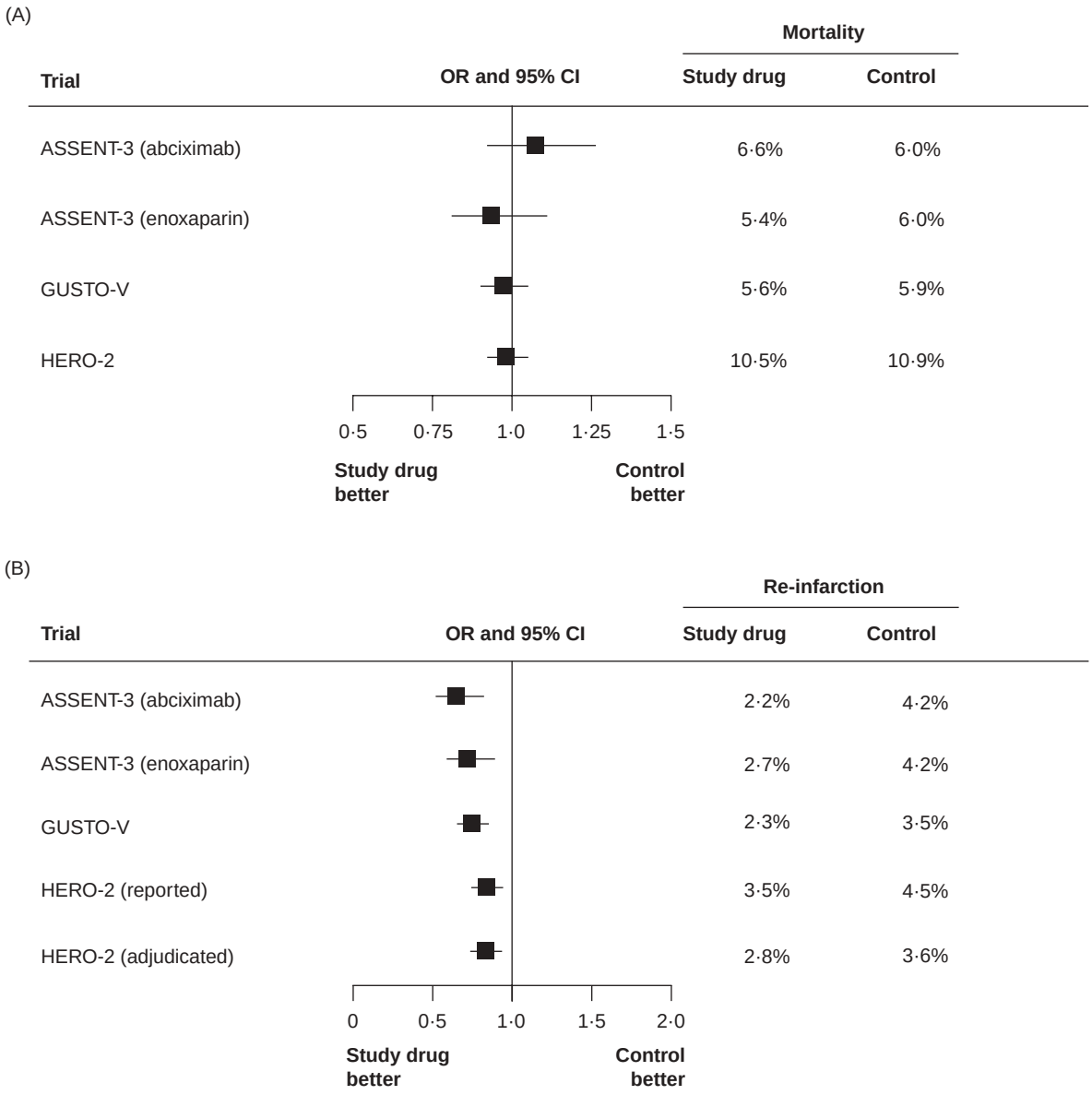


Figure 33.11 Clinical outcomes in the ASSENT-3,[46] GUSTO-V,[47] and HERO-2[48] trials: (A) mortality; (B) re-infarction

In ASSENT-3, bleeding occurred in 13·3% of elderly patients given tenecteplase plus abciximab versus 4·1% of those given tenecteplase plus unfractionated heparin ($P = 0{\cdot}0002$). In GUSTO-V, bleeding occurred in 1·9% of elderly patients given reteplase plus abciximab versus 1·2% of those given reteplase plus unfractionated heparin ($P = 0{\cdot}17$). These findings suggest that the combination of abciximab with half-dose reteplase or tenecteplase reduces the risk of re-infarction compared with full doses of these fibrinolytic agents combined with intravenous unfractionated heparin although in GUSTO-V this did not translate into a mortality benefit at 12 months, including in prespecified subgroups.[96] Based on the data currently available, no firm recommendations can be made for the use of glycoprotein IIb/IIIa inhibitors as adjuncts to either fibrinolytic therapy or percutaneous intervention. **Grade A1b**

Recommendations for use of adjunctive antithrombotic therapies

The 1999 ACC/AHA guidelines[34] and the 2000 American College of Chest Physicians (ACCP)[91] guidelines recommend that patients receiving a fibrin-specific fibrinolytic agent for acute MI should be given a 60 IU/kg bolus (maximum 4000 IU) and a 12 IU/kg/hour infusion (maximum 1000 IU/hour) of unfractionated heparin (Table 33.5). **Grade A1c** This dose is lower than that recommended in

Table 33.5 Recommendations for the use of adjunctive unfractionated heparin with fibrinolytic therapy from two consensus conferences

Fibrinolytic agent	ACC/AHA 1999[34]	ACCP 2000[91]
Fibrin-specific agents	Intravenous unfractionated heparin should be used in patients undergoing reperfusion therapy with alteplase. The recommended regimen is 60 IU/kg as a bolus at initiation of the alteplase infusion, then an initial maintenance dose of approximately 12 IU/kg/hour (maximum 4000 IU bolus and maximum 1000 IU/hour infusion for patients weighing >70 kg), adjusted to maintain the APTT at 1·5–2·0 times control (50–70 seconds) for 48 hours. Continuation of the heparin infusion beyond 48 hours should be considered in patients at high risk of systemic or venous thromboembolism	Patients receiving alteplase, reteplase or tenecteplase should be given intravenous unfractionated heparin for 48 hours. Either standard dosing (a 5000 IU bolus and 1000 IU/hour infusion) or weight adjusted dosing (a 60 IU/kg bolus (maximum 4000 IU) and 12 IU/kg/hour infusion (maximum 1000 IU/hour) may be used, both adjusted to maintain an APTT of 50–70 seconds
Streptokinase	Intravenous unfractionated heparin should be used in patients at high risk of systemic emboli (large or anterior MI, atrial fibrillation, previous embolus or known left ventricular thrombus). It is recommended that heparin be withheld for 6 hours and that APTT testing begin at that time. Heparin should be started when the APTT returns to <2 times control (approximately 70 seconds), then infused to keep the APTT at 1.5–2.0 times control (initial infusion rate approximately 1000 IU/hour). After 48 hours, a change to subcutaneous heparin, warfarin or aspirin alone should be considered	Patients at high risk of systemic or venous thromboembolism (that is, those with Q wave anterior MI, severe left ventricular dysfunction, congestive heart failure, a history of systemic or pulmonary embolism, evidence of left ventricular thrombus, or atrial fibrillation) should receive intravenous unfractionated heparin, starting not less than 4 hours after the commencement of streptokinase and when the APTT is <70 seconds. The target APTT should be 50–70 seconds, and the infusion should continue for ≥48 hours Patients who are not at high risk of systemic or venous thromboembolism should receive subcutaneous unfractionated heparin (12 500 IU) every 12 hours for 48 hours

the 1996 guidelines. The time for the first APTT measurement is not specified. Although the recent reduction in the unfractionated heparin regimen is aimed at lowering the rates of major bleeding and intracranial hemorrhage while maintaining efficacy as assessed by TIMI-3 flow rates, this is only supported by Grade C evidence.

The ACC/AHA and ACCP guidelines recommend the use of intravenous heparin in patients treated with streptokinase if they have high-risk features (Table 33.5). **Grade A1c** Our personal approach is to use intravenous heparin (commencing with a weight adjusted bolus) to achieve a high level of thrombin inhibition in patients receiving streptokinase, and to measure the APTT at 3 hours. This is based on the results of the overview (which indicated a possible saving with unfractionated heparin of 2·2 lives and 1·8 infarctions prevented per 1000 patients treated, at a cost of 3·2 transfusions and 0·3 non-fatal disabling strokes compared with a placebo or control treatment),[29] angiographic data from GUSTO-I (showing significantly better patency at 5–7 days with intravenous versus subcutaneous heparin),[6] and follow up data from GUSTO-I (showing that the 5 year survival rate of patients given streptokinase and intravenous heparin was equal to that of patients given alteplase, and higher than those given streptokinase plus subcutaneous heparin).[31]

If a fibrin-specific fibrinolytic agent is being used, the patient should receive a weight adjusted bolus of intravenous heparin followed by an infusion to maintain the APTT at 50–70 seconds for 48 hours if the patient is not undergoing PCI (see Table 33.5). The APTT should be measured at 3 hours. Further trials of adjunctive intravenous low molecular weight heparins with fibrinolytic therapy will need to be performed before recommendations can be made regarding combinations of these agents.

Future directions

Despite greater understanding of the mechanism of benefit of adjunctive antithrombin therapies, and recent large

clinical trials in patients with ST-segment elevation MI, many questions remain unanswered. It has not yet been resolved whether combinations of newer fibrinolytic agents with newer antithrombin agents and/or glycoprotein IIb/IIIa inhibitors improve clinical outcomes with acceptable bleeding risks. These regimens, along with agents such as P-selectin inhibitors[92] and tissue factor pathway inhibitors,[93] will need to be tested in combination with clopidogrel and with facilitated PCI.

Key points

- There is ongoing thrombin generation in patients with ST-segment elevation acute coronary syndromes.
- Fibrinolytic therapy results in a procoagulant state.
- Unfractionated heparin has proven efficacy in the absence of aspirin and a modest effect in the presence of aspirin.
- Unfractionated heparin has several limitations as an antithrombin agent, including variable pharmacokinetics and pharmacodynamics and relative inefficacy against clot-bound thrombin.
- Reduction of the unfractionated heparin dose may reduce the risk of major bleeding, but does not alter the risk of intracranial hemorrhage.
- Low molecular weight heparins are easier to administer than unfractionated heparin, and have been shown to reduce the risk of re-infarction when used as adjuncts to fibrinolytic therapy. However, they may increase the need for transfusion compared with unfractionated heparin.
- Bivalirudin has no effect on mortality when used as adjunctive therapy with streptokinase, but does reduce the incidence of re-infarction compared with unfractionated heparin increases the risks of minor and moderate bleeding.
- When combined with reteplase or tenecteplase, abciximab reduces the risk of re-infarction compared with unfractionated heparin, but increases the risk of major bleeding, particularly in elderly patients.

References

1. French JK, Williams BF, Hart HH *et al.* Prospective evaluation of eligibility for thrombolytic therapy in acute myocardial infarction. *BMJ* 1996;**312**:1637–41.
2. Chesebro JH, Knatterud G, Roberts R *et al.* Thrombolysis in Myocardial Infarction (TIMI) trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation* 1987;**76**:142–54.
3. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase I findings. *N Engl J Med* 1985; **312**:932–6.
4. Simes RJ, Topol EJ, Holmes DR Jr *et al.* Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. *Circulation* 1995; **91**:1923–8.
5. White HD, Norris RM, Brown MA *et al.* Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987; **317**:850–5.
6. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;**329**:1615–22 [published erratum appears in *N Engl J Med* 1994;**330**:516].
7. White HD, Cross DB, Elliott JM, Norris RM, Yee TW. Long-term prognostic importance of patency of the infarct-related coronary artery after thrombolytic therapy for acute myocardial infarction. *Circulation* 1994;**89**:61–7.
8. Hirsh J, Raschke R, Warkentin TE *et al.* Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995;**108**:258S–75S.
9. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin–antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990;**86**:385–91.
10. Eisenberg PR, Miletich JP. Induction of marked thrombin activity by pharmacologic concentrations of plasminogen activators in nonanticoagulated whole blood. *Thromb Res* 1989; **55**:635–43.
11. Lee CD, Mann KG. Activation/inactivation of human coagulation factor V by plasmin. *Blood* 1989;**73**:185–90.
12. Eisenberg PR. Role of heparin in coronary thrombolysis. *Chest* 1992;**101**(Suppl. 4):131S–9S.
13. Verheugt FW, Liem A, Zijlstra F *et al.* High dose bolus heparin as initial therapy before primary angioplasty for acute myocardial infarction: results of the Heparin in Early Patency (HEAP) pilot study. *J Am Coll Cardiol* 1998;**31**:289–93.
14. Liem A, Zijlstra F, Ottervanger JP *et al.* High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the Heparin in Early Patency (HEAP) randomized trial. *J Am Coll Cardiol* 2000;**35**:600–4.
15. Topol EJ, George BS, Kereiakes DJ *et al.* A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989;**79**:281–6.
16. Hsia J, Hamilton WP, Kleiman N *et al.* A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1990;**323**:1433–7.
17. Bleich SD, Nichols TC, Schumacher RR *et al.* Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;**66**:1412–17.
18. de Bono DP, Simoons ML, Tijssen J *et al.* Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomized double blind European Cooperative Study Group trial. *Br Heart J* 1992;**67**:122–8.
19. Turpie AGG, Robinson JG, Doyle DJ *et al.* Comparison of high-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;**320**:352–8.

20.The SCATI (Studio sulla Calciparina nell-Angina e nella Trombosi Ventricolare nell'Infarto) Group. Randomized controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet* 1989;**ii**:182–6.
21.Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). GISSI-2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990;**336**:65–71.
22.ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomized comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1992; **339**: 753–70.
23.The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–82.
24.Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;**336**:847–60.
25.Collins R, Conway M, Alexopoulos D *et al*, for the ISIS Pilot Study Investigators. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. *Eur Heart J* 1987; **8**:634–42.
26.Col J, Decoster O, Hanique G *et al.* Infusion of heparin conjunct to streptokinase accelerates reperfusion of acute myocardial infarction: results of a double blind randomized study (OSIRIS) [abstract]. *Circulation* 1992;**86**(Suppl. I):I-259.
27.O'Connor CM, Meese R, Carney R *et al*, for the DUCCS Group. A randomized trial of heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiology Study (DUCCS). *J Am Coll Cardiol* 1994;**23**:11–18.
28.Topol EJ, Califf RM, Van de Werf F *et al.* Perspectives on large-scale cardiovascular clinical trials for the new millenium. *Circulation* 1997;**95**:1072–82.
29.Collins R, MacMahon S, Flather M *et al.* Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomized trials. *BMJ* 1996; **313**:652–9.
30.Granger CB, Becker R, Tracy RP *et al.* Thrombin generation, inhibition and clinical outcomes in patients with actue myocardial infarction treated with thrombolytic therapy and heparin: results from the GUSTO-1 trial. *J Am Coll Cardiol* 1998;**31**:497–505.
31.Tardiff BE, McCants B, Hellkamp AS *et al.* Long term results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) trial: sustained benefit of fibrin-specific therapy [abstract]. *Circulation* 1999; **100**(Suppl. I):I-498–9.
32.Holmes DR Jr, Califf RM, Van de Werf F *et al.* Difference in countries' use of resources and clinical outcome for patients with cardiogenic shock after myocardial infarction: results from the GUSTO trial. *Lancet* 1997;**349**:75–8.
33.Giugliano RP, McCabe CH, Antman EM *et al.* Lower-dose heparin with fibrinolysis is associated with lower rates of intracranial hemorrhage. *Am Heart J* 2001;**141**:742–50.
34.Ryan TJ, Antman EM, Brooks NH *et al.* 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999;**34**: 890–911.
35.Granger CB, Hirsh J, Califf RM *et al.* Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;**93**:870–8.
36.Antman EM, for the TIMI-9A Investigators. Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation* 1994;**90**:1624–30.
37.The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;**90**:1631–7.
38.Antman EM, for the TIMI-9B Investigators. Hirudin in acute myocardial infarction: Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996; **94**:911–21.
39.The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775–82.
40.Cannon CP, Gibson CM, McCabe CH *et al.* TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI-10B trial. *Circulation* 1998;**98**:2805–14.
41.Van de Werf F, Cannon CP, Luyten A *et al.* Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. *Am Heart J* 1999;**137**:786–91.
42.Antman EM, Giugliano RP, Gibson CM *et al.* Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. *Circulation* 1999;**99**:2720–32.
43.Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation* 2000;**101**:2788–94.
44.Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomized trial. *Lancet* 1999; **354**:716–22.
45.The InTIME-II Investigators. Intravenous NPA for the treatment of infarcting myocardium early: InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000;**21**:2005–13.
46.The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. *Lancet* 2001;**358**: 605–13.
47.The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination

reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomized trial. *Lancet* 2001; **357**:1905–14.

48. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomized trial. *Lancet* 2001;**358**:1855–63.
49. Kontny F, Dale J, Abildgaard U, Pedersen TR, on behalf of the FRAMI Study Group. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) study. *J Am Coll Cardiol* 1997;**30**:962–9.
50. Frostfeldt G, Ahlberg G, Gustafsson G *et al.* Low molecular weight heparin (dalteparin) as adjuvant treatment to thrombolysis in acute myocardial infarction – a pilot study: Biochemical Markers in Acute Coronary Syndromes (BIOMACS II). *J Am Coll Cardiol* 1999;**33**:627–33.
51. Wallentin L, Dellborg DM, Lindahl B *et al.* The low-molecular-weight heparin dalteparin as adjuvant therapy in acute myocardial infarction: the ASSENT PLUS study. *Clin Cardiol* 2001;**24**:I-12–14.
52. Simoons ML, Krzeminska-Pakula M, Alonso A *et al.* Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction: the AMI-SK study. *Eur Heart J.* In press 2002.
53. Rao AK, Pratt C, Berke A *et al.* Thrombolysis in Myocardial Infarction (TIMI) trial – phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.
54. Ross AM, Molhoek P, Lundergan C *et al.* Randomized comparison of enoxaparin, a low molecular weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation* 2001;**104**:648–52.
55. Antman EM, Louwerenburg HW, Baars HF *et al.* Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 trial. *Circulation* 2002;**105**:1642–9.
56. Maraganore JM, Bourdon P, Jablonski I, Ramachandran KL, Fenton JW II. Design and characterization of hirulogs: a novel class of bivalent peptide inhibitors of thrombin. *Biochem J* 1990;**29**:7095–101.
57. Collen D, Matsuo O, Stassen JM, Kettner C, Shaw E. *In vivo* studies of a synthetic inhibitor of thrombin. *J Lab Clin Med* 1982;**99**:76–83.
58. Yasuda T, Gold HK, Yaoita H *et al.* Comparative effects of aspirin, a synthetic thrombin inhibitor and a monoclonal antiplatelet glycoprotein IIb/IIIa antibody on coronary artery reperfusion, reocclusion and bleeding with recombinant tissue-type plasminogen activator in a canine preparation. *J Am Coll Cardiol* 1990;**16**:714–22.
59. Haskel EJ, Prager NA, Sobel BE, Abendschein DR. Relative efficacy of antithrombin compared with antiplatelet agents in accelerating coronary thrombolysis and preventing early reocclusion. *Circulation* 1991;**83**:1048–56.
60. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;**359**:294–302.
61. Cannon CP, McCabe CH, Henry TD *et al.* A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. *J Am Coll Cardiol* 1994; **23**:993–1003.
62. Simes RJ, Granger CB, Antman EM *et al.* Impact of hirudin versus heparin on mortality and (re)infarction in patients with acute coronary syndromes: a prospective meta-analysis of the GUSTO-IIb and TIMI 9b trials [abstract]. *Circulation* 1996; **94**(Suppl. I):I-430.
63. Neuhaus K-L, Molhoek GP, Zeymer U *et al.* Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. *J Am Coll Cardiol* 1999;**34**: 966–73.
64. Zeymer U, Schroder R, Tebbe U *et al.* Non-invasive detection of early infarct vessel patency by resolution of ST-segment elevation in patients with thrombolysis for acute myocardial infarction; results of the angiographic substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 trial. *Eur Heart J* 2001;**22**:769–75.
65. White HD, Aylward PE, Frey MJ *et al.* Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). *Circulation* 1997;**96**:2155–61.
66. Andrews J, Straznicky IT, French JK *et al.* Hirulog reduces re-ischaemic episodes as assessed by continuous ST segment monitoring following acute myocardial infarction treated with streptokinase [abstract]. *J Am Coll Cardiol* 1999; **33**(Suppl. A):375A.
67. Lee KL, Woodlief LH, Topol EJ *et al.* Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41 021 patients. *Circulation* 1995;**91**:1659–68.
68. Abendschein DR, Meng YY, Torr-Brown S, Sobel BE. Maintenance of coronary patency after fibrinolysis with tissue factor pathway inhibitor. *Circulation* 1995;**92**:944–9.
69. Sitko GR, Ramjit DR, Stabilito II *et al.* Conjunctive enhancement of enzymatic thrombolysis and prevention of thrombotic reocclusion with the selective factor Xa inhibitor, tick anticoagulant peptide. *Circulation* 1992;**85**:805–15.
70. Gruber A, Harker LA, Hanson SR, Kelly AB, Griffin JH. Antithrombotic effects of combining activated protein C and urokinase in nonhuman primates. *Circulation* 1991;**84**: 2454–62.
71. Kaplinsky E. Direct antithrombin-argatroban in acute myocardial infarction (ARGAMI-2). Proceedings of the Late-Breaking Clinical Trials III Session, 47th Scientific Sessions of the American College of Cardiology; Atlanta, Georgia, USA; March 1998.
72. Peters RJG, Spickler W, Théroux P *et al.* Randomized comparison of a novel anticoagulant, vasoflux, and heparin as adjunctive therapy to streptokinase for acute myocardial infarction: results of the VITAL study (Vasoflux International Trial for

Acute Myocardial Infarction Lysis). *Am Heart J* 2001; **142**:237–43.
73. Coussement PK, Bassand JP, Convens C *et al.* A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction: the PENTALYSE study. *Eur Heart J* 2001;**22**:1716–24.
74. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81–106.
75. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**ii**:349–60.
76. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *J Am Coll Cardiol* 1992;**19**:671–7.
77. Meijer A, Verheugt FWA, Werter CJPJ *et al.* Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study: results of the APRICOT study. *Circulation* 1993;**87**:1524–30.
78. White HD, French JK, Hamer AW *et al.* Frequent reocclusion of patent infarct-related arteries between 4 weeks and 1 year: effects of antiplatelet therapy. *J Am Coll Cardiol* 1995;**25**: 218–23.
79. Gold HK, Garabedian HD, Dinsmore RE *et al.* Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators: observations in animals and humans. *Circulation* 1997;**95**:1755–9.
80. van den Merkhof LFM, Zijlstra F, Olsson H *et al.* Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty: results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study. *J Am Coll Cardiol* 1999;**33**:1528–32.
81. Montalescot G, Barragan P, Wittenberg O *et al.* Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895–903.
82. Herrmann HC, Moliterno DJ, Ohman EM *et al.* Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) trial. *J Am Coll Cardiol* 2000;**36**:1489–96.
83. Stone GW, Grines CL, Cox DA *et al.* Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**:957–66.
84. Schömig A, Kastrati A, Dirschinger J *et al.* Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 2000;**343**:385–91.
85. Kastrati A, Mehilli J, Dirschinger J *et al.* Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomized trial. *Lancet* 2002;**359**:920–5.
86. Ohman EM, Kleiman NS, Gacioch G *et al.* Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction: results of a randomized, placebo-controlled, dose-ranging trial. *Circulation* 1997;**95**:846–54.
87. Ronner E, van Kesteren HA, Zijnen P *et al.* Safety and efficacy of eptifibatide vs placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction; a phase II dose escalation, randomized, double-blind study. *Eur Heart J* 2000;**21**:1530–6.
88. Brener SJ, Zeymer U, Adgey AA *et al.* Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002;**39**:377–86.
89. Giugliano RP, Roe MT, Zeymer U *et al.* Restoration of epicardial and myocardial perfusion in acute ST-elevation myocardial infarction with combination eptifibatide + reduced-dose tenecteplase: results from the INTEGRITI trial [abstract]. *Circulation* 2001;**104**(Suppl. II):II-538.
90. The Fibrinolytic and Aggrastat ST-Elevation Resolution (FASTER) trial. Proceedings of the American College of Cardiology 51st Annual Scientific Session, Atlanta, GA, March 2002.
91. Ohman EM, Harrington RA, Cannon CP *et al.* Intravenous thrombolysis in acute myocardial infarction. *Chest* 2001; **119**(Suppl.):253S–77S.
92. Lefer AM, Campbell B, Scalia R, Lefer DJ. Synergism between platelets and neutrophils in provoking cardiac dysfunction after ischemia and reperfusion: role of selectins. *Circulation* 1998;**98**:1322–8.
93. Ott I, Malcouvier V, Schomig A, Neumann FJ. Proteolysis of tissue factor pathway inhibitor-1 by thrombolysis in acute myocardial infarction. *Circulation* 2002;**105**:279–81.
94. The Continuous Infusion Versus Double-Bolus Administra-tion of Alteplase (COBALT) Investigators. A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction. *N Engl J Med* 1997;**337**:1124–30.
95. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;**337**:1118–23.
96. Lincoff AM. One-year follow-up of the GUSTO-V trial. Proceedings of the Late Breaking Clinical Trials Session, XIVth World Congress of Cardiology. Sydney, Australia; May 2002.

34 Pain relief, general management, and other adjunctive treatments

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The prognosis of patients admitted to hospital with acute myocardial infarction (AMI) has improved greatly since the introduction of reperfusion therapies into clinical practice. Several trials testing different fibrinolytic agents, aspirin, and more recently, primary PTCA, have shown that mortality can be reduced by 20–30% when these therapies are begun in the first few hours after the onset of symptoms of AMI. The favorable effects were proportional to the patency rates obtained. Although there is no objective evidence for mortality reduction, pain relief, oxygen, bed rest, and adjunctive therapies should be considered to reduce clinical symptoms and possibly improve prognosis.

Pain relief

The relief of pain is a priority in patients with AMI, not only for humane reasons, but also because pain activates the sympathetic nervous system increasing cardiac work and myocardial oxygen consumption **Grade A1b**. Two approaches are used:

- reduction of ischemia
- direct analgesia.

Nitroglycerin by the sublingual route or by IV infusion is the most commonly used drug to reduce pain due to ischemia (see the section on Nitrates below). A double-blind randomized trial on 69 patients[1] showed that inhaled nitrous oxide can decrease pain in the absence of hemodynamic changes or other major adverse events. Few controlled data are available, so the recommendations are based mainly on empiricism and personal expertise **Grade C**.

Among direct analgesics, morphine is the drug of choice, while meperidine and pentazocine can be substituted in patients with documented hypersensitivity to morphine. Morphine, besides its analgesic effect, has useful hemodynamic actions, including peripheral vasodilation without a decrease of left ventricular (LV) filling pressure. This action, together with central reduction of tachypnea, can be particularly useful in patients with pulmonary edema.[2–5]

Effective analgesia should not be delayed because of the fear of masking the effects of anti-ischemic therapy with recommended agents – fibrinolytic agents, β blockers, aspirin, nitrates. Morphine is given at doses of 4–8 mg IV and repeated every 5–15 minutes in doses of 2–8 mg until pain is relieved. Morphine also reduces anxiety, thereby decreasing metabolic demands of the heart during the early critical phase. The decrease in heart rate resulting from the reduction of sympathetic tone and the vagomimetic action of morphine contributes to the reduction of anxiety. Usually opioids are sufficient and tranquillizers are not needed.

Adverse reactions to morphine such as severe vomiting, hypotension, and respiratory depression may limit its administration. Hypotension (systolic blood pressure <100 mmHg) can be minimized by keeping the patient supine with elevated lower extremities. In the case of excessive bradycardia, atropine may be administered IV (0·5–1·5 mg). Depression of respiration seldom occurs and can be treated with intravenous naloxone (0·1–0·2 mg, repeated after 15 minutes if necessary). Nausea and vomiting, if severe or recurrent, may be treated with a phenothiazine.

The widespread use of reperfusion therapy early after AMI has decreased the intensity and duration of pain, which is largely due to ongoing cardiac ischemia. The additional use of IV β blockers[6,7] further decreases the severity of pain by reducing cardiac work.

New approaches to analgesia after AMI include synthetic and semisynthetic narcotics like fentanyl and sufentanyl and thoracic epidural anesthesia, but clinical experience is too limited to recommend regimens and modalities.

General management

Oxygen

Grade B Experimental studies have shown that breathing oxygen can decrease myocardial injury;[8] moreover, in patients with AMI the administration of oxygen reduced ST segment elevation.[9] It is assumed that oxygen breathing might improve the ventilation/perfusion mismatch which may be seen in AMI patients. Arterial P_{O_2} is reduced for about 48 hours in many uncomplicated cases of AMI.[10]

There are no objective randomized trials on the benefit of oxygen breathing after AMI. However, in the presence of severe hypoxemia oxygen is recommended, while in uncomplicated cases its use should probably be limited to the first day or less. **Grade C**

Oxygen therapy is indicated if monitored oxygen saturation is lower than 90%. In complicated AMI, with severe heart failure, pulmonary edema or mechanical complications, supplemental oxygen is not sufficient and continuous positive pressure breathing or tracheal intubation with mechanical ventilation are sometimes required.[11] **Grade C**

Excessive oxygen can cause systemic vasoconstriction with a consequent increase in cardiac workload, an important consideration in uncomplicated patients.

Bed rest

Bed rest has been traditionally advised for patients with AMI on the assumption that it would decrease cardiac workload. However, it is now recognized that the intensive use of recommended treatments – fibrinolysis, IV β blockade, aspirin – allows a much shorter stay in bed for AMI patients. **Grade B** This may decrease the risk of thromboembolism and help to prevent the adverse effects of deconditioning.[12]

Prophylactic use of lidocaine (lignocaine)

Grade A The observation that life-threatening arrhythmias occur within the first 24–48 hours of onset of AMI in a substantial proportion of patients led to the hypothesis that the prophylactic administration of lidocaine could prevent or reduce the incidence of ventricular fibrillation and resulting early mortality.[13]

However, an overview of 14 controlled trials testing the effects of prophylactic lidocaine (administered by the IM or IV route) on a total of 9155 patients confirmed a significant reduction of 35% in the rate of ventricular fibrillation, but a strong trend to an increase of 38% in early mortality (OR 1·38, 95% CI 0·98–1·95).[14] The increase in mortality appeared to be caused by bradyarrhythmias, advanced atrioventricular

Table 34.1 Other adjunctive therapies: summary of evidence

Therapies	Study	*n*	Follow up duration	Mortality (%)		*P* value	NNT
				Treated	Control		
β blockers							
ISIS-1[19]	LSRCT	16027	7 days	3·9	4·6	0·04	143
Sleight *et al.*[18]	OV	27536	7 days	3·7	4·3	0·03	167
CAPRICORN[23]	LSRCT	1959	1.3 years	12	15	0·03	34
ACE inhibitors							
Early unselected strategy							
GISSI-3[34]	LSRCT	19394	42 days	6·4	7·2	0·03	125
ISIS-4[35]	LSRCT	58050	35 days	7·2	7·7	0·02	200
ACE-i MICG[37]	OV	98469	30 days	7·1	7·6	0·004	200
Late selected strategy							
SAVE[38]	LSRCT	2231	42 months (mean)	20·4	24·6	0·019	24
AIRE[39]	LSRCT	2006	15 months (mean)	17·0	23·0	0·002	17
TRACE[40]	LSRCT	1749		34·7	62·3	0·001	13
Nitrates							
Yusuf *et al.*[55]	OV	3041	Inhospital	13·3	18·9	0·002	18
GISSI-3[34]	LSRCT	19394	42 days	6·5	6·9	NS	–
ISIS-4[35]	LSRCT	58050	35 days	7·3	7·5	NS	–
Overview[35]	OV	81908	35 days	7·4	7·7	0·03	333
Calcium antagonists							
Teo *et al.*[62]	OV	20342	–	9·6	9·3	NS	–
Magnesium							
Teo *et al.*[67]	OV	1301	Inhospital	3·8	8·2	0·001	23
LIMIT-2[68]	LSRCT	2316	28 days	7·8	10·4	0·04	42
ISIS-4[35]	LSRCT	58050	35 days	7·6	7·2	NS	–
Overview[35]	OV	61860	35 days	7·6	7·5	NS	–

Abbreviations: LSRCT, large-scale randomized clinical trials; NNT, number of patients needed to treat to save one life; NS, non-significant; OV, overview

block, and asystole. In view of these findings, prophylactic lidocaine is no longer considered as a standard treatment in patients with AMI, but is reserved for those patients who have already experienced ventricular fibrillation. **Grade A**

Other adjunctive treatments (Table 34.1)

We will now discuss adjunctive drug therapy with β blockers, ACE inhibitors, nitrates, magnesium, and calcium-antagonists. The results of published randomized trials which were of adequate size to show reliable data in terms of mortality, together with overviews of the data, will be summarized. We will also indicate areas of doubt.

Specific therapy

β Blockers

Rationale

Early after AMI, activation of the sympathetic nervous system occurs. β Blockers reduce oxygen demand by lowering heart rate and blood pressure, and decreasing myocardial wall stress, thereby limiting infarct size, the incidence of cardiac rupture, and improving ventricular function and mortality.[15] By their β adrenergic antagonist properties, they can also prevent the life-threatening ventricular arrhythmias related to the increased adrenergic activity occurring in the first hours after the onset of AMI.[16]

Evidence from trials and overviews of early IV β blockade

Studies testing the effects of early IV β blockade on the mortality of patients with AMI show consistent results.[17] Available data on more than 27 000 patients from 27 trials show that the mortality rate of the patients allocated to the active treatment was significantly reduced by about 14% in comparison with placebo-allocated patients (from 4·3% to 3·7%; in absolute terms, six lives saved per 1000 patients treated with β blockers).[18] The largest study testing this treatment, the ISIS-1 trial, showed that the mortality reduction by atenolol treatment in patients with AMI was concentrated in the first day or two from the onset of AMI symptoms.[19] Further, this study suggested that reduction in cardiac rupture and cardiac arrest were the most notable changes in early death associated with β blocker therapy.[20] These observations may be considered as the rationale for the combined use of β blockers and fibrinolytics, which are both known to reduce mortality. In particular, in the first few days from the onset of AMI, β blockers may reduce cardiac rupture, the incidence of which may be increased by fibrinolytic induced hemorrhage of infarcted myocardium.[21,22] However, β blocker trials in AMI were conducted mostly during the 1970s and 1980s, when no fibrinolysis or primary angioplasty was performed, and adjunctive therapy was characterized by much less use of aspirin and no ACE inhibitors. Further, study populations were mostly at lower risk and patients with heart failure were usually excluded. For these reasons, the CAPRICORN trial was planned with the aim to evaluate whether long-term treatment with carvedilol (titrated up to 25 mg ×2/day) could reduce all-cause mortality in postinfarction patients (from 3 to 21 days from symptom onset) with an LV ejection fraction ⩽40% and who were receiving an ACE inhibitor for ≥48 hours.[23] All-cause mortality was reduced from 15% in the placebo group and to 12% in the carvedilol group (23% relative reduction), while the combined end point of all-cause deaths plus CV hospitalizations was not modified by the active treatment.

Recommendations

All patients with AMI, in the absence of specific contraindications, should be treated with a β blocker within 24 hours from the onset of symptoms and treatment should be continued for at least 2 years. **Grade A** Clear contraindications are pulmonary edema, asthma, hypotension, bradycardia, or advanced atrioventricular block. Even in the absence of trials of adequate size testing specifically the effects of the combination of a β blocker and a fibrinolytic, pathophysiologic premises, observational data, and the few controlled studies suggest that this treatment should be considered in association with reperfusion treatment with fibrinolysis. In the GISSI-2 trial, IV atenolol was used in conjunction with fibrinolytics in 48% of the patients.

Lack of randomized trials of early β blockade in the era of reperfusion

With the exception of the recently published CAPRICORN trial that included patients with LV dysfunction some days after AMI, the trials testing the early effects on mortality of β blockers in all-comers with AMI were conducted in the early 1980s, before the widespread use of reperfusion therapy. Trials formally testing the effects of the combination of a β blocker and a fibrinolytic are few and underpowered to provide reliable data in terms of mortality reduction. The only data available are from the TIMI-2B trial, in which 1434 patients, all treated with tPA and aspirin, were randomized to receive immediate or delayed (6–8 days) oral metoprolol.[24] Total mortality rate at 6 and 42 days was not significantly decreased by the immediate treatment, but the number of deaths was fewer, and the rate of non-fatal re-infarction was reduced in the group receiving immediate metoprolol.

More recently, data from the National Registry of Myocardial Infarction 2 showed that immediate β blocker administration in patients with AMI treated with tPA

reduces the occurrence of intracranial hemorrhage. Among patients receiving tPA, the incidence of intracranial hemorrhage was 0·7% (158/23 749) in patients receiving β blockers and 1·0% (384/3658) in patients not receiving β blockers ($P < 0·001$).[25] Multivariate analysis showed that immediate β blocker use was associated with a 31% reduction in the rate of intracranial hemorrhage. No other drugs given within the first 24 hours were associated with a reduction in the rate of intracranial hemorrhage.

Long-term use

The effects of β blocker therapy started after the acute phase of MI (5–28 days from the onset of symptoms) have been tested among more than 35 000 patients not receiving a reperfusion therapy in several placebo-controlled trials.[26] Overall, the long-term composite outcome of mortality and non-fatal infarction was reduced by 20–25%. **Grade A**

Timolol, metoprolol, and propranolol were the most extensively studied drugs.[27–29] In the Norwegian Multicenter Study,[27] patients allocated to timolol showed a 39% mortality reduction and a 28% reduction of re-infarction. The initial benefit persisted for at least 72 months in the patients who continued timolol treatment after trial termination. Similar results have been obtained by the Beta-Blocker Heart Attack Trial (BHAT),[28] in which 3837 patients were allocated to propranolol or placebo. After 25 months of treatment overall mortality was reduced by 28%. Subgroup analysis showed that the beneficial effects of β blockers were apparent among the various subgroups, but the magnitude of the benefit was greater in high-risk patients (those with large or anterior AMI or with signs or symptoms of moderate left ventricular dysfunction). This subgroup analysis of the BHAT trial has been recently confirmed by the results of the CAPRICORN trial, which showed a significant mortality reduction in post-AMI patients with LV dysfunction treated with carvedilol.[23]

Definite contraindications to β blocker therapy are pulmonary edema, asthma, severe hypotension, bradycardia, or advanced atrioventricular block. Evidence from trials and overviews suggests that all patients with AMI who do not have clear contraindications should be treated with intravenous β blockers within 24 hours from the onset of symptoms. If tolerated, the treatment should be continued for at least 2–3 years, and perhaps longer. **Grade A**
A debate is still open about whether β blockers should be prescribed to all patients without contraindications or whether they should be given only to the patients at moderate to high risk who have the most to gain from a long-term treatment.

Despite the clear evidence of benefit, observational studies showed that in clinical practice β blockers are generally underused, only 36–42% of patients receiving a β blocker at discharge.[30]

ACE inhibitors

Rationale

The rationale behind this strategy is based mainly on the fact that activation of the renin–angiotensin system occurs during the very early phase of MI, with deleterious consequences, including an increase of peripheral resistance and heart rate, decrease of coronary perfusion, and alteration in endogenous fibrinolytic activity.[31,32]

Evidence from trials and overviews

After the disappointing results of the CONSENSUS-2 trial,[33] which did not show a benefit from enalapril treatment, the results of GISSI-3 and ISIS-4 studies were published.[34,35] In the GISSI-3 trial, 6 week total mortality was significantly lower in the patients treated with lisinopril: 6 week lisinopril treatment significantly reduced mortality from 7·2% to 6·4% (in absolute terms eight lives saved per 1000 treated patients).[34]

The favorable results on mortality shown by the GISSI-3 study have been confirmed by the larger ISIS-4 trial. During the first 5 weeks there were 2088 (7·19%) deaths recorded among 29 028 captopril-allocated patients compared with 2231 (7·69%) among 29 022 patients allocated placebo.[35] This 7% relative reduction in total mortality was statistically significant ($P = 0·02$) and corresponded in absolute terms to five fewer deaths per 1000 patients treated with captopril for 1 month. The reduction in total mortality shown by CCS-1[36] was similar to that demonstrated by the larger GISSI-3 and ISIS-4 trials, but statistical significance was not achieved, presumably because of inadequate sample size.

An overview of the trials testing an early unselected approach with ACE inhibitors in 98 496 patients with AMI showed that immediate treatment is safe, well tolerated and that it produces a small, but significant reduction of 30 day mortality.[37] This benefit is quantifiable as about five extra lives saved for every 1000 patients treated with ACE inhibitors early after the onset of AMI.

With respect to the safety profile, persistent hypotension and renal dysfunction were (as expected) reported significantly more often in the patients treated with ACE inhibitors than in corresponding controls.

The overview also confirmed the important benefit achievable with early ACE inhibitor treatment. Of the total 239 lives saved by early ACE inhibitor treatment, 200 were saved in the first week after AMI.

The "selective" strategy of starting ACE inhibitors some days after AMI only in patients with clinical heart failure and/or objective evidence of LV dysfunction was tested in three trials (SAVE, AIRE, TRACE), involving about 6000 patients overall.[38–40] These trials consistently showed that long-term ACE inhibitor treatment in this selected population of patients was associated with a significant reduction of mortality. **Grade A**

Controversy: aspirin and ACE inhibitors

It has been proven that part of the hypotensive/unloading effect of ACE inhibitors is attributable to increased synthesis of vasodilatory prostaglandins such as PGE_2.[41] It has been shown that the concomitant administration of salicylate reduces the effectiveness of ACE inhibitors in patients with congestive heart failure.[42,43] However, the appropriateness of extrapolating these data to post-AMI patients in clinical practice is questionable since other studies have yielded conflicting results on the interaction between ACE inhibitor and aspirin.[44,45] In relatively unselected AMI patients enrolled in the GISSI-3 trial there was a beneficial effect from ACE inhibitors irrespective of aspirin use.[46] The GISSI-3 findings have been confirmed by the overview of the individual data of 98 496 patients enrolled in trials involving more than 1000 patients randomly allocated to receive ACE inhibitors or control starting in the acute phase of AMI. ACE inhibitor treatment was associated with a similar proportional reduction in 30 day mortality among the 86 484 patients who were taking aspirin (6%) and among the 10 228 patients who were not (10%).[47] The lack of negative interaction between aspirin and ACE inhibitors has also been reported in the overview of 12 763 AMI patients with LV dysfunction or heart failure.[48]

In conclusion, it seems that the pharmacologic interaction between salicylates and ACE inhibitors is devoid of major clinical relevance in the setting of AMI, both in terms of reduction of the unloading effect of ACE inhibitors and in terms of adverse effects on renal function. Therefore in the absence of adequate data from randomized controlled trials (RCTs), both ACE inhibitors and aspirin may be safely administered in the early phase of AMI. Since patients with left ventricular (LV) dysfunction have a mortality rate of about 50% if they experience a new infarction, prevention with aspirin should not be abandoned on the basis of inadequate data. The lack of negative interaction between aspirin and ramipril in the prevention of cardiovascular events, recently shown by the HOPE trial,[49] further supports this conclusion.

Recommendations

ACE inhibitor treatment should be started during the first day following AMI in most patients after timely and careful observation of the patient's hemodynamic and clinical status, and after administration of routinely recommended treatments (fibrinolysis, aspirin, and β blockers). **Grade A** If echocardiography shortly before discharge shows LV dysfunction, the treatment should be continued for a long period of time. In the patients showing neither clinical symptoms nor objective evidence of LV dysfunction, the treatment can be stopped and ventricular function re-evaluated after an appropriate time interval. **Grade A** These recommendations derive from the results of trials testing ACE inhibitors in patients with a recent AMI. More recently, the results of the HOPE trial have been published.[49] The HOPE trial tested the effects of ramipril versus placebo in nearly 9000 patients at increased risk of cardiovascular disease, defined as a history of MI, angina, cerebrovascular or peripheral arterial disease. People with diabetes were also included, even in the absence of a previous cardiovascular event. The trial showed a significant 22% reduction of a composite measure of MI, stroke, and death from cardiovascular causes. The HOPE findings indicate that virtually all patients with a history of cardiovascular disease should be treated with ACE inhibitors, and not just those who after an AMI have signs or symptoms of heart failure. **Grade A** The PEACE and EUROPA trials, still ongoing, will provide further data from such patients.[50]

The main contraindications to early ACE inhibitor treatment are hypotension, bilateral renal artery stenosis, severe renal failure, or a history of cough or angioedema attributed to previous treatment with ACE inhibitors. Caution is needed in patients previously receiving high-dose diuretic (>50 mg furosemide/day) therapy.

Nitrates

Rationale

Experimental and clinical studies showed that nitrates can reduce oxygen demand and myocardial wall stress during AMI by reducing pre- and afterload.[51] Further, nitrates can increase coronary blood supply to the ischemic muscle by reducing coronary vasospasm.[52] These favorable effects of reduced infarct size and improved LV function have been demonstrated in both animals and humans.[53,54]

Evidence from trials and overviews

Controlled clinical trials and overviews provide conflicting results. Yusuf *et al* carried out a meta-analysis of seven small trials testing IV nitroglycerin and three trials testing IV nitroprusside. Overall, the results on 2041 patients showed that nitrate treatment reduced mortality by about 35%.[55]

More recently, the effects of different nitrate treatments in patients with AMI has been tested in two large-scale mortality trials enrolling more than 80 000 patients, receiving currently recommended concomitant therapies (90% received aspirin and about 70% fibrinolysis).[35] Both trials showed that routine nitrate use does not produce an improvement in survival, either in the total population of patients with AMI or in the subgroups with different risks of death. A large number of patients allocated to the control groups in these trials received out-of-protocol nitrate treatment because of a specific indication (pain, angina, heart failure, hypertension), possibly obscuring a true benefit in

terms of mortality reduction. Accordingly, the ISIS-4 investigators analyzed the effects of nitrates in the subgroup of patients not receiving out-of-protocol nitrate treatment. The results of this subanalysis confirmed the main results of the study.[35]

A further trial, ESPRIM, of the nitric oxide donor molsidomine also failed to show any mortality benefit in AMI patients.[56] The overview of all existing data (the first 10 small trials plus the two recent large scale studies) confirms the negative results in terms of mortality reduction.[35]

Recommendations

Grade A Nitrates are not a recommended treatment for all patients with AMI. However, nitrates are confirmed to be well tolerated even in the context of the other treatments (β blockers, aspirin, fibrinolysis, ACE inhibitors), suggesting that their use, limited to the patients with specific indications such as angina or pump failure, is safe and likely to be beneficial in the treatment of ischemic chest pain and pump failure. **Grade A** Definite data on the short-term mortality benefit of IV nitroglycerin started in the first 24 hours after the beginning of AMI symptoms are not available.

Unclear interaction with ACE inhibitors

The results of the GISSI-3 trial suggest that nitrates can produce some additive beneficial effect when used in combination with ACE inhibitors but this was not seen in ISIS-4. Additional trials should be conducted to confirm or reject this hypothesis.[34,35]

Calcium-channel blockers

Rationale

Calcium-channel blockers can reduce oxygen demand by lowering blood pressure and reducing contractility;[57] verapamil and diltiazem also reduce heart rate.[58] These mechanisms could be beneficial in patients during AMI.

Evidence from trials and overviews

Trials testing nifedipine at different dosages either in the acute phase of MI or after discharge showed a non-significant increase of mortality.[59] Controlled clinical trials testing calcium-channel blockers other than dihydropyridines, such as diltiazem or verapamil, have also found no significant reduction of mortality. However, the DAVIT-2 trial did show a 20% reduction of the combined end point of cardiovascular mortality and re-infarction.[60] Similarly, the largest trial testing diltiazem showed a 23% reduction of deaths from cardiac causes and re-infarction in the subgroup of patients without signs of pulmonary congestion, while in the subgroup of patients with pulmonary congestion a 41% increase of these events was observed.[61] An overview of the 24 trials testing any kind of calcium-channel blocker in patients with AMI showed a non-significant increase of mortality of about 4%.[62]

Recommendations

Grade A Since individual trials and overviews revealed no statistically significant evidence of harm or benefit in terms of mortality reduction, these drugs are not recommended as standard therapy in patients in the acute phase of MI. Verapamil or diltiazem may be useful after AMI in patients intolerant of β blockade. Despite the consistent negative results of trials and overviews, the rate of use of calcium-channel blockers remains high.[30,63]

Newer drugs

Few data are available concerning the effects either of long-acting nifedipine or of newer, more selective dihydropyridines, such as felodipine or amlodipine. New trials of these drugs are planned or under way.

Magnesium

Rationale

In experimental models of AMI, high plasma levels of magnesium can prevent extensive myocardial damage, possibly through inhibition of the inward current of calcium in ischemic cardiac cells, and the reduction of coronary tone.[64,65] Infusion of magnesium in experimental models of AMI can increase the threshold for malignant arrhythmias, reducing the occurrence of ventricular fibrillation.[66] In humans, high plasma levels of magnesium reduce peripheral vascular resistance and increase cardiac output without affecting myocardial oxygen consumption. Thus, infusions of magnesium started early during AMI could theoretically reduce infarct size, prevent life-threatening arrhythmias and improve survival.

Evidence from trials and overviews

Conflicting results have been provided by the trials in which IV infusion of magnesium has been tested. A first overview by Teo *et al* of seven trials among about 1300 patients showed that mortality was reduced by 58% (from 8·2% to 3·8%) by an early intravenous infusion of magnesium.[67] The greatest part of the benefit was due to the reduction of life-threatening ventricular arrhythmias. These favorable data received further support from a large single center study, LIMIT-2, in which 2316 patients were randomized to receive IV magnesium or placebo.[68] This study showed that

the 28 day mortality rate was significantly reduced by 24% ($P = 0{\cdot}04$) (but with a lower confidence interval near zero). No difference was observed in terms of ventricular arrhythmias, but surprisingly a reduction in clinical heart failure was observed. More recently the results of the ISIS-4 trial on more than 58 000 patients did not confirm that IV magnesium can reduce mortality.[35] As expected, the current overview of all the existing data is dominated by the results of ISIS-4.[35]

Recommendations

Intravenous magnesium cannot be recommended for routine use for patients with AMI. **Grade A** Its use should be limited to the patients with specific indications (that is, patients with ventricular arrhythmias and prolonged QT interval, or those with high blood pressure not controlled by usual therapy).

A new trial

Experimental studies suggested in animal models that magnesium is effective only if administered before fibrinolysis, thereby preventing reperfusion injury.[69,70] This hypothesis is supported by animal models of AMI and by the LIMIT-2 trial, which showed a reduction of the cases of heart failure after magnesium infusion.

Even though the ISIS-4 trial showed that magnesium treatment was not effective in any of the studied subgroups of patients, including those treated with fibrinolysis within 6 hours from the onset of symptoms, the possibility that magnesium treatment can limit reperfusion injury after recanalization therapy has not been formally tested. Because of this disparity between ISIS-4 and LIMIT-2, a further trial (MAGIC) is ongoing in selected patients.

Other adjunctive therapies in search of evidence

Adenosine

The excess of mortality in the day after fibrinolytic therapy may be, at least in part, attributed to reperfusion injury. Adenosine has been shown to exert a cardioprotective action in animal studies and in small-scale clinical trials. In particular, adenosine reduced infarct size and improved LV function in animal models of reperfusion injury.

In the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial, among patients receiving IV fibrinolytic therapy within 6 hours from symptom onset, an IV infusion of adenosine reduced infarct size by 33% compared to placebo ($P = 0{\cdot}085$). Infarct size was significantly reduced by 67% ($P = 0{\cdot}014$) in patients with anterior MI, while it had no effect in those with non-anterior MI. The effect of adenosine on final infarct size appeared to be independent of the fibrinolytic (alteplase or streptokinase) and of lidocaine use.[71] Based on these promising results obtained in 236 patients, a large-scale trial, AMISTAD II, was conducted to assess the effect of two doses of adenosine versus placebo on mortality and heart failure over 6 months after MI. Although the overall analysis did not show significant improvement with adenosine versus placebo, the higher dose group showed a significant reduction in infarct size and a trend in event reduction (American College of Cardiology, 2002).

Inhibition of leukocyte adhesion

Inflammation plays a role in determining the extent of myocardial damage after ischemia and reperfusion. Anti-inflammatory treatments have yielded contrasting results in animal models of MI, but have never been proven beneficial in humans. Specific inhibition of leukocyte adhesion reduced cardiac ischemia-reperfusion injury in animals. In the Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI), 394 patients with signs and symptoms of AMI were randomized within 12 hours of symptom onset to two doses of IV bolus of a monoclonal antibody to the CD18 subunit of the β2 integrin adhesion receptors (rhu MAB CD18) or placebo. The MAB CD18 was well tolerated, but ineffective either in increasing 90 minute TIMI grade 3 flow or in decreasing MI size.[72]

Along the same line, 420 patients with TIMI flow 0 or 1 after MI were randomized to two doses of LeukArrest or placebo in the HALT-MI trial. LeukArrest is a human monoclonal antibody which binds all four integrin receptors on leukocytes. LeukArrest did not reduce infarct size or clinical and adverse event rates. The agent appeared well tolerated, except for a significant increase in the rate of major infections.[73]

Metabolic interventions

The old concept of metabolic protection of the ischemic myocardium has been tested in a randomized open trial on 407 patients with suspected MI, the ECLA Glucose-Insulin-Potassium (GIK) trial.[74] Patients were randomized to two doses of GIK or to control within 24 hours from symptom onset. Overall mortality and morbidity reduction by GIK did not reach statistical significance. However, the reduction in mortality was significant in patients who received reperfusion therapy. GIK appeared to be well tolerated even if volumes of the order of 2–3 liters had to be infused over 24 hours. A mortality trial is being conducted to verify the benefit of this cheap intervention in AMI.

Ischemia/reperfusion damage is due partly to the Na^+/H^+ exchange system. Animal experiments and a pilot study in patients suggested that inhibitors of Na^+/H^+ exchanger, amiloride derivatives (cariporide, eniporide) exerted cardioprotective effects. Two recent placebo-controlled trial have shown neutral results of NHE inhibitors versus placebo.[75,76]

In the GUARd During Ischemia Against Necrosis (GUARDIAN) trial 11 590 patients with unstable angina or non-ST-elevation MI were randomized to cariporide or placebo and followed for 36 days. No difference between cariporide and placebo was documented on the primary end point of death or MI.[75] In the Evaluation of the Safety and Cardioprotective Effects of Eniporide in AMI (ESCAMI) trial, 1389 patients with ST-elevation MI undergoing reperfusion treatments were studied. Eniporide administered before reperfusion neither reduced infarct size (the primary end point), nor improved clinical outcome.[76]

Nicorandil, has been proposed for several years with indications ranging from stable effort angina to MI. In an open study, 81 patients with a first anterior MI were randomized to control or nicorandil started IV before PTCA. Nicorandil plus PTCA improved clinical outcome and left-ventricular functional recovery in respect to PTCA alone.[77] However, the number of patients in the study was too small, even for a pilot trial, to draw any conclusion.

Conclusions

The therapeutic approaches discussed in the chapter can provide benefits only to patients who survive long enough to reach a monitored bed. The potential reduction of mortality obtainable with the use of evidence-based therapies is applicable to only about half of the population of patients suffering an AMI.[78]

Besides research efforts aimed at designing new strategies to further improve survival, the challenges are several:

- to broaden the correct use of evidence-based treatments for the patients reaching the hospital;
- to apply these or new treatments to the subgroup of patients generally excluded from randomized clinical trials (elderly patients, patients with comorbidities, etc.);
- to reduce the number of patients who die before reaching the hospital.

Appendix: long-term use of aspirin after the acute phase of myocardial infarction

Grade A Besides the favorable effects in terms of mortality reduction when used in the first 24 hours from the onset of symptoms of AMI,[79] long-term use of aspirin in the postinfarction period also results in a significant reduction of morbidity and mortality.

The Antiplatelet Trialists' Collaborative Group reviewed all the long-term trials of antiplatelet agents in secondary prevention.[80] Six randomized, placebo-controlled trials tested the effects of aspirin started between 1 week and 7 years after the initial infarct. Vascular mortality, non-fatal re-infarction and non-fatal stroke rates were significantly reduced respectively by 13%, 31%, and 42% among the patients allocated to aspirin in comparison with the placebo-allocated patients. The beneficial effects on major vascular events were apparent in all subgroups examined.

The overview also shows that, although other antiplatelet agents, such as dipyridamole or sulfinpyrazone, have been used in postinfarct patients, there is no evidence that they can be more efficacious than aspirin alone.

The benefits of aspirin were seen to be similar in the trials which evaluated doses from 160 mg to 1500 mg daily. These observations suggest that it is reasonable to recommend aspirin at 160–325 mg/day, starting early after the onset of symptoms of AMI and continuing for a long period of time (probably lifelong). **Grade A** A trial in patients with stable angina recently showed that lower doses of aspirin (75 mg/day) were associated with a significant reduction (34%) of non-fatal MI and sudden death.[81] These data suggest that lower doses of aspirin can be effective with fewer adverse effects.

References

1. Thompson PL, Lown B. Nitrous oxide as an analgesic in acute myocardial infarction. *JAMA* 1976;**235**:924–7.
2. Roth A, Keren G, Gluck A, Braun S, Laniado S. Comparison of nalbuphine hydrochloride versus morphine sulfate for acute myocardial infarction with elevated pulmonary artery wedge pressure. *Am J Cardiol* 1988;**62**:551–5.
3. Semenkovich CF, Jaffe AS. Adverse effects due to morphine sulfate. Challenge to previous clinical doctrine. *Am J Med* 1985;**79**:325–30.
4. Timmis AD, Rothman MT, Henderson MA, Geal PW, Chamberlain DA. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *BMJ* 1980;**280**: 980–2.
5. Nielsen JR, Pedersen KE, Dahlstrom CG *et al.* Analgesic treatment in acute myocardial infarction. A controlled clinical comparison of morphine, nicomorphine and pethidine. *Acta Med Scand* 1984;**215**:349–54.
6. Waagstein F, Hjalmarson A. Double blind study of the effect of cardioselective beta-blockade on chest pain in acute myocardial infarction. *Acta Med Scand* 1975;**587**:201–8.
7. Ramsdale DR, Faragher EB, Bennett DH *et al.* Ischemic pain relief in patients with acute myocardial infarction by intravenous atenolol. *Am Heart J* 1982;**103**:459–67.
8. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation* 1975;**52**:360–8.
9. Madias JE, Hood WB Jr. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. *Circulation* 1976;**53**(Suppl. I):I-198–200.
10. Fillmore SJ, Shapiro M, Killip T. Arterial oxygen tension in acute myocardial infarction: serial analysis of clinical state and blood gas changes. *Am Heart J* 1970;**79**:620–9.

11. Aubier M, Trippenbach T, Roussos C. Respiratory muscle fatigue during cardiogenic shock. *J Appl Physiol* 1981;**51**: 499–508.
12. Coats AJS, Adamopoulos S, Meyer TE, Conway J, Sleight P. Effects of physical training of chronic heart failure. *Lancet* 1990;**335**:63–6.
13. Lie KI, Wellens HJJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation* 1975;**52**:755–9.
14. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA* 1988;**260**:1910–16.
15. Yusuf S, Sleight P, Rossi PRF *et al.* Reduction in infarct size, arrhythmias, chest pain and morbidity by early intravenous beta-blockade in suspected acute myocardial infarction. *Circulation* 1983;**67**:32–41.
16. Rossi PRF, Yusuf S, Ramsdale D *et al.* Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction. *BMJ* 1983;**286**:506–10.
17. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;**27**:335–43.
18. Sleight P (for ISIS Study Group). Beta blockade early in acute myocardial infarction. *Am J Cardiol* 1987;**60**:6A–12A.
19. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction. ISIS-1. *Lancet* 1986;**ii**:57–66.
20. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. *Lancet* 1988;**i**:921–7.
21. Mauri F, DeBiase AM, Franzosi MD *et al.* GISSI: analisi delle cause di morte intraospedaliera. *G Ital Cardiol* 1987;**17**:37–44.
22. Honan MB, Harrell FE, Reimer KA *et al.* Cardiac rupture, mortality and the timing of thrombolytic therapy: a meta-analysis. *J Am Coll Cardiol* 1990;**16**:359–67.
23. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
24. Roberts R, Rogers WJ, Mueller HS *et al.* Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation* 1991;**83**:422–37.
25. Barron HV, Rundle AC, Gore JM, Gurwitz JH, Penney J, for the participants in the National Registry of Myocardial Infarction-2. Intracranial hemorrhage rates and effect of immediate beta-blocker use in patients with acute myocardial infarction treated with tissue plasminogen activator. *Am J Cardiol* 2000;**85**:294–8.
26. Yusuf S, Lessem J, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: an update of randomly allocated controlled trials. *J Hypertens* 1993;**11** (Suppl. 4):S61–73.
27. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**304**:801–7.
28. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;**247**:1707–14.
29. Hjalmarson A, Elmfeldt D, Herlitz J *et al.* Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. *Lancet* 1981;**ii**:823–7.
30. Rogers WJ, Bowlby LJ, Chandra NC *et al.* Treatment of myocardial infarction in the United States (1990 to 1993): observations from the National Registry of Myocardial Infarction. *Circulation* 1994;**90**:2103–14.
31. Liang CS, Gavras H, Black J, Sherman LG, Hood WB Jr. Renin-angiotensin system inhibition in acute myocardial infarction in dogs. Effects on systemic hemodynamics, myocardial blood flow, segmental myocardial function and infarct size. *Circulation* 1982;**66**:1249–55.
32. Ertl G, Kloner RA, Alexander RW, Braunwald E. Limitation of experimental infarct size by an angiotensin-converting enzyme inhibitor. *Circulation* 1982;**65**:40–8.
33. Swedberg K, Held P, Kjekshus J *et al.* CONSENSUS II Study Group. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. *N Engl J Med* 1992;**327**:678–84.
34. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;**343**:1115–22.
35. ISIS-4 Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**: 669–85.
36. Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995;**345**:686–7.
37. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998; **97**:2202–12.
38. Pfeffer MA, Braunwald E, Moyé LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial (SAVE). *N Engl J Med* 1992; **327**:669–77.
39. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–8.
40. The Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**: 1670–6.
41. Swartz SL, Williams GH, Hollenberg NK *et al.* Captopril-induced changes in prostaglandin production. Relationship to vascular responses in normal man. *J Clin Invest* 1980;**65**: 1257–64.

42.Hall D, Zeitler H, Rudolph W. Counteraction of the vasodilator effect of enalapril by aspirin in severe heart failure. *J Am Coll Cardiol* 1992;**20**:1549–55.
43.Pitt B, Yusuf S, for the SOLVD Investigators, University of Michigan Medical Center. Studies of left ventricular dysfunction (SOLVD): subgroup results (abstract). *J Am Coll Cardiol* 1992;**19**:215A.
44.Baur LHB, Schipperheyn JJ, van der Laarse A *et al.* Combining salicylate and enalapril in patients with coronary artery disease and heart failure. *Br Heart J* 1995; **73**:227–36.
45.Nguyen KN, Aursnes I, Kjeskshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997;**79**:115–19.
46.Latini R, Santoro E, Masson S *et al.*, for the GISSI-3 investigators. Aspirin does not interact with ACE inhibitors when both are given early after acute myocardial infarction. Results of the GISSI-3 Trial. *Heart Dis* 2000;**2**:185–90.
47.Latini R, Tognoni G, Maggioni AP *et al.*, on behalf of the Angiotensin-converting Enzyme Inhibitor Myocardial Infaction Collaborative Group. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin. Systematic overview of individual data from 96 712 randomized patients. *J Am Coll Cardiol* 2000;**35**:1801–7.
48.Flather MD, Yusuf S, Køber L *et al.*, for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;**355**:1575–81.
49.The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
50.Maggioni AP. Secondary prevention: improving outcomes following myocardial infarction. *Heart* 2000;**84**(Suppl.1):5–7.
51.Jugdutt BI, Becker LC, Hutchins GM *et al.* Effect of intravenous nitroglycerin on collateral blood flow and infarct size in the conscious dog. *Circulation* 1981;**63**:17–28.
52.Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. *N Engl J Med* 1987;**317**:1055–9.
53.Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarction size, expansion, and complications: effect of timing, dosage and infarct location. *Circulation* 1988;**78**:906–19.
54.Mahmarian JJ, Moye LA, Chinoy DA *et al.* Transdermal nitroglycerin patch therapy improves left ventricular function and prevents remodeling after acute myocardial infarction: results of a multicenter prospective randomized, double-blind, placebo-controlled trial. *Circulation* 1998;**97**:2017–24.
55.Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988;**i**: 1088–92.
56.The European Study of Prevention of Infarction with molsidomine (ESPRIM) Group. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. *Lancet* 1994;**344**:91–7.
57.Kloner RA, Braunwald E. Effects of calcium antagonists on infarcting myocardium. *Am J Cardiol* 1987;**59**:84–94B.
58.Opie LE, Buhler FR, Fleckenstein A *et al.* Working group on classification of calcium antagonists for cardiovascular disease. *Am J Cardiol* 1987;**60**:630–2.
59.Yusuf S, Furberg CD. Effects of calcium-channel blockers on survival after myocardial infarction. *Cardiovasc Drugs Ther* 1987;**1**:343–4.
60.The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II – DAVIT II). *Am J Cardiol* 1990;**66**:779–85.
61.The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;**319**:385–92.
62.Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA* 1993;**270**:1589–95.
63.Zuanetti G, Latini R, Avanzini F *et al.*, on behalf of the GISSI Investigators. Trends and determinants of calcium antagonist usage after acute myocardial infarction (the GISSI experience). *Am J Cardiol* 1996;**78**:153–7.
64.Vormann J, Fischer G, Classen HG, Thoni H. Influence of decreased and increased magnesium supply on the cardiotoxic effects of epinephrine in rats. *Arzneimittelforschung* 1983;**33**:205–10.
65.Turlapaty PDMV, Altura BM. Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science* 1980;**208**:198–200.
66.Watanabe Y, Dreifus LS. Electrophysiological effects of magnesium and its interactions with potassium. *Cardiovasc Res* 1972;**6**:79–88.
67.Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effect of intravenous magnesium in suspected acute myocardial infarction: overview of randomized trials. *BMJ* 1991;**303**:1499–503.
68.Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992;**339**:1553–8.
69.Herzog WR, Schlossberg ML, MacMurdy KS *et al.* Timing of magnesium therapy affects experimental infarct size. *Circulation* 1995;**92**:2622–6.
70.Christensen CA, Rieder MA, Silvestein EL, Gencheff NE. Magnesium sulfate reduces myocardial infarct size when administered before but not after coronary reperfusion in a canine model. *Circulation* 1995;**92**:2617–21.
71.Mahaffey KW, Puma JA, Barbagelata NA *et al.*, for the AMISTAD Investigators. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction. Results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction Study of Adenosine (AMISTAD) Trial. *J Am Coll Cardiol* 1999;**34**:1711–20.
72.Baran KW, Nguyen M, McKendall GR *et al.*, for the LIMIT AMI Investigators. Double-blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction.

Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) Study. *Circulation* 2001;**104**:2778–83.
73. Rother K. HALTing myocardial injury didn't work. *Heart Wire News* 1999; Nov.11.
74. Diaz R, Paolasso EA, Piegas LS *et al.*, on behalf of the ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. Metabolic modulation of acute myocardial infarction. The ECLA Glucose-Insulin-Potassium Pilot Trial. *Circulation* 1998; **98**:2227–34.
75. Théroux P, Chaitman BR, Danchin N *et al.*, for the GUARd During Ischemia Against Necrosis (GUARDIAN) Investigators. *Circulation* 2000;**102**:3032–8.
76. Zeymer U, Suryapranata H, Monassier JP *et al.*, for the ESCAMI Investigators. The Na^+/H^+ exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol* 2001;**38**:1644–50.
77. Ito H, Taniyama Y, Iwakura K *et al.* Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol* 1999;**33**:654–60.
78. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex difference in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment and 28-day case fatality of 3991 events in men and 1551 events in women. *Circulation* 1996;**93**:1981–92.
79. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**: 349–60.
80. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ* 1988;**296**:320–31.
81. Becker RC. Antiplatelet therapy in coronary heart disease: emerging strategies for the treatment and prevention of acute myocardial infarction. *Arch Pathol Lab Med* 1993;**117**:89–96.

35 Complications after myocardial infarction

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Introduction

Despite major changes in treatment and prevention, myocardial infarction (MI) remains a common and lethal condition. Recent statistical updates estimate that there are 7·3 million persons in the United States who have suffered a myocardial infarction, and each year there are 1·1 million new or recurrent coronary attacks, of whom 40% die.[1] Mechanical complications of myocardial infarction include acute and chronic heart failure, cardiogenic shock, ventricular aneurysm, right ventricular infarction and failure, mitral regurgitation due to papillary muscle dysfunction or rupture, rupture of the interventricular septum and rupture of the free wall of the left ventricle. Electrical complications include ventricular fibrillation, ventricular tachycardia, atrial fibrillation, and atrioventricular block. A common and important category of complication that is frequently neglected is the psychosocial and socioeconomic complications of MI.

Other chapters in this book cover the topics of left ventricular dysfunction and heart failure (Chapter 46) ventricular arrhythmias (Chapter 42) bradyarrhythmias (Chapter 74) and atrial fibrillation (Chapter 38–40). The major complications of MI, such as left ventricular (LV) dysfunction, heart failure or ventricular and atrial arrhythmias lend themselves to study with controlled clinical trials. However, for many of the acute complications of MI, clinical trials have not been performed, and clinical decision making must rely on evidence from other sources including uncontrolled trials, observational studies and inference from pathophysiologic data. The evidence base for managing the complications of MI will be discussed under the headings of clinical features and prognosis, and management.

Left ventricular dysfunction and failure

Clinical features and prognosis

Pathophysiology

Acute coronary occlusion with ST segment elevation (STEMI) affects the function of the left ventricle within seconds, even before irreversible myocardial damage has occurred.[2] Adverse remodeling of the ventricle can occur early in the course of myocardial infarction, and continues over the ensuing months and years, leading to an increase in end-diastolic and end-systolic volumes, an increase in the sphericity of the ventricle, and systolic bulging and thinning of the infarct zone, without necessarily any extension of the infarcted zone.[3] Results from autopsy studies suggested that MIs that involved greater than 40% of the left ventricle were usually fatal.[4] However, a more recent prospective study conducted in the reperfusion era showed that out of 16 patients with residual infarcts of >40%, and followed for 13 months, only one had persistent heart failure and subsequently died.[5] The likely explanation for this discrepancy lies in the inherent bias of autopsy studies and the improved management of post-MI patients in the reperfusion era. Extensive damage can occur as a consequence of one large infarction or multiple smaller ones. Non-ST elevation MI may also cause left ventricular dysfunction if there has been prior cumulative myocardial damage. Echocardiographic evidence from infarct survivors shows that up to 60–80% of the left ventricle may be akinetic or severely hypokinetic in those with a history of multiple infarctions.[6]

Prognostic markers based on left ventricular dysfunction

The extent of LV dysfunction is a strong predictor of short- and long-term prognosis after MI. The Killip and Kimball[7] classification stratifies MI patients from low to very high risk based upon clinical signs of heart failure. It remains a reasonably accurate indicator of short term survival. In patients undergoing primary PTCA, the inhospital mortality was 2·4%, 7% and 19% for class I, II and III, respectively and 6 month mortality was 4%, 10% and 28% for class I, II, and III, respectively.[8] The presence of left ventricular dysfunction as determined by Killip class may be a predictor of response to invasive coronary procedures in acute myocardial infarction.[9] The Forrester classification comprising four categories defined according to the presence or absence of pulmonary congestion and peripheral hypoperfusion requires measurement of the pulmonary artery pressure using a balloon flotation catheter.[10] Although this is safe in experienced hands, it has a recognized risk of adverse events, including ventricular tachyarrhythmias and pulmonary hemorrhage or infarction.[11]

In both postinfarction patients[12] and in a wider range of critically ill patients in intensive care units,[13] hemodynamic variables determined from right heart catheterization correlate strongly with a higher mortality even after adjusting for other prognostic variables. This association may be spurious, due to a failure to identify and adjust for all relevant variables. However, recent guidelines recommend the use of balloon flotation catheters only in severe or progressive CHF or pulmonary edema, cardiogenic shock or progressive hypotension or suspected mechanical complications of acute infarction – that is, ventricular septal defect (VSD), papillary muscle rupture, or pericardial tamponade.[11] The mechanism whereby right heart catheterization might increase mortality is uncertain.[14]

Late postinfarction mortality is also affected by the extent of left ventricular dysfunction. The presence of clinical signs of left ventricular failure is a strong indicator of a poor long-term prognosis.[15] In some patients, more detailed assessment is necessary, and the use of echocardiography or radionuclide assessment may provide information which cannot be obtained clinically.[16] Late postinfarction mortality was 3% in patients with an EF above 0·40, 12% when the EF was between 0·20 and 0·40, and 47% when it was below 0·20.[17] The measurement of left ventricular function adds incremental value to the clinical detection of left ventricular failure. Approximately two thirds of patients with an EF low enough to indicate a poor long-term prognosis for example, $<$0·40, have no radiological evidence of left ventricular failure.[18] The choice of modality for assessment of left ventricular function depends on local availability and expertise. The information obtained from assessing left ventricular function by echocardiography, radionuclide imaging or cardiac catheterization has been found to be of equivalent value in predicting 1 year prognosis.[19]

Biochemical markers

Biochemical markers of necrosis provide an index of the extent of left ventricular infarction which in turn is correlated with the extent of left ventricular dysfunction. Creatine kinase was shown in the prereperfusion era to predict short- and long-term prognosis.[20] The introduction of reperfusion into routine clinical practice has reduced the utility of CK or CK-MB to reflect the extent of left ventricular dysfunction because of early, direct release of the myocardial enzymes into the plasma during reperfusion and high, early peaking of the serum levels. The use of newer markers such as troponin is now widespread, and both troponin-I[21] and troponin-T[22] correlate well with prognosis, although their value in estimating infarct size is limited. Multivariate analysis of data from large clinical trials has provided sound evidence that prognosis can be predicted with accuracy using clinical information which is readily available during the assessment of the patient. Demographics (advanced age, lower weight), more extensive infarction (higher Killip class, lower blood pressure, faster heart rate, longer QRS duration), higher cardiac risk (smoking, hypertension, prior cerebrovascular disease), and arrhythmia were important predictors of death between 30 days and 1 year in 41 021 patients enrolled in the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) trial,[23] and in the GISSI trial.[24]

Management

Pharmacologic therapy

Since left ventricular function is a critical determinant of prognosis, there have been many attempts to limit the extent of left ventricular dysfunction during myocardial infarction. Pharmacologic attempts to achieve this after myocardial necrosis is well established have achieved limited success. Improvements in hemodynamic status have not translated to better outcomes. For example, furosemide has been shown to reduce elevated LV filling pressures without adversely affecting cardiac output,[25] but there is no evidence of improvement in outcomes with diuretic therapy in AMI. Nitrates have been shown to improve the hemodynamic status in and adverse remodeling post-AMI,[26] and nitroglycerin may increase collateral blood flow to the infarct zone and thus limit infarct size, particularly if heart rate is controlled.[27] The fact that remodeling begins soon after the onset of infarction is a justification for beginning intravenous nitroglycerin or an ACE inhibitor early, even when these drugs are not required to correct a hemodynamic abnormality. While preliminary meta-analysis of small trials of intravenous nitrates showed an apparent benefit on outcomes,[28] larger clinical trials have shown no benefit of nitrates in improving prognosis.[29,30]

In contrast to the neutral effects of nitrate vasodilators, the beneficial effects of angiotensin converting enzyme (ACE) inhibitors in the treatment of patients with left ventricular function complicating myocardial infarction have been striking. Eight large randomized, placebo-controlled trials have assessed the effect of an ACE inhibitor on mortality after MI.

ACE inhibitors unequivocally reduce mortality overall, and the benefit appears to be the greatest among patients with depressed LV function, overt heart failure, or anterior infarction.[31–38] Grade A1a

In a meta-analysis of data from all randomized trials involving more than 1000 patients in which ACE inhibitor treatment was started within 36 hours of onset of myocardial infarction, there were results available on 98 496 patients from four eligible trials.[39] Among patients allocated to ACE inhibitors there was a 7% (95% CI 2–11; $2P < 0{\cdot}004$) proportional reduction in early mortality, an

absolute reduction of 5 (SD 2) deaths per 1000 patients. While the relative benefit was similar in patients at different underlying risks, the absolute benefit was greatest in those patients with evidence of left ventricular dysfunction (that is, Killip class II to III, heart rate ≥100 bpm at entry) and in anterior MI. ACE inhibitor therapy also reduced the incidence of non-fatal manifestations of left ventricular dysfunction. During longer term follow up of patients enrolled in randomized controlled trials, ACE inhibitors have also been shown to be effective. In three long-term follow up trials involving 5966 postinfarction patients, mortality was significantly lower with ACE inhibitors than with placebo, odds ratio 0·74 (95% CI 0·66–0·83).[40] Whether low-risk postinfarction patients with normal EFs derive benefit from ACE inhibitors is still controversial. The AHA/ACC guidelines for acute myocardial infarction conclude that ACE inhibitors are supported by a class 1 recommendation for all patients with MI and LV ejection fraction less than 40%, or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from AMI.[11] The optimum timing of initiation of ACE inhibitor therapy has been studied in only a small number of direct comparative trials. In a meta-analysis of 845 patients receiving thrombolysis, ACE inhibitor treatment within 6 to 9 h after MI was compared with other usual therapy.[41] ACE inhibition could not be demonstrated to attenuate LV dilation on 3 month echocardiographic follow up. Three hundred and fifty-two patients with acute anterior myocardial infarction were randomized to early (1 to 14 days) or late (14 to 19 days) post-MI treatment with the angiotensin converting enzyme (ACE) inhibitor ramipril and were followed by echocardiography. Those receiving early ramipril had a greater improvement in ejection fraction, suggesting that such patients should be commenced on ACE inhibitor therapy early in their course of infarction.[42] In considering treatment for left ventricular dysfunction, the hemodynamic benefits need to be balanced against the possible adverse effect of extending the infarct size. In the only ACE inhibitor trial that did not show a mortality benefit, CONSENSUS-II, treatment was begun early with an intravenous ACE inhibitor.[31]

Inotropic agents

Inotropic agents are used widely in cardiogenic shock complicating myocardial infarction.

The choice of inotropic agents is dependent on the known pathophysiologic effects of the drugs rather than clinical trial evidence.[43] **Grade C5**

Digitalis may help the acute postinfarction patient with heart failure when the left ventricle is dilated and damaged, but use of this drug carries more risk than benefit when heart failure complicates a large infarction in a previously healthy ventricle.[44] Digoxin reduced the rate of hospitalization for heart failure, but did not alter total mortality, in a large randomized trial of patients with chronic heart failure, 70% of whom had ischemic heart disease as the primary cause.[45]

Reperfusion therapy

Attempts to prevent myocardial necrosis and subsequent left ventricular dysfunction, and the disappointing results of efforts to limit infarct size when myocardial necrosis is well advanced, have driven the so-called reperfusion era of treatment in myocardial infarction. However, the relationship between improvements in left ventricular function and prognosis after reperfusion therapy has been surprisingly difficult to demonstrate. Although some of the early studies demonstrated clear benefits on left ventricular function from coronary thrombolysis,[46,47] the evidence since then has been conflicting, with some groups showing a worse left ventricular function despite an improved prognosis. In a meta-analysis of ten studies enrolling 4088 patients treated with thrombolytic therapy versus control, only a modest improvement in left ventricular function was demonstrated after thrombolytic therapy.[48] By 4 days, mean LV ejection fraction was 53% versus 47% (thrombolytic *v* control therapy, $P < 0{\cdot}01$); by 10 to 28 days it was 54·1% and 51·5%, respectively. The reason for the discrepancy in the marked improvement in survival and the limited benefit on left ventricular function is not clear. Patients who have had coronary reperfusion after MI may have myocardium that is stunned[49] or even hibernating,[50] phenomena that may affect the assessment of ventricular function. Stunned myocardium has been successfully reperfused but has not regained its normal contractile function.

A study of 352 patients with anterior MI found that out of the 252 patients with abnormal LV function on day 1, 22% had complete and 36% had partial recovery of function by day 90.[51] This result highlights the potential for improvement in LV function over time due to recovery of stunned myocardium. Hibernating myocardium is underperfused and non-contractile, but is not infarcted and may gradually improve its function with revascularization. The degree of success in achieving coronary patency with thrombolysis is an obvious confounding factor.[52] The most recent analysis demonstrates that left ventricular function is improved by successful coronary reperfusion and that the previous inability to demonstrate this has been due to confounding by the following factors: the variable relationship between left ventricular function and prognosis (irrespective of reperfusion status), variable methods of measuring left ventricular function, the effects of hibernation and stunning on interpretation of left ventricular functional recovery, and the variable success in achieving coronary patency in the coronary reperfusion trials.[53]

Overall reperfusion therapy results in a modest improvement in systolic LV function. Grade A1c

Cardiogenic shock

Clinical features and prognosis

Cardiogenic shock is a syndrome characterized by hypotension and peripheral hypoperfusion, usually accompanied by high LV filling pressures. The common clinical manifestations of these hemodynamic derangements include mental obtundation or confusion, cold and clammy skin, and oliguria or anuria.[11] Cardiogenic shock is the commonest cause of inhospital mortality after MI.[54] When cardiogenic shock is not secondary to a correctable cause, such as arrhythmia, bradycardia, hypovolemia or a mechanical defect, short-term mortality is 80% or higher, depending upon the strictness of the definition. Despite the major improvements in treatment in the past two decades, the inhospital mortality in a recent international registry for patients with cardiogenic shock treated with modern therapy in the late 1990s was 66%.[55] Old age, diabetes, previous infarction and extensive infarction as assessed either by enzymatic or electrocardiographic criteria are factors commonly associated with cardiogenic shock.[54] A recent analysis of predictors of cardiogenic shock in patients treated with thrombolytic therapy showed that each decade increase in age increased the risk of cardiogenic shock by 47%.[56]

Management

Inotropic drugs have been subjected to detailed study and widespread use in cardiogenic shock, but no clearcut effect on mortality has been demonstrated.[57] Intra-aortic balloon pumping has been used to stabilize patients with cardiogenic shock; clearcut benefits on hemodynamic status and coronary blood flow have been shown, but benefits on survival, have not been shown; inhospital mortality remained at 83% despite the use of balloon pumping in a cooperative clinical trial.[58] Nevertheless, intra-aortic balloon pumping has a clear place in stabilizing the unstable cardiogenic shock patient for more definitive treatment such as coronary angioplasty or bypass surgery,[59] as has been demonstrated in a randomized trial in the setting of rescue angioplasty.[60] Newer methods of circulatory support have shown highly encouraging results,[61,62] but benefits on survival remain to be established.

Although the outcome of cardiogenic shock has been shown to be dependent on the patency of the infarct related artery, clinical trials of thrombolytic therapy have not shown a benefit in patients with established cardiogenic shock.[63] Alternative antithrombotic strategies may improve outcomes, but data is limited to observational studies.[64] There has been increased interest in alternative approaches to reperfusion in patients with cardiogenic shock. Observational studies and clinical trials suggest that an aggressive approach with early revascularization reduces the mortality of patients with cardiogenic shock after MI. For example, the 30 day mortality was 38% in 406 patients who underwent early angiography and were usually revascularized, most often with angioplasty, compared to 62% in the 1794 patients without early angiography in the GUSTO-1 trial.[65] A registry report has suggested that an aggressive approach with reperfusion therapy and intra-aortic balloon pulsation treatment of patients in cardiogenic shock due to predominant LV failure is associated with lower inhospital mortality rates than standard medical therapy.[66] This benefit persisted after adjustment for baseline differences (odds ratio 0·43; 95% CI 0·34–0·54; $P = 0·0001$). The use of early catheterization may influence the outcome by helping to direct therapy.[55] In a controlled clinical trial of an aggressive approach involving early catheterization with revascularization and intra-aortic balloon pumping, in cardiogenic shock patients (the SHOCK trial),[67] 87% of patients in the invasive arm underwent revascularization (surgical or percutaneous). There was a clear trend at 30 days towards reduced mortality in the invasive group compared with the medical therapy group (46·7% *v* 56·0%), however this difference did not reach statistical significance. There was an early hazard in the first 5 days after assignment to the invasive approach, which was possibly associated with procedure-related complications. However, after the first 5 days there was a survival benefit in favor of the revascularization group, which persisted at one year, when survival in the early revascularization group was 46·7% compared with 33·6% in those treated with early medical stabilization (relative risk for death: 0·7; 95% CI 0·54–0·95).[68]

Evidence from clinical trials supports invasive intervention in patients with cardiogenic shock post-MI. These patients should undergo coronary angiography with a view to coronary angioplasty, or in selected patients, coronary bypass surgery. Grade A1d

Right ventricular infarction and failure

Clinical features and prognosis

Right ventricular (RV) infarction typically occurs in association with inferior or posterior MI, as a consequence of total occlusion of the right coronary artery proximal to its marginal branches,[69] or of the proximal circumflex in patients with a dominant left coronary system. RV infarction was present in 54% of patients with inferior MI in one series, although clinical manifestations are usually evident in only 10–15%.[70] RV involvement is much less common in anterior infarction, with 13% being the highest incidence

reported.[71] Right ventricular involvement in inferior infarction has been reported to increase the mortality by fivefold. In one series of 200 consecutive cases,[72] the inhospital mortality in inferior MI complicated by RV infarction was 31%, compared to 6% when RV involvement was absent. RV dysfunction almost always resolves in survivors during the first few weeks. Some studies have shown that RV infarction is an independent predictor of long-term prognosis, while others have not demonstrated a difference in long-term mortality between patients with and without this complication.[69]

The clinical features of RV infarction complicating inferior MI include hypotension, an elevated jugular venous pressure and clear lung fields; however, the sensitivity of this combination of findings for the diagnosis of right ventricular infarction is less than 25%.[69] Jugular venous distension on inspiration (Kussmaul's sign) has been reported to be a sensitive and specific sign of RV infarction.[73] The hemodynamic features of RV infarction may disappear with volume depletion or may emerge only after volume loading, making the clinical diagnosis elusive in some cases.

ST segment elevation in a right precordial lead (V_{4R}) has been reported to have a sensitivity of 70% and a specificity of nearly 100% for the diagnosis of RV infarction when the electrocardiogram is recorded within the first hours after the onset of symptoms.[74] Echocardiography commonly reveals wall motion abnormalities of the right ventricle and interventricular septum. Bowing of the interatrial septum toward the left atrium indicates that the right atrial pressure exceeds the left atrial pressure,[75] and bowing of the interventricular septum into the right ventricle, compounding the dysfunction of the right ventricle;[76] both indicate a poor prognosis. Detection of a low RVEF and a segmental wall motion abnormality by radionuclide right ventriculography had a sensitivity of 92% and a specificity of 82% for identifying hemodynamically significant RV infarction in one study.[73]

Management

Volume loading can normalize blood pressure and increase cardiac output.[77] Earlier trials of RV infarction demonstrated a marked response to volume loading.[78] Many of these patients were volume depleted secondary to aggressive diuresis in response to a raised venous pressure.

Although this therapy remains very important, these trials may have exaggerated the importance of volume loading. **Grade B4**

Inotropic agents are often used in the treatment of right ventricular infarction when volume loading fails to improve cardiac output, but the effect of this on prognosis is unclear. The maintenance of atrioventricular synchrony is often critical to the maintenance of a satisfactory cardiac output; atrioventricular pacing has been shown to improve hemodynamics.[79] Successful thrombolysis appears to reduce the incidence of RV infarction.[80] Patients with inferior MI in the TIMI-II study were less likely to have RV involvement when the culprit artery was patent as compared to patients with persistent occlusion.[81] In patients with hemodynamically significant right ventricular infarction, right coronary artery reperfusion with angioplasty was associated with dramatic recovery of right ventricular function and reduced mortality.[82] In contrast, unsuccessful right coronary artery reperfusion was associated with a high mortality.

In summary, reperfusion therapy in right ventricular infarction has not been studied in randomized trials but appears to be effective. **Grade B4**

Left ventricular aneurysm

Clinical features and prognosis

Left ventricular aneurysms develop most commonly after large transmural anterior MIs, although in 5–15% of cases the site is inferior or posterior.[83] The coronary anatomy is an important determinant of the development of left ventricular aneurysm. Total occlusion of the left anterior descending artery in association with poor collateral blood supply is a significant determinant of aneurysm formation in anterior MI. Multivessel disease with either good collateral circulation or a patent left anterior descending artery is uncommonly associated with the development of left ventricular aneurysm.[84] Coronary patency also determines the likelihood of developing an aneurysm.[85] A ventricular aneurysm can often be palpated as a dyskinetic region adjacent to the apical impulse. A third heart sound and signs of heart failure may also be detected. A non-specific marker of an aneurysm is ST segment elevation that persists weeks after the acute phase of infarction. Echocardiography can delineate LV aneurysms as well as left ventriculography and has a higher sensitivity in the detection of thrombus.[86] A left ventricular aneurysm may cause no problems, but may be associated with heart failure because the left ventricle functions at a mechanical disadvantage. Ventricular tachycardia late after infarction is commonly associated with an aneurysm, but its incidence may be reduced in patients receiving thrombolysis. In a non-randomized study of patients who developed a ventricular aneurysm after myocardial infarction, inducible ventricular tachycardia was less likely in patients who received thrombolytic therapy than those who did not (8% *v* 88%; $P = 0{\cdot}0008$) and there was a reduced incidence of sudden death on subsequent follow up (0% *v* 50%; $P = 0{\cdot}002$).[87]

A ventricular aneurysm also provides a nidus for the development of an intracavitary thrombus. The risk of a clinical embolic event, based on four observational studies, is approximately 5%.[88] The risk of thromboembolism after infarction is greatest within the first few weeks.

Management

Surgical removal of a left ventricular aneurysm is indicated in patients with heart failure that is difficult to control medically, in patients with recurrent ventricular tachycardia not controlled by other means, and in patients with embolic episodes in spite of adequate anticoagulation.[89] **Grade B4**

Aneurysmectomy is often performed at the time of coronary bypass surgery, and coronary bypass of severe lesions almost always accompanies aneurysmectomy.

Pseudoaneurysm

A pseudoaneurysm is a rare complication of MI that develops when a myocardial rupture is sealed off by surrounding adherent pericardium. The aneurysmal sac may progressively enlarge but maintains a narrow neck, in contrast to a true ventricular aneurysm. In a series of 290 patients with LV pseudoaneurysms; congestive heart failure, chest pain and dyspnea were the most frequently reported symptoms, but >10% of patients were asymptomatic.[90] Physical examination revealed a murmur in 70% of patients. Almost all patients had electrocardiographic abnormalities, but only 20% of patients had ST segment elevation. Radiographic findings were frequently non-specific, however a mass was detected, in more than one half of patients. Differentiation of left ventricular pseudoaneurysms from true aneurysms may be difficult,[91] and can be assisted with echocardiography. The ratio of the maximum diameter of the orifice to the maximum internal diameter of the cavity has been recommended as a useful index to differentiate the two conditions. In one series, the ratio of the orifice of the aneurysm to the cavity was 0·25 to 0·50 for pseudoaneurysms, while the range for true aneurysms was 0·90 to 1·0.[92] Regardless of treatment, patients with LV pseudoaneurysms have a high mortality rate, but especially those who are managed non-surgically.[93]

Therefore urgent surgery should be considered in all patients with LV pseudoaneurysms. **Grade B4**

Cardiac thromboembolism

Clinical features and prognosis

Left ventricular thrombi develop in up to 40% of patients with large anterior transmural MIs.[94–96] If left untreated, up to 15% of thrombi will dislodge and result in a symptomatic embolic event.[97,98] Overall, 1·5–3·6% of patients with MIs suffer a complicating stroke, most often from a dislodged mural thrombus. This risk is higher in patients with large anterior infarctions.[99,100] Emboli are more common within the first few months after infarction than later, and with large, irregular shaped thrombi, particularly those with frond-like appendages.[97] When a thrombus is visualized by echocardiography, the risk ratio for embolization is 5·45 (95% CI 3·0–9·8) according to a meta-analysis.[101]

Management

Anticoagulation with heparin followed by warfarin for 6 months has been shown to reduce the incidence of thromboembolism in patients with documented intracavitary thrombi (OR 0·14; 95% CI 0·04–0·52).[102] The benefits in terms of reduction of embolic potential outweigh the risks of hemorrhage with anticoagulation. Meta-analysis of trials of anticoagulant therapy to prevent thrombus formation confirmed a benefit (OR 0·32; 95% CI 0·20–0·52), but no effect for antiplatelet drugs.[102] It is important to consider this evidence in the light of whether the anticoagulants are given in the presence or absence of aspirin, and the relationship to thrombolytic therapy. In a meta-analysis of all trials involving heparin administration in over 70 000 patients with acute myocardial infarction,[103] in the *absence* of aspirin, anticoagulant therapy reduced the risk of stroke to 1·1% from 2·1% ($2P = 0·01$), equivalent to 10 fewer strokes per 1000 ($2P = 0·01$). In the *presence* of aspirin, however, heparin was associated with a small non-significant excess of stroke and a definite excess of three major bleeds per 1000 ($2P < 0·0001$). The use of heparin after thrombolytic therapy was studied in a meta-analysis of six trials involving 1735 patients in which intravenous heparin was compared with placebo after thrombolysis.[104] Mortality before hospital discharge was 5·1% for patients allocated to intravenous heparin compared with 5·6% for controls (relative risk reduction of 9%, OR 0·91; 95% CI 0·59–1·39). The rates of total stroke, intracranial hemorrhage, and severe bleeding were similar in patients allocated to heparin; however, the risk of any severity of bleeding was significantly higher (22·7% *v* 16·2%; OR 1·55; 95% CI 1·21–1·98). Thrombolytic therapy may be associated with a reduced risk of intraventricular thrombus and thromboembolic events, but the analysis is confounded by the potential for thrombolytic therapy to cause hemorrhagic stroke. Thrombolytic therapy is associated with an excess of stroke of four extra strokes on day 1 compared with placebo.[105] This risk is reduced if angioplasty is used instead of thrombolytic therapy. In a meta-analysis comparing the effects of angioplasty with thrombolysis, angioplasty was associated with a significant reduction in total stroke (0·7% *v* 2·0%; $P = 0·007$) primarily due to a reduction in hemorrhagic stroke (0·1% *v* 1·1%; $P < 0·001$).[106]

Acute mitral regurgitation

Clinical features and prognosis

Mitral regurgitation complicating acute myocardial infarction is usually due to dysfunction of the papillary muscles.[107,108] The milder form of mitral regurgitation is a relatively common complication of myocardial infarction, found in 19% of postinfarction patients who undergo left ventriculography[109] and 39% of those who undergo Doppler echocardiography.[110] Mitral regurgitation is an independent predictor of cardiovascular mortality in postinfarction patients. In the SAVE trial, the relative risk was 2·00 (95% CI 1·28–3·04) in patients who had mitral regurgitation detected on catheterization early after MI. In a recent series studied with Doppler echocardiography, the hazard ratio for 1 year mortality after adjustment for other prognostic variables was 2·31 (95% CI 1·03–5·20) for mild MR and 2·85 (95% CI 0·95–8·51) for moderate or severe MR.[111] The most severe form of mitral regurgitation results from complete rupture of the head of a papillary muscle and usually leads quickly to severe heart failure or cardiogenic shock. In the SHOCK trial registry, cardiogenic shock was associated with severe mitral regurgitation in 98 of 1190 patients.[112] The mitral regurgitation patients were more likely to be female and to have non-ST elevation MI at the time of presentation, and to have inferior or posterior rather than anterior infarction. In fact one should suspect acute MR or another mechanical complication in any patient with a first inferior MI who develops heart failure or cardiogenic shock.

Early diagnosis of mitral regurgitation complicating MI is important because mitral valve surgery can be life saving. Usually the diagnosis is evident clinically with a loud pansystolic murmur maximal at the apex, and radiation to the axilla; however, if LV function is severely impaired or if left atrial pressure is very high, the murmur may be of low intensity or entirely absent. Echocardiography Doppler examination is invaluable in confirming the diagnosis.[113] However, in some cases transthoracic echocardiography is non-diagnostic and transesophageal echocardiography is required to assess the extent of the regurgitation. Transesophageal echocardiography has been demonstrated to be safe and produce a high diagnostic yield in hemodynamically unstable, critically ill patients who are suspected of having an underlying cardiovascular disorder.[114] The presence of cardiogenic shock or severe failure with preserved LV function usually indicates that an important mechanical complication is present, and further investigation should be urgently pursued. If the mitral regurgitation is acute in its onset, the left atrium may not be greatly enlarged, and the pulmonary capillary wedge pressure tracing should exhibit large v waves. Large v waves are neither highly sensitive nor highly specific for severe chronic mitral regurgitation,[115] but the correlation between giant v waves and severe acute mitral regurgitation is stronger.[116]

Management

Treatment with arterial dilators such as nitroprusside may improve hemodynamic status temporarily, by reducing afterload and the regurgitant fraction.[117]

Observational data suggest that surgery for acute mitral regurgitation should be performed acutely, even in patients who appear to stabilize with medical therapy, because subsequent deterioration is usual, abrupt, and unpredictable. Grade B4

The perioperative mortality associated with mitral valve surgery for postinfarction papillary muscle rupture is high, 27% in one series, but two thirds of the survivors were still alive at 7 years.[118] Patients with a low preoperative EF had the highest short-term and long-term mortality. The use of mitral valve repair in this situation can give excellent long-term results.[119] There is evidence from the SHOCK trial registry that transfer to a center skilled in mitral valve surgery for early operation may be helpful.[112] Early reperfusion with thrombolytic therapy[120] has been shown to reduce the frequency of mitral regurgitation after myocardial infarction. There is some evidence that angioplasty may be superior in achieving this, although this is based on an indirect comparison of clinical trial results.[121] There have been reports of striking improvement in mitral regurgitation after emergency coronary angioplasty in patients with acute myocardial infarction.[122]

Ventricular septal rupture

Clinical features and prognosis

Rupture of the interventricular septum occurs in approximately 2% of patients with acute myocardial infarction.[123] The pathology of septal rupture is determined by the location of the associated myocardial infarction and has implications for surgical repair. Septal rupture complicating anterior infarction is usually apical and involves one direct perforation; septal rupture complicating inferior infarction often involves the posterior or basal septum with complex, serpiginous defects.[124] The median time of onset of rupture was at 2·5 days in one study[123] and 7 days in another.[124] In the SHOCK trial registry of cardiogenic shock patients,[125] ventricular septal rupture occurred a median of 16 h after infarction. The patients tended to be older ($P = 0·053$), were more often female ($P = 0·002$) and less often had previous infarction ($P < 0·001$), diabetes mellitus ($P = 0·015$) or smoking history ($P = 0·033$). The inhospital mortality was higher in the shock patients with septal rupture 87% *v* 61%, $P < 0·001$. Even when most patients undergo surgical repair, inhospital or 30 day mortality remains high: 43% to 59%.[125–127] Early diagnosis may offer some hope of early repair. Most patients with septal rupture develop signs of acute right and left sided heart failure and a loud pansystolic murmur at the left sternal

border. This may be difficult to distinguish from the murmur of acute mitral regurgitation. The murmur may be unimpressive or even absent when cardiac contractility is depressed. A large proportion of patients have a systolic thrill at the left sternal border. Echocardiography with Doppler color flow mapping is very sensitive and specific in the diagnosis of this condition; this technique also localizes the defect accurately and provides important prognostic information.[128]

Management

Early closure is now recognized to yield better results than attempting to wait for days or weeks until the conditions for surgery improve. Although early surgical intervention may increase operative mortality there is reduced patient mortality overall.

This practice is based on observational data, as there have not been any controlled trials of early versus late intervention. Grade B4

In the SHOCK trial register, surgical repair was performed in 31 patients with rupture, of whom six (19%) survived. Of the 24 patients managed medically, only one survived.[125] Technical improvements in repair have resulted in improvements in outcome, but mortality remains high.[129] Transcatheter closure has been described, but with a high mortality in early reports.[130]

Free wall rupture

Clinical features and prognosis

Rupture of the free wall of the left ventricle is an almost uniformly fatal complication of MI that now probably accounts for 10–20% of inhospital deaths.[131] Older patients are at far greater risk than younger patients. In the GISSI trial, cardiac rupture was the cause of 19% of the deaths among patients 60 years old or younger and 86% of deaths among those more than 70 years old.[132] Rupture occurs most frequently in elderly women.[133] Anterior infarctions, hypertension on admission and marked or persistent ST elevation are also risk factors for rupture.[134] The usual presentation is sudden collapse, associated electrical-mechanical dissociation, and failure to respond to cardiopulmonary resuscitation. However, in some patients ventricular rupture is subacute, allowing time for ante-mortem diagnosis,[135] this clinical entity is probably underrecognized. Premonitory symptoms of chest discomfort, a sense of impending doom and intermittent bradycardia signal impending myocardial rupture in many cases,[136] and if recognized, can lead to life saving surgery.[137] There has been some evidence that thrombolytic therapy can increase the risk of cardiac rupture[138] and that the timing of rupture is accelerated to within 24 to 48 hours of treatment.[139] A meta-analysis of 58 cases of rupture involving 1638 patients from four trials showed that the odds ratio (treated/control) of cardiac rupture was directly correlated with time to treatment ($P = 0{\cdot}01$); late administration of thrombolytic therapy may increase the risk of cardiac rupture.[140]

Management

Urgent surgical repair is mandatory for acute rupture, but for subacute rupture, medical management may be effective but on balance all patients should be treated surgically if possible. Grade B4

In one recent report[141] of 81 consecutive patients presenting with acute hypotension with electrical mechanical dissociation, 19 survived with medical management alone.

Pericarditis

Clinical features and prognosis

Pericarditis occurs in approximately 25% of patients with Q wave infarctions and 9% of patients with non-Q wave infarctions,[142] and usually occurs within the first week.[143] A pericardial friction rub may be present but is not found in half of patients with typical symptoms and is not required for diagnosis or treatment.[143] On the other hand, the only evidence of pericarditis in many patients is a transient pericardial rub, with no symptoms. Pericarditis following myocardial infarction is associated with a higher risk of death in the year post-infarction, possibly due to the associated large infarction.[142]

Management

High dose aspirin and non-steroidal anti-inflammatory drugs are recommended to treat the symptoms of postinfarction pericarditis, although no randomized studies have been done to document their efficacy.

A single dose of a non-steroidal agent may be very effective, avoiding the need for long-term therapy. Grade C5

A serial echocardiographic study of patients with post-infarction pericarditis showed that patients treated with indomethacin or ibuprofen showed a greater tendency for infarct expansion, but it was not clear if the infarct expansion was due to the non-steroidal anti-inflammatory drugs or to the selection for treatment of those with larger infarctions.[144] Thrombolytic therapy reduces the incidence of pericarditis by approximately half.[143]

Pericardial effusion and tamponade

A pericardial effusion can be detected by echocardiography in one quarter of patients with acute Q wave MI.[145,146] This finding correlates with the presence of heart failure and a poor prognosis. Cardiac tamponade is a rare complication

of thrombolytic therapy for acute MI, being reported in four of 392 consecutively treated patients in one series.[147]

Dressler's syndrome

A form of postinfarction pericarditis occurring 2–11 weeks after the acute event was described in 1956 by Dressler.[148] The full syndrome includes prolonged or recurrent pleuritic chest pain, a pericardial friction rub, fever, pulmonary infiltrates or a small pulmonary effusion, and an increased sedimentation rate. There has been a striking reduction in the incidence of this postinfarction complication.[149]

Non-steroidal anti-inflammatory drugs may be required for control of Dressler's syndrome, but there are no randomized trials to confirm their efficacy. **Grade C5**

Ventricular fibrillation and sustained ventricular tachycardia

Clinical features and prognosis

Sustained monomorphic ventricular tachycardia is not common in the early postinfarction period but it is a marker of adverse prognosis. Results of the GISSI-3 database showed that sustained ventricular tachycardia occuring after the first 24 hours of MI was a strong independent predictor of 6-week mortality (hazard ratio 6·13; 95% CI 4·56–8·25).[150] Risk factors for this arrhythmia included: older age, a history of hypertension, diabetes, and myocardial infarction and non-administration of lytic therapy.

The frequency of ventricular fibrillation (VF) has declined over the past 20 years as noted by Antman *et al*, who demonstrated from the randomized trials of prevention of ventricular fibrillation that the frequency in the 1970s was 5 to 10%, dropping through the 1980s to less than 2%.[151] The reasons for this may include the admission of lower risk patients to coronary care units, wider use of beta blocking drugs and more effective treatment of ventricular dysfunction and electrolyte imbalances in the coronary care unit. The prognosis of ventricular fibrillation depends on the associated clinical state. VF occurring in the presence of hemodynamic compromise has a high hospital mortality of 80%.[152] VF occurring in the absence of cardiogenic shock, severe heart failure or hypotension (primary VF) has a good short-term prognosis[153] although one major study of primary VF showed higher hospital mortality.[154] Patients surviving early inhospital VF complicating myocardial infarction, experience no adverse effect on long-term survival following hospital discharge.[155,156]

Management of VF

Results of individual trials of prophylactic lidocaine were conflicting. Meta-analyses of the clinical trials[157,158] have shown that prophylactic lidocaine was effective in reducing the frequency of ventricular fibrillation, but paradoxically did not improve mortality and was associated with a possible adverse effect. For this reason the use of intravenous lidocaine as prophylaxis against ventricular fibrillation has been virtually abandoned.[11]

Intravenous β blockers have been shown to reduce mortality, particularly in high-risk patients, with an apparent benefit in reduction of ventricular fibrillation.[159] **Grade A1d**

Low serum potassium is associated with a higher risk of VF[160] especially in patients on diuretic therapy prior to their infarction.[161]

The potential of intravenous magnesium to reduce the risk of ventricular fibrillation early in acute myocardial infarction has been studied in several trials. A meta-analysis of nine small trials showed an apparent improvement in survival.[162] A clinical trial involving 2316 patients randomized to early magnesium or placebo showed a significant 24% reduction in mortality[163] but wider use in non-selected patients in the much larger ISIS-4 trial was disappointing, with no significant effect on short-term mortality.[164] A meta-analysis included in the ISIS-4 publication which included all of the previous magnesium trials failed to show a mortality benefit. Overall there is insufficient evidence for the routine use of intravenous magnesium early in the post-MI period.

Postinfarction ventricular premature beats and non-sustained ventricular tachycardia

Clinical features and prognosis

While frequent ventricular premature beats (more than 10 per hour) in the postinfarction patient are an independent risk factor for subsequent mortality (both total mortality and sudden death), the significance of non-sustained ventricular tachycardia in this setting is controversial.[165] The suppression of these ventricular arrhythmias has consistently failed to improve survival.

Management

Antiarrhythmic drugs

A meta-analysis of 138 randomized trials of prophylactic antiarrhythmic drug therapy involving 98 000 postinfarction patients, reported by Teo *et al* in 1993,[166] showed that the mortality of patients randomized to receive Class I agents was increased (OR 1·14; 95% CI 1·01–1·28, $P = 0·03$). The most convincing evidence of the deleterious effects of antiarrhythmic drugs for suppression of ventricular extrasystoles came from the Cardiac Arrhythmia Suppression Trial (CAST).[167] In patients randomized to Class IC drugs,

mortality was significantly higher even though these drugs effectively suppressed ventricular extrasystoles. Subsequently, the SWORD study was stopped after enrollment of only 3400 of the planned 6400 high-risk survivors of MI because of an excess mortality (4·6% *v* 2·7%, $P = 0{\cdot}005$) in patients randomized to D-sotalol.[168]

Clinical trials have shown some support for the use of the predominantly Class III drug amiodarone. Two randomized clinical trials, each with more than 1000 postinfarction patients with either frequent or repetitive ventricular extrasystoles (CAMIAT)[169] or an EF of 0·40 or less (EMIAT),[170] have compared amiodarone to placebo. EMIAT reported no difference in mortality between treatment groups but CAMIAT reported a decrease in the primary end point, a composite of resuscitated ventricular fibrillation or arrhythmic death (3·3% *v* 6·0%, RR 48%; 95% CI 4–72), and a trend toward decreased all-cause mortality. A subsequent analysis indicated that a beneficial interaction between amiodarone and beta adrenergic blocker drugs may have contributed to the benefit of amiodarone in these trials.[171] A limitation of amiodarone therapy is the high incidence of serious adverse effects seen with long-term therapy. The clinical trial evidence that is now available does not appear to be strong enough to recommend amiodarone therapy to MI survivors with asymptomatic ventricular extrasystoles or a depressed EF. However, patients with symptomatic ventricular tachycardia as a long-term complication of MI often benefit from amiodarone therapy.

Implantable defibrillator

The implanted defibrillator reduced total mortality over 27 months in MADIT, a small randomized clinical trial in a specific high-risk subgroup of postinfarction patients.[172] Eligible patients had an EF of 0·35 or less, a documented episode of unsustained ventricular tachycardia, and inducible, non-suppressible ventricular tachyarrhythmia during electrophysiologic study. The risk ratio for total mortality was 0·46 (95% CI 0·26–0·82). The AVID (Antiarrhythmics Versus Implantable Defibrillators) study included a group of patients with ventricular fibrillation or ventricular tachycardia associated with a low EF or hemodynamic compromise.[173] The effect of an implanted cardiac defibrillator was compared to therapy with amiodarone or sotalol, the treatment decision guided by Holter or electrophysiologic study. There was a statistically significant benefit of defibrillator therapy compared to drug therapy. Similar results have been reported in two smaller randomized trials, the Canadian Implantable Defibrillator Study[174] and the Cardiac Arrest Study Hamburg.[175] In a subgroup analysis of the AVID database, in patients with better-preserved left ventricular function with ejection fractions in the range of 35 to 40%, cardioverter-defibrillator therapy had no advantage over drug therapy.[176] In a meta-analysis of the defibrillator secondary prevention trials (AVID, CASH and SIDS), there was a 28% reduction in the relative risk of death in favor of defibrillator therapy over amiodarone therapy.[177] The MADIT II trial of 1200 post-MI patients with impaired left ventricular function was terminated early after observing a 30% reduction in mortality in patients randomized to receive an implantable defibrillator device compared to those receiving conventional treatment.[178]

Overall, the evidence indicates that Class I antiarrhythmic drugs should not be used to treat ventricular extrasystoles or unsustained ventricular tachycardia postinfarction. Amiodarone may be effective in some high-risk patients, but with a risk of side effects with long term use. β Blockers reduce total mortality and the incidence of re-infarction by one quarter in postinfarction patients.

Although no trial has specifically addressed the use of an implanted defibrillator in the early postinfarction period, it appears to be the treatment of choice in specific subgroups who have a history of MI and impaired LV systolic function. Grade A1a

Atrial fibrillation

Clinical features and prognosis

Atrial fibrillation is a relatively common complication of myocardial infarction. In patients with MI treated with thrombolytic therapy in the GUSTO 1 trial, atrial fibrillation was present on admission in 2·5% and developed during hospitalization in an additional 7·9% of cases.[179] Patients with atrial fibrillation more often had underlying three-vessel disease and an incompletely patent infarct-related artery. Inhospital stroke developed more often (3·1%) in patients with atrial fibrillation compared to those without atrial fibrillation (1·3%) ($P = 0{\cdot}0001$). Atrial fibrillation was more likely to complicate the inhospital course of older patients with larger infarctions, worse Killip class and higher heart rates. The unadjusted mortality was higher at 30 days (14·3% *v* 6·2%, $P = 0{\cdot}0001$) and at 1 year (21·5% *v* 8·6%, $P = 0{\cdot}0001$) in patients with atrial fibrillation. The adjusted 30 day mortality ratio was 1·3 (95% CI 1·2–1·4). In a study from the GISSI trial, the incidence of inhospital atrial fibrillation or flutter was 7·8%, and was associated with a worse prognosis.[180] After adjustment for other prognostic factors, atrial fibrillation remained an independent predictor of increased inhospital mortality, adjusted relative risk (RR) 1·98 (95% CI 1·67–2·34). Four years after acute myocardial infarction the negative influence of atrial fibrillation persisted (RR 1·78; 95% CI 1·60–1·99).

The onset of atrial fibrillation is usually after the first hospital day, and the usual underlying causes are heart failure, pericarditis, and atrial ischemia, with heart failure being by far the most common.[181] In a study based on 106 780 US

Medicare beneficiaries 65 years of age or over, patients were categorized on the basis of the presence of AF, and those with AF were further subdivided by timing of AF (present on arrival *v* developing during hospitalization);[182] 11 510 presented with AF and 12 055 developed AF during hospitalization. Patients developing AF during hospitalization had a worse prognosis than patients who presented with AF. In another study, detailed analysis of the prognosis of AF in AMI showed that AF was an independent predictor of cardiac death when it developed within 24 hours (OR 2·5; 95% CI 1·2–5·0; $P = 0·0012$) and later (OR 3·7; 95% CI 1·8–7·5; $P = 0·0005$), but not when it preceded the onset of AMI.[183]

Management

Amiodarone has been shown to be more effective than digoxin in achieving reversion to sinus rhythm.[184] In a prospective but not randomized study, the combination of amiodarone and digoxin was superior to amiodarone alone in restoring sinus rhythm faster, maintaining sinus rhythm longer, and allowing the use of a lower cumulative amount of amiodarone.[185]

Heart block and conduction disturbances

Clinical features and prognosis

Complete atrioventricular block occurred in 7·7% of patients with inferior MI in one large series.[186] In one study patients with inferior infarction complicated by complete heart block had higher inhospital mortality rates than did those without this complication: 42% *v* 14% ($P < 0·01$), adjusted odds ratio of 2·7 (95% CI 1·6–4·6).[186] In another series the inhospital mortality rate was also higher (24·2% *v* 6·3%, $P < 0·001$), but at hospital discharge the survivors had similar clinical characteristics to patients without complete atrioventricular block, and a similar mortality rate during the next year.[187] In a study of elderly patients who had suffered an acute MI, heart block was associated with increased inhospital mortality but had no effect on prognosis at 1 year among hospital survivors.[188] There is some evidence that the widespread adoption of reperfusion therapy may have reduced the incidence of this complication of MI.[189] But even in the "reperfusion era", among patients with inferior MI treated with thrombolytic therapy, the development of complete atrioventricular block is associated with a relative risk of 4·5 for 21 day mortality.[190]

Management

In patients with inferior infarction pacing is indicated if there is persistent high-grade atrioventricular block.[191] In anterior infarction, the prognostic significance of atrioventricular block is even greater than for inferior MI. Patients with anterior MI and complete atrioventricular block had a 63% inhospital mortality rate, compared with a 19% mortality rate in those without complete heart block.[186] When right bundle branch block and left anterior hemiblock develop within the first few hours of infarction prophylactic pacing may be considered; however this practice remains controversial. If the patient survives, this type of heart block usually regresses, but there is a risk of complete heart block causing death after hospital discharge.[192] A small randomized trial showed no benefit of prophylactic placement of a permanent pacemaker.[193]

Transvenous pacing is required urgently for atrioventricular block complicating anterior infarction because the escape rhythm originates below the level of the atrioventricular node and is therefore unstable and usually very slow (20–40 bpm). **Grade C5**

The development of left or right bundle branch block, as a complication of MI is a marker of a larger infarct size and a higher mortality after hospital discharge,[194] but is not an indication for pacing. A randomized trial of pacing for bundle branch block complicating MI showed no advantage.[195] Left anterior hemiblock denotes neither a larger infarct size nor a worse prognosis.[196]

Postinfarction angina and myocardial ischemia

Clinical features and prognosis

Approximately 20% of patients develop angina during hospitalization after MI. Patients with early postinfarction angina are 10 times more likely to develop infarct extension during hospitalization, have a worse long-term prognosis and have more extensive coronary disease at arteriography.[197]

Management

Coronary angioplasty can be performed with a low risk in patients with postinfarction angina.[198] In trials of angioplasty performed after thrombolytic therapy there was no important difference in early mortality, but an apparent reduction in mortality between 6 and 52 weeks.[199] A study of the effect of coronary interventional procedures on improved postinfarction outcomes could not attribute the improvement to increased procedural management because most of the procedures were directed to the lowest risk patients.[200] Early intervention with coronary bypass surgery can relieve symptoms in almost all patients with postinfarction angina, with low complication rates.[201] The timing of surgery after infarction has not been shown to be a risk factor except when surgery is performed within the first 2 to 3 days postinfarction.[202] Early surgery is not an important risk factor in patients with normal left ventricular function but when the LV function is significantly depressed, delayed

surgery is safer than early surgery.[203] The outcome of surgery performed after thrombolytic therapy depends on the hemodynamic stability of the patient at the time of surgery. When CABG was performed within 8 hours of thrombolytic therapy in the TIMI II trial, operative mortality was higher (13% to 17%) and there was an increased use of blood products when the patient was hemodynamically unstable compared with hemodynamically stable patients, who had a relatively low (2·8%) mortality.[204] Operative survivors in this group had a low 1 year mortality.

The Danish Trial in Acute MI (DANAMI) randomized 503 patients with inducible ischemia after thrombolytic therapy for MI to an invasive strategy, with coronary bypass surgery or angioplasty done in 82% of cases, or to a conservative strategy.[205] After 2·4 years of follow up, there was no difference in mortality (3·6% in the invasive group and 4·4% in the conservative group (P = NS)). But there was a reduction in re-infarction in the invasive group (5·6%) compared with the conservative group (10·5%) ($P = 0·038$), and far fewer hospitalizations for unstable angina in the invasive group (17·9% *v* 29·5%, $P < 0·00001$).

Overall invasive intervention is indicated in patients with postinfarction myocardial ischemia. **Grade A1c**

Psychosocial complications

Clinical features and prognosis

An estimated 20–50% of postinfarction patients have high levels of psychosocial stress, including anxiety, depression, denial, hostility, and social isolation.[206] A major depressive disorder may occur in as many as 15–20% of patients hospitalized with myocardial infarction,[207] and depression has been shown to have a significantly adverse effect on outcome.[208] The effects of depression are compounded by lifestyle factors, including isolation, which themselves have been shown to have an adverse effect.[209] Poor adherence to postinfarction therapies has been shown to be a possible mechanism for the adverse outcome of depressed postinfarction patients.[210] Other postulated mechanisms are an increased risk of postinfarction ventricular arrhythmias[211] and abnormalities in platelet function[212] associated with depression. The possible association between depression and ventricular arrhythmias may be explained by the finding of reduced heart rate variability (HRV) in depressed post-MI patients.[213]

Management

Cardiac rehabilitation programs provide psychological and social support to patients after MI, in addition to education about risk factors and their modification. Randomized clinical trials of formal exercise programs post infarction have shown benefits on quality of life, but have not yielded definitive results individually on prognosis. An overview that included 36 trials involving 4554 patients was suggestive of benefit. After an average follow up of 3 years, the odds ratio was 0·80 for total mortality (95% CI 0·66–0·96) but the rate of non-fatal re-infarction was not reduced.[214]

An overview of randomized trials of disease management programs in patients with known coronary disease (including myocardial infarction) showed improvements in processes of care, quality of life and functional status, and admissions to hospital (RR 0·84 (95% CI 0·76–0·94), but no reductions in all-cause mortality (RR 0·91 (95% CI 0·79–1·04)) or recurrent myocardial infarction (RR 0·94 (95% CI 0·80–1·10)).[215] The effect of a specific nursing intervention designed to improve the psychological and social status of postinfarction patients was assessed in the Montreal Heart Attack Readjustment Trial (M-HART). The 1376 patients were randomized to usual care or to a treatment plan consisting of nurse visits and telephone calls to patients exhibiting high levels of psychological stress. The intervention had no effect on mortality in men, and was associated with an increased mortality in women that was of borderline statistical significance ($P = 0·069$).[216] Berkman *et al* recently compared the use of psychosocial intervention to usual care in 2481 post-MI patients who were depressed and with a low level of social support.[217] The intervention included cognitive behavioral therapy and pharmacotherapy for non-responders with severe depression. There was no significant difference between the two groups with regard to the primary end point of death and MI over a period of 48 months. A preliminary clinical trial of sertraline did however show benefits, not only on mood, but on ventricular ectopic activity.[218]

Overall, trials of psychosocial interventions have yielded inconsistent results with regard to hard cardiovascular end points such as death and MI; there is some evidence however, that these interventions improve functional status and quality of life.

References

1. American Heart Association. *2001 Heart and stroke statistical update*. Dallas, Texas: American Heart Association, 2000.
2. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". *J Am Coll Cardiol* 1986;**8**:1467–70.
3. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 1990;**81**:1161–72.
4. Page DL, Caulfield JB, Kastor JA, DeSanctis RW, Saunders CA. Myocardial changes associated with cardiogenic shock. *N Engl J Med* 1971;**285**:133–7.
5. McCallister BD Jr, Christian TF, Gersh BJ, Gibbon RJ. Prognosis of myocardial infarctions involving more than 40% of the left

ventricle after acute reperfusion therapy. *Circulation* 1993;**88**:1470–5.
6. Fisher JP, Picard MH, Mikan JS *et al.* Quantitation of myocardial dysfunction in ischemic heart disease by echocardiographic endocardial surface mapping: correlation with hemodynamic status. *Am Heart J* 1995;**129**:1114–21.
7. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol* 1967;**20**:457–64.
8. DeGeare VS, Boura JA, Grines LL, O'Neill WW, Grines CL. Predictive value of the Killip classification in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2001;**87**:1035–8.
9. Rott D, Behar S, Leor J *et al*, Working Group on Intensive Cardiac Care, Israel Heart Society. Effect on survival of acute myocardial infarction in Killip classes II or III patients undergoing invasive coronary procedures. *Am J Cardiol* 2001; **88**:618–23.
10. Forrester JS, Diamond G, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;**295**:1356–62,1404–14.
11. Ryan TJ, Antman EM, Brooks NH *et al.* 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1999;**100**:1016–30.
12. Zion MM, Balkin J, Rosenmann D *et al.* Use of pulmonary artery catheters in patients with acute myocardial infarction: analysis of experience in 5841 patients in the SPRINT Registry. *Chest* 1990;**98**:1331–5.
13. Connors AF, Speroff T, Dawson N *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996;**276**:889–97.
14. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? *JAMA* 1996;**276**:916–18.
15. Stevenson R, Ranjadayalan K, Wilkinson P, Roberts R, Timmis AD. Short and long term prognosis of acute myocardial infarction since introduction of thrombolysis. *BMJ* 1993;**307**: 349–53.
16. Villanueva FS, Sabia PJ, Afrookteh A, Pollock SG, Hwang LJ, Kaul S. Value and limitations of current methods of evaluating patients presenting to the emergency room with cardiac-related symptoms for determining long-term prognosis. *Am J Cardiol* 1992;**69**:746–50.
17. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;**309**:331–6.
18. Gottlieb S, Moss AJ, McDermott M, Eberly S. Interrelation of left ventricular ejection fraction, pulmonary congestion and outcome in acute myocardial infarction. *Am J Cardiol* 1992; **69**:977–84.
19. Candell-Riera J, Permanyer-Miralda G, Castell J, *et al.* Uncomplicated first myocardial infarction: strategy for comprehensive prognostic studies. *J Am Coll Cardiol* 1991; **18**: 1207–19.
20. Thompson PL, Fletcher EE, Katavatis V. Enzymatic indices of myocardial necrosis: influence on short-and long-term prognosis after myocardial infarction. *Circulation* 1979;**59**: 113–19.
21. Antman EM, Tanasijevic MJ, Thompson B *et al.* Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; **335**:1342–9.
22. Ohman EM, Armstrong PW, White HD *et al.* Risk stratification with a point-of-care cardiac troponin T test in acute myocardial infarction. GUSTO III investigators. Global Use of Strategies to Open Occluded Coronary Arteries. *Am J Cardiol* 1999,**84**:1281–6.
23. Califf RM, Pieper KS, Lee KL *et al.* Prediction of 1-year survival after thrombolysis for acute myocardial infarction in the global utilization of streptokinase and TPA for occluded coronary arteries trial. *Circulation* 2000;**101**:2231–8.
24. Marchioli R, Avanzini F *et al.,* on behalf of GISSI-Prevenzione Investigators. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations; GISSI-Prevenzione mortality risk chart. *Eur Heart J* 2001;**22**:2085–103.
25. Dikshit K, Vyden JK, Forrester JS *et al.* Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after myocardial infarction. *N Engl J Med* 1973;**288**:1087–90.
26. Jugdutt BI. Effect of nitrates on myocardial remodeling after acute myocardial infarction. *Am J Cardiol* 1996;**77**:17C–23C.
27. Armstrong PW, Walker DC, Burton JR, Parker JO. Vasodilator therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin. *Circulation* 1975; **52**: 1118–22.
28. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988;**1**:1088–92.
29. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 1994;**343**:1115–22.
30. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995;**345**:669–85.
31. Swedberg K, Held P, Kjekshus J *et al.* Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. *N Engl J Med* 1992;**327**:678–84.
32. Pfeffer MA, Braunwald E, Moye LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; **327**: 669–77.
33. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;**343**:1115–22.
34. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–8.

35.Ambrosioni E, Borghi C, Magnani B. The effect of angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;**332**:80–5.
36.ISIS-IV Collaborative Group. A randomized factorial trial assessing early oral captopril, oral mononitrate and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669–85.
37.Kober L, Torp-Pedersen C, Carlsen JE *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**:1670–6.
38.Chinese Cardiac Study Collaborative Group. Oral captopril vs placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995;**345**:686–7.
39.Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation* 1998; **97**:2202–12.
40.Flather MD, Yusuf S, Kober L *et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–81.
41.de Kam PJ, Voors AA, van den Berg MP *et al.* Effect of very early angiotensin-converting enzyme inhibition on left ventricular dilation after myocardial infarction in patients receiving thrombolysis: results of a meta-analysis of 845 patients. FAMIS, CAPTIN and CATS Investigators. *J Am Coll Cardiol* 2000;**36**:2047–53.
42.Pfeffer MA, Greaves SC, Arnold JM *et al.* Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. *Circulation* 1997;**95**:2643–51.
43.McGhie AI, Golstein RA. Pathogenesis and management of acute heart failure and cardiogenic shock: role of inotropic therapy. *Chest* 1992;**102**(Suppl. 2):626S–32S.
44.Van Veldhuisen DJ, de Graeff PA, Remme WJ. Value of digoxin in heart failure and sinus rhythm: new features of an old drug? *J Am Coll Cardiol* 1996;**28**:813–19.
45.The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–33.
46.White HD, Norris RM, Brown MA *et al.* Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987; **317**:850–5.
47.Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. National Heart Foundation of Australia Coronary Thrombolysis Group. *Lancet* 1988;**1**:203–7.
48.Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. *Am J Cardiol* 1994;**74**:1220–8.
49.Bolli R. Myocardial "stunning" in man. *Circulation* 1992; **86**:1671–91.
50.Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". *J Am Coll Cardiol* 1986;**8**:1467–70.
51.Solomon SD, Glynn RJ, Greaves S *et al.* Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. *Ann Intern Med* 2001;**134**:451–8.
52.Marroquin OC, Lamas GA. Beneficial effects of an open artery on left ventricular remodeling after myocardial infarction. *Prog Cardiovasc Dis* 2000;**42**:471–83.
53.Lundergan CF, Ross AM, McCarthy WF *et al.* Predictors of left ventricular function after acute myocardial infarction: effects of time to treatment, patency, and body mass index: the GUSTO-I angiographic experience. *Am Heart J* 2001; **142**: 43–50.
54.Goldberg RJ, Gore JM, Alpert JS *et al.* Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community wide perspective, 1975–1988. *N Engl J Med* 1991;**325**:1117–22.
55.Hochman JS, Boland J, Sleeper LA *et al.* Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an international registry. *Circulation* 1995;**91**:873–81.
56.Hasdai D, Califf RM, Thompson TD *et al.* Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction. *J Am Coll Cardiol* 2000;**35**:136–43.
57.Richard C, Ricome JL, Rimailho A, Bottineau G, Auzepy P. Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. *Circulation* 1983;**67**:620–6.
58.Scheidt S, Wilner G, Mueller H *et al.* Intra-aortic balloon counterpulsion in cardiogenic shock. Report of a co-operative clinical trial. *N Engl J Med* 1973;**288**:979–84.
59.Bengtson JR, Kaplan AJ, Pieper KS *et al.* Prognosis in cardiogenic shock after acute myocardial infarction in the interventional era. *J Am Coll Cardiol* 1992;**20**:1482–9.
60.Ohman EM, George BS, White CJ *et al.*, the Randomized IABP Study Group. Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction: results of a randomized trial. *Circulation* 1994; **90**: 792–9.
61.Park SJ, Nguyen DQ, Bank AJ, Ormaza S, Bolman RM 3rd. Left ventricular assist device bridge therapy for acute myocardial infarction. *Ann Thorac Surg* 2000;**69**:1146–51.
62.Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 2001; **104**:2917–22.
63.Bates ER, Topol EJ. Limitations of thrombolytic therapy for acute myocardial infarction complicated by congestive heart failure and cardiogenic shock. *J Am Coll Cardiol* 1991;**18**: 1077–84.
64.Hasdai D, Harrington RA, Hochman JS *et al.* Platelet glycoprotein IIb/IIIa blockade and outcome of cardiogenic shock complicating acute coronary syndromes without persistent ST-segment elevation. *J Am Coll Cardiol* 2000;**36**:685–92.
65.Berger PB, Holmes DR, Stebbins AL *et al.* for the GUSTO-1 Investigators. Impact of an aggressive invasive catheterization and revascularization strategy on mortality in patients with cardiogenic shock in the Global Utilization of Streptokinase and

Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) Trial. *Circulation* 1997;**96**:122–7.
66. Sanborn TA, Sleeper LA, Bates ER *et al.* Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? *J Am Coll Cardiol* 2000;**36**(Suppl. A): 1123–9.
67. Hochman JS, Sleeper LA, Webb JG *et al.* Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK. *N Engl J Med* 1999;**341**:625–34.
68. Hochman JS, Sleeper LA, White HD *et al.* One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;**28**:190–2.
69. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med* 1993;**330**:1211–17.
70. Zehender M, Kasper W, Kauder E *et al.* Eligibility for and benefit of thrombolytic therapy in inferior myocardial infarction: focus on the prognostic importance of right ventricular infarction. *J Am Coll Cardiol* 1994;**24**:362–9.
71. Cabin HS, Clubb KS, Wackers FJT, Zaret BL. Right ventricular myocardial infarction with anterior wall left ventricular infarction: an autopsy study. *Am Heart J* 1987;**113**:16–23.
72. Zehender M, Kasper W, Kauder E *et al.* Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med* 1993;**328**: 981–8.
73. Dell'Italia LJ, Starling MR, Crawford MH *et al.* Right ventricular infarction: identification by hemodynamic measurements before and after volume loading and correlation with noninvasive techniques. *J Am Coll Cardiol* 1984;**4**:931–9.
74. Erhardt IR, Sjogren A, Wahlberg I. Single right sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. *Am Heart J* 1976;**91**:571–6.
75. López-Sendón J, López de Sá E, Roldán I *et al.* Inversion of the normal interatrial septum convexity in acute myocardial infarction: incidence, clinical relevance and prognostic significance. *J Am Coll Cardiol* 1990;**15**:801–5.
76. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation* 1990;**82**:359–68.
77. Goldstein JA, Vlahakes GJ, Verrier ED *et al.* Volume loading improves low cardiac output in experimental myocardial infarction. *J Am Coll Cardiol* 1993;**2**:270–8.
78. Lloyd EA, Gersh BJ, Kennelly BM. Hemodynamic spectrum of "dominant" right ventricular infarction in 19 patients. *Am J Cardiol* 1981;**48**:1016–22.
79. Love JC, Haffajee CI, Gore JM, Alpert JS. Reversibility of hypotension and shock by atrial or atrioventricular sequential pacing in patients with right ventricular infarction. *Am Heart J* 1984;**108**:5–13.
80. Schuler G, Hofmann M, Schwarz F *et al.* Effect of successful thrombolytic therapy on right ventricular function in acute inferior wall myocardial infarction. *Am J Cardiol* 1984;**54**: 951–7.
81. Berger PB, Ruocco NA, Ryan TJ *et al.* Frequency and significance of right ventricular dysfunction during inferior wall left ventricular myocardial infarction treated with thrombolytic therapy (results from the Thrombolysis in Myocardial Infarction [TIMI] II trial). *Am J Cardiol* 1993;**71**:1148–52.
82. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med* 1998;**338**:933–40.
83. Ba'albaki HA, Clements SD. Left ventricular aneurysm: a review. *Clin Cardiol* 1989;**12**:5–13.
84. Forman MB, Collins HW, Kopelman HA *et al.* Determinants of left ventricular aneurysm formation after anterior myocardial infarction: a clinical and angiographic study. *J Am Coll Cardiol* 1986;**8**:1256–62.
85. Popovic AD, Neskovic AN, Babic R *et al.* Independent impact of thrombolytic therapy and vessel patency on left ventricular dilation after myocardial infarction. Serial echocardiographic follow-up. *Circulation* 1994;**90**:800–7.
86. Sechtem U, Theissen P, Heindel W *et al.* Diagnosis of left ventricular thrombi by magnetic resonance imaging and comparison with angiocardiography, computed tomography and echocardiography. *Am J Cardiol* 1989;**64**:1195–9.
87. Sager PT, Perlmutter RA, Rosenfeld LE, McPherson CA, Wackers FJ, Batsford WP. Electrophysiologic effects of thrombolytic therapy in patients with a transmural anterior myocardial infarction complicated by left ventricular aneurysm formation. *J Am Coll Cardiol* 1988;**12**:19–24.
88. Ba'albaki HA, Clements SD. Left ventricular aneurysm: a review. *Clin Cardiol* 1989;**12**:5–13.
89. Cohen M, Packer M, Gorlin R. Indications for left ventricular aneurysmectomy. *Circulation* 1983;**67**:717–22.
90. Roberts WC, Morrow AG. Pseudoaneurysm of the left ventricle: an unusual sequel of myocardial infarction and rupture of the heart. *Am J Med* 1967;**43**:639–54.
91. Brown SL, Gropler RJ, Harris KM. Distinguishing left ventricular aneurysm from pseudoaneurysm. A review of the literature. *Chest* 1997;**111**:1403–9.
92. Gatewood RP, Nanda NC. Differentiation of left ventricular pseudoaneurysm from true aneurysm with two-dimensional echocardiography. *Am J Cardiol* 1980;**46**:869–78.
93. Frances C, Romero A, Grady D. Left ventricular pseudoaneurysm. *J Am Coll Cardiol* 1998;**32**:557–61.
94. Vecchio C, Chiarella F, Lupi G, Bellotti P, Domenicucci S. Left ventricular thrombus in anterior acute myocardial infarction after thrombolysis. A GISSI-2 connected study. *Circulation* 1991;**84**:512–19.
95. Nihoyannopoulos P, Smith GC, Maseri A, Foale RA. The natural history of left ventricular thrombus in myocardial infarction: a rationale in support of masterly inactivity. *J Am Coll Cardiol* 1989;**14**:903–11.
96. Funke Küpper AJ, Verheugt FWA, Peels CH, Galema TW, Roos JP. Left ventricular thrombus incidence and behavior studied by serial two-dimensional echocardiography in acute anterior myocardial infarction: left ventricular wall motion, systemic embolism and oral anticoagulation. *J Am Coll Cardiol* 1989;**13**:1514–20.
97. Stratton JR, Resnick AD. Increased embolic risk in patients with left ventricular thrombi. *Circulation* 1987;**75**:1004–11.

98. Keren A, Goldberg S, Gottlieb S *et al.* Natural history of left ventricular thrombi: their appearance and resolution in the post-hospital period of acute myocardial infarction. *J Am Coll Cardiol* 1990;**15**:790–800.
99. Thompson PL, Robinson JS. Stroke after acute myocardial infarction: relation to infarct size. *BMJ* 1978;**2**:457.
100. Konrad MS, Coffey CE, Coffey KS *et al.* Myocardial infarction and stroke. *Neurology* 1984;**34**:1403–9.
101. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 1993;**22**:1004–9.
102. Vaitkus PT, Berlin JA, Schwartz JS, Barnathan ES. Stroke complicating acute myocardial infarction: a meta-analysis of risk modification by anticoagulation and thrombolytic therapy. *Arch Intern Med* 1992;**152**:2020–4.
103. Collins R, MacMahon S, Flather M *et al.* Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996; **313**:652–9.
104. Mahaffey KW, Granger CB, Collins R *et al.* Overview of randomized trials of intravenous heparin in patients with acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 1996;**77**:551–6.
105. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
106. Weaver WD, Simes RJ, Betriu A *et al.* Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;**278**:2093–8.
107. Shelburne JC, Rubinstein D, Gorlin R. A reappraisal of papillary muscle dysfunction: correlative clinical and angiographic study. *Am J Med* 1969;**46**:862–71.
108. Izumi S, Miyatake K, Beppu S *et al.* Mechanism of mitral regurgitation in patients with myocardial infarction: a study using real-time two-dimensional Doppler flow imaging and echocardiography. *Circulation* 1987;**76**:777–85.
109. Lamas GA, Mitchell GF, Flaker GC *et al.* Clinical significance of mitral regurgitation after acute myocardial infarction. *Circulation* 1997;**96**:827–33.
110. Barzilai B, Gessler C, Pérez JE, Schaab C, Jaffe AS. Significance of Doppler-detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol* 1988;**61**:220–3.
111. Feinberg MS, Schwammenthal E, Shlizerman L, *et al.* Prognostic significance of mild mitral regurgitation by color Doppler echocardiography in acute myocardial infarction. *Am J Cardiol* 2000;**86**:903–7.
112. Thompson CR, Buller CE, Sleeper LA *et al.* Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? *J Am Coll Cardiol* 2000; **36**(Suppl. A):1104–9.
113. Patel AR, Mochizuki Y, Yao J, Pandian NG. Mitral regurgitation: comprehensive assessment by echocardiography. *Echocardiography* 2000;**17**:275–83.
114. Sohn DW, Shin GJ, Oh JK *et al.* Role of transesophageal echocardiography in hemodynamically unstable patients. *Mayo Clin Proc* 1995;**70**:925–31.
115. Fuchs RM, Heuser RR, Yin FCP, Brinker JA. Limitations of pulmonary wedge v waves in diagnosing mitral regurgitation. *Am J Cardiol* 1982;**49**:849–54.
116. Baxley W, Kennedy JW, Field B, Dodge HT. Hemodynamics in ruptured chordae tendinae and chronic rheumatic mitral regurgitation. *Circulation* 1973;**48**:1288–94.
117. Chatterjee K, Parmley WW, Swan HJC *et al.* Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus. *Circulation* 1973;**47**: 684–90.
118. Kishon Y, Oh JK, Schaff HV *et al.* Mitral valve operation in postinfarction rupture of a papillary muscle: immediate results and long-term follow-up of 22 patients. *Mayo Clin Proc* 1992;**67**:1023–30.
119. Yamanishi H, Izumoto H, Kitahara H, Kamata J, Tasai K, Kawazoe K. Clinical experiences of surgical repair for mitral regurgitation secondary to papillary muscle rupture complicating acute myocardial infarction. *Ann Thorac Cardiovasc Surg* 1998;**4**:83–6.
120. Leor J, Feinberg MS, Vered Z *et al.* Effect of thrombolytic therapy on the evolution of significant mitral regurgitation in patients with a first inferior myocardial infarction. *J Am Coll Cardiol* 1993;**21**:1661–6.
121. Kinn JW, O'Neill WW, Benzuly KH, Jones DE, Grines CL. Primary angioplasty reduces risk of myocardial rupture compared to thrombolysis for acute myocardial infarction. *Cathet Cardiovasc Diagn* 1997;**42**:151–7.
122. Shawl FA, Forman MB, Punja S, Goldbaum TS. Emergent coronary angioplasty in the treatment of acute ischemic mitral regurgitation: long-term results in five cases. *J Am Coll Cardiol* 1989;**14**:986–91.
123. Moore CA, Nygaard TW, Kaiser DL, Cooper AA, Gibson RS. Postinfarction ventricular septal rupture: the importance of location of infarction and right ventricular function in determining survival. *Circulation* 1986;**74**:45–55.
124. Edwards BS, Edwards WD, Edwards JE. Ventricular septal rupture complicating acute myocardial infarction: identification of simple and complex types in 53 autopsied hearts. *Am J Cardiol* 1984;**54**:1201–5.
125. Menon V, Webb JG, Hillis LD, Sleeper LA, *et al.* Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK. *J Am Coll Cardiol* 2000;**36**(Suppl. A):1110–6.
126. Lemery R, Smith HC, Giuliani ER, Gersh BJ. Prognosis in rupture of the ventricular septum after acute myocardial infarction and role of early surgical intervention. *Am J Cardiol* 1992;**70**:147–51.
127. Hill JD, Stiles QR. Acute ischemic ventricular septal defect. *Circulation* 1989;**79**(Suppl. I):I-112–15.
128. Helmcke F, Mahan EF, Nanda NC *et al.* Two-dimensional echocardiography and Doppler color flow mapping in the diagnosis and prognosis of ventricular septal rupture. *Circulation* 1990;**81**:1775–83.

129.Alvarez JM, Brady PW, Ross AM. Technical improvements in the repair of acute post infarction ventricular septal rupture. *J Cardiovasc Surg* 1992;**3**:198.
130.Landzberg MJ, Lock JE. Transcatheter management of ventricular septal rupture after myocardial infarction. *Semin Thorac Cardiovasc Surg* 1998;**10**:128–32.
131.Reddy SG, Roberts WC. Frequency of rupture of the left ventricular free wall or ventricular septum among necroscopy cases of fatal acute myocardial infarction since introduction of coronary care units. *Am J Cardiol* 1989;**63**:906–11.
132.Maggioni AP, Maseri A, Fresco C *et al.* Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). *N Engl J Med* 1993;**329**:1442–8.
133.Shapira I, Isakov A, Burke M, Almog C. Cardiac rupture in patients with acute myocardial infarction. *Chest* 1987; **92**:219–23.
134.Figueras J, Curos A, Cortadellas J, Sans M, Soler-Soler J. Relevance of electrocardiographic findings, heart failure, and infarct site in assessing risk and timing of left ventricular free wall rupture during acute myocardial infarction. *Am J Cardiol* 1995;**76**:543–7.
135.López-Sendón J, Gonzalez A, López de Sá E *et al.* Diagnosis of subacute left ventricular wall rupture after acute myocardial infarction: sensitivity and specificity of clinical, hemodynamic and echocardiographic criteria. *J Am Coll Cardiol* 1992;**19**: 1145–53.
136.Oliva PB, Hammill SC, Edwards WD. Cardiac rupture: a clinically predictable complication of acute myocardial infarction: a report of 70 cases with clinical-pathological correlations. *J Am Coll Cardiol* 1993;**22**:720–6.
137.Bashour T, Kabbani SS, Ellertson DG, Crew J, Hanna ES. Surgical salvage of heart rupture: report of two cases and review of the literature. *Ann Thorac Surg* 1983;**36**:209–13.
138.Pollak H, Nobis H, Miczoch J. Frequency of left ventricular free wall rupture complicating acute myocardial infarction since the advent of thrombolysis. *Am J Cardiol* 1994;**74**: 184–6.
139.Becker RC, Hochman JS, Cannon CP *et al.* Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin in Myocardial Infarction 9 Study. *J Am Coll Cardiol* 1999;**33**:479–87.
140.Honan MB, Harrell FE Jr, Reimer KA *et al.* Cardiac rupture, mortality and the timing of thrombolytic therapy: a meta-analysis. *J Am Coll Cardiol* 1990;**16**:359–67.
141.Figueras J, Cortadellas J, Evangelista A, Soler-Soler J. Medical management of selected patients with left ventricular free wall rupture during acute myocardial infarction. *J Am Coll Cardiol* 1997;**29**:512–18.
142.Tofler GH, Muller JE, Stone PH *et al.* Pericarditis in acute myocardial infarction: characterization and clinical significance. *Am Heart J* 1989;**117**:86–92.
143.Oliva PB, Hammill SC, Talano JV. Effect of definition on incidence of postinfarction pericarditis. Is it time to redefine postinfarction pericarditis? *Circulation* 1994;**90**:1537–41.
144.Jugdutt BI, Basualdo CA. Myocardial infarct expansion during indomethacin or ibuprofen therapy for symptomatic post infarction pericarditis. Influence of other pharmacologic agents during early remodelling. *Can J Cardiol* 1989;**5**: 211–21.
145.Pierard LA, Albert A, Henrard L *et al.* Incidence and significance of pericardial effusion in acute myocardial infarction as determined by two-dimensional echocardiography. *J Am Coll Cardiol* 1986;**8**:517–20.
146.Sugiura T, Iwasaka T, Takayama Y *et al.* Factors associated with pericardial effusion in acute Q wave myocardial infarction. *Circulation* 1990;**81**:477–81.
147.Renkin J, De Bruyne B, Benit E *et al.* Cardiac tamponade early after thrombolysis for acute myocardial infarction: a rare but not reported hemorrhagic complication. *J Am Coll Cardiol* 1991;**17**:280–5.
148.Dressler W. A post-myocardial-infarction syndrome: preliminary report of a complication resembling idiopathic, recurrent, benign pericarditis. *JAMA* 1956;**160**:1379–83.
149.Northcote RJ, Hutchison SJ, McGuinness JB. Evidence for the continued existence of the postmyocardial infarction (Dressler's) syndrome. *Am J Cardiol* 1984;**53**:1201–2.
150.Volpi A, Cavalli A, Turato R, Barlera S, Santoro E, Negri E. Incidence and short-term prognosis of late sustained ventricular tachycardia after myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio (GISSI-3) Data Base. *Am Heart J* 2001;**142**:87–92.
151.Antman EM, Berlin JA. Declining incidence of ventricular fibrillation in myocardial infarction. Implications for the prophylactic use of lidocaine. *Circulation* 1992;**86**:764–73.
152.Bigger JT, Dresdale RJ, Heissenbutter RH, Weld FM, Wit AL. Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance and management. *Prog Cardiovasc Dis* 1977;**19**:255–300.
153.Tofler GH, Stone PH, Muller JE *et al* and the MILIS study group. Prognosis after cardiac arrest due to ventricular tachycardia or ventricular fibrillation associated with acute myocardial infarction. *Am J Cardiol* 1987;**60**:755–61.
154.Volpi A, Maggioni A, Franzosi MG, Pampallona S, Mauri F, Tognoni G. In-hospital prognosis of patients with acute myocardial infarction complicated by primary ventricular fibrillation. *N Engl J Med* 1987;**317**:257–61.
155.Nicod P, Gilpin E, Dittrich H *et al.* Late clinical outcome in patients with early ventricular fibrillation after myocardial infarction. *J Am Coll Cardiol* 1988;**11**:464–70.
156.Volpi A, Cavalli A, Franzosi MG *et al* and the GISSI Investigators. One-year prognosis of primary ventricular fibrillation complicating acute myocardial infarction *Am J Cardiol* 1989;**63**:1174–8.
157.MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lignocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988;**260**:1910–6.
158.Da Silva RA, Hennekens CH, Lown B, Cascells W. Lignocaine prophylaxis in acute myocardial infarction: an evaluation of the randomised trials. *Lancet* 1981;**2**:855–8.
159.Norris RM, Barnaby PF, Brown MA *et al.* Prevention of ventricular fibrillation during acute myocardial infarction with intravenous propranolol. *Lancet* 1984;**2**:883–6.
160.Nordrehaug JE, Lippe GVD. Hypokalaemia and ventricular fibrillation in acute myocardial infarction. *Br Heart J* 1983; **50**:525–9.

161.Stewart DE, Ikram H, Espiner EA, Nicholls MG. Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease. *Br Heart J* 1985;**54**:290–7.
162.Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991;**303**: 1499–503.
163.Baxter GF, Sumeray MS, Walker JM. Infarct size and magnesium: insights into LIMIT-2 and ISIS-4 from experimental studies. *Lancet* 1996;**348**:1424–6.
164.ISIS Collaboration Group. ISIS-4: a randomized factorial trial assessing oral captopril, oral mononitrate and intravenous magnesium sulphate in 58 080 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**: 669–85.
165.Maggioni AP, Zuanetti G, Franzosi MG *et al.* Prevalence and prognostic significance of ventricular arrhythmias after myocardial infarction in the fibrinolytic era. GISSI-2 Results. *Circulation* 1993;**87**:312–22.
166.Teo K, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA* 1993;**270**:1589–95.
167.Echt DS, Liebson PR, Mitchell B *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324**:781–8.
168.Domanski MJ, Zipes DP, Schron E. Treatment of sudden cardiac death. Current understandings from randomized trials and future research directions. *Circulation* 1997;**95**: 2694–9.
169.Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). *Lancet* 1997;**349**:675–82.
170.Julian DG, Camm AJ, Frangin G *et al.* Randomised trial of the effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: European Myocardial Infarction Amiodarone Trial (EMIAT). *Lancet* 1997;**349**:667–74.
171.Boutitie F, Boissel JP, Connolly SJ *et al.* Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999;**99**:2268–75.
172.Moss AJ, Hall J, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillation Implantation Trial (MADIT). *N Engl J Med* 1996;**335**:1933–40.
173.The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**: 1576–83.
174.Connolly SJ, Gent M, Roberts RS *et al.* Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1287–302.
175.Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102**:748–54.
176.Domanski MJ, Sakseena S, Epstein AE *et al.* Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. *J Am Coll Cardiol* 1999;**34**:1090–5.
177.Connolly SJ, Hallstrom AP, Cappato R *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies; Antiarrythmics vs Implantable Defibrillator Study, Cardiac Arrest Study Hamburg, Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;**21**:2071–8.
178.Editorial MADIT II, the Multi-center Autonomic Defibrillator Implantation Trial II stopped early for mortality reduction, has ICD therapy earned its evidence-based credentials? *Int J Cardiol* 2002;**82**:1–5.
179.Crenshaw BS, Ward SR, Granger CB *et al.* for the GUSTO-1 Trial Investigators. Atrial fibrillation in the setting of acute myocardial infarction: the GUSTO-1 experience. *J Am Coll Cardiol* 1997;**30**:406–13.
180.Pizzetti F, Turazza FM, Franzosi MG *et al.* GISSI-3 Investigators. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. *Heart* 2001;**86**:527–32.
181.Sugiura T, Iwasaka T, Takahashi N *et al.* Factors associated with atrial fibrillation in Q wave anterior myocardial infarction. *Am Heart J* 1991;**121**:1409–12.
182.Rathore SS, Berger AK, Weinfurt KP *et al.* Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. *Circulation* 2000;**101**: 969–74.
183.Sakata K, Kurihara H, Iwamori K *et al.* Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction. *Am J Cardiol* 1997;**80**:1522–7.
184.Cowan JC, Gardiner P, Reid DS, Newell DJ, Campbell RW. A comparison of amiodarone and digoxin in the treatment of atrial fibrillation complicating suspected acute myocardial infarction. *J Cardiovasc Pharmacol* 1986;**8**:252–6.
185.Kontoyannis DA, Anastasiou-Nana MI, Kontoyannis SA, Zaga AK, Nanas JN. Intravenous amiodarone decreases the duration of atrial fibrillation associated with acute myocardial infarction. *Cardiovasc Drugs Ther* 2001;**15**:155–60.
186.Goldberg RJ, Zevallos JC, Yarzebski J *et al.* Prognosis of acute myocardial infarction complicated by complete heart block (the Worcester Heart Attack Study). *Am J Cardiol* 1992;**69**:1135–41.
187.Nicod P, Gilpin E, Dittrich H *et al.* Long-term outcome in patients with inferior myocardial infarction and complete atrioventricular block. *J Am Coll Cardiol* 1988;**12**:589–94.
188.Rathore SS, Gersh BJ, Berger PB, Oetgen WJ, Schulman KA, Solomon AJ: Acute myocardial infarction complicated by heart block in the elderly: prevalence and outcomes: *Am Heart J* 2001;**141**:47–54.

189. Harpaz D, Behar S, Gottlieb S, Boyko V, Kishon Y, Eldar M. Complete atrioventricular block complicating acute myocardial infarction in the thrombolytic era. SPRINT Study Group and the Israeli Thrombolytic Survey Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial. *J Am Coll Cardiol* 1999;**34**:1721–8.
190. Berger PB, Ruocco NA Jr, Ryan TJ, Frederick MM, Jacobs AK, Faxon DP. Incidence and prognostic implications of heart block complicating inferior myocardial infarction treated with thrombolytic therapy: results from TIMI II. *J Am Coll Cardiol* 1992;**20**:533–40.
191. Ritter WS, Atkins JM, Blomqvist CG, Mullins CB. Permanent pacing in patients with transient trifascicular block during acute myocardial infarction. *Am J Cardiol* 1976;**38**:205–8.
192. Atkins JM, Leshin SJ, Blomqvist G, Mullins CB. Ventricular conduction blocks and sudden death in acute myocardial infarction. Potential indications for pacing. *N Engl J Med* 1973;**288**:281–4.
193. Grigg L, Kertes P, Hunt D *et al.* The role of permanent pacing after anterior myocardial infarction complicated by transient complete atrioventricular block. *Aust N Z J Med* 1988;**18**: 685–8.
194. Ricou F, Nicod P, Gilpin E, Henning H, Ross J. Influence of right bundle branch block on short- and long-term survival after acute anterior myocardial infarction. *J Am Coll Cardiol* 1991;**17**:858–63.
195. Watson RD, Glover DR, Page AJ *et al.* The Birmingham Trial of permanent pacing in patients with intraventricular conduction disorders after acute myocardial infarction. *Am Heart J* 1984;**108**:496–501.
196. Bosch X, Theroux P, Roy D, Moise A, Waters DD. Coronary angiographic significance of left anterior fascicular block. *J Am Coll Cardiol* 1985;**5**:9–15.
197. Bosch X, Theroux P, Waters DD, Pelletier GB, Roy D. Early postinfarction ischemia: clinical, angiographic, and prognostic significance. *Circulation* 1987;**75**:988–95.
198. De Feyter PJ, Serruys PW, Soward A *et al.* Coronary angioplasty for early postinfarction unstable angina. *Circulation* 1986;**74**:1365–70.
199. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation* 1995;**91**:476–85.
200. Blanton C, Thompson PL. Role of coronary interventional procedures in improved postinfarction survival in the 1990s. *Am J Cardiol* 2001;**87**:832–7.
201. Levine FH, Gold HK, Leinbach RC *et al.* Safe early revascularization for continuing ischemia after acute myocardial infarction. *Circulation* 1979;**60**:I-5–I-9.
202. Kaul TK, Fields BL, Riggins SL, Dacumos GC, Wyatt DA, Jones CR. Coronary artery bypass grafting within 30 days of an acute myocardial infarction. *Ann Thorac Surg* 1995;**59**: 1169–76.
203. Hochberg MS, Parsonnet V, Gielinschky I *et al.* Timing of coronary revascularization after acute myocardial infarction. Early and late results in patients revascularized within seven weeks. *J Thorac Cardiovasc Surg* 1984;**88**:914–21.
204. Gersh BJ, Chesebro JH, Braunwald E *et al.* Coronary artery bypass graft surgery after thrombolytic therapy in the Thrombolysis in Myocardial Infarction Trial, Phase II (TIMI II). *J Am Coll Cardiol* 1995;**25**:395–402.
205. Madsen JK, Grande P, Saunamäki K *et al.* Danish multicenter randomized study of invasive vs conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). *Circulation* 1997;**96**: 748–55.
206. Balady G, Fletcher BJ, Froelicher ES *et al.* Cardiac rehabilitation programs. A statement for healthcare professionals from the American Heart Association. *Circulation* 1994;**90**: 1602–10.
207. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. *JAMA* 1993;**270**:1819–25.
208. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995;**91**:999–1005.
209. Ruberman W, Weinblatt E, Goldberg JD *et al.* Psychosocial influences on mortality after myocardial infarction. *N Engl J Med* 1984;**311**:552–9.
210. Ziegelstein RC, Fauerbach JA, Stevens SS *et al.* Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med* 2000;**160**:1818–23.
211. Follick MJ, Gorkin L, Capone RJ *et al.* Psychological distress as a predictor of ventricular arrhythmias in a post-myocardial infarction population. *Am Heart J* 1988; **116**:32–6.
212. Nair GV, Gurbel PA, O'Connor CM *et al.* Depression, coronary events, platelet inhibition, and serotonin reuptake inhibitors. *Am J Cardiol* 1999;**84**:321–3.
213. Carney RM, Blumenthal JA, Stein PK *et al.* Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001;**104**:2024–8.
214. O'Connor GT, Buring JE, Yusuf S *et al.* An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;**80**:234–44.
215. McAlister FA, Lawson FM, Teo KK, Armstrong PW. Randomised trials of secondary prevention programmes in coronary heart disease: systematic review. *BMJ* 2001;**323**: 957–62.
216. Frasure-Smith N, Lesperance F, Prince RH *et al.* Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. *Lancet* 1997; **350**:473–9.
217. Berkman LF, Jaffe AS. Enhancing Recovery In Coronary Heart Disease (ENRICHD) – Treatment of Depression and Social Isolation Post MI. Plenary Session VII. Late Breaking Trials. American Heart Association Scientific Sessions 2001.
218. Shapiro PA, Lesperance F, Frasure-Smith N *et al.* An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHAT Trial). Sertraline Anti-Depressant Heart Attack Trial. *Am Heart J* 1999;**137**:1100–6.

36 An integrated approach to the management of patients after the early phase of the acute coronary syndromes

Desmond G Julian

Changing definitions of myocardial infarction and unstable angina

The recent changes in the diagnostic criteria for myocardial infarction (MI) and unstable angina[1] make it difficult to compare contemporary trials with those undertaken many years ago. It is now appreciated that there is a spectrum of acute coronary syndromes and many cases that would previously have been classified as unstable angina would now be designated MI. It is, therefore, no longer appropriate to treat the different syndromes entirely separately. Nonetheless, there are important differences in management depending on whether or not the event is accompanied by, for example, elevation of the ST segment or raised troponin levels.

Management of the postinfarction patient

Treatment of the postinfarction patient can be divided into two categories – secondary prevention and the management of specific complications. Secondary prevention has been studied in many large and well-conducted trials and it is possible to arrive at some firm conclusions as to the optimal program. By contrast, the management of complications has seldom been submitted to randomized controlled trials, mainly for the reason that it may not be ethical to use placebo when seriously ill patients are being treated. Even in this context, however, two or more active treatments can be compared, but this has not often been undertaken.

Secondary prevention trials

Diet and dietary supplements

Although it is usual practice to advise patients after MI to adhere to a lipid lowering diet, no trials to date have shown this to be effective. Nonetheless, as drug trials have demonstrated the beneficial effect of lipid lowering on morbidity and mortality, it seems prudent to advise a diet that would have a similar effect. It has been found that, if 60% of saturated fats are replaced by other fats and if 60% of the dietary cholesterol is avoided, this would reduce blood total cholesterol level by about 0·8 mmol/l (10–15%),[2] sufficient to achieve a level below 5 mmol/l in many of those with "average" cholesterol levels.

Encouraging data have been provided from four studies in which an increase in the use of omega-3 fatty acids was tested. One study[3] suggested that advising the consumption of fatty fish at least twice a week reduced the risk of re-infarction and death. In a study from India,[4] it was claimed that patients taking a diet high in fiber, omega-3 fatty acids, antioxidants and vitamins had a 42% reduction in cardiac death, and a 45% reduction in total mortality at 1 year compared with a control group on a standard "low fat" diet. In the prematurely terminated Lyon Heart Study,[5] there was reported to be a 70% reduction in MI, coronary mortality, and total mortality after 2 years. In the fourth study, GISSI-Prevenzione,[6] 11 374 patients were randomized to omega-3 or vitamin E after hospital discharge or within 3 months of MI, according to a factorial design. Fish oil, but not vitamin E, showed significant benefit at a median time of 42 months.

Each of the first three trials is open to criticism but, in the absence of any evidence of harm, it is not unreasonable to recommend increased consumption of fatty fish, nuts, vegetables, and fruit.

Smoking

It has not been possible to conduct randomized studies of smoking cessation after MI, but observational studies show that those who quit smoking have a mortality in the succeeding years less than half that of those who continue to do so.[7] This is, therefore, potentially the most effective of all secondary prevention measures. Unfortunately, resumption of smoking is common after return home, and it is important to establish methods to prevent this. A randomized study has demonstrated the effectiveness of a program

in which specially trained nurses maintained contact with patients over several months.[8]

Cardiac rehabilitation

Two systematic reviews of exercise-based rehabilitation trials concluded that these reduced mortality after infarction by 20–25%.[9,10] A recent Cochrane review of exercise-based rehabilitation for coronary heart disease (CHD) has been published.[11] This review included not only patients who had experienced MI but also those with angina pectoris or who had undergone revascularization interventions. The outcomes in 8440 patients were reported (7683 contributing to the mortality outcome). For exercise-only interventions, there was a 31% reduction in mortality; the corresponding figure for comprehensive cardiac rehabilitation was 26%.

These claims must be viewed with caution as no single trial has shown a significant benefit, and there has been no evidence of a reduction in re-infarction. Furthermore, it is known that several negative trials of rehabilitation have gone unreported, and the studies showing large reductions in mortality were mainly undertaken before the widespread use of aspirin, β blockers, and ACE inhibitors in postinfarction patients. Nonetheless, there is no doubt that such programs improve exercise performance and a sense of wellbeing, and can be justified on that basis.

Antiplatelet and anticoagulant treatment

The effectiveness of antiplatelet drugs in unstable angina has been demonstrated in many trials, but it must be borne in mind that many patients included in these trials would now be regarded as having sustained an MI. In the US Veterans Administration Study trial of aspirin reported by Lewis *et al*,[12] the intention-to-treat analysis at 12 weeks demonstrated a risk reduction in the primary end point of death and myocardial infarction of 41%. At longer term follow up, mortality was 5·5% in the aspirin group compared with 9·6% in the control group. In the Canadian Multicenter Trial,[13] cardiac death was reduced by aspirin from 9·7% to 4·3%. No benefit was observed with sulfinpyrazone. In the Antithrombotic Trialists' Collaboration report on 12 unstable angina trials of antiplatelet therapy published up to 1997,[14] the number of vascular events was reduced by 46% from 13·3% to 8·0%.

The value of antiplatelet treatment with aspirin in the acute phase of myocardial infarction was shown clearly by the ISIS-2 trial,[15] and this has been further confirmed by the Antithrombotic Trialists' Collaboration.[14] In the latter survey of 19 288 patients included in trials up to 1997, 1 month of antiplatelet treatment was associated with 38 fewer events per 1000 patients, with non-fatal MI being reduced by 13 events per 1000, vascular deaths by 23 per 1000, and non-fatal stroke by two per 1000. Against this was an increase of one to two extracranial bleeds per 1000. In the trials analyzed, aspirin dosages ranged from 75 to 1500 mg daily. There is some evidence that the lower dosages were effective and produced fewer adverse effects.

In this report,[14] it was also observed that there were 36 fewer serious vascular events in 18 788 patients with a prior history of MI followed for a mean duration of 27 months. There were 18 fewer non-fatal infarctions, 14 fewer vascular deaths, and five fewer non-fatal strokes per 1000 patients treated. On the other hand, there were three additional major extracranial bleeds. Because few patients have contraindications to aspirin therapy, it is appropriate for most postinfarction patients.

Clopidogrel was studied as an alternative to aspirin in the CAPRIE trial of 11 630 survivors of MI.[16] This failed to show any difference between this drug and aspirin in terms of death or re-infarction. It had few side effects and can be considered an alternative for those who cannot be prescribed aspirin.

Subsequently, the CURE trial[17] has demonstrated the value of adding clopidogrel to aspirin in patients with unstable angina, many of whom would now be classified as having sustained an MI because of their enzyme/troponin levels. This combination reduced the primary end point of cardiovascular death, myocardial infarction, and stroke by 20% when administered over a mean period of 9 months. Further trials will be necessary to establish how long it is cost effective to maintain the combination.

The role of antithrombins after myocardial infarction is less clear. In the Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) study,[18] aspirin alone was compared with aspirin with intravenous heparin for 3–4 days, followed by warfarin. The primary outcome of death, MI, and recurrent angina was observed in 27% of the aspirin group compared with 10% in the anticoagulant group ($P = 0{\cdot}004$). However, the difference was no longer significant at 12 weeks.

In the Fragmin during Instability in Coronary Artery Disease (FRISC) study,[19] aspirin alone was compared with aspirin combined with low molecular weight heparin. While at 6 days, the rate of death and myocardial infarction was 4·8% and 1·8% respectively ($P = 0{\cdot}001$), the difference at 10·7% and 8·0% respectively was no longer significant at 40 days ($P = 0{\cdot}07$).

In the Thrombolysis in Myocardial Infarction (TIMI) 11B trial,[20] low molecular weight enoxaparin was compared with intravenous unfractionated heparin during the acute phase, followed by placebo subcutaneous injection for 35 days. At the specified primary outcome time of 43 days, there was a significant reduction in the composite end point of death, re-infarction, and severe recurrent ischemia.

In FRISC II,[21] patients were randomized to the low molecular weight heparin, dalteparin, or placebo. The primary end point of death or MI at 3 months occurred in

6·7% of the dalteparin patients and 8% of those on placebo ($P = 0·17$).

The use of long-term heparin therapy after MI has not been firmly established.

In a meta-analysis of oral anticoagulant trials in patients with coronary artery disease (CAD) performed between 1960 and 1999, Anand and Yusuf[22] concluded that high or moderate intensity oral anticoagulation is effective in reducing MI and stroke but at the expense of an increased risk of bleeding. Low intensity anticoagulation together with aspirin does not seem superior to aspirin alone.

Since this review, two anticoagulant trials have been presented but not yet published. In the Combination Hemotherapy And Mortality Prevention (CHAMP) study,[23] 5059 patients were randomized after an MI to aspirin 160 mg/day or a combination of aspirin 81 mg/day and warfarin titrated to an INR of 1·5–2·5 IU. There was no difference in the end points of overall mortality, cardiovascular mortality, or non-fatal MI.

In the WARIS II trial of antithrombotic therapy after MI,[24] 3630 patients were randomized to one of three regimens: aspirin alone in a dosage of 160 mg/day, warfarin alone to reach a target INR of 2·8–4, or a combination of aspirin 75 mg and warfarin with a target INR of 2·0–2·5. The primary composite end point of death, non-fatal re-infarction, or thromboembolic stroke occurred in 20% of the patients on aspirin, 16·7% of those on warfarin, and 15% of those on a combination of these drugs. The superiority of the combination over aspirin was highly significant at $P = 0·0005$, but there was no significant difference between the two warfarin groups. Major bleeding occurred at a rate of 0·15% per year in the aspirin alone group, 0·58% per year in the warfarin alone group, and 0·52%/year in the combined group. It may be concluded that the beneficial effect of aspirin after MI may be augmented by the addition of warfarin.

Whilst it is clear that adding clopidogrel to aspirin is beneficial in those who have experienced unstable angina, it is still unresolved whether adding this drug to those who have had an ST elevation MI is cost effective.

Whether antithrombins should be routinely used is uncertain. It is likely that the beneficial results of WARIS II reflect the use of a more effective anticoagulant regimen.

β Blockers

Several trials and meta-analyses undertaken in the pre-fibrinolytic era have demonstrated that β adrenoceptor blocking drugs reduce mortality and re-infarction by 20–25% in those who have recovered from acute MI.[25,26] Recently, the CAPRICORN trial of carvedilol involved 1959 postinfarction patients with a left ventricular ejection fraction of 40% or less:[27] 46% of the patients had been treated with fibrinolysis or primary angioplasty, and nearly all patients were also being treated with ACE inhibitors and aspirin. All-cause mortality was reduced from 15% to 12% ($P = 0·03$). This study confirms that β blockers add to the benefit of ACE inhibitors and are of value in patients with impaired left ventricular function, many of whom have experienced heart failure. It is not possible to say whether carvedilol is superior to the other β blockers (propranolol, metoprolol, timolol, and acebutolol), which have been shown to be effective in the postinfarction patient.

Physicians have been, in the past, reluctant to administer β blockers to patients who are or have been in cardiac failure. This has been partly responsible for the relatively low usage of β blockers in the postinfarction patient. Recent trials in heart failure (see below) have shown that patients with heart failure benefit from β blockers, provided the heart failure is stable and the dosage carefully uptitrated.

About one quarter of postinfarction patients have contraindications to β blockade because of uncontrolled heart failure, respiratory disease, or other conditions. Of the remainder, perhaps half can be defined as of low risk,[26,28] in whom β blockade exerts only a marginal benefit, bearing in mind the minor though sometimes troublesome side effects. β Blockers are most clearly indicated in the higher risk patient without contraindications.

Calcium antagonists

Trials with dihydropyridine calcium antagonists[29] have failed to show a benefit in terms of improved prognosis after MI.

One trial with verapamil[30] (DAVIT-II) suggested that it prevented re-infarction and death. Trials with diltiazem[31] have failed to show a reduction in mortality; indeed, it was increased in those with impaired left ventricular function. A review of heart rate-lowering antagonists in hypertensive postinfarction patients[32] showed a decrease in mortality and recurrent infarction in hypertensive postinfarction patients without heart failure, but an increase in those with this complication. The INTERCEPT trial[33] compared once daily diltiazem with placebo in 874 patients with acute MI, not complicated by heart failure, who had been treated with fibrinolysis. There was no significant reduction in the primary end point of a composite of cardiac death, non-fatal re-infarction, or refractory ischemia, but there was a reduction in non-fatal cardiac events and in the need for revascularization.

Nitrates

Oral or transdermal nitrates did not improve prognosis in the first few weeks after MI in the ISIS-4[34] and GISSI-3[35] trials. There have been no long-term trials of nitrates after MI.

Angiotensin converting enzyme (ACE) inhibitors

Several trials have established that ACE inhibitors reduce mortality after acute MI.[36–40] In the SAVE trial,[36] patients

who survived the acute phase of infarction were recruited to receive captopril or placebo if they had an ejection fraction less than 40% on nuclear imaging, and if they were free of manifest ischemia on an exercise test. No mortality benefit was seen in the first year, but there was a 19% mortality reduction in 3–5 years of follow up (from 24·6 to 20·4%) ($P = 0·019$). Fewer re-infarctions and less heart failure were, however, seen even within the first year. In the AIRE trial[37] postinfarction patients were randomized to ramipril or placebo after an MI that had been complicated by the clinical or radiological features of heart failure. At an average of 15 months later, the mortality was reduced from 22·6% to 16·9% (a 27% reduction) ($P = 0·002$). In the TRACE study,[38] patients were randomized to trandolapril or placebo if they had left ventricular dysfunction as demonstrated by a wall motion index of 1·2 or less. At an average follow up of 108 weeks, the mortality was 34·7% in the treated group and 42·3% in the placebo group ($P = 0·001$).

A systematic review of these trials[39] found that at a mean treatment duration of 31 months, there were 702 deaths (23·4%) of 2995 patients randomized to receive ACE inhibitor and 866 (29·1%) of 2971 randomized to control ($P < 0·0001$). Comparable figures for re-infarction were 10·8% and 13·2% ($P < 0·0057$).

In the SMILE (Survival of Myocardial Infarction Long-Term Evaluation) study,[40] 1556 patients with anterior MI were randomized to zofenopril or placebo within 24 hours of onset, the treatment being continued for 6 weeks. At 1 year, the mortality rate was significantly lower in the zofenopril group (10·0%) than in the placebo group (14·1%) ($P = 0·011$). These studies provide powerful evidence of the effectiveness of ACE inhibitors in patients who have experienced heart failure in the acute event, even if no features of this persist, who have an ejection fraction of less than 40%, or a wall motion index of 1·2 or less, provided there are no contraindications. Analysis of the results of these studies indicate that ACE inhibitors are beneficial not only in patients with poor left ventricular function even if they have not experienced heart failure, but also in those who have suffered from heart failure even if their left ventricular function is relatively good. The SMILE study suggests that ACE inhibitor therapy may be appropriate for anterior infarction even in the absence of poor ventricular function. As discussed in chapter 34, there is a case for administering ACE inhibitors to all patients with acute infarction from admission, provided there are no contraindications. Against such a policy is the increased incidence of hypotension and renal failure in those receiving ACE inhibitors in the acute stage, and the small benefit in those at relatively low risk, such as patients with small inferior infarctions.

The indications for ACE inhibitors after infarction have been radically altered following the results of the Heart Outcomes Prevention Evaluation Study (HOPE).[41] This study of ramipril versus placebo included a wide range of patients at high risk of serious cardiovascular events, but 52% of the patients had had a prior MI and 25% unstable angina. Patients with a history of clinical heart failure or a ejection fraction known to be less than 0·40 were excluded. There seemed little difference in the relative benefit observed in the different categories of patients included in the trial, and the overall results may be taken to apply to postinfarction patients. There was a very clear reduction in the primary end point of a composite of cardiovascular death, heart attack, and stroke in the ramipril arm (placebo 17·8%, ramipril 14·0% $P < 0·001$). The incidence of MI was reduced from 12·3% to 9·9%, and stroke from 4·9% to 3·4%. There were comparable reductions in overall mortality, need for hospitalization, and revascularization. It is not yet known whether similar results would be seen with other ACE inhibitors, but this question should be answered by the ongoing EUROPA trial with perindopril[42] and the PEACE trial with trandolapril.[43]

Antiarrhythmic drugs

Trials of antiarrhythmic drugs after MI have proved disappointing. A meta-analysis of 18 trials of Class I drugs showed a significant 21% increase in mortality.[44] The SWORD trial[45] of the Class III drug *d*-sotalol was stopped because of an increased mortality. The Class III agent dofetilide was studied in the DIAMOND trial of 1510 patients with recent MI and left ventricular dysfunction.[46] There was no difference between dofetilide and placebo with regard to overall mortality, cardiac mortality, or arrhythmic death. Similar results have been reported with azimilide in the Azimilide post-Infarct Survival Evaluation trial (ALIVE).[47]

Amiodarone has been studied in four trials. Two small trials were favorable, but the two larger trials – EMIAT[48] and CAMIAT[49] – failed to demonstrate a reduction in total mortality. However, there was a reduction in arrhythmic death in these studies, and a pooling of results from amiodarone trials following MI shows a significant reduction in arrhythmic death (2·6% *v* 4·2% per year) and a non-significant trend towards lower total mortality (10·9% *v* 12·3%).[50] Unlike the other Class I and III antiarrhythmic drugs, amiodarone does not appear to have an important pro-arrhythmic effect, but its use is limited by its significant side effects.

Lipid lowering agents

The Scandinavian Simvastatin Survival Study (4S)[51] clearly demonstrated the benefits of lipid lowering in a population of 4444 anginal and/or postinfarction patients with serum cholesterol levels of 5·5–8·0 mmol/l (212–308 mg/dl) after dietary measures had been tried. Overall mortality at a median of 5·4 years was reduced by 30% (from 12 to 8%) ($P = 0·0001$). This represented 33 lives saved per 1000

patients treated over this period. There were substantial reductions in coronary mortality and in the need for coronary bypass surgery. Older patients appeared to benefit as much as younger patients. Relatively few women were recruited, perhaps accounting for the failure to show a significant reduction in mortality, but coronary events were reduced as they were in men.

In the Cholesterol and Recurrent Events (CARE) trial,[52] 4159 post-MI infarction patients with "average" cholesterol levels were randomized to pravastatin or placebo at least 3 months after the acute event: 13·2% of the placebo group and 10·2% of the treatment group ($P = 0·003$) experienced a primary end point (fatal coronary event or non-fatal MI) in the trial which lasted 5 years. There was also a reduction in stroke and in the need for coronary artery bypass surgery and angioplasty. The effects appeared to be greater in women than in men, and in those with higher low density lipoprotein (LDL) levels. Indeed, no benefit was shown in patients with LDL levels below 125 mg/dl (3·25 mmol/l).

In the Long-term Intervention with pravastatin in ischemic heart disease (LIPID) study,[53] 9014 patients with a history of MI or unstable angina, and with cholesterol 4·0–7·0 mmol/l were randomized to pravastatin or placebo. After a mean follow up of 6·1 years, overall death rate was 14.1% in the placebo group and 11·0% in the pravastatin group ($P < 0·001$) – coronary death rates were 8·3% and 6·4% respectively. There were corresponding reductions in MI and need for revascularization.

The Heart Protection Study (HPS)[54] has provided further information about certain categories of patient, such as women and the elderly, poorly represented in the earlier trials. It has shown that these groups are also benefitted to a similar degree.

The trials cited above were started in postinfarction patients some months or years after the acute event. To determine whether patients would benefit from an earlier administration of lipid lowering, the MIRACL trial[55] of atorvastatin versus placebo was started within days of the onset of unstable angina in 3086 patients not scheduled for early intervention. The primary end point of death, non-fatal MI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia occurred in 14.8% of the atorvastatin patients and 17·4% of the placebo patients ($P = 0·048$). The benefit was essentially confined to the prevention of recurrent myocardial ischemia.

In the FLORIDA study,[56] patients with a recent MI and a cholesterol value less than 6·5 mmol/l on admission were started on fluvastatin or placebo immediately on discharge. The primary end point was that of myocardial ischemia on Holter monitoring; this was observed in 17% of both groups, but at 1 year 2·6% of the fluvastatin group and 4.0% of the placebo group had died. It is difficult to draw confident conclusions from these studies, but it would seem that it is safe to start lipid lowering therapy soon after the acute event, and it may be wise to do so if the patient is known to be hyperlipidemic in spite of dietary measures.

In the VA-HIT trial,[57] 2531 men with documented CHD, with HDL cholesterol at or less than 40 mg/dl (1 mmol/l), LDL cholesterol at or less than 140 mg/dl (3·6 mmol/l), and triglycerides at or less than 300 mg/dl were randomized to gemfibrozil or placebo. There was a significant reduction in the combined end point of coronary death and MI in the treatment arm, with events occurring in 21·6% of the placebo group and 17·3% of the gemfibrozil group ($P = 0·006$).There were non-significant reductions in death due to CHD, total death, and stroke, but there was a significant reduction in non-fatal MI (from 14·5% to 11·6%, $P = 0·02$).

The Bezafibrate Infarction Prevention (BIP) trial[58] randomized 3090 patients with previous MI or stable angina to bezafibrate or placebo. The primary end point of MI or sudden death occurred in 13·6% of those on bezafibrate and 15·0% in those on placebo ($P = 0·26$).

These trials have firmly established the use of statins in post-MI patients with "average" or high lipid levels. Furthermore, patients with lipid abnormalities other those studied in these trials (for example, hypertriglyceridemia) might benefit from other lipid lowering regimens.

Hormone replacement therapy (HRT)

Many epidemiologic trials have suggested that HRT might reduce cardiovascular risk substantially, but the only large-scale trial in patients with CHD – the Heart and Estrogen/progestin trial (HERS)[59] – showed a significant (52%) increase in the primary combined end point of non-fatal MI and coronary death in the first year of treatment (42·5/1000 person-years compared with 28·0 in the placebo group). There was a trend towards fewer events in the treated group in the ensuing years and, at an average of 4·1 years, there was no longer a significant difference between the two groups. The ongoing Estrogen in the Prevention of Reinfarction Trial (ESPRIT) is studying the effect of estrogen alone in a postinfarction population.

Percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery (CABG)

The role of coronary interventions in preventing recurrent infarction and death when performed in the days after MI remains uncertain. The SWIFT (Should We Intervene Following Thrombolysis?),[58] TIMI-II,[61] and TIMI IIIB trials[61] failed to show any benefit from intervention in terms of recurrent infarction and death in patients after fibrinolysis.

In the Veterans Affairs Non-Q wave Infarction Strategies in-Hospital (VANQWISH) trial,[63] patients with non-Q wave MI were randomized to an invasive or a conservative strategy. In the former, cardiac catheterization was carried out within 3 to 7 days, and, subsequently, PTCA or CABG was

carried out according to the coronary anatomy; a total of 920 patients were randomized. Death and MI occurred in 7·8% of the invasive arm and 5·7% of the conservative arm at hospital discharge ($P = 0·012$).

In the Danish Acute Myocardial Infarction (DANAMI) study,[64] however, 1008 survivors of a first acute infarction in whom ischemia could be induced were randomized to catheterization and revascularization, or standard medical therapy. There were significantly fewer non-fatal infarctions in the 2·5 year follow up period in those who underwent revascularization ($P = 0·0038$), as well as a reduction in hospitalization and in medical costs.

In the FRISC II trial,[65] there was a significant reduction in death and/or MI in those randomized to coronary angiography, followed, if appropriate, by angioplasty or CABG in patients with unstable CAD. At 6 months, there was a reduction in the composite end point of death and MI from 12·1% in the non-invasive group to 9·4% in the invasive group ($P = 0·031$). At 1 year, the comparable figures were 14.1% versus 10·4% ($P = 0·005$).[66] The benefit was predominantly in those with raised troponin levels and/or ST depression at entry. There was no evidence of a benefit in women.[67]

In TACTICS-TIMI-18,[68] 2220 patients with an acute coronary syndrome without ST elevation were all administered tirofiban, and randomized to a conservative or invasive strategy. The primary end point of death, MI, or rehospitalization at 6 months occurred in 19·4% of the conservative group, and 15·9% in the invasive group ($P = 0·025$). Death and/or MI occurred in 9·5% and 7·3% respectively ($P < 0·05$). The benefit seemed to be largely confined to those with elevation in troponin or creatine kinase, and in those without prior aspirin treatment.

It seems probable that an invasive approach is appropriate for acute coronary syndromes if there are raised cardiac markers or active ischemia and when there has not been an intervention during the acute event. The place of such a strategy in women, or in those who have not shown these features, remains uncertain.

Management of the complications of MI

Cardiac failure

On the basis of the trials with ACE inhibitors described above and the results of the Consensus[69] and SOLVD[70] trials, ACE inhibitors should be given to patients in heart failure without contraindications, in addition to diuretics and, perhaps, digitalis. The use of diuretics and digitalis is largely based on observational studies.

Several trials have established the value of β blockers in the treatment of heart failure, which, in the majority of cases, was due to ischemic heart disease. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II)[71] of patients with NYHA (New York Heart Association) classes III and IV was stopped prematurely, after it was found that the bisoprolol-treated group had a highly significantly better survival rate than the placebo group. At an average of 1·4 years, there was a 17·3% mortality rate in the placebo group compared with 11·8% in the bisoprolol group. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[72] was similar, except that the active agent was metoprolol and it included patients with NYHA class II heart failure. All-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (7·2%, per patient-year of follow up *v* 11·0%, $P = 0·00009$). In the COPERNICUS trial (Carvedilol Prospective Randomized Cumulative Survival),[73] 2289 patients with severe chronic heart failure were randomized to carvedilol or placebo. There were 190 deaths in the placebo group and 135 in the carvedilol group – a 35% reduction in the risk of death ($P = 0·0014$). By contrast, no overall benefit was seen in the BEST (Beta-blocker Evaluation Survival trial)[74] in which 2708 patients with severe chronic heart failure were randomized to receive either bucindolol or placebo. A subgroup analysis suggested that there was a benefit in non-black patients. Whether the different results in BEST were due to chance, the drug being tested, or a different population is uncertain. It would seem that β blockade is effective in patients with heart failure without contraindications.

The Randomized Aldactone Evaluation Study (RALES) study[75] concerned patients with a history of NYHA class IV heart failure and an ejection fraction of less than 40%, who had already received ACE inhibitor therapy. Patients were randomized to receive spironolactone or placebo. The trial was stopped when patients had been followed for a minimum of 18 months. Mortality was reduced by a quarter from 40% to 27% ($P = 0·001$).

It seems reasonable to suggest that patients with NYHA class II–III should receive both β blockers and ACE inhibitors, and that spironolactone should be added in the more severe cases.

Angina pectoris

There have been few randomized studies of the therapy of angina after infarction. The DANAMI[64] study referred to above suggests that PTCA and CABG have an important role in controlling symptoms and improving prognosis.

Life-threatening arrhythmias

As mentioned above, the use of antiarrhythmic drugs is potentially hazardous in the postinfarction patient. However, the findings of the EMIAT[47] and CAMIAT[48] studies have shown that amiodarone is relatively free of arrhythmogenesis, and is effective in preventing sudden death in high-risk patients without life-threatening arrhythmias. It seems an appropriate therapy for those with such arrhythmias.

The place of implantable defibrillators (ICD) in the post-infarction patient with arrhythmias remains uncertain, although recent trials have been encouraging. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT),[76] 202 patients with prior MI, together with an ejection fraction of 0·35 or less, unsustained ventricular tachycardia, and non-suppressible ventricular tachycardia on electrophysiologic study, were randomly assigned to an implantable defibrillator or conventional medical therapy. At an average follow up of 27 months, there were 15 deaths in the defibrillator group and 39 deaths in the conventionally treated group ($P = 0{\cdot}009$).

In the Antiarrhythmics versus Implantable Defibrillators (AVID) Trial,[77] in which many of the patients were post-infarction, half of those included had experienced ventricular fibrillation and the other half serious ventricular tachycardia. After three years, 25% of the patients in the defibrillator group had died compared with 36% of patients treated with antiarrhythmic drugs ($P < 0{\cdot}02$).

In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)[78] postinfarction patients with an ejection fraction of 0·30 or less were randomized to an implantable defibrillator or conventional medical therapy. At an average follow up of 20 months, 19·8% of the conventional group had died compared with 14.2% of the defibrillator group ($P = 0{\cdot}016$).

It is evident that an implantable defibrillator is highly effective in the types of patient included in these studies, but its eventual place in the prevention of sudden death following MI remains to be determined.

Limitations of the evidence available

While randomized clinical trials provide the most reliable evidence of efficacy, their findings may not readily be applied to a wide spectrum of patients with the given condition, particularly if the entry criteria are very rigidly defined. Furthermore, even though the internal validity may be beyond question, few trials are sufficiently powered to permit reliable estimates of effect in subgroups, such as women or the elderly, or in relation to concomitant therapy. The latter problem is compounded by the fact that there may be interactions between effective agents.

Subgroup analysis is rightly suspect, although it is important to differentiate between "proper subgroups" (based on baseline characteristics) and "improper subgroups" based on findings after entry into the trial.[79] Analysis of proper subgroups may be of great importance, particularly when there are marked differences in risk in various baseline characteristics so that, even if the effect of therapy is relatively the same whatever the risk, the absolute effect will be very different. In postinfarction and postunstable angina patients, it is possible to define high-, medium-, and low-risk patients on quite simple clinical and investigational criteria, and the probable effect of the secondary preventive treatment can then be estimated. Thus, one can anticipate little benefit from β blockers or ACE inhibitors in a patient with a small inferior first infarction who has had no complications in the acute phase, whereas the patient, who has had heart failure brought under control, remains at high risk and would benefit from both these therapies.

A further problem with applying trial results to practice is that of adherence to therapy. There is abundant evidence that compliance falls off if therapies have to be taken more than twice a day and when more than three types of drug are prescribed. It is now commonplace for patients to be given five or more drug therapies, and several widely recommended drugs (for example, captopril) have to be taken three or more times a day.

Increasingly, the cost of therapies is being critically scrutinized. An outstanding example is that of the statins, which are now being recommended for most patients with manifest coronary disease. As pointed out by Yusuf and Anand,[80] based on the 4S study, the cost effectiveness of this therapy in high-risk individuals is very favorable. Pedersen *et al*[81] have concluded that the drug costs of treatment are largely offset by savings that result from fewer hospitalizations and less need for revascularization.

These estimates were made on assumptions from the United States. They will be very different in countries with substantially lower hospitalization costs but are also very sensitive to the cost of the drug.

Both compliance issues and health economic considerations argue for economy in the prescription of drugs, and this will influence the integrated approach to management.

An integrated approach to post-MI and unstable angina patients

As far as secondary prevention is concerned, it is possible to base therapy on the results of well-conducted randomized clinical trials. However, one must bear in mind that it may not be feasible to undertake randomized trials with regard to certain lifestyle factors, such as smoking and diet, nor can patients with major remediable symptoms be subjected to placebo-controlled trials. One can, however, advise the cessation of smoking based on strong observational data, and recommend a "Mediterranean" diet, knowing that it is probably beneficial and unlikely to have any harmful effects. The same is true of exercise-based rehabilitation programs.

Aspirin should be administered to all patients with these diagnoses, unless contraindicated. Clopidogrel should be added, at least in the short term, to patients who have had an acute coronary syndrome without ST elevation; it is still not possible to conclude for how long it should be given, or whether it should be given to patients who have sustained an ST elevation MI.

β Blockers should be considered in all patients but the risks and benefits should be carefully weighed up in those at low risk. Calcium antagonists and nitrates should be prescribed for symptomatic reasons only, the former should probably be avoided in those with heart failure or poor left ventricular function.

ACE inhibitors should be prescribed for all patients (except those with contraindications) who have been or are in heart failure, as well as those who have poor left ventricular function. There is also a strong case for giving ramipril to patients who fulfill the criteria of the HOPE trial.

Patients with average or raised lipid levels should first be treated by dietary means, but appropriate lipid modifying therapy should be given if an adequate fall in LDL is not achieved.

PTCA and CABG should be considered in patients with recurrent angina or easily provoked ischemia. Such patients should have coronary angiography and the choice of treatment determined by the anatomical and functional findings.

Evidence-based secondary prevention therapies for postinfarction patients

- Smoking cessation **Grade B**
- Lipid lowering diet **Grade C**
- Lipid lowering drugs if diet fails **Grade A**
- Aspirin for all patients without contraindications. **Grade A** Other antiplatelet agents (for example, clopidogrel) if aspirin contraindicated. **Grade A** Clopidogrel added to aspirin in patients who have experienced non-ST segment elevation MI or unstable angina. **Grade A**
- β Blockers, particularly for high-risk patients, in the absence of contraindications. **Grade A**
- ACE inhibitors for all patients with severely impaired left ventricular function or heart failure. **Grade A**
- In the absence of heart failure, ramipril for those who fulfill the criteria for the HOPE trial. **Grade A**
- Percutaneous transluminal angioplasty or CABG for patients with persistent readily induced ischemia or angina, **Grade A** or for patients with non-ST segment elevation MI or unstable angina with raised troponin levels. **Grade A**

References

1. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined. *J Am Coll Cardiol* 2000;**36**:959–69.
2. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;**314**:112–17.
3. Burr ML, Fehily AM, Gilbert JF *et al.* The effects of changes in fat, fish and fibre intakes on death and myocardial infarction: diet and reinfarction trial. *Lancet.* 1989;**ii**:757–81.
4. Singh RB, Rastogi SS, Verma T *et al.* Randomised controlled trial of cardioprotective diet in patients with acute myocardial infarction: results of one year follow-up. *BMJ* 1992;**304**:1015–19.
5. de Lorgeril M, Renaud S, Mamelle N *et al.* Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;**343**:1454–9.
6. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;**354**:447–55.
7. Åberg A, Bergstrand R, Johansson S *et al.* Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. *Br Heart J* 1983;**49**:416–22.
8. Taylor CB, Houston-Miller N, Killen JD, De Busk RF. Smoking cessation after acute myocardial infarction: effect of a nurse-managed intervention. *Ann Intern Med* 1990;**113**:118–32.
9. O'Connor GT, Buring JE, Yusuf S *et al.* An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;**80**:234–44.
10. Oldridge NB, Guyatt GH, Fischer MD, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized trials. *JAMA* 1988;**260**:945–50.
11. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease (Cochrane Review). *Cochrane Database Syst Rev* 2001;**1**:CD001800.
12. Lewis HD, Davis J, Archibald D *et al.* Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. *N Engl J Med* 1983;**309**:396–403.
13. Cairns J, Gent M, Singer J *et al.* Aspirin, sulfinpyrazone or both in unstable angina: results of a Canadian Multicenter trial. *N Engl J Med* 1985;**313**:1369–75.
14. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002;**324**:71–80.
15. ISIS-2 (Second International Study of Infarct Survival Collaborative Group). Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected myocardial infarction. ISIS-2. *Lancet* 1988;**ii**:349–60.
16. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
17. The Clopidogrel in Unstable Angina to Prevent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
18. Cohen M, Adams P, Parry G *et al.* on behalf of the Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Combination antithrombotic therapy in unstable angina and non-Q wave infarction in non-prior aspirin users: primary end-points from the ATACS trial. *Circulation* 1994;**89**:81–8.
19. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low molecular weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561–8.
20. Antman EM, McCabe CH, Gurfinkel EP *et al.* Enoxaparin prevents death and cardiac ischemic events in unstable

angina/non-Q wave myocardial infarction. *Circulation* 1999; **100**:1593–1601.
21. Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) investigators. Low molecular-mass heparin in unstable coronary artery disease: FRISC II prospective randomised multicenter study. *Lancet* 1999;**354**:701–7.
22. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999; **282**:2058–67.
23. CHAMP. Presented at American Heart Association 1999.
24. WARIS II. Presented at the European Society of Cardiology. Stockholm. September 2001.
25. Yusuf S, Lessem J, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: An update of randomly allocated controlled trials. *J Hypertens* 1993;**11** (Suppl. 4):S61–S73.
26. The Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. *Eur Heart J* 1988; **9**:8–16.
27. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
28. Furberg CD, Hawkins CM, Lichstein F. Effect of propranolol in postinfarction patients with mechanical and electrical complications. *Circulation* 1983;**69**:761–5.
29. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol* 1991;**67**:1295–7.
30. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after myocardial infarction (the Danish Verapamil Infarction Trial II-DAVIT II). *Am J Cardiol* 1990;**66**:779–85.
31. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;**319**:385–92.
32. Messerli FH, Hansen JF, Gibson RS, Schechtman KB, Boden WE. Heart-rate lowering calcium antagonists in hypertensive post-myocardial infarction patients. *J Hypertens* 2001; **19**:977–82.
33. Boden WE, Wiek H van G, Scheldewaert RG *et al.* Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo controlled trial. *Lancet* 2000; **355**:1751–6.
34. ISIS-4 (Fourth International Study on Infarct Survival) Collaborative group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate and intravenous magnesium in 58,000 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669–85.
35. Gruppo Italiano per lo Studio della Sopravivenza nell'infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal nitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343**:1115–22.
36. Pfeffer MA, Braunwald E, Moyé LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;**327**:669–77.
37. AIRE (Acute Infarction Ramipril Efficacy) Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–8.
38. Køber L, Torp-Pedersen C, Carlsen JE *et al.* A clinical trial of the angiotensin converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**:1670–6.
39. Flather MD, Yusuf S, Køber L *et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;**355**:1575–81.
40. Ambrosioni E, Borghi C, Magnani B. The effect of angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 1995;**332**:80–5.
41. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
42. Pfeffer MA, Domanski M, Rosenberg Y *et al.* Prevention of events with angiotensin-converting enzyme inhibition (the PEACE study design). Prevention of Events with Angiotensin-Converting Enzyme Inhibition. *Am J Cardiol* 1998;**82**: 25H–30H.
43. Fox KM, Henderson JR, Bertrand ME, Ferrari R, Remme WJ, Simoons ML. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). *Eur Heart J* 1998;**19**(Suppl. J):J52–5.
44. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA* 1993;**270**:1589–95.
45. Waldo AL, Camm AJ, deRuyter H *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348**:7–12.
46. Køber L and others. Effect of dofetilide in patients with recent myocardial infarction and left ventricular dysfunction: a randomised study. *Lancet* 2000;**356**:2052–8.
47. ALIVE, Presented at the American Heart Association. November 2001.
48. Julian DG, Camm AJ, Frangin G *et al.* Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997;**349**:667–74.
49. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997;**349**:675–82.
50. Connolly SJ. Meta-analysis of antiarrhythmic drug trials. *Am J Cardiol* 1999; **84**(Suppl. 1):90–3.
51. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary

heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
52. Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**: 1001–9.
53. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad base of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–54.
54. Heart Protection Study presented at the American Heart Association, November 2001.
55. Schwartz GG, Olsson AG, Ezekowitz MD *et al.* Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–18.
56. FLORIDA, Presented at the American Heart Association, 2000.
57. Rubens HB, Robins SJ, Collins D *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;**341**:410–18.
58. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The bezafibrate infarction prevention (BIP) study. *Circulation* 2000;**102**:21–7.
59. Hulley S, Grady D, Bush T *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**290**:605–13.
60. SWIFT (Should we intervene following thrombolysis ?) Study Group. SWIFT trial of delayed elective intervention *v* conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. *BMJ* 1991;**302**:555–60.
61. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial, *N Engl J Med* 1989;**320**:618–27.
62. Anderson HV, Cannon CP, Stone PH *et al.* One-year results of the thrombolysis in myocardial infarction (TIMI) IIIB clinical trial. *J Am Coll Cardiol* 1995;**26**:1643–50.
63. Boden WE, O'Rourke RA, Crawford MH *et al.* Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;**338**:1785–92.
64. Madsen JK, Grande P, Saunamaki K *et al.* Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in Acute Myocardial Infarction (DANAMI). *Circulation* 1997;**96**: 748–55.
65. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicenter study. *Lancet* 1999; **354**:708–15.
66. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 2000;**356**:9–16.
67. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E, FRISC II Study Group Investigators. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol* 2001;**38**:41–8.
68. Cannon CP, Weintraub WS, Demopoulos LA *et al.* Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001; **344**: 1879–87.
69. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive failure. *N Engl J Med* 1987; **316**:1429–44.
70. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
71. CIBIS-II Investigators Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999;**353**:9–13.
72. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999, **353**:2001–7.
73. Packer M, Coats AJS, Fowler MB *et al.* Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–8.
74. The beta-blocker evaluation of survival trial investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;**344**:1659–67.
75. Pitt B, Zannad F, Remme WJ *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–17.
76. Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *New Engl J Med* 1996; **335**:1933–40.
77. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of anti-arrhythmic therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**: 1576–83.
78. Moss AJ, Zareba W, Hall JH *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
79. Yusuf S, Wittes J, Probstfield, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**:93–8.
80. Yusuf S, Anand S. Cost of prevention. The case of lipid-lowering. *Circulation* 1996;**93**:1774–6.
81. Pedersen TR, Kjekshus J, Berg K *et al.* Cholesterol lowering and the use of healthcare resources. *Circulation*; 1996;**93**: 1796–802.

Part IIIc

Specific cardiovascular disorders: Atrial fibrillation and supraventricular tachycardia

A John Camm and John A Cairns, Editors

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

37 Atrial fibrillation: antiarrhythmic therapy

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Definition of the arrhythmia

The clinical classification of atrial fibrillation has caused much controversy, as ideally it would encompass multiple etiologies, risk factors and precipitating agents, various clinical presentations, variable temporal patterns of behavior, all of which might have an important influence on the selection of the therapeutic strategy and ultimately, determine the effect of treatment.[1] Attempts to classify atrial fibrillation according to etiology or underlying heart disease have been instantly marred by the fact that any process in the atrial tissue that causes infiltration, inflammation, scarring or stretch may lead to the development of atrial fibrillation. Furthermore, the primary pathologies underlying or promoting the occurrence of atrial fibrillation vary, probably, more than for any other cardiac arrhythmia, ranging from autonomic imbalance through organic heart disease to metabolic disorders, such as diabetes mellitus and hyperthyroidism.

Recently approved by the ESC/AHA/ACC Task Force on the management of atrial fibrillation, the classification of atrial fibrillation includes two equally important elements: temporal patterns of the evolution of the arrhythmia which may determine further treatment, and the response to medical interventions (Figure 37.1, Table 37.1).[2] First onset atrial fibrillation is the first clinical presentation of the arrhythmia where the patient is still in atrial fibrillation when evaluated and the episode has been present for less than 48 hours. The new onset, or recent onset atrial fibrillation category is included, but not infrequently the duration of atrial fibrillation is uncertain because the patient is often unaware of symptoms. The paroxysmal form of atrial fibrillation is determined by recurrent episodes of the arrhythmia that typically last from minutes to hours, occasionally days, but eventually self-terminate. Persistent atrial fibrillation is present when the arrhythmia is not self-terminating, but sinus rhythm can be restored by pharmacologic

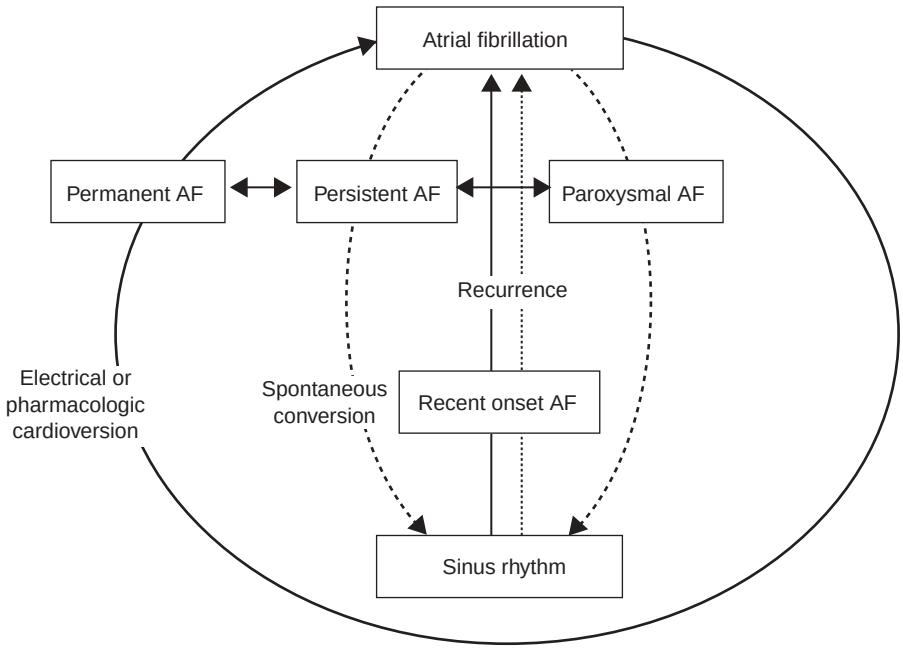

Figure 37.1 Classification of atrial fibrillation, based on the time course of the arrhythmia, and possible transition between the three forms of atrial fibrillation

Table 37.1 Classification of atrial fibrillation

Type	Duration and character	Therapeutic strategy
First detected	Usually <48 hours; usually patient is still in AF when diagnosed	Electrical or pharmacologic cardioversion ± prophylaxis with Class I or III AAD
Paroxysmal	Self-terminating; <2–7 days, frequently <24 hours Spontaneous conversion occurs frequently	Conversion and prevention with Class IC or III AAD and/or Rate control therapy during paroxysm
Persistent	<2–7 days Not self-terminating; usually electrical cardioversion needed to restore sinus rhythm	Electrical cardioversion ± AADs + warfarin pericardioversion
Permanent	Restoration and/or maintenance of sinus rhythm not feasible	Control of the ventricular rate + warfarin or aspirin

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation

means or, more commonly, by electrical cardioversion. In these patients, atrial fibrillation has usually lasted for weeks or months. Once the arrhythmia is terminated medically, it does not change the designation of the form. Permanent atrial fibrillation is sustained and attempts to restore or maintain sinus rhythm have been abandoned because of frequent recurrence, physician or patient decision, or inability to cardiovert the patient.

Natural history and pathophysiology

Natural history

Atrial fibrillation is the most common cardiac arrhythmia and the incidence increases with age. The Framingham Heart Study showed that the biennial prevalence ranged from 6·2 and 3·8 cases per 1000 in men and women aged 55–64 years, respectively, up to 75·9 and 62·8 per 1000 in men and women aged 85–94 years. Men were 1·5 times more likely to develop atrial fibrillation than women.[3]

Patients with atrial fibrillation are characterized in both sexes by a higher age, the presence of diabetes, hypertension, congestive heart failure, and valve disease. Coronary artery disease is a risk factor for atrial fibrillation only in men.[3] Other predictors are cardiomyopathy and obesity. Echocardiographic predictors include large atria, diminished left ventricular function, and increased left ventricular wall thickness. In the past, rheumatic heart disease was the most common cause of atrial fibrillation, but at present more patients have atrial fibrillation on the basis of coronary artery disease and systemic hypertension.

Mechanisms of atrial fibrillation

Moe and coworkers[4] postulated that atrial fibrillation is maintained by multiple re-entering wavelets circulating randomly in the myocardium and that the stability of the fibrillatory process depends on the average number of wavelets. This hypothesis was confirmed experimentally by Allessie and colleagues,[5] who estimated that the critical number of wavelets to sustain atrial fibrillation was approximately four to six. Atrial fibrillation may also present itself as a focal arrhythmia amenable to ablation. It then occurs in the absence of heart disease in relatively young patients.

Atrial fibrillation has the tendency to become more persistent over time. This is illustrated by the fact that about 30% of patients with paroxysmal atrial fibrillation eventually will develop persistent atrial fibrillation.[6] Also, pharmacologic and electrical cardioversion, and maintenance of sinus rhythm thereafter become more difficult the longer the arrhythmia exists.[7,8] This relates to progression of the underlying disease and possibly also to electrical remodeling of the atria.[9]

Modulating factors

The onset and persistence of atrial fibrillation may be modulated by the autonomic nervous system. Coumel and coworkers distinguished vagal and adrenergic atrial fibrillation.[10] However, the distinction between both mechanisms is not always clear. This implies that it is more appropriate to speak of autonomic imbalance rather than either an increased vagal or an increased sympathetic tone.

Vagally mediated atrial fibrillation

Vagally mediated atrial fibrillation occurs more frequently in men than in women, usually at a younger age (30–50 years). It only rarely progresses to permanent atrial fibrillation and it predominantly occurs in the absence of structural heart disease.[10] Attacks occur at night, end in the morning, and neither emotional stress nor exertion trigger the arrhythmia. On the contrary, when patients feel that atrial

fibrillation may start (repeated atrial extrasystoles), some observe that they can prevent an arrhythmia by doing exercise. The arrhythmia frequently starts after exercise or stress. Rest, the postprandial state, and alcohol are other precipitating factors. The pathophysiologic mechanism may relate to vagally induced shortening of the atrial refractory period.

Adrenergic tone in atrial fibrillation

Adrenergic atrial fibrillation is more frequently associated with structural heart disease (ischemic heart disease) than its vagal counterpart.[10] Typically, it occurs during day time and is favored by stress, exercise, tea, coffee or alcohol. Attacks terminate often within a few minutes. It is less frequently observed than vagal atrial fibrillation. The underlying mechanism is unknown.

Familial atrial fibrillation

A hypothesis of genetic predisposition to atrial fibrillation or even specific genetically predetermined forms of the arrhythmia has been confirmed by identification of a gene defect linked to chromosome 10q in three Spanish families, 21 of 49 members of which presented with atrial fibrillation at a relatively young age, ranging from 2 to 46 years.[11] Candidate genes for the familial form of the arrhythmia include genes encoding channel or pore proteins and genes encoding the α- and β adrenergic receptors or signaling proteins. Of interest, since these receptors are involved in normal and abnormal cardiac automaticity, it is tempting to speculate that the basis for familial atrial fibrillation lies in abnormal atrial automaticity or triggering mechanisms.

Recently, a missense mutation in the lamin A/C gene has been found to be a cause of dilated cardiomyopathy associated with progressive conduction system disease, atrioventricular block, atrial fibrillation, congestive heart failure, stroke and sudden death.[12] Similarly, a missense mutation Arg663His in the β-cardiac myosin heavy chain has been identified in patients with specific phenotype of familial hypertrophic cardiomyopathy presenting with moderate left ventricular hypertrophy, predominantly localized in the proximal segment of the interventricular septum, and a 47% prevalence of atrial fibrillation.[13] Although the incidence of familial AF is to be determined, further exploration may reveal a number of possible targets for medical therapy for the prevention or reversal of the arrhythmia.

Clinical impact

Atrial fibrillation causes palpitations, chest pain, dyspnea, and fatigue. Some patients experience presyncope or even drop attacks, especially at arrhythmia onset or termination. All patients with longer lasting atrial fibrillation develop left ventricular dysfunction, even those without underlying heart disease. This is often indicated as tachycardiomyopathy. Conversely, many patients with atrial fibrillation have preexistent heart failure. Furthermore, atrial fibrillation is associated with excess thromboembolic complications, especially in elderly patients.

However, in at least one third of patients, no obvious symptoms or noticeable degradation of quality of life are observed.[14] In the ALFA (Etude en Activité Liberale sur le Fibrillation Auriculaire) study of 756 patients with atrial fibrillation from general practice in France, of 86 participants who reported no symptoms, 63 (73%) presented with permanent atrial fibrillation, 14 (16%) were diagnosed with recent onset atrial fibrillation, and only 9 (11%) had a paroxysmal form of the arrhythmia.[15] Pharmacologic treatment of the atrial fibrillation has long been known potentially to convert a symptomatic form of the arrhythmia to an entirely asymptomatic variety. In the PAFAC (Prevention of Atrial Fibrillation After Cardioversion) study of more than 1000 patients with atrial fibrillation, antiarrhythmic drug therapy rendered 90% of arrhythmia recurrences completely asymptomatic, as detected in this study by daily transtelephonic ECG monitoring.[16] These observations challenged the validity of symptoms for the reliable detection of recurrence of atrial fibrillation and for the assessment of the efficacy of antiarrhythmic drug therapy.

Hemodynamic consequences and mortality

Atrial fibrillation reduces cardiac output and may lead to heart failure.[17,18] Apart from loss of atrial kick, excessive rate response and rhythm irregularity, two other pathogenetic factors should be mentioned, namely progression of underlying cardiovascular disease and development of tachycardia-related cardiomyopathy.[19] In fact, associated heart disease creates the background hemodynamic derangement which is modulated by the other factors. Tachycardiomyopathy may occur in the absence of heart disease and it may be concealed – that is, heart failure due to tachycardiomyopathy cannot be distinguished from that due to the underlying cardiovascular disease, but may be demonstrable only after restoration of sinus rhythm or adequate rate control.[19,20]

Several cohort and retrospective studies have shown that the relative risk of death in subjects with atrial fibrillation is roughly twice that found in subjects in sinus rhythm.[17,18,21] The reduced survival relates to progression of the underlying cardiovascular disease and stroke. The prognostic impact of atrial fibrillation in patients with heart failure is still uncertain.[22,23]

Progressive increase of atrial size

Atrial enlargement is a cause but also a consequence of atrial fibrillation.[24,25] Atrial enlargement is associated with

an increased risk for thromboembolic complications and a high arrhythmia recurrence rate following cardioversion. In addition, drugs used to convert the arrhythmia may be less effective. Restoration of sinus rhythm may reverse the process of atrial enlargement, even in patients with mitral valve disease.[26]

Increased number of thromboembolic complications

Atrial fibrillation is the most common cardiac cause of systemic emboli, usually cerebrovascular.[27] In the presence of atrial fibrillation, the risk of stroke shows an approximately fivefold increase unrelated to age.[27] The proportion of atrial fibrillation-related stroke increases significantly with age from 6·7 for ages 50–59 years to 36·2 for ages 80–89 years. The risk for stroke in lone atrial fibrillation is still uncertain. The cardiac embolus often results in occlusion of a major cerebral artery. The ensuing infarct is often large and may be fatal.[28] Apart from symptomatic strokes, atrial fibrillation has been associated with an increased risk of silent strokes.[28] Risk factors for stroke in atrial fibrillation include rheumatic heart disease, age >65 years, hypertension, previous stroke or transient ischemic attack, diabetes, recent heart failure, and echocardiographic atrial or ventricular enlargement.[27,29,30]

Antiarrhythmic therapy of atrial fibrillation

Essentially, there are three antiarrhythmic strategies: acute pharmacologic termination; drug prevention in paroxysmal atrial fibrillation and persistent atrial fibrillation post cardioversion; and control of the ventricular rate during a paroxysm of atrial fibrillation or during the presence of persistent or permanent atrial fibrillation. Drug treatment to convert or prevent atrial fibrillation aims at prolonging the wavelength or reducing the triggers for atrial fibrillation. The former can be achieved by Class IA or III antiarrhythmic drugs or even the Class IC drugs flecainide and propafenone which prolong refractoriness at short cycle lengths. The latter, for example, through β blockers in the case of adrenergic atrial fibrillation.

Paroxysmal atrial fibrillation

Defining the temporal pattern of atrial fibrillation requires a careful history, an electrocardiogram, and frequently a 24 hour Holter monitor. This implies that the definite pattern cannot always be established on the first consultation. Which strategy will be chosen in the individual patient should depend on the frequency of the paroxysms, the triggers for the arrhythmia, the accompanying symptoms, and the underlying heart disease (Figure 37.2).

The three possible strategies for the pharmacologic treatment of paroxysmal atrial fibrillation will be discussed below.

Acute conversion of paroxysmal atrial fibrillation

If the arrhythmia is not self-limiting, antiarrhythmic drugs can be administered to restore sinus rhythm. Pharmacologic cardioversion is considered to be most effective if initiated within 7 days after the onset of the arrhythmia in which case restoration of sinus rhythm can be achieved in nearly 70% of patients, but the success rate is lower in atrial fibrillation of longer duration.[31] The high rate of spontaneous conversion suggests that a placebo group is required to determine the effects of antiarrhythmic drug therapy.[32] Furthermore, although antiarrhythmic drugs reduce the time to conversion to sinus rhythm, the high rates of spontaneous conversion in recent onset atrial fibrillation may result in an insignificant difference between the intervention and the placebo arms. Figure 37.3 shows conversion rates on placebo and the different antiarrhythmic drugs in recent onset atrial fibrillation. It demonstrates that with time the cumulative conversion rate increases both on placebo and drugs.

Recently published guidelines of ESC Committee and AHA/ACC Task Force members on the management of atrial fibrillation have stated that in atrial fibrillation of less than 7 days' duration, propafenone and flecainide (oral or intravenous), ibutilide or dofetilide should be the first line choice if pharmacologic cardioversion of the arrhythmia is considered.[2] High dose amiodarone (intravenous and in combination with oral administration), and oral quinidine have been shown to be more effective than placebo for converting atrial fibrillation into sinus rhythm and may be used as second choice therapy in selected patients. As the success rate of pharmacologic cardioversion is progressively reduced with increased duration of the arrhythmia, the choice of antiarrhythmic drugs is limited to dofetilide, ibutilide, and possibly, amiodarone. Antiarrhythmic drugs proven to be effective for cardioversion of atrial tachyarrhythmias and recommended by the committee are summarized in Table 37.2.

Conversion rates up to 90% are found 1 hour after intravenous flecainide or propafenone. Both drugs can also be administered orally with success rates reported to be 50–80%.[33–35] The advantage of Class IC antiarrhythmic drugs is their ability to expediently restore sinus rhythm within a short period of time. Thus, cardioversion rates for flecainide and propafenone given as a single dose of 200–300 mg and 450–600 mg respectively were 59% and 51% at 3 hours compared with 18% in the placebo arm, reaching 78% and 72% at 8 hours compared with 39% on placebo.[33] In the third Propafenone in Atrial Fibrillation Italian Trial (PAFIT-3), intravenous infusion of propafenone at a dose of 2 mg/kg restored sinus rhythm within the first hour in nearly half patients with recent onset atrial fibrillation (1–72 hours) compared with 14% on placebo.[36]

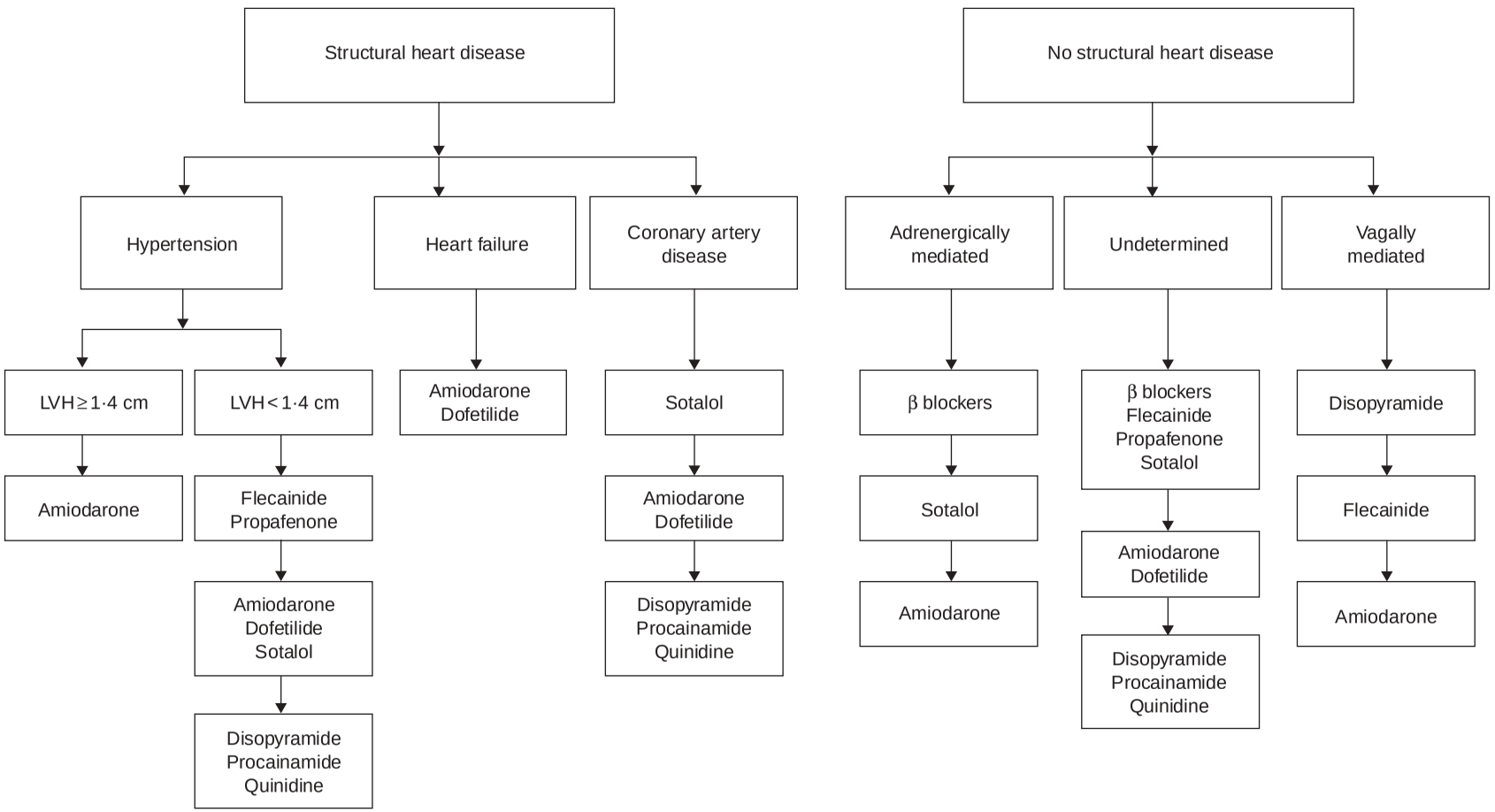

Figure 37.2 Selection of the optimal antiarrhythmic agent to prevent atrial tachyarrhythmias. *No left ventricular dysfunction; LVH, left ventricular hypertrophy

Drug treatment of atrial fibrillation: summary

Type	Strategy	Drugs	Recommendation level
Paroxysmal	(1) Terminate paroxysm	(1) Class IC AAD IV or oral or procainamide IV	**Grade A**
		Class IA, IC in WPW	**Grade B**
		Class III drugs (ibutilide, dofetilide)	**Grade A**
		Amiodarone in hemodynamically compromised patients (cardioversion)	**Grade A**
	(2) Prevent paroxysm	(2) Class IC	**Grade A**
		Class III AAD (sotalol, dofetilide, azimilide[a])	**Grade A**
		Amiodarone (first choice in hemodynamically compromised patients)	**Grade A**
		Disopyramide/flecainide in vagally induced AF	**Grade B**
		β blockers in adrenergically induced AF	**Grade B**
	(3) Rate control during paroxysm	(3) Digitalis	**Grade B**
		±	
		β blockers	
		±	
		Calcium-channel blockers	
Persistent	Serial cardioversion	DC electrical cardioversion[b]	**Grade A**
	±	±	
	Serial antiarrhythmic drug therapy	Sotalol (initiate in hospital)	**Grade B**
	+	Class IC drug (not in patients with significant structural heart disease)	**Grade B**
	Patient counseling (report to hospital at recurrence)	Amiodarone (first choice in hemodynamically compromised patients)	**Grade B**
Permanent	Accept AF, rate control therapy:	Digitalis	**Grade A**
		±	
	if duration AF >36 months	β blockers	
	or	±	
	age >70 years and NYHA III + IV	Calcium-channel blockers	
	or		
	after failure of serial cardioversion therapy		

[a] Investigational agent.
[b] Drugs usually ineffective.
Abbreviation: WPW, Wolff–Parkinson–White syndrome

Ibutilide has been shown to act as much as twice more effectively for conversion of atrial flutter than atrial fibrillation (63% *v* 31%).[37] In 319 patients with persistent atrial tachyarrhythmias (18·5% atrial flutter) of duration up to 45 days, intravenous ibutilide at a dose of 1 mg or 2 mg was more effective than intravenous d,1-sotalol at a dose of 1·5 mg/kg in conversion of atrial fibrillation to sinus rhythm in less than 1 hour (20% with 1 mg, 44% with 2 mg *v* 11%) and was particularly effective in termination of atrial flutter (56% with 1 mg, 70% with 2 mg *v* 19%).[38] In another randomized study in patients with atrial flutter, the comparison also was in favor of ibutilide which was significantly superior

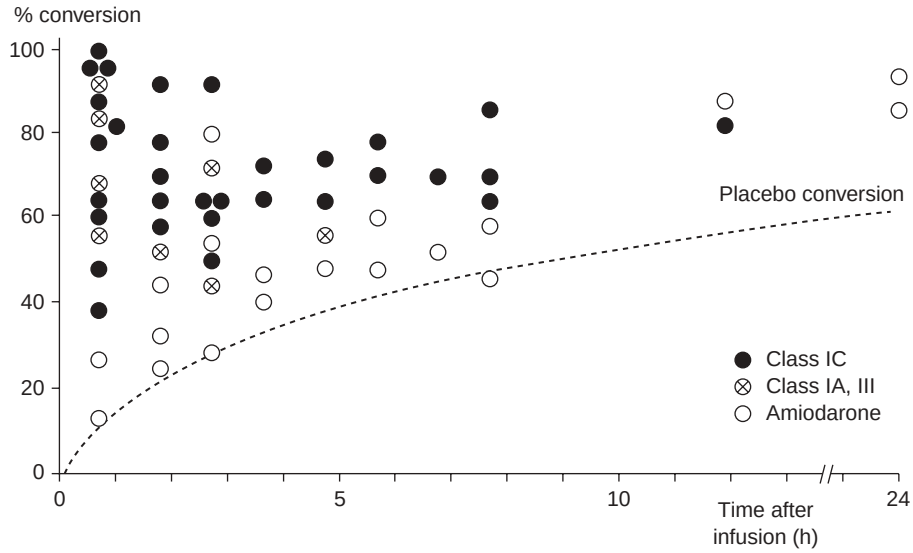

Figure 37.3 Conversion of paroxysmal atrial fibrillation (<3 days). Conversion rates in relation to time after start of the infusion found in studies investigating the efficacy of Class IC (flecainide and propafenone), Class IA and III drugs (procainamide, quinidine, sotalol, ibutilide, dofetilide) and amiodarone are presented. The curve indicating placebo conversion was constructed from placebo conversion rates found in the above studies. Class IC drugs appear most efficacious. Note the late onset of conversion on amiodarone. (Modified after Fresco *et al.*[7])

Table 37.2 Antiarrhythmic drugs for pharmacologic cardioversion of atrial fibrillation of less and more than 7 days duration. Grade A

Drug	Route of administration	Dose
Flecainide	Oral or IV	200–300 mg or 1·5–3·0 mg/kg over 10–20 min
Propafenone	Oral or IV	450–600 mg or 1·5–2·0 mg/kg over 10–20 min
Dofetilide	Oral	125–500 mg twice daily[a]
Ibutilide	IV	1 mg over 10 min; repeat 1 mg if necessary
Amiodarone	Oral or IV	Inpatient: 1200–1800 mg daily in divided doses until 10 g total; then 200–400 mg daily Outpatient: 600–800 mg daily until 10 g total; then 200–400 mg daily 5–7 mg/kg over 30–60 min IV; then 1200–1800 mg daily oral until 10 g total; then 200–400 mg daily
Procainamide	IV	1000 mg over 30 min (33 mg/min) followed by 2 mg/min infusion
Quinidine	Oral	750–1500 mg in divided doses over 6–12 hours + a rate slowing drug

[a] Dose depends on creatinine clearance: >60 ml/min – 500 mg; 40–60 ml/min – 250 mg; 20–40 ml/min – 125 mg twice daily.

to procainamide (76% *v* 14%).[39] However, the efficacy of ibutilide decreased significantly with duration of the arrhythmia more than 7 days: from 71% to 57% for atrial flutter and from 46% to only 18% for atrial fibrillation. Furthermore, as many controlled studies of ibutilide have enrolled patients with mild or moderate underlying heart disease, these results may not be generalizable to patients with markedly depressed left ventricular function.

Dofetilide has been shown to convert 30·3% of 96 patients with atrial tachyarrhythmias within 3 hours from the start

of intravenous infusion of 8 micrograms/kg for 30 minutes compared with a 3·3% conversion rate on placebo.[40] The conversion rates were significantly higher for atrial flutter than for atrial fibrillation (64% *v* 24%). Two large prospective studies, DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality ON Dofetilide in Congestive Heart Failure) and SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide), have recently evaluated effects of oral dofetilide on the conversion rate and maintenance of sinus rhythm in patients with atrial fibrillation. In the DIAMOND study of 1518 patients with symptomatic heart failure and an ejection fraction ⩽35%, therapy with dofetilide 1000 micrograms was associated with a greater rate of spontaneous conversion to sinus rhythm (44% *v* 14%).[41] In the SAFIRE-D study of 325 patients with persistent atrial fibrillation and/or atrial flutter, cardioversion rates were 6·1%, 9·8%, and 29·9% for 125, 250, and 500 micrograms of dofetilide twice daily compared with 1·2% of spontaneous conversion in the placebo arm.[42]

However, as far as late conversion has been studied, amiodarone may produce sinus rhythm in over 80% within 24 hours. An advantage of amiodarone is its ability to lower ventricular rates before conversion, whereas Class IC drugs may increase the ventricular rate due to conversion of atrial fibrillation to atrial flutter with 2:1 atrioventricular conduction, and, therefore, should be administered in conjunction with β blockers. Amiodarone is especially recommended in hemodynamically compromised patients since it is less negatively inotropic.[43] A meta-analysis of 12 randomized controlled studies has shown that intravenous amiodarone was moderately effective in converting atrial fibrillation compared with placebo (63% *v* 44%), with the maximum effect at 24 hours (74% *v* 55%).[44] There is evidence from a randomized, controlled study suggesting that higher than usual intravenous dose amiodarone and the combination of intravenous and oral routes of administration may enhance the cardioversion rate.[45]

Quinidine is usually administered in conjunction with rate slowing agents, preferably with β blockers and when given in a cumulative daily dose of up to 1350 mg has been shown to cardiovert 50–77% of patients with recent onset atrial fibrillation.[46,47]

For acute conversion, sotalol must be considered ineffective. This has only become apparent after the drug has been used as an "active" comparator in trials studying new Class III agents.[38,48] The rate of conversion of atrial fibrillation with sotalol did not exceed 19% and was significantly lower for conversion of atrial flutter (11%).[38] On the other hand, sotalol is effective for the *prevention* of atrial fibrillation. This discrepancy relates to its property to prolong the refractory period predominantly at *lower* atrial rates, but not during rapid atrial fibrillation, due to its reverse use dependency.

The availability of studies on the efficacy of procainamide and disopyramide is limited, precluding definite conclusions. Procainamide has been found to convert at least 65% of the patients with atrial fibrillation within approximately 1 hour. Its lack of efficacy (compared to Class IC drugs) may relate to the rather low dose used in the procainamide studies: up to a maximum of 1 g in 30 minutes, sometimes followed by a low maintenance infusion.

Digitalis, β blockers, and calcium-channel blockers are ineffective for the acute conversion of atrial fibrillation.[7,49,50] The DAAF (Digitalis in Acute Atrial Fibrillation) study has shown that there was no difference in cardioversion rates at 16 hours between intravenous digoxin and placebo (51% *v* 46%).[51] Moreover, the drug has been shown to facilitate AF due to its cholinergic effects which may cause a non-uniform reduction in conduction velocity and effective refractory periods of the atria, and to delay the reversal of remodeling after restoration of sinus rhythm.[52,53]

Self-administered oral drug conversion may be applied if the patient is clinically stable and if the agent has been shown to be safe and effective in that patient.[7]

Prevention of paroxysmal atrial fibrillation

Paroxysmal atrial fibrillation is a chronic disease: the first attack will not be the last in over 90% of patients, despite antiarrhythmic prophylaxis. As a consequence the end point of treatment used in controlled drug studies has been "attack-free rate" or "time to first recurrence". Therefore, when considering drug efficacy, it might be more appropriate to focus on quality of life but firm data concerning this issue are available only for His bundle ablation. In this respect, it is important to note that up to 50% of patients discontinue drug therapy for loss of quality of life due to adverse effects and drug inefficacy. Moreover, too many studies looked at drug effects in mixed populations, including both paroxysmal and persistent atrial fibrillation. Finally, older drugs like procainamide have not been tested extensively in appropriate placebo-controlled studies. Useful data concerning these agents have or will become available only after they have been used as active comparators in studies on Class IC and the new Class III drugs. Therefore, this paragraph contains clinically useful conclusions which, however, are not all evidence-based.

Prophylactic antiarrhythmic drug therapy is usually not recommended after a first episode of the arrhythmia which may self-terminate or require electrical or pharmacologic cardioversion and in patients with infrequent, self-limiting, and well-tolerated paroxysms of the arrhythmia. However, this approach can be appropriate in a small proportion of patients as paroxysmal atrial fibrillation tends to evolve to persistent and eventually to a permanent form. Prophylactic antiarrhythmic drug therapy is, therefore, recommended for a vast majority of patients with paroxysmal tachyarrhythmia when paroxysms occur frequently (1 episode per 3 months) and are associated with significant symptoms or lead to

worsening left ventricular function; for patients with persistent atrial fibrillation when the likelihood of maintenance of sinus rhythm is uncertain, especially in the presence of risk factors for recurrence (left atrial enlargement, evidence for depressed atrial function, left ventricular dysfunction, underlying cardiovascular pathology, long duration of the arrhythmia, and advanced age).[54]

The efficacy of propafenone for the prevention of recurrent atrial fibrillation has been assessed in several uncontrolled studies and four placebo-controlled trials.[55–57] In the Propafenone Atrial Fibrillation Trial (PAFT), the likelihood of maintenance of sinus rhythm at 6 months after cardioversion was 67% in the propafenone-treated group compared with 35% with placebo.[56] The UK PSVT (Paroxysmal Supraventricular Tachycardia) study showed that propafenone given at doses of 600 mg and 900 mg daily was effective for suppression of recurrences of the arrhythmia but a dose of 900 mg was associated with a less favorable adverse event profile.[57] Propafenone has proven to be efficacious and safe in patients with supraventricular tachyarrhythmias in meta-analysis involving over 3100 patients.[58] All-cause mortality associated with propafenone was 0·3%. There are now two ongoing studies of the effectiveness of propafenone for the maintenance of sinus rhythm: the North American Recurrence of Atrial Fibrillation Trial (RAFT) and its European equivalent, ERAFT.

Several placebo-controlled and comparative trials of another Class IC antiarrhythmic drug, flecainide, including the Flecainide Multicenter Atrial Fibrillation Study, have found that the efficacy of flecainide in the prevention of first recurrence of AF or flutter and the reduction of the total time spent in the arrhythmia comparable to that of quinidine, with fewer adverse effects.[59–63] In a placebo-controlled, crossover study Anderson and colleagues included 53 patients with two or more attacks of atrial fibrillation within a 4 week baseline period.[61] The median dose of flecainide was 300 mg, which is well above the clinical dose currently instituted (150–200 mg daily). During therapy with flecainide, the median time to the first recurrence was significantly prolonged (15 days *v* 3 days, $P < 0{\cdot}001$). Similarly, the time interval between subsequent attacks lengthened, from 6 to 27 days during flecainide compared to placebo ($P < 0{\cdot}001$). The efficacy of flecainide was maintained during a mean follow up of 17 months.[62] Naccarelli included 239 patients randomized to flecainide (maximum dose 300 mg) or quinidine (maximum dose 1500 mg/day) and followed them for 12 months. Inadequate response caused 10% and 12% terminations of the drug, respectively. However, 30% of the quinidine patients stopped the drug due to adverse effects, versus only 18% of the flecainide group.[63]

Following the publication of the Cardiac Arrhythmias Suppression Trial (CAST I), and the Stroke Prevention Atrial Fibrillation (SPAF I) study showing a three- to sixfold increase in risk for all-cause and cardiac mortality with Class I antiarrhythmic agents, particularly in patients with structural heart disease,[64,65] a shift has been made to more frequent use of Class III antiarrhythmic drugs, the action of which is based on prolongation of action potential duration. These include amiodarone, sotalol, and dofetilide, a new, investigational agent azimilide, and iodine-free benzofurane derivative dronedarone with affinity for multiple potassium channels. However, the likelihood of remaining free from recurrence of the arrhythmia over the long term is not satisfactory with any of the antiarrhythmic drugs which are presently available but probably, higher for dofetilide (Figure 37.4).

Selected randomized trials of the efficacy of class III antiarrhythmic drugs for conversion of atrial fibrillation and maintenance of sinus rhythm are summarized in Table 37.3.

In randomized comparative and placebo-controlled studies, sotalol has proven to be effective in the prevention of recurrent atrial fibrillation. Sotalol has also been shown to exert additional beneficial effects by suppressing symptoms associated with relapse into atrial fibrillation due to its rate slowing action.[66–69] In 253 patients with atrial fibrillation or flutter, therapy with d,l-sotalol at a dose of 240 mg daily resulted in a significant increase in the median time to first recurrence of symptomatic arrhythmia documented as assessed by transtelephonic monitoring.[69] In the PAFAC study of more than 1000 patients, the recurrence rates during 1 year of daily transtelephonic ECG monitoring were 50% for sotalol, 38% for the combination of quinidine and verapamil, and 77% for placebo.[70] Furthermore, sotalol proved to be inferior to amiodarone in the Canadian Trial of Atrial Fibrillation (CTAF).[71] Sotalol was less effective and had higher rates of withdrawal than dofetilide in the European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD) study.[72]

In the CTAF study, therapy with amiodarone at a dose of 200 mg/day resulted in a 57% reduction in risk for recurrence of the arrhythmia compared with sotalol and propafenone.[71] However, difficulties with the methodology of the trial, particularly the delay in logging recurrences of the arrhythmia in the amiodarone-treated group, reduce confidence in its results. Data from the CHF-STAT (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) substudy showed that amiodarone was effective for the prevention of recurrence of atrial fibrillation in patients with congestive heart failure NYHA Classes II and III.[73] In this study, patients who received amiodarone were twice as less likely to develop new atrial fibrillation compared with placebo (4% *v* 8%).

Dofetilide has been recently introduced as a safe and effective Class III antiarrhythmic drug for treatment of atrial tachyarrhythmias in patients with underlying heart pathology. In the DIAMOND-CHF study, treatment with dofetilide 500 micrograms twice daily was associated with a significantly greater probability of remaining in sinus rhythm at 1 year

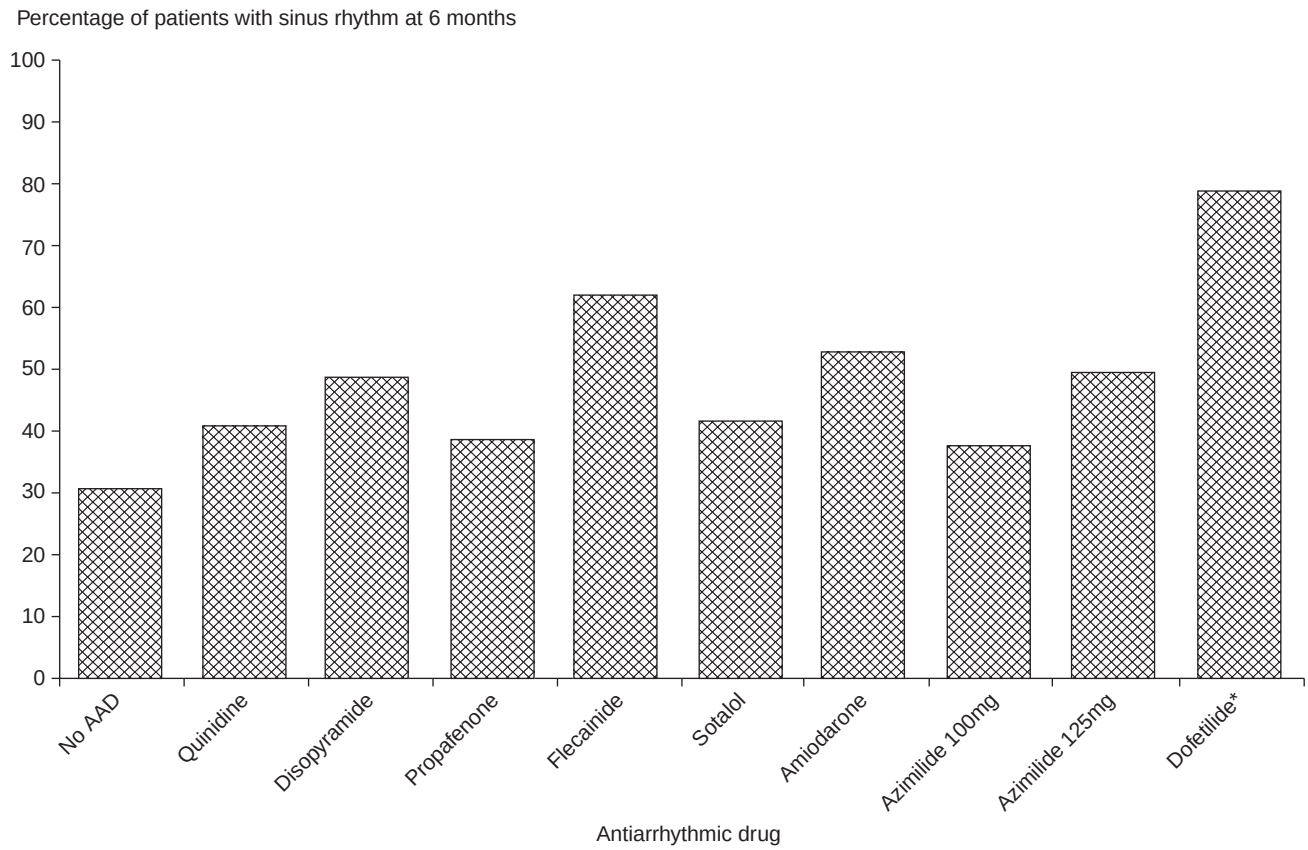

Figure 37.4 Likelihood of remaining free from recurrence of atrial fibrillation or atrial flutter with prophylactic antiarrhythmic drug therapy* at 1 year

Table 37.3 Randomized, controlled studies of efficacy of Class III antiarrhythmic drugs for conversion and/or maintenance of sinus rhythm in patients with atrial fibrillation and flutter

Study	Drug	Patients (*n*)	Follow up	Cardioverted *v* control/ placebo	Remained in SR *v* control	Torsade de pointes
Ibutilide Repeat Dose Study[37]	Ibutilide 1·5 mg or 2 mg IV	266	24 hours	47% *v* 2%; 63% *v* 31% flutter *v* AF	–	8·3% (required cardioversion 1·7%)
Ibutilide/Sotalol Comparator Study (ISCS)[38]	Ibutilide 1 mg or 2 mg IV, d,l-sotalol 1·5 mg/kg IV	319	72 hours	56–70% *v* 19% on sotalol in atrial flutter; 20–44% *v* 11% in AF	–	0·9% on ibutilide 2 mg; none on sotalol
Sotalol Multicenter Study Group[48]	d,l-sotalol 160 or 320 mg	49	To first recurrence	–	73% on sotalol 320 mg; 40% on sotalol 160 mg *v* 29% on placebo	None
D,l-Sotalol Atrial Fibrillation/ Flutter Study Group[69]	d,l-sotalol 160, 240 or 320 mg	253	24 weeks	–	Increased time to first episode: 106–229 days *v* 27 days on placebo	None

Table 37.3 Continued

Study	Drugs (*n*)	Patient	Follow up control/ placebo	Cardioverted *v* control/ placebo	Remained in SR *v* control	Torsade de pointes
PAFAC	Sotalol quinidine + verapamil	1182	1 year; daily TTE	–	Recurrence rates: 50% on sotalol *v* 38% on quinidine + verapamil *v* 77% on placebo	1% (all on sotalol)
Randomized, placebo-controlled study in recent onset AF[45]	Amiodarone IV 125 mg/h for 24 hours; maximum dose 3 g	100	1 month	92% *v* 64%	88%	Not stated
CTAF[71]	Amiodarone 200 mg	403	16 months	–	65% *v* 37% on sotalol or propafenone (57% risk reduction)	None
CHF-STAT[73]	Amiodarone 800 mg for 2 weeks; 400 mg for 50 weeks; then 200 mg	667; 103 AF	4–5 years	31·3% *v* 7·7%	–	–
DDAFF[57]	Dofetilide 8 μg/kg IV	96	3 hours	30·3% *v* 3·3% 64% flutter *v* 24% AF	–	3%
DIAMOND[41]	Dofetilide 500 μg	1518	18 months	59% *v* 34%	79% *v* 46%	3·3%
SAFIRE-D[42]	Dofetilide 250, 500, 1000 μg	225	1 year	6·1%, 9·8%, 19·9% *v* 1·2%	40%, 37%, 58% *v* 25%	0·8%
EMERALD[74]	Dofetilide 250, 500, 1000 μg	671	Phase 1: 72 h; Phase 2: 2 years	6%, 11%, 29% *v* 5% on sotalol at 72 hours	40%, 52%, 66% *v* 21% on placebo at 1 year	3 torsades de pointes; 1 sudden death
ASAP[76]	Azimilide 50, 100, 125 mg	384	180 days	–	17%, 38%, 83%[a]	0·99%
Meta-analysis of 4 SVA studies[77]	Azimilide 35, 50, 100, 125 mg	1380	Time to first recurrence	–	1·32–1.34 1·49–1.86[c]	0·9% at 100 and 125 mg *v* 0% on placebo
ALIVE (unpublished)	Azimilide 100 mg	3381	1 year	26·8% *v* 10·8% ($P = 0·076$)	New AF: 0·49% *v* 1·15% ($P = 0·04$)	0·3% *v* 0·1% on placebo

[a] Indicates a reduction in risk of AF recurrence compared with placebo.
[b] Indicates hazards ratios for the time to first recurrence of the arrhythmia compared with placebo.
[c] In patients with structural heart disease.
Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; DCC, direct current cardioversion; SR, sinus rhythm; SVA, supraventricular arrhythmia

compared with placebo (79% *v* 42%) and a significant reduction in the development of new cases of atrial fibrillation (1·98% *v* 6·55%).[41] In the SAFIRE-D study, 58% of patients treated with the maximal dose of dofetilide (1000 micrograms daily) remained in sinus rhythm at 1 year compared with 25% in the placebo group.[42] The preliminary results of the EMERALD study have shown that therapy with dofetilide at different dose regimens 250, 500, and 1000 micrograms daily was associated with a higher likelihood of maintenance of sinus rhythm compared with placebo (40%, 52%, and 66% *v* 21%, respectively).[74] In the EMERALD study, dofetilide was effective for maintenance of sinus rhythm in the subgroups of patients with high risk of recurrence of the arrhythmia, including those with significantly dilated left atrium, left ventricular dysfunction, and atrial fibrillation of more than 30 days' duration.[75]

Finally, azimilide, a new antiarrhythmic agent which blocks both fast and slow components of the delayed potassium rectifier current, has been shown to significantly prolong the time to first symptomatic arrhythmia episode compared with placebo (the hazard ratio 1·58) in 384 patients with atrial fibrillation.[76] Meta-analysis of four randomized controlled studies of the effectiveness of a range of azimilide doses in 1380 patients with atrial tachyarrhythmias has shown that each of the two highest doses (100 and 125 mg/day) significantly prolonged the time to first recurrence.[77] Patients with a history of coronary artery disease or congestive heart failure derive significantly greater benefit from azimilide than those with other underlying cardiovascular pathologies. In the ALIVE (AzimiLide post Infarct survival Evaluation Trial) of over 3000 post myocardial infarction patients with left ventricular dysfunction, fewer patients who started the trial in sinus rhythm developed atrial fibrillation on azimilide compared with placebo (0·49% *v* 1·15%), and there was a clear tendency to higher pharmacologic conversion rates in the azimilide arm than in the placebo arm (26·8% *v* 10·8%).

In patients suffering from vagally induced atrial fibrillation, β blockers and digitalis should be avoided as these drugs may provoke attacks. Quinidine, disopyramide, and flecainide may be effective due to their vagolytic effect. Propafenone is also considered ineffective due to its β blocking properties.

In patients with adrenergic-dependent atrial fibrillation, underlying cardiac disorders should be treated. After that, patients usually benefit from a β blocker. Class IA and IC drugs are generally ineffective, although some patients may respond to propafenone. At this point it should be stressed that firm data concerning this issue are missing since unequivocal identification of vagal or adrenergic atrial fibrillation may be impossible. This has precluded large, controlled studies on drug efficacy in predominantly vagally or adrenergically induced atrial fibrillation.

Finally, although β blockers have been predominantly used for rate control, recent data suggest that therapy with β blockers appears to be effective in the prevention of recurrence of persistent atrial fibrillation after cardioversion, especially in the presence of hypertension as underlying pathology.[78,79] In a randomized, crossover study, the efficacy of atenolol at a dose of 50 mg daily was comparable to that of low-dose sotalol (160 mg daily) and better than placebo for suppression of recurrent atrial fibrillation, reduction in duration of episodes of the arrhythmia and associated symptoms.[80] Bisoprolol at a dose of 5 mg daily has been shown to maintain sinus rhythm during 1 year after electrical cardioversion in 58% of patients with persistent atrial fibrillation, an effect comparable to that of sotalol (59%).[81]

Control of the ventricular rate during paroxysmal atrial fibrillation

Digitalis, β blockers or calcium-channel blockers may be necessary to control the ventricular rate when a relapse occurs. This holds especially in hemodynamically compromised patients who may decompensate during the attack. These agents may also prevent rate-dependent proarrhythmias (rapid atrioventricular conduction, excessive QRS widening, and ventricular tachycardia) of Class IA and IC drugs during a recurrence of atrial fibrillation, but conclusive data on this issue are lacking.[82] If amiodarone or sotalol are used to prevent atrial fibrillation, addition of conventional rate control drugs is not necessary. Controlling the ventricular rate in patients with paroxysmal atrial fibrillation in the setting of a sick sinus syndrome may be impossible

Table 37.4 Review of controlled studies on maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation with Class I antiarrhythmic drugs

Study (1st author)	Year	Patients (*n*)	Duration AF (mth; mean)	Age (yr; mean)	Underlying heart disease (%)			Lone AF
					CAD	VHD	SH	
Quinidine *v* no treatment								
1 Södermark	1975	176	<36	58	35	27	9	8
2 Byrne-Q	1970	92	<120	54	16[b]	56	—[b]	20
3 Hillestad	1971	100	?	54	10	70	?	8
4 Lloyd	1984	53	<36	46	11	70	5	6

Table 37.4 Continued

Study (first author)	Year	Patients (*n*)	Duration AF (mth; mean)	Age (yr; mean)	Underlying heart disease (%)			Lone AF
					CAD	VHD	SH	
5 Boissel	1981	212	?	?	1	70	4	20
6 Hartel	1970	175	?	?	18	30	2	11
Disopyramide 450–500 mg *v* no treatment								
7 Karlson	1988	90	4[a]	60	16	13	13	40
Procainamide 3000 mg *v* propranolol 60 mg								
8 Szekely	1970	166-23	NA	NA	8	78	NA	5
Flecainide 150–300 mg *v* no treatment								
9 Van Gelder	1989	73	6–11[a]	58	27	37	10	18
Propafenone 900 mg *v* disopyramide 750 mg								
10 Crijns	1996	56	5[a]	60	12	28	16	40
Quinidine sulfate 1200 mg *v* sotalol 160–320 mg								
11 Juul-Möller	1990	183	5	59	16	6	26	52
Propafenone 450–900 mg (mean 737 ± 177) *v* sotalol 320–950 mg (mean 335 ± 18)								
12 Reimold	1993	53[c]	55	61	16	30	19	19
Quinidine 1200 mg *v* amiodarone 2000 mg/week								
13 Vitolo	1981	54	79% < 6	53	56	44	0	0

Study	Follow up (mth)	Patients in SR at 1 mth (%)		Patients in SR at 6 mth (%)		Stat. sig.	Death on (*n*/*n*)		Drug-related death
		AA	Ctrl	AA	Ctrl		AA	Ctrl	
1	12	90	50	51	28	Yes	5/91	2/75	0
2	12	NA	NA	54	16	Yes	1/45	0/43	1
3	12	60	46	40	21	Yes	1/48	0/52	0
4	6	70	82	48	39	No	2/26	0/25	1
5	3	NA	NA	75[d]	56[d]	Yes	2/103	1/104	1
6	3	NA	NA	69[d]	41[d]	Yes	1/88	0/87	1
7	12	70	39	54	30	Yes	2/44	0/46	0
8	12	66	61[e]	25	13	No	NA	NA	NA
9	12	70	54	49	36	No	0/36	0/37	0
10	6	76	71[f]	55	67	No	0	0	0
11	6	80	70[g]	49	42[g]	No	1/97	1/86[g]	0[i]
12	12	61	59[h]	37	30[h]	No	2/28	0/25	2[j]
13	6	NA	NA	83	43[g]	Yes	0/28	0/26[g]	0

Abbreviations: AA, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; CTR, control group; lone AF, atrial fibrillation without underlying heart disease; SH, systemic hypertension; SR, sinus rhythm; Stat. sig., statistically significant; VHD, valvular heart disease

[a] Median value.

[b] Ischemic and/or hypertensive heart disease.

[c] For persistent atrial fibrillation only.

[d] Follow up 3 months.

[e] Control drug: propranolol.

[f] Control drug: disopyramide.

[g] Long acting quinidine.

[h] Control drug: propafenone.

[i] Two severe proarrhythmias on each drug early after start of the drug.

[j] Sudden deaths (one documented torsade de pointes) after recent dosage increase.

Modified from Crijns *et al*,[84] where details of the studies are given.

without implanting an artificial pacemaker. This relates to possible sinus node or atrioventricular conduction disturbances caused by negative chronotropic drugs. In Wolff–Parkinson–White syndrome complicated by atrial fibrillation acute rate control (as well as conversion to sinus rhythm) may be achieved by procainamide or flecainide.[83]

Prevention of recurrences of persistent atrial fibrillation

Persistent atrial fibrillation does not disappear spontaneously and is difficult to terminate with drugs. First choice therapy for restoration of sinus rhythm is DC electrical cardioversion. However, the Achilles' heel of cardioversion is that atrial fibrillation frequently relapses if left untreated. Recurrences happen predominantly during the first month after cardioversion (Table 37.4, Figure 37.5).[84] Preliminary data from our institution indicate that there is a vulnerable period which is confined to the first week after the shock.

The notion that about 50% of patients will maintain sinus rhythm for over 1 year after cardioversion should be taken with caution since most studies show a progressive pattern of relapses but do not give information beyond 1 year. After a single shock (without prophylactic drugs) the 4 year arrhythmia-free survival rate presumably does not exceed 10%.[8] This means that most patients need prophylactic therapy after cardioversion. However, even when using a serial antiarrhythmic approach only around 30% of patients maintain sinus rhythm for 4 years (Figure 37.5).[8]

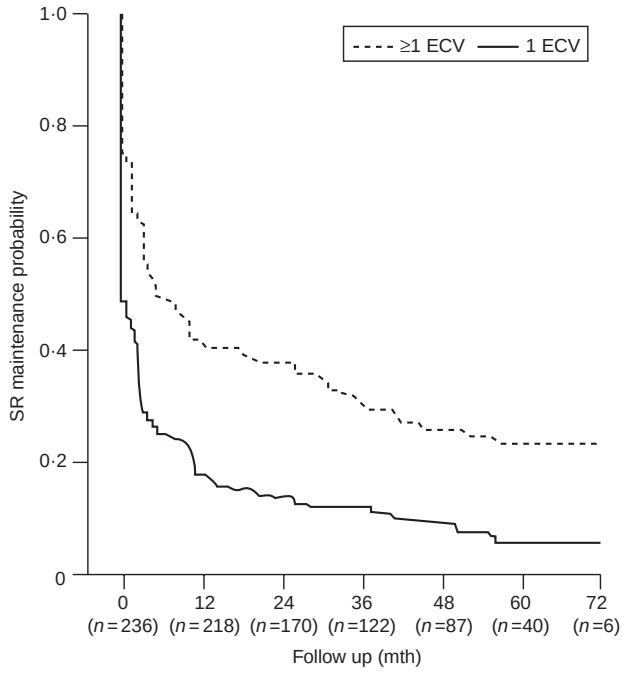

Figure 37.5 Kaplan–Meier plots depicting the probability of maintenance of sinus rhythm (SR) after serial electrical conversions (≥1 ECV) compared to a single cardioversion without drug prescription (1 ECV). *n*, number of patients at risk during serial cardioversion therapy. (From Van Gelder *et al*[8] with permission.)

Most prophylactic drugs are equally effective, except for amiodarone which appears to be more efficacious. Quinidine has been studied most frequently. A meta-analysis of six controlled trials showed that quinidine was superior to no treatment (50% *v* 25% of the patients remained in sinus rhythm during one year, respectively). However, the total mortality was significantly higher in the quinidine group: 12 of 413 patients (2·9%) *v* 3 of 387 patients (0·8%) respectively ($P < 0{\cdot}05$).[85] Also, a recent registry demonstrated a relatively high incidence of sudden death with quinidine.[86] Of 570 patients aged younger than 65 years, 6 patients died suddenly, all shortly after restoration of sinus rhythm. These findings make it questionable whether there is still a role for quinidine in the prophylaxis of atrial fibrillation.

Only a few controlled trials evaluated the Class IC drugs flecainide and propafenone and the Class III drug sotalol, showing that they are comparable to Class IA drugs (Table 37.4). However, differences may be observed in the adverse event profile which may guide the choice for one particular drug (see below). In general, Class IC drugs and sotalol are better tolerated than Class IA drugs and amiodarone. On the other hand, all except amiodarone cause significant proarrhythmia. Limited prospective comparative data of amiodarone are available but a favorable outcome has been reported when amiodarone is instituted as a last resort agent. The drug is particularly useful in atrial fibrillation complicated by heart failure. Unfortunately, its use is limited by potentially severe non-cardiac adverse effects. However, low dose amiodarone (200 mg daily) is effective and gives only few adverse events.[87] Gosselink *et al* included 89 patients with chronic atrial fibrillation who had failed previous treatment aimed at maintenance of sinus rhythm. These patients were treated with a mean dose of amiodarone of 204±66 mg. Actuarially, 53% of these patients were still in sinus rhythm after a follow up of 3 years. Adverse events occurred in three patients and were a reason for discontinuation in only one patient.[87] β Blockers are only effective in preventing early but not late recurrences,[88] presumably by suppressing adrenergic-dependent premature beats in the early phase after cardioversion. It is uncertain when to start β blockade and which patients benefit. Obviously, these issues warrant further evaluation.

Rate control in atrial fibrillation

Although increased morbidity and mortality conveyed by atrial fibrillation provide a clear impetus to rhythm control as the first line strategy, there is no direct evidence that rhythm control confers additional benefit over rate control with regard to improved survival or reduced risk for stroke. Furthermore, rate control appears to be more appropriate as a primary strategy in a substantial proportion of patients with atrial fibrillation, including those with a permanent

form of the arrhythmia, patients with heart failure and mildly symptomatic, longstanding atrial fibrillation, patients with persistent arrhythmia and failed repeat cardioversions and serial prophylactic antiarrhythmic drug therapy, and those in whom risk/benefit ratio from using specific antiarrhythmic agents is shifted towards increased risk.

To date, there are four studies which have addressed the issue of rate versus rhythm control in a systematic fashion (Table 37.5).

The PIAF (Pharmacological Intervention in Atrial Fibrillation) trial[89] and the pilot STAF (Strategies of Treatment of Atrial Fibrillation) study[90] in patients with persistent atrial fibrillation were not powered to determine survival benefit but showed that both strategies yielded similar results with regard to symptoms, functional status and quality of life improvement. Despite repeat cardioversions and serial antiarrhythmic drug therapy, 56% PIAF patients and 40% STAF patients, who were assigned to rhythm control, maintained sinus rhythm at 1 year. Of note, although there was no difference in the incidence of composite primary end point events (death, cardiovascular event or systemic embolism) in the rhythm control and the rate control groups (9 and 10 events, respectively) in the STAF population, 18 of these occurred while patients were in atrial fibrillation, providing indirect evidence that maintenance of sinus rhythm is protective.

The preliminary results of the RACE (RAte Control versus Electrical cardioversion) study of 522 patients with persistent AF have also shown no difference in the primary composite end point of cardiovascular death, hospital admissions for heart failure, thromboembolic events, major bleedings, pacemaker implantation, and adverse effects of antiarrhythmic drug therapy between the two strategies (22·6% *v* 17·2%) (unpublished results at the time of this chapter going to press). This study was designed to prove non-inferiority of rate control, and indeed, a −5·4% absolute difference with 90% confidence intervals ranging from −11·0% to 0·4% showed a non-significant trend in favor of the rate control strategy. After 3 years of follow up, sinus rhythm was maintained in less than half the patients randomized to rhythm control, implying that the strategies appear equal not because atrial fibrillation and sinus rhythm were associated with the equivalent risk for prespecified end points, but due

Table 37.5 Randomized studies of rhythm and rate control strategies in atrial fibrillation

Study	Patients (*n*)	Follow up	Rhythm control	Rate control	Patients in SR[a]	Primary end point
PIAF[89]	252	1 yr	*n* = 127 Amiodarone, repeat DCC	*n* = 125 Diltiazem	56% *v* 10%	Symptomatic improvement 55% *v* 61% (n.s.)
STAF[90]	200	2 yr	*n* = 200 Amiodarone, repeat DCC	*n* = 200 Digoxin β blockers Calcium blockers	40% *v* 12% at 1 yr, 26% *v* 11% at 2 yr; 23% *v* 0% at 3 yr	Composite end point (all-cause mortality, cardiovascular events, CPR, TE) 9 *v* 10; 18/19 events occurred during AF
RACE[b]	522	2·3 yr	*n* = 266 Serial DCC + sotalol, propafenone or flecainide, amiodarone	*n* = 256 Digoxin β blockers Calcium blockers	40% *v* 10%	Composite end point (cardiovascular death, admissions for CHF, TE, bleeding, pacemaker implantation, adverse effects of AAD) 22·6% *v* 17·2%; in HTN 30·8% *v* 17·3%
AFFIRM[b]	4060	3·5 yr	*n* = 2033 Amiodarone, sotalol, propafenone, procainamide, quinidine, flecainide	*n* = 2027 Digoxin, β blockers Calcium blockers	60% *v* 38% at 5 yr	All-cause mortality 27% *v* 26% (n.s.)

[a]Rhythm *v* rate control.
[b]Preliminary results.
Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; DCC, direct current cardioversion; HTN, hypertension; SR, sinus rhythm; TE, thromboembolism

to the fact that that it was not possible to achieve rhythm control in a significant proportion of patients assigned to this strategy. This is in consistency with the inclusion criteria for the RACE study, allowing participation of patients with persistent atrial fibrillation who may have had the arrhythmia as long as 12 months' duration and who had undergone one or two electrical cardioversions in the past 2 years. Despite an aggressive rhythm control strategy, including three antiarrhythmic drugs (sotalol, propafenone or flecainide, and amiodarone) and serial cardioversions, the likelihood of maintenance of sinus rhythm in this selected group of patients is expected to be low, thus favoring the rate control strategy. Likewise in the STAF study, atrial fibrillation was an underlying rhythm in more than two thirds of the RACE patients at the time of the primary end point events.

The largest to date AFFIRM (Atrial Fibrillation Follow up Investigation of Rhythm Management) study of 4060 patients over 65 years or under 65 years but with at least one risk factor for stroke, which was designed to assess mortality benefit of different strategies in atrial fibrillation, has shown no difference in the primary end point of all-cause mortality as well as quality of life and functional status between the two strategies (unpublished results at the time of this chapter going to press). However, likewise the results of the RACE study, the conclusions drawn from the AFFIRM trial, which pertained to older patients in whom rate control is generally considered to be preferential, can only be applied to selected groups of patients with atrial fibrillation and cannot be extrapolated on younger patients who are more likely to be symptomatic and to have impaired quality of life associated with the arrhythmia, even if good rate control has been achieved.

The aim of rate control in atrial fibrillation is to improve symptoms, functional status and quality of life and to prevent the progression of left ventricular dysfunction and heart failure. There is no accepted definition for adequate rate control at rest or exercise. To compensate for loss of atrial contribution, the ventricular rate during AF should probably be about 10–20% higher than a corresponding rate during sinus rhythm. The rate is generally considered controlled if the ventricular rate response is between 60 and 80 beats/min at rest and between 90 and 115 beats/min during moderate exercise.[2]

Rate control therapy in atrial tachyarrhythmias is based mainly on depression of conduction through the atrioventricular node. This is achieved by digitalis, calcium-channel blockers and β blockers. The evidence in favor of sotalol or amiodarone as rate slowing agents is poor. In permanent atrial fibrillation, digoxin usually provides rate control at rest by prolongation of atrioventricular nodal conduction and refractoriness through vagal stimulation, by direct effects on the atrioventricular node, and by increasing the amount of concealed conduction in the atrioventricular node due to the increased rate at which atria discharge. Due to sympathetic overdrive it does not prevent an excessive heart rate increase during daily life exercise, especially in younger, active patients, in which case concomitant use of multiple drugs may be necessary to provide an adequate ventricular rate response, such as β blockers and non-dihydropyridine calcium antagonists. On the other hand, β blockers but also verapamil and diltiazem may reduce peak heart rate too much, thereby limiting the exercise tolerability and quality of life. These agents should be titrated to provide control of both resting and daily life exercise heart rate. In active patients it is necessary to monitor peak exercise heart rate which should not be blunted too much by drugs. Digoxin is accepted as primary rate control treatment in atrial fibrillation complicated by heart failure, but this advice lacks a solid scientific basis. In the light of the positive studies on β blockers in heart failure it seems worthwhile to evaluate their rate controlling effects in this setting. Finally, there is a delay of 30–60 minutes before onset of the therapeutic effect of digoxin, and a peak effect develops after 4–6 hours which limits the use of digoxin in emergency settings.

β blockers, including propranolol, atenolol, metoprolol or esmolol, may be particularly useful in the presence of high adrenergic tone. In the recent crossover, open label study of five drug regimens, the combination of digoxin and atenolol has been shown to be superior to digoxin, atenolol, and diltiazem alone, and the combination of digoxin with diltiazem for rate control, especially during exercise.[91] In randomized, placebo-controlled studies, non-dihydropyridine calcium antagonists, verapamil and diltiazem, have proven effective for rate control in acute atrial fibrillation as they have a rapid onset of action and slow heart rate by 25% within 3–7 minutes of administration but their effects are transient, and repeat doses or a continuous intravenous infusion may be required to maintain adequate rate control.[92,93]

Finally, there are data suggesting that amiodarone may provide adequate rate control during atrial fibrillation if it fails to restore and/or maintain sinus rhythm. In the CHF-STAT study, amiodarone produced a sustained and significant slowing of the mean and maximal ventricular rate responses in the range of 16–20% and 14–22%, respectively.[73] However, the efficacy and safety of amiodarone purely for rate control have not been tested prospectively. Agents that may be administered for control of the ventricular rate response in atrial fibrillation are listed in below.

Atrial fibrillation after cardiac surgery

The incidence of atrial fibrillation after cardiac surgery is 27–37% following coronary bypass surgery and exceeds 50% after valvular surgery.[94–97] Postoperative AF occurs predominantly during the first 4 days and is associated with increased morbidity and mortality, largely due to stroke and circulatory failure, and longer hospital stay. More than 90%

Agents for rate control in atrial fibrillation

Drug	Dose	Level of evidence
Digoxin	Loading dose: 250 micrograms every 2 hours; up to 1500 micrograms; maintenance dose 125–250 micrograms daily	**Grade A**
Diltiazem	120–360 mg daily	**Grade A**
Verapamil	120–360 mg daily	
Metoprolol	50–200 mg daily	**Grade A**
Atenolol	50–100 mg daily	
Propranolol	80–240 mg daily	
Amiodarone	800 mg daily for 1 week; then 600 mg daily for 1 week; then 400 mg daily for 4–6 weeks; maintenance dose 200 mg daily	**Grade C**

patients present with a paroxysmal or first onset form of the arrhythmia.[96] Atrial flutter and atrial tachycardias, including multifocal atrial tachycardia, are also not uncommon.

Clinical factors that convey a higher risk for the development of postoperative atrial tachyarrhythmias include advanced age, male sex, a previous history of atrial fibrillation, hypertension, congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, chronic renal failure, previous cardiac surgery, left atrial enlargement, inadequate cardioprotection and hypothermia, right coronary artery grafting, and a longer bypass time.[98] Recent observations suggest that the incidence of postoperative atrial tachyarrhythmias is lower with minimally invasive techniques, especially for valvular surgery. The pathophysiology of atrial fibrillation after cardiac surgery relates to perioperative changes in atrial electrophysiology, including increased dispersion of atrial refractoriness, decreased atrial conduction velocity, and changes in atrial transmembrane potential. A rhythm control strategy, including electrical or pharmacologic restoration of sinus rhythm with subsequent prophylactic antiarrhythmic therapy should be considered in hemodynamically unstable or highly symptomatic patients with postoperative atrial fibrillation. Low energy internal atrial defibrillation using temporary implanted epicardial coils may be particularly effective in high-risk patients with contraindications to pharmacologic therapy.[99]

Rate control may be preferable in the absence of hemodynamic compromise or poorly tolerated symptoms as atrial fibrillation after coronary bypass surgery appears to be self-limited and there is a high likelihood of spontaneous conversion to sinus rhythm within 6 weeks after discharge.[100] Although digoxin and non-dihydropyridine calcium antagonists (verapamil, diltiazem) are effective in slowing atrioventricular conduction, β blockers should be considered the first line choice because of their beneficial effects on hyperadrenergic postoperative state and a high probability of restoring sinus rhythm (see below).

Short-acting β blocking agents for intravenous administration, such as esmolol, may be preferable in the presence of increased risk for bradyarrhythmias, hypotension, and bronchospasm. In a small series of patients, intravenous infusion of esmolol was associated with a significantly higher rates of conversion to sinus rhythm compared with intravenous diltiazem (66·6% *v* 13·3% at 6 hours and 80% *v* 66·6% at 24 hours).[101] However, diltiazem produced a more rapid rate slowing effect than digoxin (median time to 20% or more decrease in ventricular rates were 2 min and 228 min, respectively).[102] At 2 and 6 hours, the proportion of patients who achieved adequate rate control was significantly higher in the diltiazem-treated group compared with the digoxin-treated group (75% *v* 35% and 85% *v* 45%). This difference disappeared only after 12–14 hours of treatment. There is evidence from a retrospective study of 38 hemodynamically unstable patients with atrial tachyarrhythmias suggesting that intravenous amiodarone may provide adequate rate control resulting in a significant hemodynamic improvement and may also potentiate reversion to sinus rhythm.[103]

The role of β blocker therapy in controlling atrial tachyarrhythmias after cardiac surgery is well established. Two meta-analyses of randomized controlled studies have shown that treatment with β blockers may reduce the incidence of atrial fibrillation by approximately 50%.[104,105] β blockade should always be started or continued as soon as possible after cardiac surgery. There is indirect evidence that adding digoxin may further reduce the occurrence of atrial arrhythmias or increased the success rate of pharmacologic cardioversion.[104,106,107]

Class IA and IC antiarrhythmic drugs have been proven to be moderately effective in the prevention of atrial tachyarrhythmias after cardiac surgery. The preliminary results from the Clinical Outcomes from the Prevention of Postoperative Arrhythmia (COPPA) II study of 293 patients who had undergone coronary bypass have shown that treatment with propafenone 675 mg daily reduced the incidence of postoperative atrial fibrillation to 12·4% compared with 22·7% on placebo.[108] However, there was no difference in the prevalence of atrial fibrillation between patients treated with propafenone at a lower dose of 450 mg daily and the placebo group. Of note, in addition to the study drug or placebo, 93% of patients received digoxin and 84% received β blockers.

Propafenone administered intravenously at a dose of 2 mg/kg produced a more rapid effect on restoration of sinus rhythm compared with intravenous procainamide given at a dose of 20 mg/kg to maximum of 1000 mg (59% *v* 18% at 15 minutes) but there was no significant difference in the conversion rates at 1 hour (76% *v* 61%).[109] However, procainamide was associated with a significantly higher

Principles of management of atrial tachyarrhythmias after cardiac surgery

Strategy	Therapy	Effectiveness	Level of evidence
Prophylaxis (before and/or after surgery)	β blockers	Effectiveness proven	**Grade A**
	Class III antiarrhythmic drugs (sotalol, amiodarone)	Effectiveness mainly proven	**Grade A**
	Class IA and IC antiarrhythmic drugs (procainamide, propafenone)	Possibly effective	**Grade A**
	Digoxin	Ineffective alone, possibly increases the effectiveness of the above	**Grade A**
	Calcium-channel blockers	Ineffective	**Grade B**
Pharmacologic cardioversion	Ibutilide	Effectiveness proven, especially for atrial flutter	**Grade A**
	Amiodarone Class IA and IC antiarrhythmic drugs (procainamide, propafenone)	Possibly effective	**Grade A**
Electrical cardioversion	Low energy internal cardioversion	Effective and preferable in high-risk patients	**Grade B**
Rate control	β blockers	Effectiveness proven	**Grade A**
	Calcium antagonists	Effectiveness proven	**Grade A**
	Digoxin	Effectiveness proven	**Grade A**
	Amiodarone	Possibly effective	**Grade B**
Anticoagulation	Warfarin or LMWH	Effective, required if AF persists more than 24–48 h	**Grade B**
Atrial pacing	Single, dual site or biatrial	Possibly effective but controversy exists	**Grade B**

Abbreviations: AF, atrial fibrillation; LMWH, low molecular weight heparin

incidence of hypotension than propafenone (27% *v* 7%) which was clinically relevant and required discontinuation of the drug in 9% cases. Procainamide does not appear to be more effective than placebo in the prevention of atrial fibrillation but it has not been studied systematically.[110,111] Finally, quinidine has been shown to reduce recurrence of atrial fibrillation in patients who developed the arrhythmia after coronary bypass surgery as assessed by serial 24 hour Holter monitoring and regular physical examination during a 3 month period of follow up, but it was associated with a 16·6% rate of adverse effects.[112]

Sotalol has been reported to reduce the incidence of postoperative atrial fibrillation by 20% to 67% compared with placebo and to have a relatively safe profile in randomized, controlled studies.[113–117] Sotalol may be more effective in the prevention of atrial fibrillation as compared with β blockers because of its potential incremental benefit due to Class III antiarrhythmic drug properties. However, in a randomized study of 429 patients who had undergone cardiac surgery, both low- and high-dose propranolol (40 or 80 mg daily) and low- and high-dose sotalol (120 or 240 mg daily) were comparably effective in reducing the incidence of atrial fibrillation to 14 and 19% or to 11% and 14% respectively.[118] In another series of patients, sotalol proved to be superior to metoprolol resulting in a twofold decrease in atrial fibrillation.[119]

There is compelling evidence from randomized, controlled studies that treatment with amiodarone may reduce the incidence and duration of postoperative atrial fibrillation, and is also effective for control of the ventricular rate.[120–128] Although in some studies amiodarone did not statistically alter the occurrence of atrial tachyarrhythmias, favorable trends were noted for selected groups of patients. The Amiodarone Reduction in Coronary Heart (ARCH) study of 300 patients who had undergone coronary bypass surgery has shown a significant reduction in the incidence of postoperative atrial fibrillation with intravenous amiodarone compared with placebo (35% *v* 47%) without significant risk from the active agent.[126] In the Atrial Fibrillation Suppression Trial (AFIST), there was a significant difference in favor of amiodarone for symptomatic atrial fibrillation

(4·2% *v* 18%).[127] However, adverse events, especially bradycardia necessitating chronotropic support or pacing, may limit its feasibility. Thus, temporary atrial pacing was required due to bradycardia in 40–48% patients who received prophylactic amiodarone compared with 28% patients in the placebo group.[128] Recent meta-analysis of 42 randomized trials of amiodarone, sotalol and β blockers has shown that each of the three drug treatments prevented postoperative atrial fibrillation with odds ratios of 0·48, 0·35, and 0·39, respectively.[129]

Magnesium sulphate (administered intravenously during the first 4–5 days) has been reported to significantly reduce the incidence and the number of episodes of atrial fibrillation.[130,131] In the recent randomized, controlled study of 200 patients who had undergone elective coronary bypass surgery, infusion of 6 mmol of magnesium sulphate the day before, immediately after and for 4 consecutive days after the intervention was associated with a 2% incidence of postoperative atrial fibrillation compared with 21% in the placebo arm.[130] The favorable effects of magnesium may relate to restoration of electrolyte balance after surgery. Alternatively, the stimulating effects of magnesium on the sodium/potassium pump may act beneficially by inducing a calcium-channel blocking effect. However, magnesium infusion did not confer additional benefit in patients already treated with propranolol (22·4% compared with 19·5% on propranolol alone)[132] and was less effective than intravenous amiodarone (the cumulative rates of atrial fibrillation were 23% and 14% respectively).[126] Finally, glucose–insulin–potassium infusion started at anesthetic induction and continued for 12 hours postoperatively significantly decreased the incidence of atrial fibrillation compared with placebo (15% *v* 60%) in diabetic patients.[133]

Several new Class III antiarrhythmic drugs, ibutilide and dofetilide, have recently proven effective for pharmacologic cardioversion of atrial tachyarrhythmias after cardiac surgery. In 302 patients, 101 of whom presented with atrial flutter, intravenous ibutilide given at three dose regimens (0·25, 0·5, or 1 mg) was associated with significantly higher conversion rates (40%, 47%, and 57%, respectively) compared with placebo (15%).[112] Conversion rates at all doses were higher for atrial flutter than for atrial fibrillation, reaching 78% versus 44% with a dose of 1 mg. Pretreatment with ibutilide was associated with a trend towards lower energy levels required for external defibrillation. Of note, there was a suggestion of a benefit of concomitant therapy with digoxin: 65% patients treated with digoxin were successfully cardioverted with 1 mg of ibutilide compared with 31% patients who did not receive digoxin. Dofetilide administered intravenously at a dose of 4 or 8 micrograms/kg was associated with a non-significant trend towards higher incidence of restoration of sinus rhythm compared with placebo (36% and 44% *v* 24%).

However, in virtually all randomized studies antiarrhythmic drug therapy, probably except for amiodarone, accomplished no reduction in the length of hospital stay. Selected randomized, controlled trials of prophylactic antiarrhythmic drug therapy for postoperative atrial fibrillation are listed in Table 37.6.

The potential role of preventative atrial pacing for postoperative atrial fibrillation has been investigated in a number of randomized studies, but the efficacy of this therapeutic modality has not yet been proven. This issue will be discussed in more details in the following sections.

Persistent and permanent atrial fibrillation in the setting of heart failure – evidence base for "upstream" therapy

In patients with atrial fibrillation in the setting of heart failure, management should be aimed initially at adequate therapy of heart failure. Thereafter, electrical cardioversion may be considered in younger patients with a short arrhythmia duration who have been successfully re-compensated. In case of an early relapse (<6 months after the last shock) recardioversion should be performed after pretreatment with amiodarone.[87] Repeat cardioversions with intervals longer than 6 months between each shock is an appropriate manner to prevent progression of heart failure.

Effective conventional treatment of congestive heart failure delays progression of left ventricular dysfunction and reduces mitral regurgitation and consequently, may prevent left atrial dilation and stretch which are considered to be important constituents of the substrate for atrial tachyarrhythmias by creating "a critical mass" necessary for multiple wavelet re-entry and stretch-related abnormal automaticity in the atria. Experimental evidence suggests that angiotensin enzyme converting (ACE) inhibitors may provide additional "antiarrhythmic" benefit by reducing adverse electrophysiologic effects of angiotensin II due to lessening the extent of fibrosis within the atrial myocardium.[135,136]

The beneficial effect of an ACE inhibitor on the frequency of atrial fibrillation was first shown in the TRACE (Trandolapril Cardiac Evaluation) study of 1749 post myocardial infarction patients with left ventricular dysfunction.[137] In the trandolapril group, significantly fewer patients developed atrial fibrillation during follow up compared with the placebo group (2·8% *v* 5·3%), reflecting a 55% risk reduction. Pretreatment with an ACE inhibitor before electrical cardioversion in patients with congestive heart failure and persistent atrial fibrillation increased a likelihood of restoration of sinus rhythm (33% in the ACE inhibitor-treated group *v* 7% in the untreated group) and exhibited a trend towards fewer recurrences of the arrhythmia.[138] Furthermore, angiotensin II AT_1-receptor blocker irbersartan has been shown to promote pharmacologic cardioversion of persistent atrial fibrillation by oral amiodarone (32% compared with 23% on amiodarone alone) and to reduce the recurrence rate

Table 37.6 Clinical evidence of the efficacy of antiarrhythmic therapy with Class I and III antiarrhythmic drugs for conversion and/or prophylaxis of atrial tachyarrhythmias after cardiac surgery

Study (first author)	Patients (*n*)	Treatment arm	Control arm	Incidence of AF *v* placebo	Adverse effects
Laub[110]	46	Procainamide IV 12 mg/kg, then 2 mg/min started within 1 h after surgery	Placebo	3·9/day at risk *v* 10·6 day at risk	–
Gold[111]	100	Oral procainamide (weight adjusted dose) for 4 days after surgery	Placebo	38% *v* 26% but reduced duration of AF (16 *v* 28 patient-days)	Hypotension
COPPA II[108]	293	Oral propafenone 675 mg Oral propafenone 400 mg started within 24 h for 15 days or until discharge	Placebo	12·4% *v* 22·5% *v* 22·7%	–
Geelen[109]	62	Propafenone IV 2 mg/kg in 10 min	Procainamide IV 20 mg/kg (maximum 1000 mg)	Conversion rates: 59% *v* 18% at 15 min ($P<0·001$); 76% *v* 61% at 1 h (difference n.s.)	Hypotension in 7% in the propafenone arm 27% in the procainamide arm (9% severe)
Nystrom[120]	101	Oral sotalol	β blocker	10% *v* 29% ($P=0·028$)	Sotalol stopped or dose reduced in 10% *v* none in the control arm
Suttorp[117]	300	Sotalol 240 mg started from the 4th h for 6 days after surgery	Placebo	16% *v* 33%	Sotalol stopped in 1%; placebo stopped in 3%
Suttorp[118]	429	Sotalol 120 mg *or* Sotalol 240 mg started from the 4th h for 6 days after surgery	Propranolol 40 mg Propranolol 80 mg	13·9% *v* 18·8% 10·9% *v* 13·7% (difference n.s.)	Either low-dose drug stopped in 2·9%; either high-dose drug stopped in 10·7%
Evrard[113]	206	Oral sotalol 160 mg from the 1st day after surgery	Matched control patients; no β blockers	16% *v* 48% ($P<0·0001$); 20% reduction	Sotalol stopped in 7·8% *v* none in the control arm
Pfisterer[114]	255	Oral sotalol 160 mg started 2 h before until discharge	Placebo	26% *v* 46% ($P=0·0012$); 43% reduction	Sotalol stopped in 5·6%; placebo stopped in 3·9% (difference n.s.)
Matsuura[115]	80	Oral sotalol 80 mg for 14 days after surgery	Matched control patients	15% *v* 37·5% ($P=0·05$)	Hypotension on sotalol in 7·5%
Gomes[116]	85	Oral sotalol 80–120 mg 24–48 h before and 4 days after surgery	Placebo	12·5% *v* 38% ($P=0·008$); 67% reduction	Sotalol stopped (bradycardia, hypotension) in 5% *v* none in the control arm

Table 37.6 Continued

Study (first author)	Patients (*n*)	Treatment arm	Control arm	Incidence of AF *v* placebo	Adverse effects
Parikka[119]	191	Oral sotalol 120 mg after surgery	Oral metoprolol 75 mg	16% *v* 30% ($P < 0{\cdot}01$)	–
Daoud[121]	124	Oral amiodarone 600 mg started for a minimum of 7 days before surgery, then 200 mg until discharge	Placebo	25% *v* 53% ($P = 0{\cdot}04$)	Major morbidity and mortality events occurred in 12% and 5% in the amiodarone arm *v* 10% and 3% in the placebo arm
Lee[122]	140	Amiodarone 150 mg IV, then 400 mg/kg/h for 3 days before and 5 days after surgery	Placebo	12% *v* 34% ($P < 0{\cdot}01$); longer stay in intensive care in the placebo arm	–
Reddle[123]	143	Oral amiodarone 2000 mg 1–4 days before surgery and 400 mg for 7 days after surgery	Placebo	24·7% *v* 32·8% (difference n.s.) Amiodarone + β blockers: 16·7% *v* 32·8% in the remaining patients	–
Solomon[124]	102	Amiodarone IV 1000 mg/day for 48 h, then 400 mg/day	Propranolol IV 1 mg every 6 h for 48 h, then 80 mg/day until discharge	16% *v* 32·7% ($P = 0{\cdot}05$)	–
Treggiari-Venzi[125]	155	Amiodarone IV 900 mg/d for 72 h	Magnesium sulphate 4000 mg/d for 72 h Placebo	14% *v* 23% *v* 27% (difference n.s.)	–
ARCH[126]	300	Amiodarone IV 100 mg/d for 2 days	Placebo	35% *v* 47% ($P = 0{\cdot}01$)	Major morbidity and mortality events occurred in 2·5% and 0% in the amiodarone arm *v* 4·9% and 1·4% in the placebo arm
AFIST[127]	220	Oral amiodarone 600 mg for 5 days or 1600 mg for 1 day before surgery, then 800–1200 mg on the day of surgery and 800 mg for 1–4 days after surgery	Placebo	22·5% *v* 38·0%; 4·2% *v* 18·0% for symptomatic AF	Bradycardia and hypotension on amiodarone in 7·5% and 14·2% *v* 7·5% and 10·0% in the placebo arm

Table 37.6 Continued

Study (first author)	Patients (*n*)	Treatment arm	Control arm	Incidence of AF *v* placebo	Adverse effects
VaderLugt[107]	302 (101 with flutter)	Ibutilide IV 0·25 mg, 0·5 mg, 1 mg	Placebo	Conversion rates: 40%, 47%, 57% *v* 15% in the placebo arm; at 1 mg 44% for AF, 78% for flutter	All ibutilide *v* placebo: hypotension 2·8% *v* 1·3%; ventricular arrhythmias 8·3% *v* 1·2%, torsade de pointes 1·8% *v* 1·2%
Frost[134]	98 with AF/flutter	Dofetilide IV 8 microgram/kg Dofetilide IV 4 microgram/kg	Placebo	Conversion rates: 44% *v* 33% *v* 24% (difference n.s.)	Ventricular tachycardia in 9·3% on high-dose dofetilide

Abbreviaiton: AF, atrial fibrillation

at 2 months of follow up (14% *v* 30%).[139] Finally, in a series of 750 patients with advanced heart failure who were evaluated for heart transplantation, an increase in use of ACE inhibitors and amiodarone between 1985 and 1993 was associated with an improvement in the 2 year survival rate from 39% to 66% in those with atrial fibrillation.[140]

Although β blockers are usually ineffective for long term maintenance of sinus rhythm, except for adrenergically mediated atrial fibrillation, therapy with β blockers in patients with heart failure may confer benefit in terms of prevention or delay in the development of the arrhythmia likely due to an overall beneficial effect in heart failure. In the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) study of 1959 patients with myocardial infarction and left ventricular dysfunction, therapy with carvedilol reduced risk of the development of atrial fibrillation or flutter by nearly two thirds.[141] However, it is unclear whether it translates into survival benefit. Although the subgroup analysis of CIBIS (Cardiac Insufficiency Bisoprolol Study) II data has shown that bisoprolol reduced all-cause mortality in patients with sinus rhythm (relative risk 0·58) but not in patients presenting with atrial fibrillation (relative risk 1·16),[142] the preliminary data from the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study have suggested that in the subgroup of patients with atrial fibrillation carvedilol was associated with a better survival compared with placebo, but this effect was less pronounced than in patients with sinus rhythm.

These observations open the possibility of exploitation of ACE inhibitors and angiotensin II AT_1-receptor blockers to prevent or delay atrial remodeling in atrial fibrillation and introduce the concept of "upstream" therapy targeting the underlying disease process, such as heart failure or hypertension, that may favor the atrial arrhythmia by disorganized hemodynamics or the development of atrial pathology.

Tolerability and safety of antiarrhythmic drugs

The most important adverse effects of drugs used in atrial fibrillation are ventricular proarrhythmia, heart failure, enhanced atrioventricular nodal conduction, and exacerbation of sick sinus syndrome (or atrioventricular conduction disturbances). The latter may be the basis for atrial fibrillation and can be unmasked by all antiarrhythmic drugs, including digitalis.

Class IA and III drugs predominantly cause polymorphic ventricular tachycardia or torsade de pointes,[143,144] and Class IC drugs, incessant monomorphic ventricular tachycardias and ventricular fibrillation.[145,146] In contrast to the quinidine-like drugs, ventricular proarrhythmia or sudden death due to Class IC drugs is virtually absent in patients *without* overt heart disease. Patients treated with quinidine or sotalol may experience sudden death especially *early* after onset of therapy or after dosage increases.[86] Amiodarone shows a low incidence of torsade de pointes and may even be instituted after proarrhythmic events on Class IA drugs. Class III agent, dofetilide, has been shown to exhibit reverse use-dependence, that is, a decline in its ability to prolong action potential duration and effective refractory period at higher heart rates, a property which is associated with potentially proarrhythmic QT prolongation during bradycardia. The incidence of torsade de pointes in the DIAMOND study was 3·3%, the majority of which occurred within the first 3 days.[147]

Proarrhythmic effects of ibutilide are also likely to be due to marked prolongation of ventricular repolarization, favoring the occurrence of early after-depolarizations. The incidence of sustained torsade de pointes associated with ibutilide infusion for conversion of atrial fibrillation or flutter was reported to be 1·7%, with the majority of episodes occurring within 1 hour of drug administration, although patients with a high risk of the development of proarrhythmia, that is, with a history of torsade de pointes and baseline QT interval prolongation, were excluded.[148] Torsade de pointes occurred in 0·9% of patients receiving azimilide at doses of 100 mg and 125 mg.[149]

Electrocardiographic signs, potentially useful in the prediction of proarrhythmia with Class IA and III drugs, include acute and excessive QT prolongation, pause-related TU wave changes, and increased QT dispersion. Torsade de pointes may occur, especially if there is a pre-existing QT prolongation, and is enhanced by bradycardia (for example, occurring after sudden conversion of "rapid" atrial fibrillation to "slow" sinus rhythm). Late proarrhythmia may occur after addition of drugs, like diuretics or during intercurrent bradycardia. Recently, it was demonstrated that women are more susceptible than men.[150] Ventricular proarrhythmia with Class IC drugs should be expected in patients with previous sustained ventricular tachycardia and in those with structural heart disease receiving a high dose. It occurs predominantly late after institution of the drug, and especially during higher heart rates. In this respect, it is considered useful to perform an exercise test after institution of the drug. During higher heart rates conduction slowing may become more prominent. Excessive broadening of the QRS complex during high heart rates may be a marker of future ventricular proarrhythmia necessitating dose reduction or termination of the drug.

Patients using Class IA and IC drugs may experience high ventricular rates during breakthrough atrial fibrillation or flutter. These agents do not suppress and may even augment atrioventricular conduction by anticholinergic stimulation. AV conduction is further reinforced by exercise and anxiety. Therefore patients using these drugs prophylactically must be cautioned to avoid exercise during a recurrence of atrial fibrillation. Digoxin, a β blockers or a calcium-channel blocker may be added but there are no clinical data to support this approach.

Depending on dose and duration of therapy, Class IA and IC drugs especially may cause heart failure, mainly through cardiodepression. Disopyramide allegedly has the largest negative inotropic effects and may cause heart failure early but also late (months) after initiation, especially in patients with a history of cardiac insufficiency. The other Class IA drugs, as well as β blockers (including sotalol) and calcium-channel blockers, rarely cause heart failure in patients with atrial fibrillation. Heart failure induced by amiodarone has not been described.

Where to initiate antiarrhythmic drug therapy

The issue of the proper site for initiation of antiarrhythmic drug therapy for atrial tachyarrhythmias revolves around considerations of risk and practicality.[151] Inhospital initiation under monitored conditions conveys benefits of accurate assessment of the efficacy and prompt recognition of adverse effects, such as bradycardia, conduction abnormalities, excessive QT interval prolongation, proarrhythmias, and intolerance or idiosyncrasy. It should, therefore, be considered in patients in atrial fibrillation in whom sinus node function or QT interval duration during sinus rhythm are unknown and patients at anticipated high risk of developing adverse effects, irrespective of the underlying rhythm. For some antiarrhythmic agents, for example, dofetilide, there is formal mandate for inhospital initiation.

In the absence of proarrhythmic concerns and formal labeling, convenience and cost effectiveness favor out-of-hospital initiation, for example, oral propafenone and flecainide in patients with lone atrial fibrillation or atrial fibrillation associated with hypertension without significant left ventricular hypertrophy. The same approach is valid for amiodarone, given its long elimination half life period and low probability of developing torsade de pointes, especially if transtelephonic monitoring is used to provide the surveillance of heart rate, PR and QT interval durations, QRS width, and the assessment of the efficacy of treatment. Table 37.7 summarizes current recommendations on inhospital or out-of-hospital initiation of antiarrhythmic drug treatment.

Table 37.7 Inhospital versus out-of-hospital initiation of antiarrhythmic drug therapy

Drug	Underlying rhythm	
	Atrial fibrillation/flutter	Sinus rhythm
Quinidine	Inpatient	Inpatient
Procainamide	Inpatient	Inpatient
Flecainide	Outpatient [a]	Outpatient
Propafenone	Outpatient [a]	Outpatient
Sotalol	Inpatient	Outpatient [c]
Dofetilide	Inpatient	Inpatient
Azimilide [b]	Inpatient	Inpatient
Amiodarone	Outpatient [c]	Outpatient [c]

[a] No sinus node dysfunction.
[b] An investigational drug.
[c] With transtelephonic monitoring.

As a general rule, antiarrhythmic drugs should be started at a lower dose with upward titration, reassessing the ECG as each dose change is made or concomitant drug therapies are introduced.[2] Of note, even with inhospital initiation, antiarrhythmic agents impose risk of developing proarrhythmia later in the course of therapy, which may be facilitated

by progression of underlying heart disease, electrolyte abnormalities, drug interactions, and changes in absorption, metabolism or clearance.

Conclusion

Rational antiarrhythmic treatment of atrial fibrillation starts with establishing whether one is dealing with the paroxysmal, persistent or permanent subtype. Only then the goal of treatment can be identified: to restore sinus rhythm with the option of prophylactic drug treatment or to adopt atrial fibrillation as the dominant rhythm. Antiarrhythmic treatment is further guided by the duration of the arrhythmia, the tendency for recurrence after conversion, and the potential adverse effects of drugs. At some stage during treatment, rate control is useful in all three subtypes of atrial fibrillation but especially in the *permanent* form. The termination of *paroxysmal* atrial fibrillation is enhanced by intravenous drugs. For fibrillation Class IC drugs are first choice whereas Class III drugs may effectively terminate atrial flutter. Restoration of sinus rhythm in *persistent* atrial fibrillation is most effectively achieved by electrical cardioversion but to reduce post-shock recurrence usually antiarrhythmics are indispensable. Despite drugs, the latter approach will at best postpone progression from persistent to permanent atrial fibrillation.

Most patients cannot be cured from atrial fibrillation: almost all will experience recurrence of the arrhythmia earlier or later after the first attack despite drug treatment. Therefore the primary goal of treatment is to reduce morbidity (and possibly also mortality) rather than simply mending the rhythm at any price. Currently, rhythm and rate control strategies are being evaluated concerning their effect on morbidity and mortality. These studies may help to better define the role of the different antiarrhythmic treatments.

Upstream therapy aimed at the underlying pathology and better identification and modification of risk factors is likely to make possible intervention early in the course of the disease when preventative or corrective strategies are most efficient.

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References

1. Lévy S. Classification system of atrial fibrillation. *Curr Opin Cardiol* 2000;**15**:54–57.
2. Fuster V, Rydén LE, Asinger RV *et al.* Task Force Report: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J* 2001:1852–923.
3. Benjamin EJ, Levy D, Vaziri SM *et al.* Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham study. *JAMA* 1994;**271**:840–4.
4. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther* 1962;**140**:183–8.
5. Allessie MA, Lamers WJEP, Bonke FIM, Hollen SJ. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology and arrhythmias*. New York: Grune and Stratton, 1985.
6. Godtfredsen J. Atrial fibrillation. Etiology, course and prognosis. A follow up study of 1212 cases. Thesis, University of Copenhagen, 1975.
7. Fresco C, Proclemer A, on behalf of the PAFIT-2 Investigators. Management of recent onset atrial fibrillation. *Eur Heart J* 1996;**17**(Suppl. C):C41–7.
8. Van Gelder IC, Crijns HJGM, Tieleman RG *et al.* Value and limitation of electrical cardioversion in patients with chronic atrial fibrillation – importance of arrhythmia risk factors and oral anticoagulation. *Arch Intern Med* 1996;**156**:2585–92.
9. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;**92**:1954–68.
10. Coumel P. Neural aspects of paroxysmal atrial fibrillation. In Falk RH, Podrid PJ, eds. *Atrial fibrillation: mechanisms and management*. New York: Raven Press, 1992.
11. Brugada R, Tapscott T, Czernuszewicz GZ *et al.* Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;**336**:905–11.
12. Bharati S, Sasaki D, Siedman S, Vidaillet H. Sudden death among patients with a hereditary cardiomyopathy due to a missense mutation in the rad domain of the lamin a/c gene. *J Am Coll Cardiol* 2001:**37**:174A (Abstract).
13. Gruver EJ, Fatkin D, Dodds GA *et al.* Familial hypertrophic cardiomyopathy and atrial fibrillation caused by Arg663His beta–cardiac myosin heavy chain mutation. *Am J Cardiol* 1999;**83**:13H–18H.
14. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Intervent Cardiac Electrophysiol* 2000;**4**:369–82.
15. Levy S, Maarek M, Coumel P *et al.*, on behalf of the College of French Cardiologists. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA Study. *Circulation* 1999;**99**:3028–35.
16. Fetsch T, Breithardt G, Engberding R *et al.* Can we believe in symptoms for detection of atrial fibrillation in clinical routine? The results of the PAFAC study. *Circulation* 2001;**104**:II–699 (Abstract).
17. Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow up study. *Am J Med* 1995;**98**:476–84.
18. Önundarson PT, Thorgeirsson G, Jonmundsson E, Sigfusson N, Hardarson Th. Chronic atrial fibrillation – epidemiologic features and 14 years follow-up: a case control study. *Eur Heart J* 1987;**8**:521–7.
19. Crijns HJGM, Van den Berg MP, Van Gelder IC, Van Veldhuisen DJ. Management of atrial fibrillation in the setting of heart failure. *Eur Heart J* 1997;**18**(Suppl. C):C45–9.

20.Van Gelder IC, Crijns HJGM, Blanksma PK *et al.* Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol* 1993; **72**: 560–6.
21.Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation. *N Engl J Med* 1982;**306**:1018–22.
22.Carson PE, Johnson GR, Dunkman WB *et al.* The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V–HeFT studies. *Circulation* 1993;**87**(Suppl. VI): VI-102–10.
23.Stevenson WG, Stevenson LW, Middlekauff HR *et al.* Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996;**28**:1458–63.
24.Keren G, Etzion T, Sherez J *et al.* Atrial fibrillation and atrial enlargement in patients with mitral stenosis. *Am Heart J* 1987;**114**:1146–55.
25.Sanfilippo AJ, Abascal VM, Sheehan M *et al.* Atrial enlargement as a consequence of atrial fibrillation. *Circulation* 1990; **82**:792–7.
26.Gosselink ATM, Crijns HJGM, Hamer JPM, Hillege H, Lie KI. Changes in atrial dimensions after cardioversion: role of mitral valve disease. *J Am Coll Cardiol* 1993;**22**:1666–72.
27.Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. *Arch Intern Med* 1987;**147**:1561–4.
28.Petersen P. Thromboembolic complications of atrial fibrillation and their prevention: a review. *Am J Cardiol* 1990; **65**: 24C–8C.
29.The Stroke Prevention in Atrial Fibrillation investigators. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. *Ann Intern Med* 1992;**116**:1–5.
30.The Stroke Prevention in Atrial Fibrillation investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;**116**:6–12.
31.Costeas C, Kassotis J, Blitzer M, Reiffel JA. Rhythm management in atrial fibrillation – with a primary emphasis on pharmacological therapy: part 2. *PACE* 1998;**21**:742–52.
32.Slavik RS, Tisdale JE, Borzak S. Pharmacologic conversion of atrial fibrillation: a systematic review of available evidence. *Prog Cardiovasc Dis* 2001;**44**:121–52.
33.Capucci A, Villani GQ, Piepoli MF, Aschieri D. The role of oral IC antiarrhythmic drugs in terminating atrial fibrillation. *Curr Opin Cardiol* 1999;**14**:4–8.
34.Azpitarte J, Alvarez M, Baun O *et al.* Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation: results of a randomized double-blind, controlled study. *Eur Heart J* 1997;**18**:1649–54.
35.Boriani G, Biffi M, Capucci A *et al.* Conversion of recent-onset atrial fibrillation to sinus rhythm. Effects of different drug protocols. *PACE* 1998;**21**:2470–4.
36.Bianconi L, Mennuni M, and PAFIT-3 Investigators. Comparison between propafenone and digoxin administered intravenously to patients with acute atrial fibrillation. *Am J Cardiol* 1998;**82**:584–8.
37.Stambler BS, Wood MA, Ellenbogen KA *et al.*, and the Ibutilide Repeat Dose Investigators. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;**94**:1613–21.
38.Vos MA, Golitsyn SR, Stangl K *et al.*, for the Ibutilide/Sotalol Comparator Study Group. Superiority of ibutilide (a new class III agent) over d, l–sotalol in converting atrial flutter and atrial fibrillation. *Heart* 1998;**79**:568–75.
39.Volgman AS, Carberry PA, Stambler B *et al.* Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol* 1998;**31**:1414–19.
40.Norgaard BL, Wachtell K, Christensen PD *et al.* Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: a multicenter, randomized, double blind, placebo–controlled study. *Am Heart J* 1999;**137**:1062–9.
41.Pedersen OD, Bagger H, Keller N *et al.*, for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. Efficacy of dofetilide in the treatment of atrial fibrillation–flutter in patients with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Substudy. *Circulation* 2001; **104**:292–6.
42.Singh S, Zoble RG, Yellen L *et al.*, for the Dofetilide Atrial Fibrillation Investigators. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE–D) Study. *Circulation* 2000;**102**:2385–90.
43.Hou Z-Y, Chang M-S, Chen C-Y *et al.* Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**:521–8.
44.Pinski SL, Labadet C, Villamil A. Is intravenous amiodarone effective in converting atrial fibrillation: a meta-analysis. *Circulation* 2001;**104**:II-700 (Abstract).
45.Vardas PE, Kochiadakis GE, Igomenidis NE *et al.* Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation. *Chest* 2000;**117**:1538–45.
46.Di Benedetto S. Quinidine versus propafenone for conversion of atrial fibrillation to sinus rhythm. *Am J Cardiol* 1997; **80**:518–19.
47.Hohnloser SH, Van de LA, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol* 1995;**26**:852–8.
48.Sung RJ, Tan HL, Karagounis L *et al.*, for the Sotalol Multicenter Study Group. Intravenous sotalol for termination of supraventricular tachycardia and atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebocontrolled study. *Am Heart J* 1995;**129**:739–48.
49.Falk RH, Knowlton AA, Bernard SA, Gotlieb NE, Battinelli NJ. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. *Ann Intern Med* 1987;**106**:503–6.
50.Noc M, Stajer D, Horvat M. Intravenous amiodarone versus verapamil for acute conversion of paroxysmal atrial fibrillation to sinus rhythm. *Am J Cardiol* 1990;**65**:679–80.
51.The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Results of a randomized, placebo-controlled multicenter trial in 239 patients. *Eur Heart J* 1997;**18**:649–54.

52.Sticherling C, Oral H, Horrocks J *et al.* Effects of digoxin on acute, atrial fibrillation-induced changes in atrial refractoriness. *Circulation* 2000;**102**:2503–8.
53.Tieleman RG, Blaau Y, Van Gelder IC *et al.* Digoxin delays recovery from tachycardia-induced electrical remodeling of the atria. *Circulation* 1999;**100**:1836–42.
54.Van Gelder IC, Crijns HJGM, Van Gilst WH *et al.* Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. *Am J Cardiol* 1991;**68**:41–6.
55.Connolly SJ, Hoffest DL. Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. *Am J Cardiol* 1989;**63**: 817–19.
56.Stroobandt R, Stiels B, Hoebrechts R, on behalf of the Propafenone Atrial Fibrillation Trial Investigators. Propafenone for conversion and prophylaxis of atrial fibrillation. *Am J Cardiol* 1997;**79**:418–23.
57.UK Propafenone PSVT Study Group. A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. *Circulation* 1995;**92**:2550–7.
58.Reimold SC. Avoiding drug problems. The safety of drugs for supraventricular tachycardia. *Eur Heart J* 1997;**18**:C40–4.
59.Van Gelder IC, Crijns HJ, Van Gilst WH *et al.* Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1989;**64**:1317–21.
60.Pietersen AH, Hellemann H, for the Danish–Norwegian Flecainide Multicenter Atrial Fibrillation Study Group. Usefulness of flecainide for prevention of paroxysmal atrial fibrillation and flutter. *Am J Cardiol* 1991;**67**:713–17.
61.Anderson JL, Gilbert EM, Alpert BL *et al.* Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. *Circulation* 1989; **80**:1557–70.
62.Anderson JL, Platt ML, Guarnieri T *et al.*, and the Flecainide Supraventricular Tachycardia Study Group. Flecainide acetate for paroxysmal supraventricular arrhythmias. *Am J Cardiol* 1994;**74**:578–84.
63.Naccarelli GV, Dorian P, Hohnloser SH, Coumel P, for the Flecainide Multicenter Atrial Fibrillation Group. Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter. *Am J Cardiol* 1996; **77**:53A–9A.
64.Echt DS, Liebson PR, Mitchell LB *et al.*, and the CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–8.
65.Flaker GC, Blackshear JL, McBride R *et al.* Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;**20**:527–32.
66.Lee SH, Chen SA, Tai CT *et al.* Comparisons of oral propafenone and sotalol as an initial treatment in patients with symptomatic paroxysmal atrial fibrillation. *Am J Cardiol* 1997;**79**:905–8.
67.Bellandi F, Simonetti I, Leoncini M *et al.* Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 2001;**88**:640–5.
68.Wanless RS, Anderson K, Joy M, Joseph SP. Multicenter comparative study of the efficacy and safety of sotalol in the prophylactic treatment of patients with paroxysmal supra-ventricular tachyarrhythmias. *Am Heart J* 1997;**133**: 441–6.
69.Benditt DG, Williams JH, Jin J *et al.*, for the D, l-Sotalol Atrial Fibrillation/Flutter Study Group. Maintenance of sinus rhythm with oral d, l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. *Am J Cardiol* 1999;**84**:270–7.
70.Fetsch T, Breithardt G, Engberding R *et al.* Prevention of atrial fibrillation after cardioversion – results of the PAFAC trial. *Circulation* 2001;**104**:II-699 (Abstract).
71.Roy D, Talajic M, Dorian P *et al.*, for the Canadian Trial of Atrial Fibrillation Investigators. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 2000;**342**: 913–20.
72.Toivonen L, Greenbaum R, Campbell T *et al.* Dofetilide is better tolerated than sotalol for the prevention of recurrence of atrial fibrillation and flutter. *Eur Heart J* 2000;**21**:123 (Abstract).
73.Deedwania PC, Singh BN, Ellenbogen K, for the Department of Veterans Affairs CHF–STAT Investigators. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF–STAT). *Circulation* 1998;**98**:2574–9.
74.European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD). *Circulation* 1999; **99**:2486–91.
75.Santini M, Greenbaum R, Lehman R *et al.* Oral dofetilide is effective for maintenance of sinus rhythm in patients with atrial fibrillation/flutter independent of patient characteristics. *Eur Heart J* 2000;**21**:327 (Abstract).
76.Pritchett ELC, Page RL, Connolly SJ *et al.* Antiarrhythmic effects of azimilide in atrial fibrillation: efficacy and dose–response. *J Am Coll Cardiol* 2000;**36**:794–802.
77.Connolly SJ, Schnell DJ, Page RL *et al.* Dose–response relations of azimilide in the management of symptomatic, recurrent atrial fibrillation. *Am J Cardiol* 2001;**88**:974–9.
78.Kühlkamp V, Schirdewan A, Stangl K *et al.* Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 2000;**36**:139–46.
79.Tieleman RG, Van Noord T, Van Gelder IC *et al.* Beta-blockers prevent subacute recurrences after cardioversion of persistent atrial fibrillation in patients with hypertension but not in lone atrial fibrillation patients. *PACE* 2001;**24**:675 (Abstract).
80.Steeds RP, Birchall AS, Smith M, Channer KS. An open label, randomized, crossover study comparing sotalol and atenolol in the treatment of symptomatic paroxysmal atrial fibrillation. *Heart* 1999;**82**:170–5.
81.Plewan A, Lehmann G, Ndrepepa G *et al.* Maintenance of sinus rhythm after electrical cardioversion of persistent atrial fibrillation: sotalol vs bisoprolol. *Eur Heart J* 2001;**22**:1504–10.
82.Marcus FI. The hazard of using type IC antiarrhythmic drugs for the treatment of paroxysmal atrial fibrillation. *Am J Cardiol* 1990;**66**:366–7.

83. Crozier I. Flecainide in the Wolff–Parkinson–White syndrome. *Am J Cardiol* 1992;**70**:26A–32A.
84. Crijns HJGM, Gosselink ATM, Van Gelder IC *et al.* Drugs after cardioversion to prevent relapses of chronic atrial fibrillation. In: Kingma JH, van Hemel NM, Lie KI, eds. *Atrial fibrillation, a treatable disease?* Dordrecht: Kluwer Academic Publishers, 1992.
85. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990;**82**:1106–16.
86. Carlsson J, Tebbe U, Rox J *et al.*, for the ALKK study group. Cardioversion of atrial fibrillation in the elderly. *Am J Cardiol* 1996;**78**:1380–4.
87. Gosselink ATM, Crijns HJ, Van Gelder IC *et al.* Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA* 1992;**267**:3289–93.
88. Szekely P, Sideris DA, Batson GA. Maintenance of sinus rhythm after atrial defibrillation. *Br Heart J* 1970;**32**:741–6.
89. Hohnloser SH, Kuck KH, Lilienthal J, for the PIAF Investigators. Rhythm or rate control in atrial fibrillation – Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000;**356**:1789–94.
90. Carlsson J, Tebbe U. Rhythm control versus rate control in atrial fibrillation: results from the STAF Pilot Study (Strategies of Treatment in Atrial Fibrillation). *PACE* 2001;**24**:561 (Abstract).
91. Farshi R, Kistner D, Sarma JSM *et al.* Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover, open–label study of five drug regimens. *J Am Coll Cardiol* 1998;**22**:304–10.
92. Ellenbogen KA, Dias VC, Plumb VJ *et al.* A placebo-controlled trial of continuous intravenous diltiazem infusion for 24 hour heart rate control during atrial fibrillation and atrial flutter: a multicenter study. *J Am Coll Cardiol* 1991;**18**:891–7.
93. Platia EV, Michelson EL, Porterfield JK, Das G. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. *Am J Cardiol* 1989;**63**:925–9.
94. Mathew JP, Parks R, Savino JS *et al.*, for the Multicenter Study of Perioperative Ischaemia Research Group. Atrial fibrillation following coronary artery bypass graft surgery. *JAMA* 1996; **276**:300–6.
95. Aranki SF, Shaw DP, Adams DH *et al.* Predictors of atrial fibrillation after coronary artery surgery: current trends and impact on hospital resources. *Circulation* 1996;**94**:390–7.
96. Kowey PR, Stebbins D, Igidbashian L *et al.* Clinical outcome of patients who develop PAF after CABG surgery. *PACE* 2001;**24**:191–3.
97. Asher CR, Miller DP, Grimm RA *et al.* Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. *Am J Cardiol* 1998;**82**:892–5.
98. Bharucha DB, Kowey PR. Management and prevention of atrial fibrillation after cardiovascular surgery. *Am J Cardiol* 2000;**85**:20D–4D.
99. Liebold A, Wahba A, Birnbaum DE. Low-energy cardioversion with epicardial wire electrodes: new treatment of atrial fibrillation after open heart surgery. *Circulation* 1998;**98**:883–6.
100. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Arch Intern Med* 2002;**135**:1061–73.
101. Mooss AN, Wurdeman RL, Mohiuddin SM *et al.* Esmolol versus diltiazem in the treatment of postoperative atrial fibrillation/atrial flutter after open heart surgery. *Am Heart J* 2000;**140**:176–80.
102. Tisdale JE, Padhi ID, Goldberg AD *et al.* A randomized, double blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary bypass surgery. *Am Heart J* 1998;**135**:739–47.
103. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594–8.
104. Kowey PR, Taylor JE, Rials SJ, Marinchak RA. Meta-analysis of the effectiveness of prophylactic drug therapy in preventing supraventricular arrhythmia early after coronary artery bypass grafting. *Am J Cardiol* 1992;**69**:963–5.
105. Andrews TC, Reimold SC, Berlin JA, Antman EM. Prevention of supraventricular arrhythmias after coronary artery bypass surgery. A meta-analysis of randomized trials. *Circulation* 1991;**84**(Suppl. III):III-236–44.
106. Kowey PR, Dalessandro DA, Herbertson R *et al.* Effectiveness of digitalis with or without acebutolol in preventing atrial arrhythmias after coronary artery surgery. *Am J Cardiol* 1999:1114–17.
107. VanderLugt JT, Mattioni T, Denker S *et al.*, for the Ibutilide Investigators. Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery. *Circulation* 1999;**100**:369–75.
108. SoRelle R. Late-breaking clinical trials at the American Heart Association Scientific Sessions 2001. *Circulation* 2001; **104**:E9046–8.
109. Geelen P, O'Hara GE, Roy N *et al.* Comparison of propafenone versus procainamide for the acute treatment of atrial fibrillation after cardiac surgery. *Am J Cardiol* 1999; **84**:345–7.
110. Laub GW, Janeira L, Muralidharan S *et al.* Prophylactic procainamide for prevention of atrial fibrillation after coronary bypass grafting: a prospective, double-blind, randomized, placebo-controlled pilot study. *Crit Care Med* 1993;**21**: 1474–8.
111. Gold MR, O'Gara PT, Buckley MJ, DeSanctis RW. Efficacy and safety of procainamide in preventing arrhythmias after coronary artery bypass surgery. *Am J Cardiol* 1996;**78**:975–9.
112. Yilmaz AT, Demirkilic U, Arslan M *et al.* Long-term prevention of atrial fibrillation after coronary by-pass surgery: comparison of quinidine, verapamil, and amiodarone in maintaining sinus rhythm. *J Cardiac Surg* 1996;**11**:61–4.
113. Evrard P, Gonzalez M, Jamart J *et al.* Prophylaxis of supraventricular and ventricular arrhythmias after coronary artery grafting with low-dose sotalol. *Ann Thorac Surg* 2000;**70**:151–6.
114. Pfisterer ME, Kloter-Weber UC, Huber M *et al.* Prevention of supraventricular tachyarrhythmias after open heart operation by low-dose sotalol: a prospective, double-blind, randomized, placebo-controlled study. *Ann Thorac Surg* 1997;**64**: 1113–19.
115. Matsuura K, Takahara Y, Sudo Y, Ishida K. Effect of sotalol in the prevention of atrial fibrillation following coronary artery bypass grafting. *Jpn J Thorac Cardiovasc Surg* 2001; **49**:614–17.

116.Gomes JA, Ip J, Santoni-Rugiu F, Mehta D *et al.* Oral d, l sotalol reduces the incidence of postoperative atrial fibrillation in coronary artery bypass surgery patients: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999;**34**:334–9.
117.Suttorp MJ, Kingma JH, Peels HO *et al.* Effectiveness of sotalol in preventing supraventricular tachyarrhythmias shortly after coronary bypass grafting. *Am J Cardiol* 1991;**68**: 1163–9.
118.Suttorp MJ, Kingma JH, Tjon Joe Gin RM *et al.* Efficacy and safety of low and high dose sotalol versus propranolol in the prevention of supraventricular tachyarrhythmias early after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 1990;**100**:921–6.
119.Parikka H, Toivonen L, Heikkila L *et al.* Comparison of sotalol and metoprolol in the prevention of atrial fibrillation after coronary artery bypass surgery. *J Cardiovasc Pharmacol* 1998;**31**:67–73.
120.Nystrom U, Edvardsson N, Berggren H *et al.* Oral sotalol reduces the incidence of atrial fibrillation after coronary artery bypass. *Thorac Cardiovasc Surg* 1993;**41**:34–7.
121.Daoud EG, Stickberger SA, Man KC *et al.* Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med* 1997;**337**:1785–91.
122.Lee SH, Chang CM, Lu MJ *et al.* Intravenous amiodarone for prevention of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg* 2000;**70**:157–61.
123.Reddle JD, Khurama S, Marzan R *et al.* Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1999;**138**:144–50.
124.Solomon AJ, Greenberg MD, Kilborn MJ, Katz NM. Amiodarone versus a beta-blocker to prevent atrial fibrillation after cardiovascular surgery. *Am Heart J* 2001;**142**: 811–15.
125.Treggiari-Venzi MM, Waeber JL, Perneger TV *et al.* Intravenous amiodarone or magnesium sulphate is not cost–beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery. *Br J Anaesth* 2000;**85**:690–5.
126.Guarnieri T, Nolan S, Gottlieb SO *et al.* Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the Amiodarone Reduction in Coronary Heart (ARCH) Trial. *J Am Coll Cardiol* 1999; **34**:343–7.
127.Giri S, White CM, Dunn AB *et al.* Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. *Lancet* 2001;**357**:830–6.
128.Dorge H, Schoendube FA, Schoberer M *et al.* Intraoperative amiodarone as prophylaxis against atrial fibrillation after coronary operations. *Ann Thorac Surg* 2000;**69**:1358–62.
129.Crystal E, Connolly SJ, Sleik K *et al.* Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. *Circulation* 2002;**106**:75–80.
130.Nurozler F, Tokozoglu L, Pasaoglu I *et al.* Atrial fibrillation after coronary bypass surgery: predictors and the role of $MgSO_4$ replacement. *J Cardiac Surg* 1996;**11**:421–7.
131.Toraman F, Karabulut EH, Alhan HC *et al.* Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg* 2001; **72**:1256–61.
132.Solomon AJ, Berger AK, Trivedi KK, Hannan RL, Katz NM. The combination of propranolol and magnesium does not prevent postoperative atrial fibrillation. *Ann Thorac Surg* 2000; **69**:126–9.
133.Lasar HL, Chipkin S, Philippides G, Bao Y, Apstein C *et al.* Glucose–insulin–potassium solutions improve outcomes in diabetics who have coronary artery operations. *Ann Thorac Surg* 2000;**70**:145–50.
134.Frost L, Mortensen PE, Tingleff J *et al.* Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in acute termination of atrial fibrillation or flutter after coronary bypass surgery: Dofetilide Post-CABG Study Group. *Int J Cardiol* 1997;**58**:135–40.
135.Goette A, Staack T, Röcken C *et al.* Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000;**35**:1669–77.
136.Li D, Shinagawa K, Pang L *et al.* Effects of angiotensin-converting enzyme inhibition on the development of atrial fibrillation substrate in dogs with ventricular tachycardia-induced congestive heart failure. *Circulation* 2001;**104**:2608–14.
137.Pederson OD, Bagger H, Køber L *et al.*, for the TRACE Study Group. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999;**100**:376–80.
138.Van Noord T, Van Gelder IC, Van Den Berg M *et al.* Pretreatment with ACE inhibitors enhances cardioversion outcome in patients with persistent atrial fibrillation. *Circulation* 2001;**104**:II-699 (Abstract).
139.Hernandez-Madrid A, Rebollo JG, Rodriguez A *et al.* A prospective and randomized study on the effect of antiotensin II type 1 receptor blocker irbesartan in maintaining sinus rhythm in patients with persistent atrial fibrillation. *J Am Coll Cardiol* 2002;**39**:103A (Abstract).
140.Stevenson WG, Stevenson LW, Middlekauff HR. Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996;**28**:1458–63.
141.McMurray JJ, Dargie HJ, Ford I *et al.* Carvedilol reduces supraventricular and ventricular arrhythmias after myocardial infarction: evidence form the CAPRICORN study. *Circulation* 2001;**104**:II-700 (Abstract).
142.Lechat P, Hulot JS, Escolano S *et al.*, on behalf of the CIBIS II Investigators. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial. *Circulation* 2001;**103**:1428–35.
143.Hohnloser SH, Van Loo A, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol* 1995;**26**:852–8.
144.Jackman WM, Friday KJ, Andersen JL *et al.* The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;**31**:115–72.
145.Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989;**111**:107–11.
146.Flaker GC, Blackshear JL, McBride R *et al.*, on behalf of the Stroke Prevention in Atrial Fibrillation Investigators. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;**20**:527–32.

147. Torp-Pedersen C, Møller M, Bloch-Thomsen PE *et al.*, for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med* 1999;**341**:857–65.
148. Kowey PR, Vanderlught JT, Luderer JR. Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter. *Am J Cardiol* 1996;**78**:46A–52A.
149. Pritchett ELC, Page RL, Connolly SJ *et al.* Antiarrhythmic effects of azimilide in atrial fibrillation: efficacy and dose–response. *J Am Coll Cardiol* 2000;**36**:794–802.
150. Lehmann MH, Hardy S, Archibald D, Quart B, MacNeilx DJ. Sex differences in risk of torsade de pointes with d, l-sotalol. *Circulation* 1996;**94**:2534–41.
151. Reiffel JA. Drug choices in the treatment of atrial fibrillation. *Am J Cardiol* 2000;**85**:12D–19D.

38 Atrial fibrillation: antithrombotic therapy

John A Cairns

Definitions, incidence and natural history

Although oral anticoagulant prophylaxis against embolic stroke in rheumatic atrial fibrillation had been in wide use, it remained for the Framingham study[1–5] to demonstrate that the annual incidence of stroke was similar among patients with rheumatic and non-rheumatic atrial fibrillation. These observations, together with evidence of increased safety and maintained efficacy of lower-dose warfarin,[6,7] prompted the initiation of several well designed randomized controlled trials of anticoagulant and antiplatelet therapy for non-rheumatic atrial fibrillation (Table 38.1). Non-rheumatic atrial fibrillation was generally defined by the exclusion of echocardiographic mitral stenosis. The terms non-valvular atrial fibrillation and non-rheumatic atrial fibrillation are not entirely synonymous, although they are often used interchangeably. The term non-rheumatic atrial fibrillation is generally preferred.

In the Framingham study[4] patients were stratified according to the presence or absence of rheumatic heart disease, and the risk of stroke was adjusted for age and blood pressure. In comparison with patients without atrial fibrillation, the risk ratio for stroke was 17·6 for those with rheumatic atrial fibrillation and 5·6 for those with non-rheumatic atrial fibrillation. However, the absolute annual rate of stroke was virtually the same in the two groups (4·5% per year for the rheumatic group and 4·2% per year for the non-rheumatic group). The most reliable and current information comes from an analysis of the placebo groups in the recent clinical trials[8–13] where the annual incidence of stroke ranged from 3% to 7% (mean 4·5%) (Table 38.2), and the annual incidence of stroke plus other systemic emboli ranged from 3% to 7·4%. Patients were selected for entry into these trials according to a variety of criteria, including the absence of contraindications to warfarin and in some instances to aspirin, and the willingness to participate in a clinical trial. Hence, generalizations to a wider population must be made cautiously, but it is likely that these rates of stroke and other systemic embolism are reasonably close to those in the general population. In early case series, 50–70% of embolic strokes resulted in either death or severe neurologic deficit,[14] and in the recent randomized trials as many as half the strokes resulted in death or permanent disability.

Table 38.1 Non-rheumatic atrial fibrillation: designs of randomized trials

Trial	Sample size	Warfarin	INR	Aspirin
BAATAF[8]	420	Open	1·5–2·7	
CAFA[9]	383	Blind	2·0–3·0	
SPINAF[10]	536	Blind	1·5–2·5	
AFASAK[11,12]	1007	Open	2·8–4.2	75 mg/day
SPAF[13]	1330	Open	2·0–4.5	325 mg/day

Abbreviations: AFASAK, Copenhagen Atrial Fibrillation Aspirin Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; INR, international normalized ratio; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation

Several cohort studies[14] have demonstrated a reasonably consistent lower annual stroke risk in patients with paroxysmal or transient atrial fibrillation than in those with chronic atrial fibrillation. On the other hand, the SPAF trial found similar annual rates of ischemic stroke in patients with recurrent (3·2%) and chronic (3·3%) atrial fibrillation,[15] and a meta-analysis of the control groups in five large trials showed no difference.[16] These findings take precedence over earlier perceptions. There is a widespread perception that the risk of stroke is less with atrial flutter than with atrial fibrillation. A large retrospective database analysis confirmed a higher risk with atrial fibrillation, but the risk with atrial flutter was higher than in patients without this arrythmia.[17]

The term "lone atrial fibrillation" is generally used to describe patients who have atrial fibrillation in the absence of other clinically or echocardiographically demonstrable heart disease.[14] The definition is frequently extended to require the exclusion of diabetes mellitus and hypertension, and, in some series, an age younger than 60 years is required to fulfill the criteria. In general, stroke rates are much lower in patients with lone atrial fibrillation, and discrepancies among studies are most likely explained by differences in age, the presence of cardiovascular risk factors and the chronicity of atrial fibrillation.[18,19] Studies suggest

Table 38.2 Non-rheumatic atrial fibrillation: outcomes of randomized trials of warfarin

Trial	Ischemic stroke				Major bleed* Absolute increase events/ 1000 pt/yr
	Control events/ 1000 pt/yr	Warfarin events/ 1000 pt/yr	Relative risk reduction (%)	Absolute risk reduction events/ 1000 pt/yr	
BAATAF[8]	30	4	87	26	2
CAFA[9]	38	26	32	12	15
SPINAF[10]	43	9	79	34	6
AFASAK[11,12]	50	32	36	18	8
SPAF[13]	70	23	67	47	−1
Overview[16]	45	14	68	31	3

*Major bleed defined as intracranial bleeding, a bleeding event requiring 2 U of blood, or an event requiring hospital admission.

that as the study population ages, a decreasing proportion of patients with atrial fibrillation is free of other heart disease.

Antithrombotic management

Anticoagulant therapy

Five randomized controlled trials of warfarin versus control or placebo for the primary prevention of thromboembolism among patients with non-rheumatic (non-valvular) atrial fibrillation have been reported (Tables 38.1, 38.2). The trials generally enrolled patients with chronic atrial fibrillation detected on a routine or screening electrocardiogram (mean age 69 years). AFASAK[11] and SPINAF[10] excluded patients with intermittent atrial fibrillation, whereas the proportion of intermittent atrial fibrillation in CAFA[9] was 7%, in BAATAF[8] 16% and in SPAF[13] 34%. Previous stroke or transient ischemic attack was infrequent. Treatment allocation was randomized in all trials. There was a double-blind comparison of warfarin to placebo in CAFA and SPINAF, and an open label comparison in BAATAF. AFASAK compared warfarin, aspirin and aspirin placebo. SPAF allocated patients as being warfarin eligible (group 1) or warfarin ineligible (group 2). Group 1 patients were randomized to open label warfarin or usual therapy; group 2 patients were randomized to open label warfarin, aspirin or aspirin placebo. The INR range in these trials varied from 1·2–2·5 to 2·8–4·2.

Four of the trials were stopped early by their Data and Safety Monitoring Boards because interim analyses were strongly positive, whereas the fifth[9] was stopped early because of the strongly positive results from two other trials. The primary outcomes varied somewhat among the trials. However, it is possible to determine the rates of ischemic stroke and major bleeding (intracranial, transfusion of 2 or more units, hospitalization) from each trial, to make comparisons and to pool the results. The Atrial Fibrillation Investigators overview[16] was a collaborative prospective meta-analysis which provides reliable summary data based on individual patient information. The overall risk of ischemic stroke was 4·5% per year, identical to that documented in the Framingham study. This was reduced to 1·4% per year with warfarin, a reduction of 31 strokes for every 1000 patients treated ($P < 0{\cdot}001$). A major concern with warfarin is hemorrhage, which was carefully documented in each trial. The rate of major hemorrhage with warfarin was 1·3% per year versus 1% per year in controls, an increase of three major hemorrhages per 1000 patients treated, including an excess of intracranial hemorrhage of two per year for every 1000 patients treated. Hence, the overall picture is one of major benefit from warfarin, with only a modest increase in the risk of major hemorrhage and cerebral hemorrhage. **Grade A**

The European Atrial Fibrillation Trial compared warfarin, aspirin and placebo in patients with non-rheumatic atrial fibrillation who had experienced a transient ischemic attack (TIA) or stroke within the preceding 3 months.[20] The risk of recurrence was 12% among the placebo patients, dramatically higher than the 4·5% annual risk in the overall population of patients with non-rheumatic atrial fibrillation. The relative risk reduction on warfarin was 66% ($P < 0{\cdot}001$), virtually identical to that calculated in the overview of the five major randomized controlled trials, but the absolute reduction of strokes was much greater (80 per year per 1000 versus 31 per year per 1000) because of the high baseline risk of stroke in this population. Major bleeding was more frequent (excess of 21 per year per 1000), but the risk benefit ratio was strongly in favor of warfarin over placebo. **Grade A**

Additional analyses from the five trials have provided useful data on the prognostic stratification of patients as regards the risk of stroke.[16] The Atrial Fibrillation Investigators overview has demonstrated that the statistically significant multivariate predictors of stroke are previous stroke or TIA,

increasing age, history of hypertension, congestive heart failure or myocardial infarction, and diabetes. The Stroke Prevention in Atrial Fibrillation investigators have also demonstrated that echocardiographic increased left atrial size and LV dysfunction are important determinants of the risk of stroke.[21] The annual risk of stroke is about 4·5% among the total group of patients with non-rheumatic atrial fibrillation. However, patients under 60 years of age with no risk factors have an annual risk of <1% (there were no strokes among 112 such patients in the Atrial Fibrillation Investigators' overview). Patients of any age with no echocardiographic or clinical risk factors have an annual risk of only 1%, but this rises to 5% with the presence of enlarged left atrium or LV dysfunction, and to 7·2% with the presence of congestive heart failure, previous stroke or hypertension. When two or three clinical risk factors are present, the annual risk of stroke rises to 17·6%[22]. **Grade A**

The short-term risk of stroke appears to be higher in patients with recent-onset atrial fibrillation than in those with atrial fibrillation for more than 1–2 years.[23,24] Among patients with atrial fibrillation who have experienced an embolic event, the risk of recurrence in subsequent months appears to be considerably higher than the overall incidence. The high rate of recurrence, although not observed in every study, suggests that there is some urgency in initiating anticoagulation following the occurrence of embolic stroke in patients with atrial fibrillation. However, such therapy can increase the risk of hemorrhagic transformation of an embolic brain infarction. Based on a review of the literature and the results of the only available randomized clinical trial, the Cerebral Embolism Study Group recommended anticoagulation therapy for patients with small and moderate-sized embolic infarcts if a CT scan performed 24 hours after stroke onset did not show hemorrhage. In patients with a large infarction it was recommended that anticoagulant therapy be delayed until the CT scan was performed at 7 days to exclude delayed hemorrhage[25]. **Grade B**

The risk of stroke in patients with thyrotoxic atrial fibrillation is substantial, although the mechanism and the relative role of congestive heart failure are uncertain. The risk of stroke is also substantial among patients with hypertrophic cardiomyopathy and atrial fibrillation. Patients with atrial fibrillation and thyrotoxicosis or hypertrophic cardiomyopathy are considered to be at high risk when assigning treatment algorithms[26]. **Grade B**

Aspirin therapy

Comparisons of aspirin and placebo resulted in a somewhat less impressive risk reduction for stroke of about 16% (NS) in AFASAK,[11] 44% ($P = 0{\cdot}02$) in SPAF[13] and 17% (NS) in the European Atrial Fibrillation Trial (EAFT)[20] (Table 38.3). A meta-analysis of these trials found an overall reduction of 21% ($P = 0{\cdot}05$) in the rate of ischemic stroke with aspirin compared to placebo.[27] A more recent meta-analysis, including the European Stroke Prevention Study 2 (ESPS-II),[28] the Low Dose Aspirin, Stroke and Atrial Fibrillation pilot study (LASAF)[29] and atrial fibrillation patients from the United Kingdom TIA Study (UK-TIA)[30] confirmed a statistically significant 22% relative risk reduction ($P \leq 0{\cdot}05$) in the rate of all strokes (ischemic plus hemorrhagic).[31] Hence, aspirin can be expected to reduce the risk of ischemic stroke and all strokes, with a relative risk reduction of about one third that of warfarin and with a somewhat lower risk of major bleeding.

Aspirin *v* warfarin

The SPAF II trial studied 715 patients aged 75 years or less and 385 patients aged over 75 years, with each group randomly allocated to either warfarin or aspirin.[32] The incidence of

Table 38.3 Non-rheumatic atrial fibrillation trial outcomes: aspirin

Trial	All strokes (ischemic and hemorrhagic)			
	Control events/ 1000 pt/yr	Aspirin events/ 1000 pt/yr	Relative risk reduction (%)	Absolute risk reduction events/ 1000 pt/yr
AFASAK[11]	48	39	17	9
SPAF[13]	60	35	44	25
EAFT[20]	122	103	11	19
ESPF II[28]	207	138	29	69
LASAF[29]	22	27 (125 mg/day)	−17	−5
	6	22 (125 mg/2 days)	67	16
UK-TIA[30]	67	58 (300 mg/day)	17	9
	67	60 (1200 mg/day)	14	7
Overview[31]	80	63	22	17

ischemic stroke was less with warfarin than with aspirin in each group (P = NS), but intracranial hemorrhage was more frequent with warfarin and the overall rate of stroke (ischemic plus hemorrhagic) was little different with warfarin than with aspirin. The rate of all strokes with residual deficit was lower with warfarin than with aspirin in the ≤75 year old group (P = NS), but slightly higher in the >75 year old group (mean age 80 years) (P = NS). When patients with clinical risk factors (congestive heart failure, increased blood pressure, previous stroke) were examined there was a strong trend towards a greater reduction of stroke with warfarin than with aspirin in both groups.

In an attempt to better delineate the relative benefits of warfarin versus aspirin, particularly in patients at high risk of stroke, the SPAF III trial was undertaken.[33] Patients at high risk of embolic stroke because of impaired LV function, systolic hypertension, prior thromboembolism, or female gender and aged over 75 were randomly allocated warfarin, INR 2–3 or warfarin 1–3 mg/day plus aspirin 325 mg/day. This trial was discontinued early after a mean follow up of 1·2 years, because the rate of the composite primary outcome of ischemic stroke or systemic embolus was significantly higher in those given combination therapy than in those given adjusted dose warfarin (7·9% *v* 1·9% per year, risk increase 216%, $P < 0{\cdot}0001$). Rates of disabling stroke and of the composite of ischemic stroke, systemic embolus or vascular death were also significantly and markedly increased. The rates of major bleeding were similar in the two treatment groups. It is clear that in high-risk patients, targeting INR in the range of 1·2–1·5 does not provide adequate protection against thromboembolism.

Direct comparisons of warfarin and aspirin were undertaken in AFASAK,[11] SPAF-II,[32] EAFT,[20] AFASAK-II[34] and PATAF[35] (Table 38.4). AFASAK-II randomized 339 patients into a primary prevention trial which compared warfarin (INR 2–3) to aspirin (300 ml/day). PATAF randomized 272 patients into a primary prevention trial which compared warfarin (INR 2·5–3·5) to aspirin (150 mg/day). When these five trials are looked at in aggregate,[31] there is a highly statistically significant 36% (95% CI 14–52) relative risk reduction of all strokes (ischemic plus hemorrhagic) with warfarin, equivalent to an absolute risk reduction of approximately 14 events per 1000 patients per year. Major non-cerebral bleeding was somewhat more frequent with warfarin than with aspirin.

Risk of hemorrhage

The efficacy of warfarin for the prevention of ischemic stroke must be balanced against the risk of major hemorrhage, particularly cerebral hemorrhage, which is usually fatal. The risk of major hemorrhage is related to the intensity of anticoagulation, the patient's age, and the fluctuation of INR.[36,37] It is likely to be higher in clinical practice than in the rigorous setting of a clinical trial.[36,37] The 3·1% absolute reduction of ischemic stroke observed in the initial five randomized controlled trials was accompanied by an absolute excess risk of major hemorrhage of only 0·3%. The INR ranged from a low of 1·5 to a high of 4·5. The most widely recommended INR range for patients with NRAF is 2·0–3·0, with a target of 2·5.[26,38] However, the greatest reductions in the rate of ischemic stroke were observed in the two trials with the lowest INR ranges.[8,10] In SPAF II,[32] the greater efficacy of warfarin over aspirin for the prevention of ischemic stroke was outweighed by excess cerebral hemorrhage in the patients over age 75 years (mean 80 years), suggesting that a somewhat lower INR might be preferable. On the other hand, analysis of the INR levels in relation to ischemic stroke and cerebral hemorrhage in EAFT (mean patient age 71 years)[39] found no treatment effect below an INR of 2·0, most major bleeding complications occurred at an INR of 5·0 or above, and the rate of

Table 38.4 Non-rheumatic atrial fibrillation trial outcomes: warfarin *v* aspirin

Trial	All strokes (ischemic and hemorrhagic)			
	Warfarin events/ 1000 pt/yr	Aspirin events/ 1000 pt/yr	Relative risk reduction (%)	Absolute risk reduction events/ 1000 pt/yr
AFASAK[11]	22	39	45	17
SPAF-II[32]				
Age ≤ 75	17	19	10	2
Age ≥ 75	50	55	10	5
EAFT[20]	39	109	67	70
AFASAK-II[34]	31	25	−23	−6
PATAF[35]	7	10	20	3
Overview[31]	26	40	36	14

thromboembolic events was lowest at an INR from 2·0 to 3·9. The authors recommended a target INR of 3·0, with values below 2·0 and above 5·0 to be avoided.

For most patients who are candidates for warfarin an INR range of 2·0–3·0 with a target of 2·5 appears optimal.[26,38] However, those with a previous TIA or minor stroke may benefit from a somewhat higher range of 2·0–3·9 with a target of 3·0,[39] whereas those at higher risk of cerebral hemorrhage, particularly patients over the age of 75, may benefit from a somewhat lower INR range of 1·6–2·5 with a target of 2·0[26]. **Grade A/B**

Cardioversion

The presence of atrial fibrillation increases the risk of systemic embolism, whatever the nature and severity of the underlying heart disease. Accordingly, there is a strong rationale for cardioversion in patients with atrial fibrillation, and maintenance of sinus rhythm to prevent stroke and systemic embolism. Although there is no reliable information in the literature that cardioversion via electrical or pharmacologic means reduces the risk for systemic embolism, this goal remains an expectation, along with a resolution of symptoms related to the atrial fibrillation itself. The strongest predictor of initial and persistent success with cardioversion is short duration of the atrial fibrillation before cardioversion. In general, it may be expected that atrial fibrillation occurring in conjunction with a viral illness, with alcohol or other pharmacologic excess, or in association with thyrotoxicosis or pulmonary embolus, has a high likelihood of reversion with persistence of sinus rhythm if there has been resolution of the precipitating cause. The rate of initial success in restoring sinus rhythm ranges from 76% to 100%, but persistence of sinus rhythm during the next 12 months is noted in 25–81% of patients only.[40–43] Although maintenance of sinus rhythm is more likely with chronic antiarrhythmic drug therapy, a meta-analysis of six randomized placebo-controlled trials of quinidine therapy[41] revealed a statistically significant tripling of mortality during treatment. Other reviews of the use of class I antiarrhythmic therapy in ischemic heart disease indicate a statistically significant excess in mortality.[44] Clinical trials have evaluated class I, II and III drugs for maintenance of sinus rhythm, and individual patient characteristics will influence drug selection.[26] There is no clear evidence yet as to whether antiarrhythmic drug therapy to maintain sinus rhythm reduces the incidence of thromboembolism, congestive failure or death.[45,46]

Although no study has rigorously documented the incidence of systemic embolism following electrical cardioversion, an increased incidence is likely. The best available study,[47] using a prospective cohort design, demonstrated a reduction of postcardioversion systemic embolism from 5·3% to 0·8% among anticoagulated patients. Other studies of less rigorous design have also indicated benefit from anticoagulation. It is generally believed that a newly formed thrombus will become organized and adherent to the left atrial wall within 2 weeks of formation. Transesophageal echocardiography (TEE) reveals that in the majority of patients thrombus resolves, rather than simply becoming firmly adherent to the wall of the left atrium or left atrial appendage.[48] Accordingly, anticoagulation is usually recommended for about 3 weeks before cardioversion.[26,38] **Grade B** A study that pooled data from 32 studies found that 98% of thromboembolic events occurred within 10 days of cardioversion of atrial fibrillation or flutter.[49] However, evidence exists that even after successful electroversion, atrial contraction may not normalize for some weeks,[50,51] and therefore maintenance of anticoagulation for about 4 weeks following cardioversion seems prudent.[26,38] **Grade B** There is no evidence that the incidence of thromboembolism is less with pharmacologic than with electrical cardioversion, and so accordingly anticoagulant management should not differ.[26] **Grade C**

New-onset atrial fibrillation is generally not thought to warrant anticoagulation if cardioversion is undertaken within 48 hours of its onset. The commencement of intravenous heparin immediately upon diagnosis may be prudent while decisions as to the appropriateness of electrical cardioversion and the preparation for the procedure are undertaken. **Grade B** Emergency cardioversion may be required because of ischemia or hemodynamic compromise in some situations, and if atrial fibrillation has been present for more than 48 hours heparinization may offer some benefit before cardioversion.

The potential role of TEE for the detection of atrial thrombi and the simplification and shortening of the anticoagulation regimen in association with cardioversion was studied in a consecutive series of 230 patients.[52] Atrial thrombi were detected in 15%. Of 196 patients without thrombi, 95% were successfully cardioverted without prolonged anticoagulation, and none had a clinical thromboembolic event. However, a subsequent study[53] and a meta-analysis of several clinical studies[54] indicate that the absence of thrombi on TEE does not mean that a period of 4 weeks of anticoagulation following cardioversion may be safely omitted. **Grade B**

The Assessment of Cardioversion utilizing Echocardiography (ACUTE) pilot study[55] was followed by a multicenter randomized prospective of trial of 1222 patients with atrial fibrillation of more than 2 days' duration.[56] All patients were anticoagulated and assigned to either therapy guided by the findings on TEE or conventional therapy. If TEE showed no thrombus, the patient underwent cardioversion and continued on anticoagulant therapy for 4 weeks. If thrombus was detected, warfarin was given for 3 weeks, TEE was repeated and, if the thrombus had resolved, cardioversion was performed and warfarin continued for 4 weeks. If thrombus was still detected, there was no cardioversion

Table 38.5 Choice of antithrombotic therapies for patients with non-rheumatic atrial fibrillation

Clinical risk factors	Age (yrs)		
	<65	65–75	>75
No	Aspirin definite (A)	Aspirin > warfarin (A) INR target 2·5	Warfarin > aspirin (B) Consider INR target 2·0
Yes	Warfarin definite (A) INR target 2·5	Warfarin definite (A) INR target 2·5	Warfarin definite (A) Consider INR target 2·0

attempted but warfarin was continued for 4 weeks. The patients randomized to no TEE received warfarin for 3 weeks and then underwent cardioversion followed by a further 4 weeks of warfarin. At 8 weeks after the assignment of management strategy there was no significant difference between the two therapeutic groups in the rate of embolic events or in the prevalence of sinus rhythm. The TEE strategy resulted in fewer total hemorrhagic events, most of them minor. Right or left heart thrombi were identified in 13·8% of patients who underwent TEE. Of those patients with thrombi detected, 88·2% had a thrombus in the left atrial appendage. The results of this study indicate that in centers where TEE is readily available and the interpretations reliable, a TEE-guided management strategy can offer a safe, cost effective and convenient alternative to standard anticoagulant regimens. **Grade A** Patients may be anticoagulated and screened by TEE and cardioversion performed immediately if no thrombus is detected, and then receive at least 4 further weeks of anticoagulation. If thrombus is detected, patients should undergo at least 3 weeks of anticoagulation prior to cardioversion, followed by a further 4 weeks of anticoagulation. Among those patients with atrial thrombi detected, the value of repeat TEE after the initial 3 weeks of anticoagulation is uncertain.

Summary recommendations

Patients with persisting atrial fibrillation should generally receive chronic antithrombotic therapy with warfarin or aspirin (Table 38.5). **Grade A** Young patients with atrial fibrillation in the absence of other cardiac abnormality and who are free of a history of hypertension, cerebral vascular disease, congestive heart failure or diabetes mellitus, are at very low risk of thromboembolic events. Aspirin is generally preferable to warfarin, and even no antithrombotic therapy may be acceptable. **Grade A** Warfarin is more effective than aspirin for the prevention of embolic strokes, but the risk of major hemorrhage, including cerebral hemorrhage, is greater. Accordingly, its use should generally be confined to patients who have a substantial risk of embolic stroke. **Grade A** The optimal INR for most patients is 2·0–3·0, with a target of 2·5. Very elderly patients have a higher risk of cerebral hemorrhage while taking warfarin, and it is possible that the optimal risk–benefit ratio may be achieved with an INR range of 1·6–2·5, with a target of 2·0, although some authorities would recommend a target of 2·5 for all patients. **Grade B**

The most powerful predicator of cerebral embolism is previous TIA or stroke, but substantial increased risk is also associated with a history of congestive heart failure, hypertension or diabetes mellitus and echocardiographic evidence of left atrial enlargement or left ventricular dysfunction. The risk–benefit ratio of warfarin in such patients is increased.

Patients undergoing cardioversion should generally receive oral anticoagulation for about 3 weeks prior to the procedure and for 4 weeks afterwards. **Grade B** If the atrial fibrillation has been present for less than 48 hours, initial heparin therapy before cardioversion, followed by 4 weeks of warfarin therapy after cardioversion, are probably sufficient; in appropriate centers TEE-guided management can offer a safe, cost effective and convenient alternative to standard anticoagulant regimens. **Grade A**

References

1. Kannel WB, Abbott RD, Savage DD *et al.* Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983;**106**:389–96.
2. Kannel WB, Abbot RD, Savage DD *et al.* Epidemiologic features of chronic atrial fibrillation: the Framingham Study. *N Engl J Med* 1982;**306**:1018–22.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. *Arch Intern Med* 1987; **147**:1561–4.
4. Wolf PA, Dawber TR, Thomas E Jr *et al.* Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology* 1978;**28**:973–7.
5. Wolf PA, Kannel WB, McGee DL *et al.* Duration of atrial fibrillation and eminence of stroke: the Framingham Study. *Stroke* 1983;**14**:664–7.
6. Hull R, Hirsh J, Jay R *et al.* Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982;**307**:1676–81.

7. Turpie AGG, Gunstensen J, Hirsh J *et al.* Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet* 1988;**i**:1242–5.
8. The Boston Area Anticoagulation Trial of Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–11.
9. Connolly SJ, Laupacis A, Gent M *et al.* for the CAFA Study Coinvestigators. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;18:349–55.
10. Ezekowitz MD, Bridgers SL, James KE *et al.* Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;**327**:406–12.
11. Petersen P, Boysen G, Godtfredsen J *et al.* Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989;**i**:175–9.
12. Petersen P, Boysen G. Letter to Editor. *N Engl J Med* 1990; **323**:482.
13. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study: final results. *Circulation* 1991;**84**:527–39.
14. Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation: risk of stroke and role of antithrombotic therapy. *Circulation* 1991;**84**:469–81.
15. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL, for the Stroke Prevention in Atrial Fibrillation Investigators. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. *J Am Coll Cardiol* 2000;**35**:183–7.
16. Atrial Fibrillation Investigators. Risk factors for stroke and efficiency of antithrombotic therapy in atrial fibrillation analysis of pooled later from five randomized controlled trials. *Arch Intern Med* 1994;**154**:1449–57.
17. Biblo LA, Yuan Z, Quan KJ, Mackall JA, Rimm AA. Risk of stroke in patients with atrial flutter. *Am J Cardiol* 2001;**87**: 346–9, A9.
18. Brand FN, Abbott RD, Kannel WB *et al.* Characteristics and prognosis of lone atrial fibrillation: 30-year follow-up in the Framingham Study. *JAMA* 1985;**254**:3449–53.
19. Kopecky SL, Gersh BJ, McGoon MD *et al.* The natural history of lone atrial fibrillation: a population-based study over three decades. *N Engl J Med* 1987;**317**:669–74.
20. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993;**342**: 1255–62.
21. The Stroke Prevention in Atrial Fibrillation Investigation. Prevention of thromboembolism in atrial fibrillation: II Echocardiographic features of patients at risk. *Ann Intern Med* 1992;**116**:6–12.
22. The Stroke Prevention in Atrial Fibrillation Investigation. Prevention of thromboembolism in atrial fibrillation: I Clinical features of patients at risk. *Ann Intern Med* 1992;**116**:1–5.
23. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;**17**:622–6.
24. Wolf PA, Kannel WB, McGee DL *et al.* Duration of atrial fibrillation and eminence of stroke: the Framingham Study. *Stroke* 1983;**14**:664–7.
25. Cerebral Embolism Study Group. Cardioembolic stroke, early anticoagulation, and brain hemorrhage. *Arch Intern Med* 1987;**147**:636–40.
26. Fuster V, Rydén LE, Asinger RW *et al.* ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). *J Am Coll Cardiol* 2001;**38**:266i–lxx.
27. Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from 3 randomized trials. *Arch Intern Med* 1997;**157**:1237–40.
28. Diener HC, Lowenthal A. Antiplatelet therapy to prevent stroke: risk of brain hemorrhage and efficacy in atrial fibrillation. *J Neurol Sci* 1997;**153**:112.
29. Posada IS, Barriales V, for the LASAF Pilot Study Group. Alternate-day dosing of aspirin in atrial fibrillation. *Am Heart J* 1999;**138**:137–43.
30. Benavente O, Hart R, Koudstaal P, Laupacis A, McBride R. Antiplatelet therapy for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. In: Warlow C, Van Gijn J, Sandercock P, eds. Stroke Module of the Cochrane Database of Systematic Reviews. Oxford: *The Cochrane Collaboration*, 1999. CD-ROM available from BMJ Publishing Group (London).
31. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**:492–501.
32. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;**343**:687–91.
33. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: the Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet* 1996;**348**:633–8.
34. Gullov AL, Koefoed BG, Petersen P *et al.* Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation. Second Copenhagen Atrial Fibrillation, Aspirit, and Anticoagulation Study. *Arch Intern Med* 1998;**158**:1513–21.
35. Hellemons BS, Langenberg M, Lodder J *et al.* Primary prevention of arterial thromboembolism in patients with nonrheumatic atrial fibrillation in general practice (the PATAF study) [Abstract]. *Cerebrovasc Dis* 1997;**7**(Suppl 4):11.
36. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in patients taking warfarin. *Ann Intern Med* 1994; **120**:897–902.
37. Fihu SD, Callahan CM, Martin DC *et al.* The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996;**124**:970–9.
38. Albers GWM, Dalen JE, Laupacis A *et al.* Antithrombotic therapy in atrial fibrillation. *Chest* 2001;**119**:194S–206S.
39. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial

fibrillation and recent cerebral ischemia. *N Engl J Med* 1995; **333**:5–10.
40. Brodsky MA, Allen BJ, Capparelli EV *et al.* Factors determining maintenance of sinus rhythm after chronic atrial fibrillation with left atrial dilatation. *Am J Cardiol* 1989;**63**:1065–8.
41. Coplen SE, Antman EM, Berlin JA *et al.* Prevention of recurrent atrial fibrillation by quinidine: a meta-analysis of randomized trials (abstract). *Circulation* 1989;**80**(Suppl II):II–633.
42. Dittrich HC, Erickson JS, Schneiderman T *et al.* Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. *Am J Cardiol* 1989;**63**: 193–7.
43. Lundstrom T, Ryden L. Chronic atrial fibrillation: long-term results of direct current conversion. *Acta Med Scand* 1988; **223**:53–9.
44. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from the randomized controlled trials. *JAMA* 1993;**270**:1589–95.
45. Planning and Steering Committees of the AFFIRM study for the NHLBI AFFIRM investigators. Atrial fibrillation follow-up investigation of rhythm management: the AFFIRM study design. *Am J Cardiol* 1997;**79**:1198–202.
46. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000;**356**: 1789–94.
47. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. *Am J Cardiol* 1969;**23**:208.
48. Collins LJ, Silverman DI, Douglas PS, Manning WJ. Cardioversion of nonrheumatic atrial fibrillation: reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. *Circulation* 1995;**92**:160–3.
49. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. *Am J Cardiol* 1998;**82**:1545–7, A8.
50. Manning WJ, Leeman DE, Gotch PJ *et al.* Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. *J Am Coll Cardiol* 1989; **13**:617–23.
51. Padraig GO, Puleo PR, Bolli R *et al.* Return of atrial mechanical function following electrical cardioversion of atrial dysrhythmias. *Am Heart J* 1990;**120**:353–9.
52. Manning WJ, Silverman DI, Keightly CS *et al.* Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation – final results of a prospective 4.5 year study. *J Am Coll Cardiol* 1995; **25**:1354–61.
53. Black IW, Fatkin D, Sagar KB *et al.* Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation: a multicenter study. *Circulation* 1994;**89**:2509–13.
54. Moreyra E, Finkelhor RS, Debul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *Am Heart J* 1995;**129**:71–5.
55. Klein AL, Grimm RA, Black IW *et al.* Cardioversion guided by transesophageal echocardiography: the ACUTE Pilot Study. *Ann Intern Med* 1997;**126**:200–9.
56. Klein AL, Grimm RA, Murray RD *et al.* Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–20.

39 Atrial fibrillation: non-pharmacologic therapies

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The increasing public health burden of atrial fibrillation (AF) is now well recognized and its adverse impact on cardiovascular health and survival for individuals is being fully assessed. Prevalence in the United States has been variously estimated between two and three million, and this has been projected to increase to 5·6 million by 2050. It is the most common arrhythmia, particularly in the elderly. By the age of 80 years, over 9% of the population can suffer from the arrhythmia.[1] In patients with AF, there is a near doubling of cardiovascular mortality in men and a 50% increase in women.[2] While the importance of antithrombotic therapy is now undisputed, the management of this arrhythmia remains controversial. Recent clinical trials and practice guidelines have attempted to provide some insight for clinicians, but major issues remain unclear. Furthermore, epidemiologic data are derived largely from persistent or permanent AF populations, but most rhythm control trials have been conducted primarily in paroxysmal AF patients, from which extrapolation of strategies to other types of AF is problematic. While trials such as RACE,[3] STAF,[4] and AFFIRM[5] have not shown improved morbidity or mortality with rhythm control, it is also clear that effective rhythm control was not often achieved in these studies. In STAF, only 23% of the patients actually achieved freedom from AF on amiodarone therapy.[4] The inability to maintain rhythm control is due to the limited efficacy of antiarrhythmic drugs, which has been repeatedly documented in clinical trials. There is also an absence of good strategies to deal with recurrent AF. This has been limited to cardioversion in an occasional study, and a paucity of options has further compromised development of a sound rhythm control strategy.[6] Recently, an increasing number of non-pharmacologic options have become available and can supplement or even attempt to replace drug therapy in selected patients. In addition, they may be useful strategies in primary prevention approaches. It can be anticipated with some degree of certainty that the current approach of using antiarrhythmic drugs alone is likely to be modified shortly, and refocused on a combined pharmacologic and non-pharmacologic approach, or "hybrid" therapy.

Currently, available non-pharmacologic strategies revolve around implantable device therapy and ablative approaches. Devices available include cardiac pacemakers and pacemaker-defibrillators. Ablation therapy may be classified into catheter-based and intraoperative techniques. Several options now exist for each of these approaches; a classification of current non-pharmacologic strategies is shown in Table 39·1. Several major therapeutic options in current practice will be discussed in this chapter, while those in evaluation will be alluded to. Finally, hybrid therapy is gaining ground, with combinations of non-pharmacologic and pharmacologic methods for longer-term AF management.

Single site atrial pacing

Atrial pacing performed from the high right atrium has been widely reported to reduce the recurrence of AF and progression to permanent AF in observational reports. The Danish Trial of Physiologic Pacing in sick sinus syndrome reported reduction in the incidence of persistent or permanent AF with atrial-based pacing in patients with sick sinus syndrome.[7] **Grade A** This result has been corroborated in the MOST[8] and CTOPP[9] trials. It is particularly effective in patients with sick sinus syndrome alone, reducing the relative risk of AF development by 50%.[8] Clinical investigation of atrial pacing techniques for management of AF in symptomatic or high-risk populations has been the subject of a series of prospective clinical trials.[10–15] Approaches have included high right atrial, septal and dual site atrial pacing. Analysis of the benefit of atrial pacing is complicated by incomplete knowledge of its electrophysiologic effects and interactions with a heterogeneous AF population, by limited knowledge of the natural history of AF, and by the lack of standardized end points for quantifying clinical benefit.[16] Many studies lack a control group without atrial pacing therapy to judge efficacy.[17]

The efficacy of high right atrial pacing alone for prevention of symptomatic paroxysmal AF has been evaluated in clinical studies and remains currently unproven. **Grade A** In a randomized crossover two-phase clinical trial, Gillis and coworkers noted no prolongation in the time to recurrent AF compared to placebo.[10] In patients with refractory AF as the sole arrhythmia, the Jewel AF device experience showed that high right atrial pacing appeared to reduce frequency but not AF burden initially, but more detailed analysis failed to confirm long-term benefit.[11]

Table 39.1 Classification of non-pharmacologic therapies in atrial fibrillation

Therapy	References
Rhythm control strategies	
Device therapy	
Atrial Pacing	
• Single site	
(i) High right atrial	10–15, 20
(ii) Septal	18,19
• Multisite	
(i) Dual site right atrial	23–29
(ii) Biatrial	
Atrial defibrillators	
• Stand alone atrioverter with demand pacing	30
• Atrioventricular pacemaker defibrillator	11, 17
Ablation therapy	
Intraoperative or thoracoscopic	
• His bundle ablation (surgical ligation, mechanical, cryothermia)	33, 34
• Corridor procedure (mechanical)	
• Biatrial maze (mechanical)	35, 36
• Left atrial isolation (mechanical)	
• Pulmonary vein isolation (mechanical or cryothermia)	38
• Epicardial linear ablation (radiofrequency)	37
• Radial incision (mechanical)	39
Transcatheter	
• Trigger ablation	
(i) Focal pulmonary vein (radiofrequency)	22, 40–43
(ii) Pulmonary vein isolation (radiofrequency or ultrasound)	43–46
(iii) Atrial flutter/atrial tachycardia (radiofrequency)	
• Substrate ablation	
(i) Linear ablation (radiofrequency)	
Biatrial	
Right atrial	47, 48
Left atrial	
Rate control strategies	
Catheter AV junctional ablation + pacemaker (DC shock or radiofrequency)	49–51
Catheter AV junctional modification (radiofrequency)	52
Stroke prevention strategy	
Percutaneous left atrial appendage transcatheter occlusion (PLAATO)	53

Thus, in an effort to improve efficacy, several new directions have evolved for single site atrial pacing. These include several new algorithms for ensuring overdrive atrial pacing. The Medtronic AT 500 pacemaker is a DDDRP device which employs two algorithms, atrial preference pacing and atrial rate stabilization, in addition to having antitachycardia pacing capabilities. Atrial preference pacing changes the base pacing rate in response to atrial premature beats, with a programmable increment. Atrial rate stabilization intercedes after premature beats altering the post-ectopic escape interval by reducing it markedly and then slowly easing down to the base pacing rate. Antitachycardia pacing, illustrated in Figure 39·1, can terminate common and non-isthmus-dependent atrial flutter by burst, ramp, or combination rapid pacing sequences. In a non-randomized study, Israel *et al*[12] evaluated 325 patients for efficacy of atrial antitachycardia pacing and device safety, and secondarily, for reliability of atrial tachyarrhythmia detection. Fifty-three per cent of atrial tachycardia episodes were terminated with antitachycardia pacing; there was an 88% complication-free survival at 3 months and 97% reliable detection of atrial tachyarrhythmia episodes. While preventive pacing algorithms were found to increase the median percentage of atrial pacing from 62% to 97%, the frequency and duration of episodes were unchanged. The ATTEST study[13] randomized patients with the AT 500 pacemaker after implantation to all preventive pacing and antitachycardia pacing on or off. Antitachycardia pacing in this study also terminated 53% of

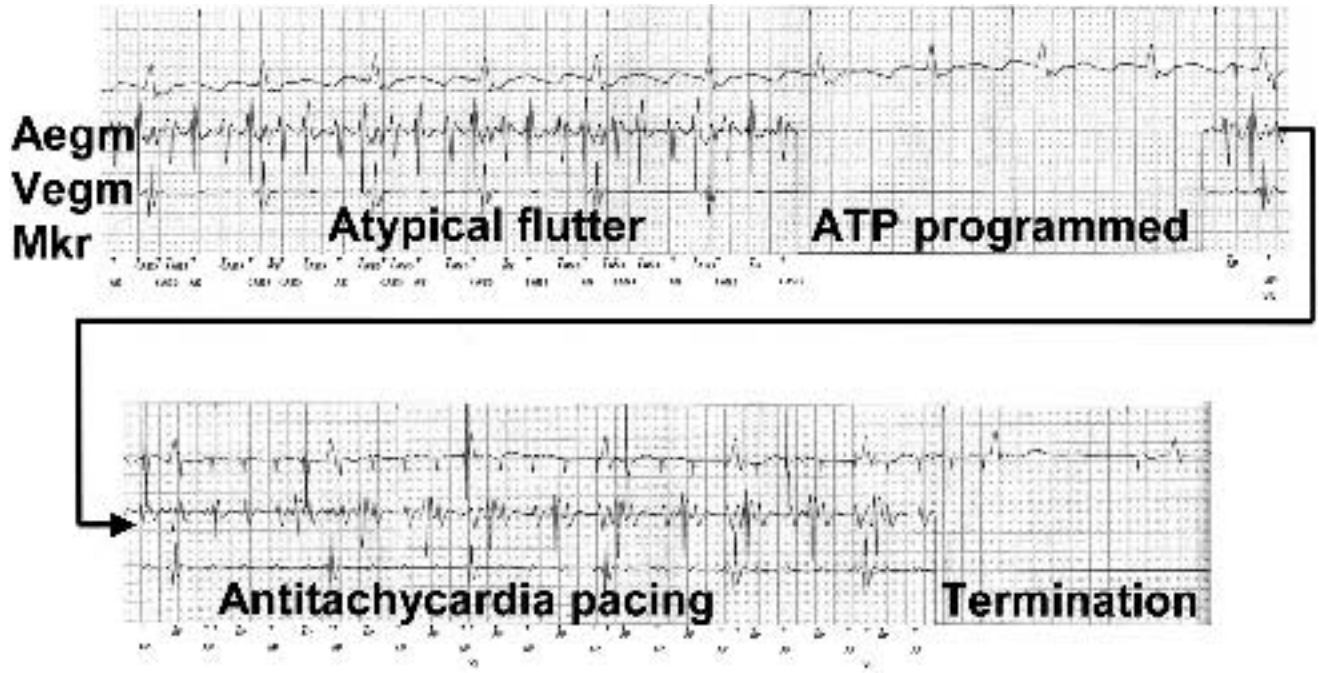

Figure 39.1 Antitachycardia pacing for restoration of sinus rhythm. Left panel represents atrial fibrillation, middle panel represents antitachycardia pacing, right panel represents restored sinus rhythm afterwards

episodes, and positive predictive value for atrial tachycardia detection was 99%. While quality of life improved in both groups, there was no significant difference in frequency or burden of atrial tachyarrhythmia episodes. PROVE, a randomized crossover trial, is evaluating a similar device, the Talent DR 213 pacemaker, combining atrial overdrive pacing with an automatic rest rate function. Preliminary results from 78 patients show 84% prevalence of atrial pacing, a mean 48% shortening of episode duration with overdrive pacing and rest rate, and a slight improvement in quality of life.[14] The ADOPT-A study evaluated a new pacing algorithm, dynamic atrial overdrive, used in St Jude Medical Integrity pacemakers, in patients with AF, and found an approximately 25% decrease in AF burden and some improvement in quality of life.[15] **Grade A**

Alternate site pacing has also been investigated. Single site pacing at a septal location was performed in two prospective randomized studies. Bailin *et al*[18] randomized 120 patients with paroxysmal AF to high septal pacing or right atrial appendage pacing. Patients with high septal pacing had a significantly higher rate of survival free from chronic AF at one year (75% *v* 47%), but no decrease in AF event frequency. A control no treatment arm was absent in this trial. The Atrial Septal Pacing Efficacy Clinical Trial (ASPECT) randomized patients to septal or non-septal RA lead implantation, and pacing prevention using an AT 500 pacemaker. Septal pacing was not associated with a reduction in AF frequency or burden.[19] **Grade B**

Another approach using atrial pacing is high right atrial pacing in combination with other antiarrhythmic therapies, such as drugs. In an early experience from our group, antiarrhythmic drug therapy combined with high right atrial pacing prolonged arrhythmia-free intervals but no long-term data was available on rhythm control.[20] Similarly, we have employed linear ablation with drug therapy and dual site or high right atrial pacing in pilot clinical experience.[21,22] We have noted a decrease in progression to permanent AF (<30% at 3 years) and device datalogs confirm resolution of persistent and permanent AF in a subgroup who underwent right atrial maze procedures.[22] In these refractory patients, early AF recurrence was often observed after intervention, which subsequently resolved after 2–3 months with restoration of rhythm control. **Grade C**

Dualsite right atrial pacing

Current experience with secondary prevention of AF with dual site RA pacing has usually been performed in patients with recurrent, symptomatic, and frequent drug-refractory AF.[23] This method is illustrated in Figures 39.2 and 39.3, which show a representative chest radiograph and electrocardiogram for a patient with dual site right atrial pacing system. The additional atrial pacing lead is inserted just outside the coronary sinus ostium for stability and left atrial synchronization. The ECG shows a biphasic P wave in the

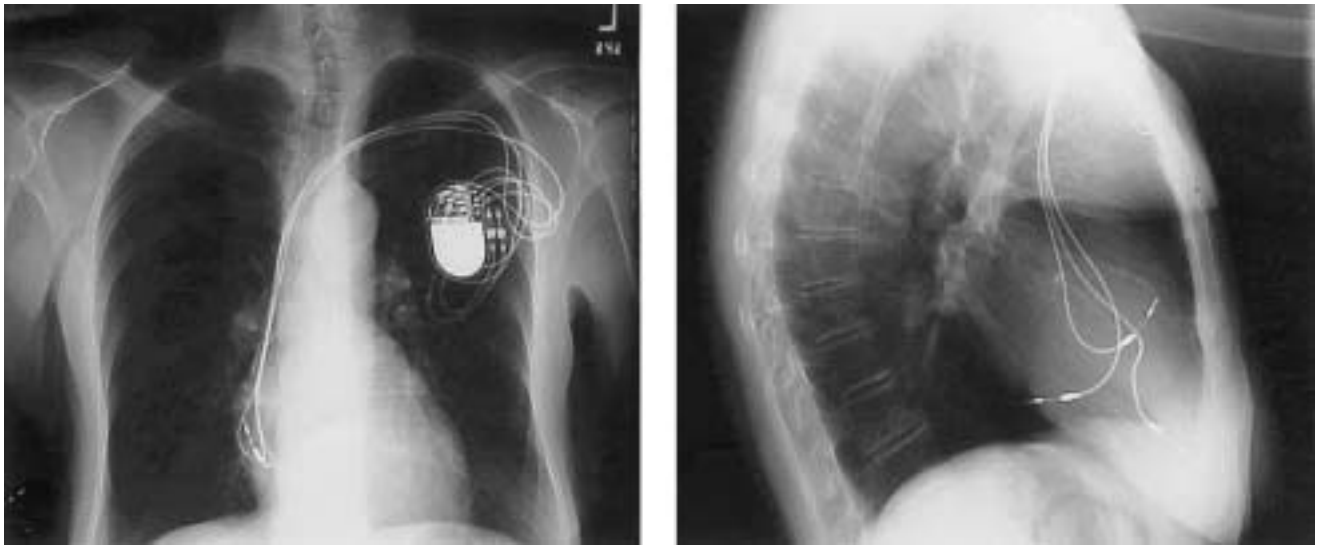

Figure 39.2 Posteroanterior (left) and lateral (right) radiographic views of a dual site right atrial pacemaker system for atrial fibrillation. Two leads are placed in the right atrium, at the high right atrium and outside the ostium of the coronary sinus. A standard right ventricular lead can be placed in patients with AV conduction abnormalities.

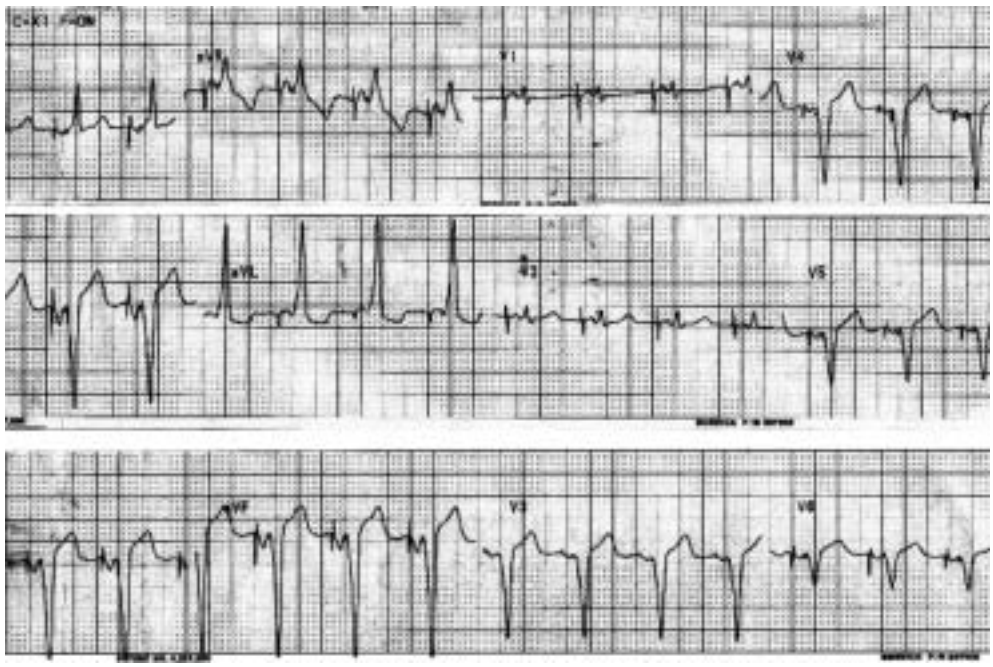

Figure 39.3 Representative electrocardiogram for a patient with a dual site atrial pacemaker for atrial fibrillation treatment. Note that during dual site pacing there is a biphasic P wave in leads II, III, and aVF with abbreviation of total P wave duration.

inferior leads with abbreviation of P wave duration. In our pilot experience, trends to benefit with dual site right atrial pacing were seen in 3 month crossover interim analyses[23] but significant benefit of dual site over high right atrial or septal pacing was only obvious after one year.[20] In our long-term experience, now encompassing over 125 patients with follow up averaging 3 years and ranging to 7 years, the overall patient survival is 80% at 5 years. Freedom from any recurrence of symptomatic AF after institution of pacing was 45% at 5 years and we achieved rhythm control in over 90% of patients at 3 years or more of follow up. The overall stroke incidence is 0·8% per year.[24] Similar efficacy rates can be achieved in paroxysmal, persistent, and permanent AF.

The safety of dual site right atrial pacing can also be assessed. Lead dislodgment rates are well within estimates for any type of atrial pacing and long-term dislodgment concerns have been obviated by the dual right atrial lead technique. The remaining complications have been largely similar to those in any pacemaker implant procedure. Precipitation of angina in a patient with advanced coronary disease and exertional angina occurred in one patient. The major issue has been late intolerance to antiarrhythmic drugs with frequent replacement of class 1 agents with class 3 drugs.

A non-randomized parallel cohort experience from Europe in patients with bradycardias requiring pacing and paroxysmal AF shows similar efficacy.[25] Of 83 patients, 30 had dual site right atrial pacing systems and 53 had single site high right pacemaker implanted. Patients with dual site systems had longer duration of AF (8·1 *v* 3·8 years for high RA systems, $P < 0{\cdot}001$) and more failed drug trials (2·4 *v* 1·6 for high RA systems, $P < 0{\cdot}05$). During a mean follow up of 18 months, symptomatic paroxysmal AF recurred in 9 patients after dual RA pacing as compared to 24 patients after high RA pacing ($P = 0{\cdot}03$). Permanent AF supervened in only one patient after dual RA pacing and in 12 patients after high RA pacing ($P < 0{\cdot}05$). In an observational study, biatrial triggered pacing in patients with intra-atrial conduction delay and recurrent atrial flutter and fibrillation, performed by Revault d'Allonnes and colleagues, resulted in a 64% incidence of rhythm control at a mean follow up of 33 months.[26] A majority of these patients were on antiarrhythmic drug therapy.

Several small, randomized trials have now been reported in addition to several single-center pilot experiences. In a short-term randomized, 12 week comparative study of patients without bradycardia, Lau *et al* reported an increase in mean time to first AF recurrence from 15 to 50 days in patients during dual site pacing as compared to no pacing.[27] In a prospective crossover trial with 6 month treatment periods in patients with recurrent symptomatic AF without structural heart disease, Ramdat Misier and coworkers have shown a significant increase in time to recurrent AF and interventions for symptomatic AF recurrence.[28]

The Dual-Site Atrial Pacing for Prevention of Atrial Fibrillation Trial (DAPPAF) was a longer-term multicenter crossover study with 6 month treatment arms comparing dual site right atrial, high right atrial, and support pacing.[29] It enrolled patients with frequent, symptomatic, and drug-refractory AF with bradyarrhythmias requiring cardiac pacemaker insertion. After dual site right atrial pacing system implant, optimization of drug and pacing therapies was performed. The three modes of pacing were then randomly selected for 6 month periods. Patient tolerance and adherence to the pacing mode was superior in dual RA pacing as compared to support ($P < 0{\cdot}001$) and high RA pacing ($P = 0{\cdot}006$). Freedom from any symptomatic AF recurrence trended to be greater with dual RA (hazard ratio 0·715, $P = 0{\cdot}07$) but not with high RA pacing ($P = 0{\cdot}19$) compared to support pacing. Combined symptomatic and asymptomatic AF frequency in patients was significantly reduced during dual RA pacing as compared to high RA pacing ($P < 0{\cdot}01$). However, in antiarrhythmic drug-treated patients, dual RA pacing increased symptomatic AF-free survival compared to support pacing ($P = 0{\cdot}011$), and high RA pacing (hazard ratio 0·669, $P = 0{\cdot}06$). In drug-treated patients with <1 AF event per week, dual RA pacing significantly improved AF suppression compared to support pacing (hazard ratio 0·464, $P = 0{\cdot}004$) and high RA pacing (hazard ratio 0·623, $P = 0{\cdot}006$). Lead dislodgment was uncommon (1·7%) with coronary sinus and high RA lead stability being comparable. Thus, the DAPPAF trial showed improved adherence to pacing and rhythm control in the dual site mode, especially when combined with antiarrhythmic drugs, supporting the use of a hybrid approach to rhythm management. **Grade A**

The implantable atrial defibrillator

Catheter-based internal cardioversion of atrial fibrillation was first employed in 1969 and early studies were performed by Mirowski and colleagues. The development of implantable device technology was achieved in the late 1990s and a prototype device was used in pilot studies.[30] Transcatheter atrial defibrillation is often achieved at energies quite similar to ventricular defibrillation. While early enthusiasm suggested that this would be feasible at very low energies (2 J or less) using right atrial and coronary sinus electrodes, more extensive clinical experience suggested significantly higher energy requirements well above the pain threshold.[31] While the initial atrial cardioverter permitted shocks up to 6 J and ventricular pacing, higher energy requirements, risk of ventricular proarrhythmia without ventricular defibrillation and pain related to the therapy limited its adoption. While ventricular proarrhythmia resulting from atrial defibrillation shocks was rare in animal studies, it has been documented in both experimental and clinical studies, particularly in diseased hearts. Initial clinical experience was modest but encouraging and suggested that effective and safe atrial defibrillation was feasible.[30]

The first generation atrial defibrillation device was succeeded by a commercially available dual chamber atrioventricular defibrillator.[11] This device, shown in Figure 39·4, includes atrial and ventricular antitachycardia pacing, cardioversion, and defibrillation. Initial studies have been conducted in patients with atrial fibrillation who may or may not have coexisting lethal ventricular tachyarrhythmias.[11,17] Due to its extensive electrical therapy and monitoring capability, the future of this technology in a hybrid therapy format is quite promising. Dual chamber AV defibrillators

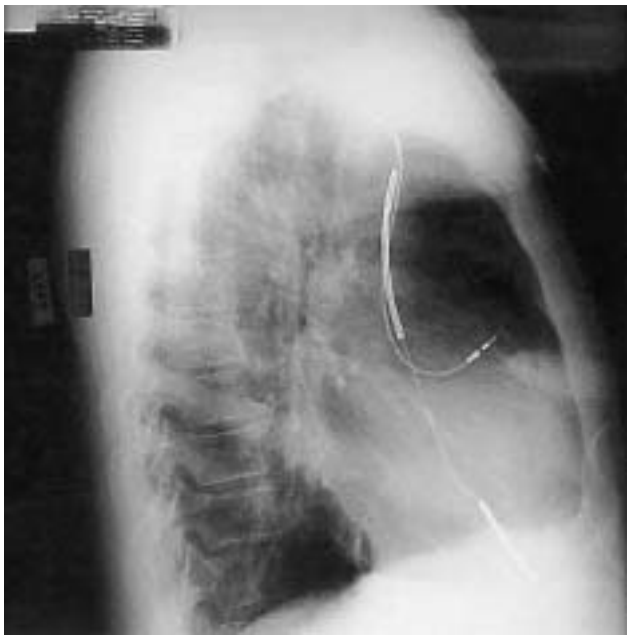

Figure 39.4 Lateral radiograph of atrioventricular defibrillator showing atrial and ventricular defibrillation electrode catheter and an additional atrial pacing lead in the high right atrium

are approved for use in patients with drug-refractory and symptomatic AF and in patients with coexisting symptomatic atrial and ventricular tachyarrhythmias. **Grade B**

In comparison to the widely used ventricular defibrillator, the atrial defibrillator requires insertion of an additional atrial defibrillation electrode used for atrial pacing, AF detection, and atrial shock delivery. Atrial tachyarrhythmia detection is based on two zones, one for monomorphic tachycardias and another for AF events. Antitachycardia pacing is available as well as shock therapy. Burst and ramp pacing is effective in both intra-atrial re-entrant tachycardia and common atrial flutter. Fifty hz pacing trains have been demonstrated to be effective in atypical atrial flutter.[32] Atrial shocks are used if pacing therapies are ineffective. In clinical studies, reliable atrial defibrillation has been obtained with shock energies up to 27 J. A full range of ventricular defibrillation functions is available as in conventional defibrillators.

Newer iterations include prevention algorithms such as continuous atrial pacing for AF prevention. Enhanced monitoring capabilities include atrial and ventricular arrhythmia detection. Device-based testing is available and a handheld patient activator permits delivery of shock therapy on demand by the patient or physician. Combination devices combining atrial defibrillation with the pacing strategies discussed above may offer improvement in AF management. One multicenter crossover study evaluated the use of a dual chamber ICD with both pacing and shock therapies, in patients otherwise indicated for an implantable ventricular ICD who also had recurrent atrial tachyarrhythmias. The device resulted in a significant reduction in atrial tachyarrhythmia burden.[11] Nevertheless, there have been no controlled trials that compare efficacy, survival, quality of life, or cost in patients treated with implantable atrial defibrillators versus other therapies.

Intraoperative ablation

The first surgical interventions for AF were ligation or cryosurgical ablation of the His bundle followed by implantation of a pacemaker.[33,34] Subsequent efforts included the corridor procedure and left atrial isolation, but definitive treatment awaited the maze procedure, developed by Cox and coworkers.[35] Several refinements of the original technique have been performed. The principle is to compartmentalize both atria so that AF cannot be maintained. Both right and left atrial appendages are resected. The pulmonary vein ostia are isolated, and linear right atrial and left atrial lesions are connected to anatomic structures to form an "electrical maze". Revisions have addressed the problem of sinus node dysfunction, though abnormal hemodynamic function may still exist. Currently, the maze procedure has become an add-on technique during other cardiac surgery procedures including mitral valve replacement and repair,[36] and coronary artery bypass surgery. **Grade B** Furthermore, new techniques described below have limited the extent of the maze. New developments include partial isolation of the pulmonary veins and LA linear ablation[37] or epicardial radiofrequency isolation of the pulmonary veins during thoracoscopy or cardiac surgery.[38] Another recent refinement, introduced to maintain more physiologic atrial transport function, is the radial incision approach, in which incisions radiate from the sinus node to the atrioventricular annular margins and parallel atrial coronary arteries.[39]

Catheter ablation for rhythm control: trigger ablation

Catheter-based approaches to rhythm control in AF utilize focal or linear ablation of the initiating trigger, or introduce linear lesions to modify the substrate maintaining fibrillation. Substantial effort is currently being devoted to trigger ablation, particularly in the pulmonary venous system. Atrial premature beats and monomorphic atrial tachycardias or flutter are the most common triggers for AF. Techniques for isthmus and non-isthmus dependent atrial flutter ablation use linear radiofrequency lesions in critical regions for flutter circuits. Recently, investigative work has focused on ablation of such premature beats or focal tachycardias arising in the pulmonary venous system, as well as mapping of atrial tachycardias and

atrial flutter, including non-isthmus dependent atypical forms. Both biatrial contact mapping with multipolar catheters placed in the RA and LA, and also three-dimensional mapping methods have been used.[22,40–43] Three-dimensional mapping can help locate triggers, propagation patterns, zones of slow conduction and re-entry, and refine the focal ablation methodology.[22] An endocardial balloon electrode permits mapping of the atrium obtaining virtual electrogram recordings from up to 3000 endocardial sites which are reconstructed using a Silicon Graphics computer workstation as a three-dimensional image. Specific sites of slow or low amplitude propagation can be defined that could potentially limit efficacy and, in addition, provide insight into the mechanisms of early AF recurrences. These sites can be prophylactically ablated. This can be combined with biatrial catheter mapping and pulmonary vein recordings. Figure 39·5 shows catheter placement in three of the four pulmonary veins in a patient with recurrent refractory AF. The veins can be visualized with angiography and ablation can be performed at the trigger site inside the vein, or partial disconnection of the focus from the left atrium using a spiral electrode configuration for circumferential mapping. Using circumferential electrode arrays on catheters (Lasso or Helix catheters), partial ablation at the site of the connecting muscle bundle can be performed in an effort to avert pulmonary vein stenosis.

Early data from many clinical centers documented elimination of these triggers with modest short-term success ranging from 14% to 63%. In addition, multiple triggers are common, and in some patients ablation within the veins had significant adverse effects including pulmonary vein stenosis. Evolving technology and techniques may address many of these issues. Newer energy sources such as ultrasound are undergoing such clinical trials and early results show modest efficacy and increased safety.[43] Pulmonary vein isolation may have greater success if all four veins are isolated, but remains a demanding and tedious procedure with measurable procedural risk. However, the vast majority of these patients still require adjuvant drug therapy for clinical benefit. Long-term success remains dependent on the number of triggering sites and few data are available in organized clinical trials. The frequency of asymptomatic and symptomatic AF has also not been addressed in a controlled clinical trial with the radiofrequency technique. **Grade C**

Pulmonary vein triggers have been directly ablated within the vein, and usually require ablation in multiple or all veins for success. Ablation within the vein has been extensive in early studies but more segmental in recent reports to reduce the risk of pulmonary vein stenosis. Subclinical effects on pulmonary vein flow velocity can occur in many patients (range 25–80%) but clinically significant stenosis occurs in up to 8% of patients. Table 39·2 summarizes efficacy and safety data on this approach in several large reports.[40–46] Another major challenge is the paucity of patients demonstrating spontaneous arrhythmia at the time of study, limiting map-directed targeted ablation. More recently, anatomic approaches to isolate the pulmonary veins by circumferential periostial ablation methods using radiofrequency[44–46] or ultrasound[43] energy have been employed. While there has been demonstrable efficacy, no definite improvement in outcome or safety can be documented at the present time. Furthermore, recurrent AF is common and often has not been systematically monitored in these studies, using advanced or implantable monitoring for asymptomatic as

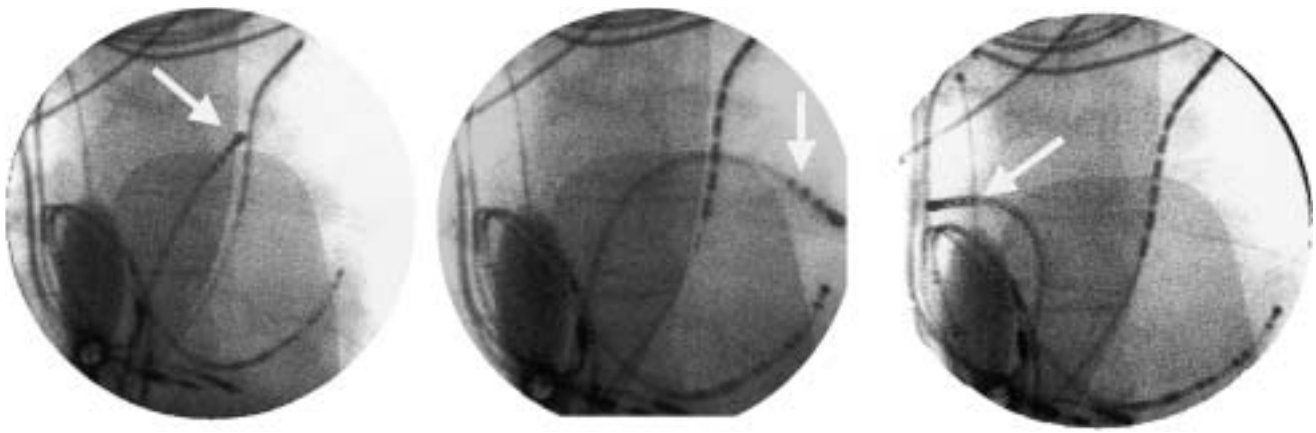

Figure 39.5 Biatrial catheter mapping of refractory atrial fibrillation with three-dimensional mapping of the right atrium. Multielectrode catheters are placed in the right atrium, coronary sinus, left pulmonary artery and transeptally into the pulmonary veins. The arrow points out the individual pulmonary veins in this patient, which are mapped for triggers and then ablated at the focus. There is a pre-existing dual site atrial pacemaker system in this patient with permanent leads in the high right atrium, coronary sinus ostium, and right ventricle.

Table 39.2 Efficacy and safety of pulmonary vein trigger ablation or isolation

Series	Method	Patients (*n*)	Mean follow up (mth)	% AF eliminated	% PV stenosis
Map-directed ablation					
Chen[40]	PVA	79	6	86s	42 (TEE)
Haissaguerre[41]	PVA	225	Not specified	70s	2 (clinical)
Gerstenfeld[42]	PVA	71	6	23s 31c	8 (angiography)
Natale[43]	PVA	293	10	81s 86c	11·5 (CT)
Anatomic ablation					
Pappone[44]	PVI	251	10·4	85pa 68perm	0 (TEE)
Kanagaratnam[45]	PVI	71	29	21s 83c	36 (CT)
Oral[46]	PVI	70	5	70pa 22pers	3 (CT)
Natale[43]	CUVA	30	12	47s 80c	3 (CT)

Abbreviations: c, with drugs; CT, by computed tomography; CUVA, catheter ultrasound vein ablation; pa, paroxysmal; pers, persistent; perm, permanent; PVA, pulmonary vein ablation; PVI, pulmonary vein isolation; s, without drugs; TEE, by transesophageal echocardiography

well as symptomatic AF. These patients require adjuvant drug or device therapy for clinical benefit.

Catheter ablation for rhythm control: substrate ablation

Linear atrial lesions have been employed in the left and right atrium for substrate compartmentalization. In these approaches, contiguous radiofrequency energy lesions are used to create linear ablative lesions, producing lines of block for electrical propagation of triggering or perpetuating arrhythmias in the atrium. During linear ablation, three-dimensional mapping allows assessment of anatomic contiguity of ablation lesions for confluent linear line development. Pacing techniques are used for assessment of the linear lesion's integrity. In addition, new arrhythmias that may develop in compartments can be identified and treated. Left atrial compartmentalization has been modified due to safety concerns and more recent approaches use pulmonary vein ostial or posterior left atrial compartmentalization alone. Again, formal clinical trials of these new approaches are lacking and are awaited.

Right atrial linear compartmentalization has been employed, initially as monotherapy with limited success. Adjuvant drug therapy was often required for modest benefit.[47] Kocheril[48] has reported beneficial effects in paroxysmal AF, and interim results of a large clinical trial have shown benefit in symptomatic AF suppression in over 65% of patients (Cardima Inc., unpublished data). Most patients do require adjuvant antiarrhythmic drug therapy for clinical success but the technique is quite safe in clinical application. Finally, adjuvant pacing therapies such as dual site pacing can be examined. Recently, we have reported successful AF suppression with atrial pacing after right atrial linear compartmentalization in patients with drug-refractory persistent and permanent AF.[22] In these patients, device datalogs documented elimination of persistent or permanent AF, with the vast majority having non-sustained atrial arrhythmias or brief asymptomatic AF. In summary, ablative AF therapies are in rapid evolution. Early empiric application has been troubled by efficacy and safety concerns. Mapping guided assessment of mechanisms and interventional therapies in the atrium can refine techniques with potential for improving efficacy and safety. **Grade C**

Rate control strategies: catheter ablation and modification of the AV conducting system

As device and ablation therapy advances, permitting restoration of sinus rhythm in more patients, the role of catheter-induced complete AV block to control rapid ventricular response in AF is becoming limited to a smaller population of highly refractory and symptomatic patients. This approach was initially performed operatively with cryoablation. Subsequently, it was performed by catheter using direct current, and ultimately with radiofrequency current. The first prospective, international study of safety and efficacy of the approach was the Catheter Ablation Registry,[49] which evaluated 136 patients treated with direct current energy from 1987 to 1990. The registry reported successful induction of complete heart block in 83% of surviving patients, but an inhospital mortality rate of 5·1%. Patients who died in the hospital were more likely to have had prior sudden cardiac death, congestive heart failure, reduced ejection fraction, and QT prolongation. The Ablate and Pace Trial[50] similarly evaluated radiofrequency ablation. It

reported successful ablation of AV conduction in 155 of 156 patients, with no procedural mortality. **Grade B** There was 85·3% 1 year survival, with five sudden cardiac deaths in this period. There were significant improvements in quality of life indices, and slight significant 1 year improvement in New York Heart Association functional class from 2·1 to 1·9. A sustained improvement in left ventricular ejection fraction was only noted in patients with reduced systolic function, indicating that tachycardia-induced cardiomyopathy may be reversed with this approach. Long-term experience with the ablate and pace strategy at the Mayo Clinic, for an average of 3 years, has been reported.[51] Patients were compared with two control groups: age- and sex-matched Minnesota residents, and patients with atrial fibrillation managed with drug therapy. While the observed survival rate was significantly lower than in the Minnesota residents, it was equal when high-risk patients with previous myocardial infarction, congestive heart failure, or drug therapy after ablation were excluded. Survival was equal between the ablation and drug therapy cohorts, suggesting that rate control by AV junctional ablation does not negatively affect long-term survival. Nevertheless, the concern of sudden cardiac death remains, particularly in patients with left ventricular systolic dysfunction.

An alternative to AV junctional ablation and permanent pacemaker placement is modification of AV junctional conduction.[52] This approach typically involves application of radiofrequency energy to the basal portions of Koch's triangle. Experience has been mixed, with results varying widely between series, and the procedure is now employed uncommonly. Progression to complete AV block has been reported as well as loss of efficacy in rate control in a significant proportion of patients. Prospective trial data is lacking for this procedure.

Stroke prevention strategy

While the goal of most device therapy for atrial fibrillation is the restoration of sinus rhythm or rate control, one experimental approach involves implantation of a device to decrease the risk of stroke. Percutaneous left atrial appendage transcatheter occlusion, or PLAATO, involves the insertion of an occlusion device by catheter into the left atrial appendage, the location of over 90% of atrial thrombi, via a transseptal puncture approach. The device is sized for the patient's appendage and anchored in place. It is currently undergoing initial clinical trials in humans in patients deemed not to be candidates for anticoagulation.[53]

Conclusions

An increasingly wide variety of non-pharmacologic approaches now exists for the management of medically refractory AF, spanning devices, surgical approaches, and percutaneous catheter interventions, and with goals including sinus rhythm restoration and maintenance, rate control, and stroke prevention (Table 39.3) Evidence-based application is largely

Table 39.3 Benefits of non-pharmacologic therapy options to treat symptomatic atrial fibrillation

Procedure	Restores sinus rhythm	Restores hemodynamics	Decreases risk of stroke	Need for implantable device (pacemaker/ defibrillator)
Surgical maze procedure	Yes	Yes	Yes	No (usually)
Surgical pulmonary vein isolation/limited maze	Yes	Possibly	Unknown	No
High right atrial pacing/septal pacing	No	No	No	Yes
Dual site atrial pacing	Yes	Improved	Yes	Yes
Implantable atrial/AV defibrillator	Yes	Yes	Unknown	Yes
Catheter-based maze procedure	Yes	Yes	Yes	No
Catheter ablation in pulmonary veins or isolation	Yes	Unknown	Unknown	No
Catheter ablation of AV junction	No	No	No	Yes
Catheter-based modification of AV conduction	No	No	No	No

becoming available for pacing therapies in specific populations, while defibrillation and ablation remain in the technologic evolution and refinement stage with largely observational data. It is becoming clear that non-pharmacologic approaches offer improved efficacy in a rhythm control strategy. They are likely to be implemented in a "hybrid" therapy strategy in a staged or simultaneous manner in the future to achieve effective rhythm control.

Levels of evidence for efficacy and safety of procedures to prevent or manage atrial fibrillation

● Surgical maze procedure	**Grade B**
● Left atrial isolation	**Grade B**
● Corridor procedure	**Grade B**
● Surgical pulmonary vein isolation/ partial maze	**Grade B**
● High right atrial pacing in sick sinus syndrome	**Grade A**
● Dual site right atrial pacing	**Grade A**
● Implantable atrial/AV defibrillator	**Grade B**
● Catheter-based ablation of AV conduction	**Grade A**
● Catheter-based modification of AV conduction	**Grade B**
● Catheter-based maze procedure	**Grade C**
● Catheter ablation of pulmonary veins or isolation	**Grade B**

References

1. Go AS, Hylek EM, Phillips KA *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001; **285**:2370–5.
2. Saksena S, Domanski MJ, Benjamin EJ *et al.* Report of the NASPE/NHLBI round table on future research directions in atrial fibrillation. *Pacing Clin Electrophysiol* 2001;**24**: 1435–51.
3. Crijns HJ. Rate control vs. electrical cardioversion for persistent atrial fibrillation. A randomized comparison of two treatment strategies concerning mortality and morbidity: the RACE study. *ACC 2002 late-breaking clinical trials.*
4. Carlsson J. Mortality and stroke rates in a trial of rhythm control versus rate control in atrial fibrillation: results from the STAF pilot phase (strategies of treatment of atrial fibrillation). *ACC 2001 late-breaking clinical trials.*
5. Wyse DG. Survival in patients presenting with atrial fibrillation: the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. *ACC 2002 late-breaking clinical trials.*
6. Crijns HJ, van Noord T, van Gelder IC. Recurrence of atrial fibrillation and the need for new definitions. *Eur Heart J* 2001;**22**:1769–71.
7. Andersen HR, Nielsen JC, Thomsen PEB *et al.* Long-term follow-up of patients from a randomized trial of atrial versus ventricular pacing for sick sinus syndrome. *Lancet* 1997; **350**:1210–16.
8. Lamas GA, Lee K, Sweeney M *et al.* Ventricular pacing or dual chamber pacing for sinus node dysfunction. *N Engl J Med* 2002;**346**:1854–62.
9. Connolly SJ, Kerr CR, Gent M *et al.* Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000;**342**:1385–91.
10. Gillis AM, Wyse DG, Connolly SJ *et al.* Atrial pacing perialation for prevention of paroxysmal atrial fibrillation. *Circulation* 1999;**99**:2553–8.
11. Friedman PA, Dijkman B, Warman EN *et al.* Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. *Circulation* 2001;**104**:1023–8.
12. Israel CW, Hügl B, Unterberg C *et al.* on behalf of the AT500 Verification Study Investigators. Pace-termination and pacing for prevention of atrial tachyarrhythmias: results from a multicenter study with an implantable device for atrial therapy. *J Cardiovasc Electrophysiol* 2001;**12**:1121–8.
13. Lee MA, Weachter R, Pollack S *et al.* Can preventive and antitachycardia pacing reduce the frequency and burden of atrial tachyarrhythmias? The ATTEST study results. North American Society of Pacing and Electrophysiology 23rd Annual Scientific Sessions 2002.
14. Funck RC, Adamec R, Lurje L *et al.*, on behalf of the PROVE Study Group. Atrial overdriving is beneficial in patients with atrial arrhythmias: first results of the PROVE study. *PACE* 2000;**23**:1891–3.
15. Carlson MA for the ADOPT-A investigators: the Atrial Dynamic Overdrive Pacing Trial (ADOPT-A): Presented at Late Breaking Clinical Trials Session, North American Society of Pacing and Electrophysiology 22nd Annual Scientific Sessions 2001.
16. Saksena S. Definitions and endpoints for device clinical trials in atrial fibrillation – a pressing need. *J Interv Card Electrophysiol* 1997;**1**:173–4.
17. Saksena S, Sulke N, Manda V *et al.*, on behalf of the Worldwide Jewel AF Investigators. Reduction in frequency of atrial tachyarrhythmia episodes using novel prevention algorithms of an atrial pacemaker defibrillator. *Pacing Clin Electrophysiol* 2000; **23**:581.
18. Bailin SJ, Adler S, Guidici M. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann bundle: results from a multicenter randomized trial. *J Cardiovasc Electrophysiol* 2001;**12**:912–17.
19. Padeletti L, Purerfellner, Adler S *et al.* Atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial fibrillation: ASPECT study results. North American Society of Pacing and Electrophysiology 23rd Annual Scientific Sessions 2002.
20. Delfaut P, Saksena S, Prakash A, Krol RB. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single and dual site right atrial pacing for arrhythmia prevention. *J Am Coll Cardiol* 1998;**32**:1900–8.
21. Prakash A, Saksena S, Krol RB *et al.* Catheter ablation of inducible atrial flutter in combination with atrial pacing and antiarrhythmic drugs (hybrid therapy) improves rhythm control in patients with refractory atrial fibrillation. *J Interv Card Electrophysiol* 2002;**6**:165–74.
22. Filipecki A, Saksena S, Prakash A *et al.* Atrial pacing improves rhythm control after linear right atrial ablation in refractory

permanent and persistent atrial fibrillation. *Pacing Clin Electrophysiol* 2001:**24**:707.
23. Saksena S, Prakash A, Hill M. Prevention of recurrent atrial fibrillation with chronic dual site right atrial pacing. *J Am Coll Cardiol* 1996;**28**:687–94.
24. Saksena S, Lin WH, Prakash A, Filipecki A. Long-term outcome of dual site right atrial pacing in patients with drug-refractory paroxysmal versus persistent or permanent atrial fibrillation. *J Am Coll Cardiol* 2002;**39**:84A.
25. Leclercq JF, DeSisti A, Fiorello P *et al.* Is dual site better than single site atrial pacing in the prevention of atrial fibrillation? *Pacing Clin Electrophysiol* 2000;**23**:2101–7.
26. D'Allonnes GR, Pavin D, Leclercq C *et al.* Long-term effects of biatrial synchronous pacing to prevent drug refractory atrial tachyarrhythmia: a nine-year experience. *J Cardiovasc Electrophysiol* 2000;**11**:1081–91.
27. Lau CP, Tse HF, Yu CM *et al.*, for the New Indication for Preventive Pacing in Atrial Fibrillation (NIPP-AF) Investigators. Dual-site atrial pacing for atrial fibrillation in patients without bradycardia. *Am J Cardiol* 2001;**88**: 371–5.
28. Ramdat Misier AR, Linde C, Beukema WP *et al.* Dual-site right atrial pacing improves quality of life in patients with drug refractory atrial fibrillation. *Pacing Clin Electrophysiol* 2000;**24**:555.
29. Saksena S, Prakash A, Ziegler P *et al.* The Dual Site Atrial Pacing for Permanent Atrial Fibrillation (DAPPAF) trial: improved suppression of drug refractory atrial fibrillation with dual site atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2001;**38**:598–9.
30. Wellens HJ, Lau CP, Luderitz B *et al.* Atrioverter: an implantable device for the treatment of atrial fibrillation. *Circulation* 1998; **98**:1651–6.
31. Saksena S, Prakash A, Mongeon L *et al.* Clinical efficacy and safety of atrial defibrillation using biphasic shocks and current nonthoracotomy endocardial lead configurations. *Am J Cardiol* 1995;**76**:913–21.
32. Giorgberidze I, Saksena S, Mongeon L *et al.* Effects of high-frequency atrial pacing in atypical atrial flutter and atrial fibrillation. *J Interv Card Electrophysiol* 1997;**1**:111–23.
33. Dreifus LS, Nichols H, Morse D. Control of recurrent tachycardia of Wolff–Parkinson–White syndrome by surgical ligature of the AV bundle. *Circulation* 1968;**38**:1030–6.
34. Camm J, Ward DE, Spurrell RA, Rees GM. Cryothermal mapping and cryoablation in the treatment of refractory cardiac arrhythmias. *Circulation* 1980;**62**:67–74.
35. Cox JL, Schuessler RB, D'Agostino HJ Jr *et al.* The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;**101**:569–83.
36. Kosakai Y. Treatment of atrial fibrillation using the Maze procedure: the Japanese experience. *Semin Thorac Cardiovasc Surg* 2000;**12**:44–52.
37. Kottkamp H, Hindricks G, Hammel D *et al.* Intraoperative radiofrequency ablation of chronic atrial fibrillation: a left atrial curative approach by elimination of anatomic "anchor" reentrant circuits. *J Cardiovasc Electrophysiol* 1999;**10**:772–80.
38. Sie HT, Beukema WP, Ramdat Misier AR *et al.* The radiofrequency modified maze procedure. A less invasive surgical approach to atrial fibrillation during open-heart surgery. *Eur J Cardiothorac Surg* 2001;**19**:443–7.
39. Nitta T, Lee R, Schuessler RB, Boineau JP, Cox JL. Radial approach: a new concept in surgical treatment for atrial fibrillation I. Concept, anatomic and physiologic bases and development of a procedure. *Ann Thorac Surg* 1999;**67**:27–35.
40. Chen SA, Hsieh MH, Tai CT *et al.* Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 1999;**100**: 1879–86.
41. Haissaguerre M, Shah DC, Jais P *et al.* Mapping-guided ablation of pulmonary veins to cure atrial fibrillation. *Am J Cardiol* 2000;**86**:K9–19.
42. Gerstenfeld EP, Guerra P, Sparks PB *et al.* Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. *J Cardiovasc Electrophysiol* 2001;**12**:900–8.
43. Natale A. Presentation at 16th Annual Course on diagnosis and treatment of cardiac arrhythmias, Milwaukee, 18 April 2002.
44. Pappone C, Oreto G, Rosanio S *et al.* Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001; **104**:2539–44.
45. Kanagaratnam L, Tomassoni G, Schweikert R *et al.* Empirical pulmonary vein isolation in patients with chronic atrial fibrillation using a three-dimensional nonfluoroscopic mapping system: long-term follow-up. *Pacing Clin Electrophysiol* 2001;**24**:1774–9.
46. Oral H, Knight BP, Tada H *et al.* Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation* 2002;**105**:1077–81.
47. Garg A, Finneran W, Mollerus M *et al.* Right atrial compartmentalization using radiofrequency catheter ablation for management of patients with refractory atrial fibrillation. *J Cardiovasc Electrophysiol* 1999;**10**:763–71.
48. Kocheril AG. Right atrial mapping and linear ablation for paroxysmal atrial fibrillation. *J Intervent Card Electrophysiol* 2001;**5**:505–10.
49. Evans GT, Scheinman MM, Bardy G *et al.* Predictors of in-hospital mortality after DC catheter ablation of atrioventricular junction: results of a prospective, international, multicenter study. *Circulation* 1991;**84**:1924–37.
50. Kay GN, Ellenbogen KA, Giudici M *et al.* The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. *J Intervent Card Electrophysiol* 1998;**2**:121–35.
51. Ozcan C, Jahangir A, Friedman PA *et al.* Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1043–51.
52. Kuck K-H, Kunze K-P, Schluter M *et al.* Transcatheter modulation by radiofrequency current of atrioventricular nodal conduction in patients with atrial fibrillation or flutter. In: Luderitz B, Saksena S, eds. *Interventional electrophysiology.* Mount Kisco, NY: Futura Publishing, 1991.
53. Sievert H, Lesh MD, Trepels T *et al.* Percutaneous left atrial appendage transcatheter occlusion (PLAATO) to prevent stroke in patients with atrial fibrillation: first human experience. *J Am Coll Cardiol* 2002;**39**:6A.

40 Supraventricular tachycardia: drugs *v* ablation

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"Supraventricular tachycardia", or SVT, is a rather imprecise term used to describe certain types of narrow complex tachycardia. The term is misleading because not all narrow complex tachycardias are "supraventricular" in origin. For example, ventricular tachycardias originating from the His bundle or its environs have a narrow QRS morphology. Also, not all supraventricular tachycardias have narrow complexes. Pre-excited tachycardias (in which the QRS complex is broad because of antegrade conduction through an accessory pathway) and SVTs with aberrant conduction, are cases in point. Furthermore, some "supraventricular" tachycardias involve mechanisms that are not confined to atrial or AV nodal tissue. SVTs involving accessory pathways are absolutely dependent upon conduction through the ventricles for their maintenance.

Ideally, arrhythmias should be described in a manner that reflects the underlying electrophysiological mechanism and the anatomical structures involved. This is not always possible when limited data are available from electrocardiogaphic recordings. In these instances a descriptive term can be applied to the electrocardiogram (for example, "narrow QRS tachycardia") until a more precise mechanism is known. In this way no assumption is made about the arrhythmia mechanism. The term "supraventricular tachycardia" is thus a term used to describe a range of arrhythmias with different mechanisms and involving different components of the cardiac conducting system. The following arrhythmias are encompassed by the term:

- **atrioventricular re-entrant tachycardia [AVRT]** – mediated by re-entry, and involving an accessory pathway and the AV node
- **atrioventricular nodal re-entrant tachycardia [AVNRT]** – mediated by a re-entry circuit involving the atrioventricular (AV) node and its atrial inputs
- **atrial flutter** – involving a re-entry circuit around large scale atrial structure(s), for example, veins, valve orifices
- **atrial tachycardias** – tachycardias involving a smaller scale intra-atrial re-entry circuit or an automatic focus
- **atrial fibrillation** – tachycardias involving multiple complex intra-atrial re-entry circuits.

The use of precise terminology is important. An understanding of the underlying mechanism helps determine whether a pharmacological or non-pharmacological treatment strategy is likely to be helpful. If drug treatment is chosen, the choice of drug used will in part be governed by the underlying arrhythmia mechanism. For radiofrequency ablation to succeed, the arrhythmia mechanism must be understood.

The common SVTs encountered in emergency departments are characterized by sudden onset of palpitation in young and middle-aged adults, with an ECG showing a regular, rapid, narrow complex tachycardia. These tachycardias can be terminated using vagal maneuvers or intravenous adenosine, and mainly involve the first two mechanisms listed above. Management of these tachycardias is the main focus of this chapter.

Issues to consider

Most supraventricular tachycardias are not life-threatening, and are problematic because of the symptoms they cause. For patients with well-tolerated occasional or short-lived episodes of palpitation it is reasonable to adopt a conservative approach and not to recommend drug treatment or ablation. If the arrhythmia does cause significant symptoms, the initial decision between drug treatment or ablation is a matter of patient preference. Patients need to be made aware of the likelihood of achieving symptom control, and of the potential risks of each strategy. For patients with specific occupations (for example, pilots), curative treatment with ablation may be a prerequisite to continuing work. For patients with a history of poor compliance with medication, ablation may also be the favored option. Some patients favor a tiered approach, in which a trial and error approach to drug treatment is used at first, with the option of ablation if symptoms persist or if drugs are poorly tolerated.

Drug treatment for SVTs

There are several categories of drugs that can be used as prophylaxis against SVT. The occurrence of these arrhythmias depends on there being an electrophysiological substrate, and a trigger. The substrate may be fixed, in the case of an accessory pathway mediated tachycardia, or may be dependent on

autonomic tone, as in some cases of AV nodal re-entrant tachycardia. Here, the ability of the AV node and its input pathways to maintain tachycardia is dependent on the relative conduction times and refractory periods of the tissues involved. These change dramatically in the presence of sympathetic or vagal stimulation. The trigger for SVT usually takes the form of a critically timed ectopic beat.

Drug treatments may alter substrate, trigger, or both. β Blockers can reduce the frequency of the ectopic beats that potentially trigger tachycardia, as well as altering the conduction properties of the tachycardia circuit to reduce the likelihood of tachycardia being maintained.[1] Some drugs are prescribed because of their effect on the AV nodal component of the re-entry circuit (for example, digoxin, verapamil). Others are used because of a direct effect on the refractory period of conducting tissue (for example, sotalol, dofetilide, amiodarone – potassium-channel blockers)[2] or on excitability and cardiomyocyte depolarization (for example, flecainide, propafenone, quinidine, disopyramide, amiodarone – sodium-channel blockade). Note that amiodarone has mixed properties, including partial beta blockade and calcium-channel blockade. Sodium-channel blockers such as flecainide more potently inhibit conduction through accessory pathways than through the AV node.[3,4] These agents are thus theoretically favorable in the management of atrioventricular re-entrant tachycardia.

How effective are drugs?

There is comparatively little information about the effectiveness of antiarrhythmic drugs for treatment of SVTs. In particular there are few studies that offer information about long-term symptom control, or adverse drug effects, in this setting. Published studies tend to be comparative and with short-term follow up. Other studies are limited in their usefullness because no attempt is made to tailor treatment to the tachycardia mechanism; in most studies all regular SVTs are treated the same. Atrial flutter and atrial fibrillation, which do not share a common mechanism, have been considered together in other trials. The high success rates for radiofrequency ablation have discouraged comparative studies of ablation versus pharmacological management for most SVTs. A summary of drug trials is given in Table 40.1.[5–13]

Both flecainide and propafenone have been shown to be more effective than placebo at preventing paroxysmal SVT.[5,6] In randomized studies, reported mainly in the mid-1990s, success rates for flecainide ranged from 73% to 93%, at the expense of an incidence of adverse effects of up to 53%. The doses used in these trials varied, as did the definitions of success and adverse effects. In some studies success has been defined as a reduction in the incidence or severity of symptom episodes, rather than abolition of the arrhythmia. It is also clear that clinical adverse effects are a significant limiting

Table 40.1 Summary of drug trials

	Patients (*n*)	Follow up (months)	Drugs	Success rate (%)	Adverse effects (%)
Drugs for "SVT" trial					
Pritchett, 1991[5]	14	1	Flecainide	86	23–53
			Placebo	29	
UK Propafenone	52	3	Propafenone	67–91	2–26
PSVT group, 1995[6]			Placebo	29–41	0–4
Chimienti, 1995[7]	135	12	Flecainide	93	10
			Propafenone	86	8
Hellestrand, 1996[8]	102	48	Flecainide	87	9
Weindling, 1996[9]	106	12	Digoxin ± propranolol	70	0
Dorian, 1996[10]	121	8	Flecainide	86	19
			Verapamil	73	24
Hopson, 1996[11]	67	12	Flecainide	73	64
Drugs for paroxysmal atrial flutter or artial fibrillation					
Pritchett, 1991[5]	28	1	Flecainide	61	23–55
			Placebo	7	31
UK Propafenone	48	3	Propafenone	60–96	3–40
PSVT group, 1995[6]			Placebo	30–32	3–4
Chimienti, 1995[7]	200	12	Flecainide	77	16
			Propafenone	75	14
Hopson, 1996[11]	67	12	Flecainide	56	56
Aliot, 1996[12]	97	12	Flecainide	62	9
			Propafenone	53	17

factor in the use of these drugs. For paroxysmal atrial fibrillation, amiodarone appears to be the most effective prophylactic agent but is not a desirable or realistic treatment option for young patients without structural heart disease, because of its unfavorable adverse effect profile with long-term use.[14] Class IC (flecainide and propafenone) and Class III (d.l sotalol) antiarrhythmic drugs can also be effective at reducing the incidence of symptoms in patients with paroxysmal atrial fibrillation, and are often used as first-line treatment.[5,6,15]

Proarrhythmia

Antiarrhythmic drugs can cause unwanted, sometimes life-threatening arrhythmias. These drugs work by slowing conduction, prolonging repolarization, or by altering automaticity. While these properties can be used to advantage, they can also increase the likelihood of arrhythmia under certain circumstances.[16–18] For example, sodium-channel blockade can have a differential slowing effect on conduction in diseased and healthy tissue, creating an environment in which re-entry is more likely to occur. Furthermore, anisotropy of conduction (that is, different speeds of conduction along the longitudinal and transverse axes between cardiomyocytes) may be exaggerated. These phenomena may explain the increased incidence of sudden death when Class IC drugs (flecainide and encainide) were used in patients with ischemic heart disease in the CAST study.[19] Prolongation of refractoriness through potassium-channel antagonism (for example, with sotalol) also causes proarrhythmia, increasing the risk of polymorphic ventricular tachycardia.[20] This may be caused by exaggerating the differences in refractoriness in diseased and healthy ventricular myocardium, or by a triggering mechanism.

Several risk factors have been identified for occurrence of proarrhythmia. These are: female gender (Class III drugs), history of VT or VF, ischemic heart disease, structural heart disease, and cardiac failure. Most patients with paroxysmal SVT are young and do not have structural heart disease, and are thus not at high risk of proarrhythmia. The incidence of ventricular proarrhythmia in patients treated with flecainide or propafenone for supraventricular arrhythmia is less than 2%, compared with 4–33% when used to treat ventricular arrhythmia.[16,21] Although this risk is small, it is still part of the decision making process when considered in the context of the small risk of serious complication from radiofrequency ablation. Another form of "proarrhythmia" can also occur when Class IC antiarrhythmics are used to treat atrial flutter. These agents slow atrial conduction without significantly affecting the AV nodal refractory period. This causes slowing of atrial flutter, enabling 1:1 atrioventricular conduction to occur.[22] This can paradoxically increase the ventricular rate to well over 200 beats per minute and may lead to hemodynamic compromise.

Ablation for "common" SVTs

For patients with SVTs mediated by atrioventricular nodal re-entry or atrioventricular re-entry via an accessory pathway, it is now accepted that catheter ablation is more effective than drug treatment. Catheter ablation has a more positive impact on quality of life and is more cost effective when assessed for long-term efficacy.[23–25] Catheter ablation is now an accepted first-line treatment for otherwise healthy patients with recurrent, symptomatic tachycardias.

Accessory pathway mediated tachycardias

These tachycardias involve conduction through an accessory atrioventricular connection, usually comprising tissue with electrophysiological properties similar to that of Purkinje tissue. The most common indication here for catheter ablation is *orthodromic* atrioventricular re-entrant tachycardia, during which atrioventricular conduction occurs via the AV node, and ventriculo-atrial re-entry occurs through the accessory pathway. This arrhythmia can occur in patients with manifest electrocardiographic evidence of pre-excitation – Wolf–Parkinson–White syndrome – or in patients with an apparently normal resting electrocardiogram, who may have a concealed accessory pathway. (A less common variant, *antidromic* atrioventricular re-entry, can occur in which the accessory pathway forms the antegrade limb of the circuit, resulting in a broad complex tachycardia.) Initial approaches to curative treatment of this tachycardia involved surgical division of the accessory pathway, and subsequently direct current ablation, but these techniques were rapidly superseded by radiofrequency ablation. Early reports suggested procedural success rates in excess of 95%, with failures and recurrences more frequent when right-sided accessory pathways were treated.[26,27] With refinement of catheter technology, success rates continue to improve and not surprisingly catheter ablation is established as a first-line treatment for this condition in otherwise uncomplicated cases.[28]

Patients with Wolf–Parkinson–White syndrome can also present with pre-excited atrial fibrillation. In some cases the accessory pathway refractory period is very short, allowing rapid, repetitive ventricular stimulation in response to atrial fibrillation. This gives rise to extremely rapid ventricular rates and can precipitate ventricular fibrillation and death. For this reason catheter ablation should be seriously considered in any patient with manifest pre-excitation and palpitation. It is less clear whether asymptomatic patients with pre-excitation should undergo electrophysiological studies.[29] Assessment of accessory pathway refractory period in the EP laboratory is a poor predictor of risk of sudden death because many autonomic variables alter this parameter. It is not clear that the benefit of catheter ablation in asymptomatic patients outweighs the risks of the procedure except in specific circumstances, for example, for competitive athletes or pilots.

AV nodal re-entrant tachycardia

This arrhythmia has a very similar presentation to atrioventricular re-entrant tachycardia. The electrocardiogram typically shows a regular, rapid, narrow complex tachycardia with rate between 160 and 240 beats per minute. For many years the electrophysiology of this arrhythmia was poorly understood. Surgical mapping and autopsy studies have shown that this tachycardia involves atrial as well as AV nodal tissue, and it is sometimes referred to as para AV nodal re-entrant tachycardia.[30,31] Identification that patients with this tachycardia have multiple AV nodal inputs with different electrophysiological properties, and anatomical correlation of a posterior AV nodal extension with the electrophysiological location of a slowly conducting AV nodal input, led to the development of the technique of slow pathway ablation.[32] This technique involves ablation of atrial tissue inferior to the compact AV node, typically at a site anterior to the coronary sinus ostium adjacent to the tricuspid annulus. Initial success rates exceeded 80% at the expense of a 2% risk of development of atrioventricular block requiring permanent pacing.[27,33] With modern catheters and temperature controlled ablation techniques, success rates now exceed 95% and the risk of AV block is approximately 1%.[28]

Atrial flutter

In most cases atrial flutter is mediated by a right atrial macro re-entry circuit with a critical pathway of conduction between the inferior vena cava and the tricuspid annulus. This cavo-tricuspid isthmus zone forms the target for contemporary ablation techniques.[34] Rarer forms of atrial flutter use other anatomic barriers as their substrate (for example, the pulmonary veins, an atrial septal defect, or a surgical scar) and are collectively referred to as atypical atrial flutter. The technique of flutter ablation involves the production of a line of interconnected ablation lesions to create conduction block between two anatomical barriers in a critical part of the flutter circuit. In the case of typical atrial flutter, this line is created in the cavo-tricuspid isthmus. Success rates for catheter ablation of typical atrial flutter were initially limited by an inability to produce full-thickness lesions in patients with pectinate ridges extending into the isthmus region.[35] The use of large tipped catheters or "cooled tip" catheters has allowed delivery of more energy into the atrial myocardium, and has increased success rates over 95%.[36] AV block can complicate flutter ablation, particularly if the line of block is created in the medial (septal) aspect of the cavo-tricuspid isthmus.[28]

Atrial tachycardia

Atrial tachycardias can have an automatic or re-entrant mechanism. Drug treatments have generally proven disappointing, although flecainide may have a role in their management.[37] Until recently catheter ablation techniques were also of limited use, because of the very large area of potential atrial surface area from which these tachycardias can originate. Furthermore, patients with re-entrant atrial tachycardias often have extensive atrial disease and may have more than one focus for tachycardia. The development of non-fluoroscopic mapping systems, which allow three-dimensional mapping of atrial activation during tachycardia, has proved very helpful in allowing the electrophysiologist to pinpoint the focus or circuit (Figure 40.1).[38] Quoted success rates for treatment of these tachycardias now range from 80–90%.[39]

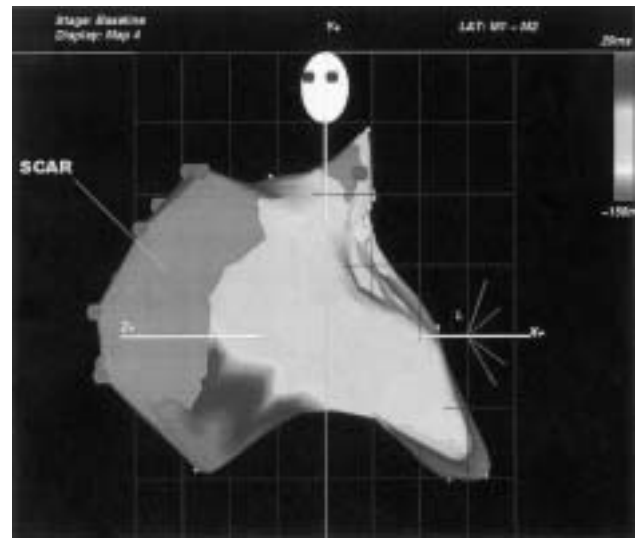

Figure 40.1 Non-fluoroscopic mapping of the right atrium of a patient with suspected right atrial tachycardia. A large zone of atrial infarction is identified by voltage mapping and the patient is subsequently shown to have scar-related atrial flutter.

Atrial fibrillation

Atrial fibrillation is the most common atrial arrhythmia and is the cause of much morbidity because of hemodynamic effects and embolic complications. The arrhythmia itself comprises multiple, interacting, intra-atrial re-entry circuits or wavelets that produce a complex, rapid, irregular atrial rhythm.[40] Atrial fibrillation is most likely to be maintained in enlarged, diseased atria because re-entry is promoted by slow conduction and by long conduction pathways. In these situations atrial fibrillation is likely to be persistent (that is, will not spontaneously terminate) or permanent (that is, will not terminate with pharmacological or electrical cardioversion). Paroxysmal atrial fibrillation can occur in patients with structurally normal hearts and may be initiated by ectopic beats originated from sleeves of atrial tissue extending into the pulmonary veins, or less commonly the superior vena

cava.[41,42] Ablation techniques have evolved extremely rapidly in recognition of these mechanisms and can be divided into those directed at ectopic triggers (focal ablation) and at preventing intra-atrial re-entry (linear ablation).

Focal ablation for paroxysmal atrial fibrillation

This technique involves transseptal puncture to pass catheters from the right atrium into the left atrium, and the use of multi-electrode catheters in the ostia of the pulmonary veins to identify the conduction pathways into and out of these veins. The superior pulmonary veins are the most common sources of ectopic triggers and form the targets for ablation.[43] Two approaches may be adopted – electrical isolation of the culprit veins identified from spontaneous ectopic beat activity, or the anatomical approach in which as many pulmonary veins as possible are isolated in an attempt to eliminate all ectopic triggers.[44] Initial techniques involved ablation deep within the veins and were associated with a significant incidence of pulmonary vein stenosis.[45] It is now generally accepted that radiofrequency energy should be applied at or close to the ostia to minimize this risk. Success rates for pulmonary vein ablation are currently around 60% in experienced centers, with success defined as lack of symptomatic recurrence of atrial fibrillation in the medium term (few long-term data are yet available). It is now recognized that pulmonary vein ectopic impulses may be involved in the maintenance of atrial fibrillation as well as its initiation. Ablation of these foci in some patients with persistent atrial fibrillation can acutely terminate the arrhythmia.[46] The response to antiarrhythmic drugs may be improved by modifying the triggering focus. Recurrences occur because of multiple pulmonary vein triggers, triggers occurring within the atria themselves, or incomplete isolation of veins.

Linear ablation

Linear ablation procedures are designed to compartmentalize atrial tissue to prevent intra-atrial re-entry. These procedures owe much to the early experience with the surgical maze and corridor procedures.[47] Current techniques involve the production of linear lesions around the pulmonary vein ostia, across the superior aspect of the left atrium, and connecting the mitral valve annulus to the pulmonary vein ostial lines. Specially designed compliant, multi-electrode ablation catheters have been developed for this purpose. At present linear ablation is still considered an experimental procedure.[48]

The pace and ablate strategy

For patients with persistent, symptomatic atrial fibrillation, total AV nodal ablation offers a means of controlling heart rate and of regularizing the ventricular rhythm. A physiological (rate responsive) permanent pacemaker is implanted and used to govern heart rate. This technique is effective at improving quality of life in selected patients, especially those with palpitation. Its effectiveness is less clear-cut in patients with non-specific symptoms such as fatigue and dyspnea, in which the underlying cardiac condition may be the main

Table 40.2 Potential problems of drugs and ablation for treatment of SVTs

Antiarrhythmic drugs	Ablation
Proarrhythmia $<$2% if otherwise normal heart $>$4% in other patients (that is, structural or coronary disease)	Potentially life-threatening complication (for example, cardiac tamponade, stroke, myocardial infarction) – very rare No deaths in 1998 NASPE registry
Non-cardiac side effects 8 to 60% with Class IC drugs[11] 24% with verapamil[10]	AV block requiring pacemaker 0·15% (AVRT) to 1% (AVNRT)
Failure to control arrhythmia up to 30% with short-term follow up	Inability to ablate target 2·6% (AVNRT) 6% (AVRT) up to 28% (atrial tachycardia) 14% (atrial flutter)[a]
Compliance issues	Pneumothorax (avoided by coronary sinus cannulation via femoral vein route) Tricuspid regurgitation (rare) Vascular complications (rare)

[a] This figure is likely to improve with the use of large tipped catheters and cooled tip catheters that can produce a larger lesion.

cause. Total AV nodal ablation is thus best reserved for patients with atrial fibrillation who have palpitation and for whom AV nodal blocking drugs are ineffective or cause significant adverse effects.

Risks of ablation

In discussing treatment options with patients, the risks of treatment are an important factor (Table 40.2). The risks of antiarrhythmic drugs, especially proarrhythmia, have already been covered. For catheter ablation there are uncommon but important risks. Most patients worry about the risk of a disabling or life-threatening complication. Cardiac tamponade can occur because of transseptal puncture, catheter trauma or ablation in thin-walled tissue. This risk is therefore greatest with left-sided accessory pathways and with ablation of focal atrial arrhythmias, at around 0·7%. For other tachycardias the risk is significantly less. Fatalities were reported particularly during early experience with catheter ablation but in the 1998 NASPE prospective catheter ablation registry there were no deaths reported in more than 3300 procedures. This registry was voluntary and open to reporting bias, but nonetheless death is a very uncommon complication. Other reported complications included myocardial infarction, pneumothorax, pericarditis, tricuspid regurgitation, and femoral artery pseudoaneurysm. AV block requiring pacemaker implantation affected 1 in 100 patients treated for AVNRT, 1 in 650 patients treated for AVRT, and 1 in 150 patients treated for atrial flutter. Complication rates for focal and linear ablation techniques are less well reported but there is concern about the potential for thromoembolic complication when multiple radiofrequency applications are made in the left atrium.

Recommendations	Evidence Grade
● Propafenone and flecainide are effective antiarrhythmic drugs for the prophylactic management of paroxysmal supraventricular tachycardia.	**Grade A**
● Sotalol and amiodarone are effective prophylactic therapies for paroxysmal atrial flutter.	**Grade B**
● Potential proarrhythmic complications and other adverse effects of antiarrhythmic therapy should be considered when choosing antiarrhythmic therapy.	**Grade C**
● The choice between ablation and antiarrhythmic drug therapy for the initial treatment of paroxysmal supraventricular tachycardia is dependent on patient preference.	**Grade C**
● Verapamil is a safe first-line treatment for pSVT but has a relatively high rate of failure and side effects.	**Grade B**
● Flecainide and propafenone reduce symptoms from pSVT in most cases and should be considered for individuals who do not have underlying coronary artery disease.	**Grade B**
● RF ablation should be offered as first-line treatment for individuals with pSVT.	**Grade B**
● RF ablation is the treatment of choice in individuals who present with pre-excited atrial fibrillation.	**Grade C**
● RF ablation should be offered as first-line treatment for individuals with paroxysmal or persistent atrial flutter.	**Grade B**
● Pulmonary vein ablation should be considered a second-line treatment for paroxysmal atrial fibrillation in the absence of structural heart disease in selected individuals, where antiarrhythmic drug therapy has failed.	**Grade C**
● The "ablate and pace" strategy should be used to palliate symptoms in patients with atrial fibrillation in whom rate control is not achieved using drugs.	**Grade B**

References

1. Frishman WH, Cavusoglu E. Beta-adrenergic blockers and their role in the therapy of arrhythmias. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia: mechanisms, diagnosis and management.* Baltimore, Maryland: Williams and Wilkins, 1995.
2. Gill J, Heel RC, Fitton A. Amiodarone. An overview of its pharmacological properties, and review of its therapeutic use in cardiac arrhythmias. *Drugs* 1992;**43**:69–110.
3. Estes NAM, Garan H, Ruskin JN. Electrophysiologic properties of flecainide acetate. *Am J Cardiol* 1984;**53**(Suppl. B): 26B–9B.
4. Hellestrand KJ, Bexton RS, Nathan AW *et al.* Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in men. *Br Heart J* 1982;**48**:140–8.
5. Pritchett ELC, Datorre SD, Platt ML *et al.* Flecainide acetate treatment of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation – dose response studies. *J Am Coll Cardiol* 1991;**17**:297–303.
6. UK Propafenone PSVT Study Group. A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. *Circulation* 1995;**92**:2550–7.
7. Chimienti M, Cullen Jr MT, Casadei G for the Flecainide and Propafenone Italian Study Investigators. Safety of flecainide versus propafenone for the long-term management of symptomatic paroxysmal supraventricular tachyarrhythmias. Report from the Flecainide and Propafenone Italian Study (FAPIS) Group. *Eur Heart J* 1995;**16**:1943–51.
8. Hellestrand KJ. Efficacy and safety of long-term oral flecainide acetate in patients with responsive supraventricular tachycardia. *Am J Cardiol* 1996;**77**:83A–8A.
9. Weindling SN, Saul JP, Walsh EP. Efficacy and risks of medical therapy for supraventricular tachycardia in neonates and infants. *Am Heart J* 1996;**131**:66–72.
10. Dorian P, Naccarelli GV, Coumel P *et al.* A randomised comparison of flecainide versus verapamil in paroxysmal

supraventricular tachycardia. The Flecainide Multicenter Investigators Group. *Am J Cardiol* 1996;**77**:89A–95A.
11. Hopson JR, Buxton AE, Rinkenberger RL *et al.* Safety and utility of flecainide acetate in the routine care of patients with supraventricular tachyarrhythmias: results of a multicenter trial. The Flecainide Supraventricular Tachycardia Study Group. *Am J Cardiol* 1996;**77**:72A–82A.
12. Aliot E, Denjoy I. Comparison of the safety and efficacy of flecainide and propafenone in hospital out-patients with symptomatic atrial fibrillation/flutter. The Flecainide AF French Study Group. *Am J Cardiol* 1996;**77**:66A–71A.
13. Orejarena LA, Vidaillet H Jr, DeStefano F *et al.* Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol* 1998;**31**:150–7.
14. Gooselink AT, Crijns HJ, Van Gelder IC *et al.* Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA* 1992;**267**:3289–93.
15. Chung MK, Schweikert RA, Wilkoff BL *et al.* Is hospital admission for initiation of antiarrhythmic therapy with sotalol for atrial arrhythmias required? Yield of in-hospital monitoring and prediction of risk for significant arrhythmia complications. *J Am Coll Cardiol* 1998;**32**:169–76.
16. Stanton MS, Prystowsky EN, Fineberg NS *et al.* Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. *J Am Coll Cardiol* 1989;**14**:209–15.
17. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med* 1992;**117**:141–50. [Published erratum in *Ann Intern Med* 1992;**117**:446.]
18. Friedman PL, Stevenson WG. Proarrhythmia. *Am J Cardiol* 1998;**82**:50N–8N.
19. Echt DS, Liebson PR, Mitchell LB *et al.* Mortality and morbidity in patients receiving encainide, flecainide or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–8.
20. Reiffel JA. Impact of structural heart disease on the selection of class III antiarrhythmics for the prevention of atrial fibrillation and flutter. *Am Heart J* 1998;**135**:551–6.
21. Pritchett E, Wilkinson WE. Mortality in patients treated with flecainide and encainide for supraventricular arrhythmias. *Am J Cardiol* 1991;**67**:976–80.
22. Nathan AW, Hellestrand KJ, Bexton RS *et al.* Proarrhythmic effects of the new antiarrhythmic agent flecainide acetate. *Am Heart J* 1984;**107**:222–8.
23. Bathina MN, Mickelsen S, Brooks C *et al.* Radiofrequency catheter ablation versus medical therapy for initial treatment of supraventricular tachycardia and its impact on quality of life and healthcare costs. *Am J Cardiol* 1998; **82**:589–93.
24. Weerasooriya HR, Murdock CJ, Harris AH *et al.* The cost- effectiveness of treatment of supraventricular arrhythmias related to an accessory atrioventricular pathway: comparison of catheter ablation, surgical division and medical treatment. *Aust NZ J Med* 1994;**24**:161–7.
25. Ikeda T, Sugi K, Enjoji Y *et al.* Cost effectiveness of radiofrequency catheter ablation versus medical treatment for paroxysmal supraventricular tachycardia in Japan. *J Cardiol* 1994; **24**:461–8.
26. Jackman WM, Beckman KJ, McClelland JH *et al.* Catheter ablation of accessory pathways (Wolff–Parkinson–White syndrome) by radiofrequency current. *N Engl J Med* 1991; **324**:1605–11.
27. Sathe S, Vohra J, Chan W *et al.* Radiofrequency catheter ablation for paroxysmal supraventricular tachycardia: a report of 135 procedures. *Aust NZ J Med* 1993;**23**:317–24.
28. Scheinmann MM, Huang S. The 1998 NASPE prospective catheter ablation registry. *Pacing Clin Electrophysiol* 2000; **23**:1020–8.
29. Fitzsimmons PJ, McWhirter PD, Peterson DW *et al.* The natural history of Wolff–Parkinson–White syndrome in 228 military aviators: a long-term follow-up of 22 years. *Am Heart J* 2001;**142**:530–6.
30. Keim S, Werner P, Jazayeri M *et al.* Localization of the fast and slow pathways in atrioventricular nodal re-entrant tachycardia by intra-operative ice-mapping. *Circulation* 1992; **86**: 919–25.
31. Inoue S, Becker AE. Posterior extensions of the human compact atrioventricular node: a neglected anatomic feature of potential clinical significance. *Circulation* 1998;**97**:188–93.
32. Jackman WM, Beckman KJ, McClelland JH *et al.* Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow pathway conduction. *N Engl J Med* 1992;**327**:313–18.
33. Kugler JD, Danford DA, Deal BJ *et al.* Radiofrequency catheter ablation for tachyarrhythmias in children and adolescents. The Pediatric Electrophysiology Society. *N Engl J Med* 1994; **330**:1481–7.
34. Cosio FG, Lopez-Gil M, Goicolea A, Arribas F, Barroso JL. Radiofrequency ablation of the inferior vena cava-tricuspid valve isthmus in common atrial flutter. *Am J Cardiol* 1993; **71**:705–9.
35. Chen SA, Chiang CE, Wu TJ *et al.* Radiofrequency catheter ablation of common atrial flutter: comparison of electrophysiologically guided focal ablation and linear ablation technique. *J Am Coll Cardiol* 1996;**27**:860–8.
36. Jaïs P, Hocini M, Gilet T *et al.* Effectiveness of irrigated tip catheter ablation of common atrial flutter. *Am J Cardiol* 2001;**88**:433–5.
37. Anderson JL, Jolivette DM, Fredell PA. Summary of efficacy and safety of flecainide for supraventricular arrhythmias. (Review). *Am J Cardiol* 1988;**62**:62D–6D.
38. Hoffman E, Reithmann C, Nimmermann P *et al.* Clinical experience with electroanatomic mapping of ectopic atrial tachycardia. *Pacing Clin Electrophysiol* 2002;**25**:49–56.
39. Poty H, Saoud N, Haissaguerre M *et al.* Radiofrequency catheter ablation of atrial tachycardias. *Am Heart J* 1996;**131**:481–9.
40. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn* 1962;**140**:183–8.
41. Haïssaguerre M, Jaïs P, Shah DP *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
42. Tsai CF, Tai CT, Hseih MH *et al.* Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava. Electrophysiological characteristics and results of radiofrequency ablation. *Circulation* 2000;**102**;67–74.
43. Haïssaguerre M, Jaïs P, Shah DC *et al.* Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 1996;**7**:1132–44.
44. Hassiguerre M, Jais P, Shah DC *et al.* Electrophysiological end-point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. *Circulation* 2000;**101**: 1409–17.

45. Robbins IM, Colvin EV, Doyle TP *et al.* Pulmonary vein stenosis after catheter ablation of atrial fibrillation. *Circulation* 1998;**98**:1769–75.
46. Pappone C, Oreto G, Rosanio S *et al.* Atrial electroanatomic remodelling after circumferential radiofrequency pulmonary vein ablation. *Circulation* 2001;**104**:2539–44.
47. Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG. Five year experience with the maze procedure for atrial fibrillation. *Ann Thorac Surg* 1993;**56**:814–24.
48. Maloney JD, Milner L, Barold S, Czerska B, Markel M. Two-staged biatrial linear and focal ablation to restore sinus rhythm in patients with refractory chronic atrial fibrillation: procedure experience and follow-up beyond 1 year. *Pacing Clin Elecrophysiol* 1998;**21**:2527–32.

Part IIId

Specific cardiovascular disorders: Ventricular arrhythmias, bradyarrhythmias and cardiac arrest

A John Camm, Editor

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

41 Prevention and treatment of life-threatening ventricular arrhythmia and sudden death

Eugene Crystal, Stuart J Connolly, Paul Dorian

Introduction

Arrhythmic death and risk stratification

Epidemiologic studies and carefully conducted clinical trials have consistently demonstrated that deaths in patients with severe heart disease are often due to ventricular arrhythmia. The evidence for this comes from several sources, including recordings made by paramedics, Holter monitor studies, and postmortem classification based on suddenness of hemodynamic collapse.[1] Although not all sudden deaths are due to ventricular tachycardia or fibrillation, there is substantial evidence from paramedic monitoring and Holter reports that most are.[2] Although different schemes have been used to classify death according to presumed mechanisms, there is considerable evidence that between one quarter and half of cardiac deaths are sudden and due to arrhythmia. Thus prevention of the sudden death is an important clinical goal.

Over the past two decades methods of risk stratification have been developed and evaluated, in order to target therapy to the subpopulation at greatest risk of sudden death. Techniques have been used in clinical trials of antiarrhythmic agents to select a population at high risk of arrhythmic death. These include some clinical characteristics (decreased left ventricular ejection fraction (LVEF), recent myocardial infarction, New York Heart Association (NYHA) functional class of heart failure), and the use of investigations such as measurement of ventricular ectopy on the 24-hour Holter, programmed ventricular stimulation, signal averaged ECG and heart rate variability. Although all of these techniques identify patients at increased risk of arrhythmic death, and total death as well, there is no evidence that any technique selectively detects increased risk of arrhythmic death.[3] Thus powerful markers of total death, such as poor LVEF, are now used in trials to identify patients at risk of arrhythmic death.

To summarize, risk stratification is necessary to select patients at high enough risk of events to justify intervention; however, left ventricular damage, a powerful risk factor for overall cardiac death risk, may be the most efficient means of selecting patients who are at high risk of arrhythmic death.

Pharmacologic interventions and sudden cardiac death

Classification of antiarrhythmic drugs

There have been a number of attempts to classify antiarrhythmic drugs. The most widely used classification is based on the influence of drugs on different phases of the action potential of myocytes (Table 41.1). This system is relatively simple compared to other classifications, but is limited because of the mixed abilities of most antiarrhythmic drugs.

Table 41.1 Classification of antiarrhythmic drugs*

	Action	Drugs
Class IA	Depression of action potential upstroke, slow conduction, prolong repolarization	Quinidine, procainamide, disopyramide
Class IB	Little effect on upstroke in normal tissue, depression of upstroke in abnormal tissue, shortening of repolarization	Lidocaine, mexiletine
Class IC	Marked depression of upstroke, marked slow conduction, slight effect on repolarization	Flecainide, propafenone, encainade, ajmaline, moricizine
Class II	β Blockers	
Class III	Prolong repolarization	Amiodarone, sotalol, dofetilide, azimilide, ibutilide
Class IV	Calcium-channel blockers	Verapamil, diltiazem

*Many drugs have properties of more than one class, but are classified according to their major effects.

Trials of antiarrhythmic therapy in patients with sustained ventricular arrhythmia

There have been only a few randomized trials of antiarrhythmic therapy in patients with prior sustained ventricular arrhythmia. These have used active controls and the primary outcome has been arrhythmia recurrence or death. Steinbeck *et al*[4] conducted a prospective randomized trial in 170 patients to investigate whether electrophysiologic study (EPS)-guided antiarrhythmic therapy improves the long-term outcome of patients with spontaneous and inducible sustained ventricular arrhythmia compared with metoprolol therapy not guided by EPS. EPS-guided therapy consisted of serial EPS testing of inducibility under different antiarrhythmic agents (in sequence: propafenone → disopyramide → sotalol → amiodarone) to identify one that would suppress an initially inducible sustained arrhythmia. There were 55 patients whose arrhythmia was never inducible during the baseline EPS, thereby precluding further serial drug testing, and these patients were treated with metoprolol. The 2 year incidence of the composite outcome of symptomatic arrhythmia recurrence or sudden death was the same for EPS-guided therapy as for metoprolol (46% *v* 48%).

In the Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) study[5,6] patients with inducible VT and any (i) history of cardiac arrest, (ii) sustained VT or (iii) syncope, were randomly assigned to undergo serial testing of the efficacy of the antiarrhythmic drugs either by EPS or by 24 hour Holter monitoring. Patients ($n = 486$) received long-term treatment with the first antiarrhythmic drug that was predicted to be effective on the basis of either repeat EPS or 24 hour Holter. The primary conclusion of ESVEM was that therapy guided by EPS and that guided by Holter monitoring are equally effective.[6] The secondary outcome, related to the efficacy of individual study drug, was very interesting.[5] Sotalol, a β blocking drug with class III activity, was more effective than the class I drugs tested (imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine). The actuarial probability of a recurrence of arrhythmia after a prediction of drug efficacy by either strategy was significantly lower for patients treated with sotalol than for patients treated with the other drugs (risk ratio (RR) 0·43; 95% CI 0·29, 0·62). With sotalol there were lower risks of death from any cause (RR 0·50; 95% CI 0·30, 0·80), death from cardiac causes (0·50; $P = 0 \cdot 02$) and death from arrhythmia (0·50; $P = 0 \cdot 04$). The cumulative percentage of patients in whom a drug was predicted to be effective and in whom it remained effective and tolerated was also higher for sotalol than for the other drugs ($P < 0 \cdot 001$). Sotalol was more effective than the other six antiarrhythmic drugs in preventing death and recurrences of arrhythmia.

In the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) study, antiarrhythmic drug therapy was evaluated in survivors of out of hospital VF.[7] Amiodarone without EPS or Holter guidance was compared to class I antiarrhythmic agents (quinidine, procainamide, their combination, or flecainide), selected by serial EPS or Holter monitoring. Most of the 228 randomized patients had coronary artery disease with a prior myocardial infarction, and the mean left ventricular ejection fraction was 35±10%. During a mean follow up of 6 years, amiodarone improved survival compared to the class I agents (53% *v* 40%, $P = 0 \cdot 007$).

These trials provide evidence that, in survivors of sustained ventricular arrhythmia, amiodarone and sotalol are superior to class I agents.

Recommendation

Grade A Where antiarrhythmic drugs are to be used to prevent the recurrence of ventricular tachyarrhythmia, amiodarone and sotalol are superior to class I antiarrhythmic agents.

Trials of antiarrhythmic therapy in patients with asymptomatic non-sustained ventricular arrhythmia, at risk of sudden death

Asymptomatic non-sustained ventricular arrhythmia on Holter monitor was determined in the 1980s to be a predictor of death in patients surviving myocardial infarction, and these patients were targeted in several trials of antiarrhythmic therapy on the assumption that decreasing asymptomatic ventricular arrhythmia would decrease the occurrence of sudden cardiac death This hypothesis was first tested in the International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT)[8] and then in the pivotal Cardiac Arrhythmia Suppression Trial (CAST).[9] In IMPACT, 630 patients with recent myocardial infarction were randomly assigned to treatment with mexiletine or placebo.[8] Despite a decrease in the frequency of complex ventricular arrhythmia, after an average follow up of 9 months, the mortality on mexiletine was 7·6% and on placebo was 4·8% (P = NS).

In the Cardiac Arrhythmic Suppression Trial (CAST)[9] 1727 patients with recent onset of myocardial infarction and with asymptomatic, or mildly symptomatic, ventricular arrhythmia (≥ 6 ventricular extrasystoles per hour), suppressible by a class I antiarrhythmic drug (encainade, flecainide or moricizine), were randomized to the active antiarrhythmic drug or placebo and followed for arrhythmic death. The trial was halted early because of an increased incidence of arrhythmic cardiac death and non-fatal cardiac arrests in patients treated with encainade and flecainide (4·5% *v* 1·2%, RR 3·6, 95% CI 1·7, 8·5).

These results led to reappraisal of class I drug therapy for sudden death prophylaxis. In a meta-analysis of the results

of 138 trials of antiarrhythmic prophylactic therapy in patients after myocardial infarction,[10] there were 660 deaths among 11 712 patients allocated to receive class I agents and 571 deaths among 11 517 corresponding control patients (51 trials: odds ratio (OR) 1·14; 95% CI 1·01, 1·28; $P = 0 \cdot 03$). There is therefore considerable evidence that class I antiarrhythmic drugs are harmful when used as prophylactic agents in high-risk patients.

Amiodarone is a class III antiarrhythmic agent which has been extensively studied in patients at risk of sudden arrhythmic death. Amiodarone has several properities other than class III effect, including an antiadrenergic effect. The two largest trials (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, CAMIAT[11] and European Myocardial Infarction Amiodarone Trial, EMIAT[12]) both showed a reduction in arrhythmic death but no significant reduction in overall death. Meta-analysis of data from all 13 randomized controlled trials of amiodarone (89% of patients, after myocardial infarction) showed a significant reduction in total mortality (OR 0·87, 95% CI 0·78–0·99) and a significant reduction in arrhythmic death (OR 0·71, 95% CI 0·59, 0·85).[13,14] Analysis of the interaction between the treatment and baseline factors suggested an important positive relationship between β blocker use and amiodarone effect,[15] such that patients on β blockers received a significantly greater benefit from amiodarone than those not on β blockers.

D-Sotalol, a pure class III agent, was evaluated for prevention of sudden death in a placebo controlled trial of 3121 patients with recent myocardial infarction and left ventricular ejection fraction <40%, or symptomatic heart failure with a remote myocardial infarction (Survival with Oral d-sotalol, or SWORD trial).[16] Among 1549 patients assigned to d-sotalol there were 78 deaths (5·0%) compared to 48 (3·1%) among the 1572 patients assigned to placebo (RR 1·65, 95% CI 1·15, 2·36). Presumed arrhythmic deaths (RR 1·77, 95% CI 1·15, 2·74) accounted for the excess mortality in the d-sotalol group. This proarrhythmic fatal effect of d-sotalol was greater in patients with a left ventricular ejection fraction of 31–40% than in those with lower ejection fractions (RR 4·0 *v* 1·2, $P = 0 \cdot 007$).

Another pure class III compound, dofetilide, was tested in patients with symptomatic heart failure. In the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) 1518 patients were randomized to dofetilide or placebo.[17,18] The study treatment was initiated in hospital and included 3 days of cardiac monitoring and dose adjustment. During a median follow up of 18 months, 311 patients in the dofetilide group (41%) and 317 patients in the placebo group (42%) died (OR, 0·95; 95% CI 0·81, 1·11). Treatment with dofetilide significantly reduced the risk of hospitalization for worsening CHF, rate of conversion and risk of recurrence of atrial fibrillation. There were 25 cases of *torsades de pointes* in the dofetilide group (3·3%), compared to none in the placebo group. Dofetilide has also been tested in a randomized trial of 1510 patients with severe left ventricular dysfunction (LVEF ≤ 35%) after recent myocardial infarction (DIAMOND MI trial). The primary end point was all-cause mortality. No significant difference was found between the dofetilide and placebo groups in overall mortality (31% *v* 32%). The cardiac mortality (26% *v* 28%) and arrhythmic mortality (17% *v* 18%) were also similar. There were seven cases of *torsades de pointes* ventricular tachycardia, all in the dofetilide group.[19]

In the Azimilide Postinfarct Survival Evaluation (ALIVE) trial the effect of azimilide, another pure class III agent, was evaluated in 3717 patients with recent myocardial infarction, with LVEF < 35% and with low heart rate variability. Azimilide had no effect on mortality (HR = 1·0).[20]

β Blockers in patients at risk of sudden death

β Blockers are the single type of agent most frequently studied in postmyocardial infarction patients for the prevention of death, with more than 12 large trials reported. A meta-analysis of the β blocker trials, reported in 1985, showed a significant reduction in mortality during treatment after myocardial infarction.[21] The data from this meta-analysis also indicated a highly significant 30% reduction in sudden cardiac death with β blockers. The risk of non-sudden death was also decreased by 12%, but this difference was not significant. Recent β blocker trials in CHF patients also show a reduction in both overall and sudden cardiac death.[22–24]

In summary, antiarrhythmic drugs have been extensively evaluated in randomized trials as prophylactic agents against death, but little tested against recurrence of arrhythmia. β Blockers are effective against arrhythmic death (about 20–30% reduction) and non-arrhythmic deaths, and reduce overall mortality significantly. Amiodarone has a moderate effect against sudden death and a neutral effect on other deaths, therefore its overall effect on total mortality is modest. Class I antiarrhythmic drugs are harmful, probably owing to proarrhythmic effects. Pure class III agents are at best neutral, and in the case of one agent, d-sotalol, actually harmful.

β Blocker therapy is indicated in all patients at high risk for sudden death, and amiodarone is the treatment of choice for control of specific arrhythmias where concern about possible proarrhythmic effects is an issue (especially in patients with ischemic heart disease and/or left ventricular dysfunction).

Pure class III antiarrhythmic agents clearly do not reduce mortality when used prophylactically in high-risk patients. The different results of D-sotalol, dofetilide and azimilide trials are probably due to differences in the design of the studies and differences in risk of *torsades de pointes* between the agents.

Recommendations

Grade A β Blockers are indicated in patients with myocardial infarction or congestive heart failure for the prevention of death.

Grade A Amiodarone is the antiarrhythmic drug of choice where there is an above average risk of proarrhythmia.

Grade A Class I antiarrhythmics should be avoided in patients with coronary artery disease or left ventricular dysfunction.

Other pharmacologic interventions decreasing risk of sudden cardiac death

The effect of angiotensin converting enzyme (ACE) inhibitors on the risk of sudden cardiac death (SCD) following myocardial infarction has been demonstrated in randomized trials.[25–27] A recent meta-analysis[28] incorporated data from 15 trials that included 15 104 patients having 900 SCDs. ACE inhibitor therapy resulted in a significant reduction in total mortality (OR 0·83; 95% CI 0·71, 0·97), cardiovascular death (OR 0·82, 95% CI 0·69, 0·97) and SCD (OR 0·80; 95% CI 0·70, 0·92). Also, the meta-analysis suggested that a reduction in SCD risk with ACE inhibitors was an important component of overall survival benefit, the magnitude of effect on SCD being the same as on overall mortality.

Interestingly, in the Heart Outcome Prevention Evaluation Study (HOPE),[29] involving cardiovascular patients without a significant decrease in (LVEF $>$ 40%), the ACE inhibitor, ramipril, significantly decreased the incidence of cardiac arrest (RR 0·62, 95% CI 0·41, 0·94). The mechanism by which ACE inhibitors reduce SCD is poorly understood. In addition to attenuation of remodeling, and thereby reducing the substrate for ventricular tachyarrhythmia, they provide significant neurohumoral modulation and protection from future ischemic events.

In the Randomized Aldactone Evaluation Study (RALES)[30] aldactone was evaluated in patients having NYHA III–IV. After a mean follow up of 24 months the incidence of heart failure symptoms was significantly decreased (RR 0·71, 95% CI 0·54, 0·95). The magnitude of this effect was similar to the effect on total mortality (RR 0·70, 95% CI 0·68, 0·72).

In the GISSI-Prevenzione Trial[31] treatment with *n*-3 polyunsaturated fatty acids in 11 324 postmyocardial infarction patients significantly decreased the incidence of sudden cardiac death (RR 0·74, 95% CI 0·58, 0·93), also significantly decreasing total cardiac mortality and coronary mortality by the same ratio (RR 0·78 and 0·80, respectively, both significant).

Thus, accumulated evidence supports the wide use of the above-mentioned interventions in appropriate patients. However, there is no evidence of a primary antiarrhythmic action and so these agents cannot be recommended as antiarrhythmic agents.

Grade A. ACE inhibitors and spironolactone should be used in patients with congestive heart failure.

ICD treatment trials

ICD therapy

Electrical shock therapy is the most effective acute treatment for life-threatening ventricular arrhythmia. The concept of an implantable device able to diagnose ventricular tachyarrhythmia and to deliver shock therapy automatically was developed in the 1970s. ICD therapy has been the subject of intensive validation since its introduction into clinical practice. The first ICD was implanted in 1980; since then there have been many refinements to the initial technology and improvements continue to occur at a brisk pace. The fundamental therapy is the direct current (DC) shock capable of cardioversion/defibrillation. Overdrive pacing therapy for the termination of VT and bradycardia pacing are available. Therapy can be tiered so that if overdrive pacing fails to convert VT, or transforms it to a more malignant arrhythmia, defibrillation/cardioversion can be deployed subsequently. Detection of VT or VF is achieved by automatic counting of the heart rate. Automatic gain control allows the device to detect VF as well as VT. Major recent refinements are a reduction in size and the addition of atrial electrodes which allow dual chamber pacing, as well as use of the atrial electrogram to improve the specificity of VT and VF detection.

Implantation is generally done under anesthesia in the operating room or the electrophysiology laboratory, with intraoperative testing for pacing and defibrillation thresholds. The operative mortality with modern endocardial systems is $<$1%.[32,33] The ICD is associated with a number of complications: pneumothorax or vascular complications of implantation; heart perforation; pericarditis; and infectious complications. The rate of infection with non-thoracotomy systems is 0·6–4·1%.[34] A troublesome complication is the painfulness of virtually all cardioversion/defibrillator shocks. The availability of overdrive pacing therapy, which is painless, reduces the frequency of shocks even in fast VT, but many patients still require shocks periodically.[35,36]

ICD therapy has achieved considerable sophistication in the detection and treatment of VT and VF. There is no doubt that it is an effective therapy for the termination of episodes of VT and VF. This has been clear for many years from the fact that VT or VF, artificially induced in hospital, can be reliably terminated by the ICD. Modern ICDs now provide an ECG collection and telemetry ability that allows inspection of the cardiac electrograms immediately before and after discharges of the ICD. It is now possible to directly confirm the success of the ICD against episodes of spontaneously occurring VT

and VF. Thus it is safe to conclude that the ICD is very effective for many episodes of VT and VF, preventing their fatal outcomes.

Assessment of ICD effectiveness

Assessment of the overall effectiveness of the ICD is made complex by the fact that in the vast majority of patients VT and VF are not isolated conditions but late complications of ischemic heart disease or cardiomyopathy. In fact, VT and VF only rarely occur in the absence of serious structural heart disease. The typical patient receiving an ICD is at risk of dying not only from recurrence of VT or VF, but also from recurrent myocardial infarction and congestive heart failure. Thus although the ICD is clearly effective against VT and VF, it was not entirely obvious that it would prolong life in the average patient treated. Several trials have addressed this issue.

ICD for survivors of sudden death

There have been four randomized trials which evaluated the ICD as a treatment for patients with previous documented sustained VT or VF. A small (60 patients) Dutch trial randomized patients with inducible sustained cardiac arrhythmia after cardiac arrest to either ICD or conventional therapy (which included antiarrhythmic drugs and VT ablation and VT surgery).[37] During 24 months of follow up patients in the ICD group had non-significantly lower overall, cardiac and sudden cardiac mortality.

Three secondary prevention ICD trials have been conducted. CASH[38] enrolled patients with prior VF, whereas the Canadian Implantable Defibrillator Study (CIDS) and the Antiarrhythmic versus Implantable Defibrillator (AVID) study enrolled both patients with prior VF as well as patients with hemodynamically unstable VT.[39,40] CIDS also enrolled patients with decreased LV function, syncope and inducible VT.

AVID was the first of these three trials to report its results.[40] There were 1016 patients randomized to receive either an ICD or drug therapy, which was specified as either amiodarone or sotalol. In patients eligible for either drug, allocation was random. Forty-five per cent of patients had VF and the rest had VT. Only 13 of 509 patients randomized to drug therapy were actually discharged from hospital on sotalol; the rest received amiodarone. The mean dose of amiodarone at 1 year was 331 mg/day and 87% of patients remained on amiodarone at 1 year. There was a significant imbalance in β blocker use between ICD and amiodarone patients, with 45% of ICD patients receiving this therapy compared to 13% of drug therapy patients. There was a reduction in mortality with the ICD. Over a mean follow up of 18 months, crude death rates were $15{\cdot}8 \pm 3{\cdot}2\%$ for the ICD *v* $24{\cdot}0 + 3{\cdot}7\%$ for drug therapy ($P < 0{\cdot}02$). The relative risk reductions at 1, 2 and 3 years were $39 \pm 20\%$, $27 \pm 21\%$ and $31 \pm 21\%$ ($\pm$95% CI). The treatment effect is quite large in terms of relative risk reduction (approximately one third) but the prolongation of life is modest, at only just over 3 months.

CASH was initially planned as a 400 patient study with four treatment arms: ICD, amiodarone, metoprolol and propafenone. The propafenone arm was terminated prematurely owing to excessive mortality compared to the other treatments (61% higher all-cause mortality rate than in ICD patients during a follow up of 11 months). The study continued to recruit patients in the remaining three arms; 99 were assigned to ICDs, 92 to amiodarone and 97 to metoprolol. The primary end point was all-cause mortality. The study was terminated when all patients had concluded a minimum 2 year follow up. Over a mean follow up of 57 ± 34 months, therapy with an ICD was associated with a 23% (non-significant) reduction in all-cause mortality rates compared to treatment with amiodarone/metoprolol.

In CIDS a total of 659 patients were randomly assigned to treatment with the ICD or with amiodarone. The primary outcome measure was all-cause mortality and the secondary outcome was arrhythmic death. At 5 years, 85·4% of patients assigned to amiodarone were still receiving it at a mean dose of 255 mg/day, 28·1% of ICD patients were also receiving amiodarone, and 21·4% of amiodarone patients had received an ICD. A non-significant reduction in the risk of death was observed with the ICD, from 10·2% per year to 8·3% per year (19·7% relative risk reduction; 95% CI −7·7 to 40; $P = 0{\cdot}142$). A non-significant reduction in the risk of arrhythmic death was observed, from 4·5% per year to 3·0% per year (32·8% relative risk reduction; 95% CI −7·2 to 57·8; $P = 0{\cdot}094$).

A meta-analysis of the three trials provides a summary of the benefit of the ICD in the secondary prevention.[41] Individual patient data from AVID, CASH and CIDS were merged into a database. Analysis of the data showed that the estimates of ICD benefit from the three studies were consistent with each other ($P_{\text{heterogeneity}} = 0{\cdot}306$). It also showed a significant reduction in death from any cause with the ICD, with a summary hazard ratio (ICD *v* amiodarone) of 0·72 (95% CI 0·60, 0·87; $P = 0{\cdot}0006$). For the outcome of arrhythmic death the hazard ratio was 0·50 (95% CI 0·37, 0·67; $P < 0{\cdot}0001$). Survival was extended by a mean of 4·4 months by the ICD over a follow up period of 6 years. Patients with left ventricular ejection fraction ≤35% derived significantly more benefit from ICD therapy than those with better left ventricular function (HR 1·2, 95% CI 0·86, 1·76 in patients with LVEF > 35% *v* HR 0·66, 95%CI in patients with LVEF ≤ 35%, $P_{\text{interaction}} = 0{\cdot}011$).

At present, when managing a patient with life-threatening sustained VT or VF the balance of evidence now favors ICD therapy over amiodarone. In light of the modest prolongation of life conferred by the ICD and its high cost, where resources are limited, amiodarone may be used as reasonable alternative.

Recommendations
Grade A ICD is the treatment of choice for patients with cardiac arrest or sustained ventricular tachycardia.

ICD for inducible VT/VF

Two randomized trials have evaluated the ability of the ICD to reduce the risk of death in patients who have not experienced sustained ventricular tachyarrhythmia but who are at high risk of sudden death because they have been shown to have low LVEF, spontaneous non-sustained VT, and inducible sustained ventricular tachyarrhythmia. These are the Multicenter Automatic Defibrillator Implantation Trial (MADIT)[42] and the Multicenter Unsustained Tachycardia Trial (MUSTT).[43,44]

In MADIT, patients with left ventricular ejection fraction <35% and recent myocardial infarction were further screened by programmed ventricular stimulation. Patients found to have inducible VT or VF became eligible for the study if inducibility of the tachycardia could not be suppressed by procainamide.[42] There were 196 patients randomized to either receive an ICD or "conventional" therapy. The choice of conventional therapy was at the discretion of the investigator. Amiodarone and β blockers, the only proven effective drugs against VT and VF, were used predominantly but sporadically (in 45% and 5%, respectively, of "conventional" patients at last contact). The trial was terminated prematurely when about 75% of patients had been enrolled, owing to a benefit of ICD treatment. The hazard ratio was 0·46 (95% CI 0·26, 0·82; $P = 0 \cdot 009$), indicating a greater than 50% reduction in death with ICD therapy. When the specific causes of death were examined, the ICD not only reduced arrhythmic death (13 ν 3), but there appeared to be reduction in non-arrhythmic cardiac death (13 ν 7) and deaths of unknown cause (6 ν 0), which is not explained and not biologically plausible. There was a marked imbalance in the use of β blocker therapy in favor of the ICD group, but this did not explain the benefit observed with the ICD.

The Multicenter Unsustained Tachycardia Trial (MUSTT) was a randomized trial of electrophysiologically guided antiarrhythmic therapy in patients with coronary artery disease, a left ventricular ejection fraction ≤0·40 and asymptomatic, non-sustained ventricular tachycardia.[43] Seven hundred and four patients who satisfied these criteria, and in whom sustained ventricular tachyarrhythmia was induced by programmed stimulation, were randomly assigned to receive either antiarrhythmic drug tailored by electrophysiological testing, including drugs and ICDs (if drugs failed to suppress inducibility), or no antiarrhythmic therapy at all. The primary end point of cardiac arrest or death from arrhythmia was reached in 25% of those receiving electrophysiologically guided therapy, and in 32% of those assigned to no antiarrhythmic therapy (relative risk 0·73; 95% CI 0·53–0·99), representing a reduction in risk of 27%. Five year total mortality was 42% in patients receiving EPS-guided therapy, versus 48% in controls (RR 0·80, 95% CI 0·64, 1·01). In a non-randomized analysis the primary end point was less frequent among the patients who received ICDs compared to patients discharged without receiving defibrillator treatment (relative risk 0·24; 95% CI, 0·13–0·45; $P < 0 \cdot 001$). In contrast, the primary end point in those who received antiarrhythmic drugs was not less frequent than in the patients assigned to no antiarrhythmic therapy.

The results of these two trials provide suggestive evidence that the ICD reduces risk of death when used as a prevention therapy in patients with coronary disease, reduced left ventricular function and inducible VT. However, the small size of MADIT and the indirect inference about the role of ICD in MUSTT make it hard to conclude definitely that the ICD benefits these patients.

Recommendation
Grade B The ICD may be considered for patients with LVEF ≤ 40% and with inducible sustained VT.

ICD as a primary prevention of sudden cardiac death

In two other randomized trials, ICDs were tested in patients without spontaneous or inducible life-threatening ventricular arrhythmia: the Coronary Artery Bypass Graft Patch Trial (CABG-Patch)[45] and the Second Multicenter Autonomic Defibrillator Implantation Trial (MADIT II).[46]

The rationale for the CABG-Patch trial was developed at a time when a thoracotomy was required for implantation of an ICD. Patients requiring CABG, who were identified to be at high risk of sudden death, were thought to be good candidates for prophylactic ICD implantation because the detrimental effect of a major surgical procedure to implant the ICD was already accounted for.[45] Thus in the CABG-Patch Trial, patients scheduled for CABG and with LVEF ≤35% were further stratified for risk of arrhythmic death by signal averaged ECG. High-risk patients were randomized either to receive or not to receive an ICD at the time of CABG. The trial randomized 900 patients. Antiarrhythmic drug use was similar between the two groups. There were 52 patients randomized to ICD who either never received a device or who had it removed. There were 196 deaths (101 in the ICD group and 95 in the control group) for a crude mortality rate of 21·8% during an average follow up of 32 ± 16 months. The hazard ratio was 1·07 (95% CI 0·81, 1·42), indicating no benefit from the ICD in this patient population. Secondary analysis showed that the ICD did reduce arrhythmic death, but the benefit was offset by an unexplained increase in non-arrhythmic death.[47]

MADIT II is the second completed trial of ICDs in patients at risk of future sudden death without evidence of sustained VT or VF.[46,48] The target population were patients with LVEF ≤30%, excluding patients with recent (<1 month) myocardial infarction, CABG or PTCA (<2 months); and patients justifying the MADIT I criteria for ICD implantation. There were 1232 patients randomly assigned to receive an ICD (742 patients) or conventional medical therapy (490 patients). During an average follow up of 20 months, the mortality rates were 19·8% in the conventional therapy group and 14·2% in the defibrillator group (HR 0·69, 95% CI 0·51, 0·93).

The discrepancy between the results of the CABG-Patch Trial and MADIT may be explained by differences in severity of left ventricular dysfunction of the target populations (≤30% in MADIT II *v* ≤35% in CABG-Patch). All patients in the CABG-Patch population had CABG performed at the very start of the study. MADIT II enrolled patients who had either been previously revascularized or who were not suitable for revascularization.

There are other ongoing prospective randomized controlled trials evaluating the efficacy of ICD therapy in patients at risk of VT/VF without spontaneous or inducible sustained ventricular arrhythmia. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is a randomized placebo controlled trial designed to determine whether amiodarone or the ICD will decrease overall mortality in patients with coronary artery disease or non-ischemic cardiomyopathy who are in New York Heart Association (NYHA) class II or III heart failure with a left ventricular ejection fraction ≤35%.[49] The primary end point in SCD-HeFT is total mortality.

The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) is a randomized comparison of ICD therapy versus no ICD therapy in survivors of acute myocardial infarction at risk of sudden cardiac death.[50] The study aims to enroll 675 patients shortly after their infarction (day 6 to day 40) who have reduced left ventricular function (LVEF ≤ 0·35) and impairment of cardiac autonomic function, shown by depressed heart rate variability (standard deviation of normal to normal R–R intervals 70 ms) or elevated average 24 hour heart rate (mean 24 hour R–R interval 750 ms, assessed by Holter monitoring). Patients will be followed for approximately 3 years on average, with subsequent data analysis based on the intent to treat principle. Primary outcome is all-cause mortality.

Results from SCD-Heft and DINAMIT are expected during 2003. At present the evidence of superiority of ICD in patients with low (≥30%) left ventricular ejection fraction is confined to the partially reported results of MADIT II, but counterbalanced by a neutral effect from CABG-Patch.

However, the MADIT II result is likely to be important because of the simple clear design of that study and the clear result in favor of ICD therapy. Left ventricular dysfunction is a major determinant of the degree to which patients can benefit from the ICD. In the secondary prevention trials CIDS and AVID, and in MADIT I, the benefit of the ICD is much greater in these patients with poor LV function than in those whose LV is well preserved. The results of MADIT II, which enrolled patients with severe LV dysfunction, add further evidence in support of this view. Although the occurrence of a sustained ventricular arrhythmia remains the main indication for an ICD today, it is likely that in the future reduced LV function will be the primary determinant of need.

Recommendation

Grade A The ICD is indicated for patients with coronary artery disease and LVEF ≤ 30%.

Combined ICD and antiarrhythmic drug therapy

ICDs and antiarrhythmic drugs should not be considered as exclusive alternatives.[51] In fact, many ICD patients receive concomitant antiarrhythmic therapy to help control supraventricular tachyarrhythmia, recurrent ventricular arrhythmia and frequent ICD shocks. Indeed, the ICD does not prevent VT/VF, only its fatal consequences. Conversely, the ICD is able to protect patients from the occasional proarrhythmic action of antiarrhythmic drugs. In one recent placebo controlled trial sotalol was shown to be effective in preventing shocks in ICD patients.[52]

Cost of ICD therapy

The high cost of modern ICD systems is a considerable obstacle against their wider use in many areas, making the treatment available to only a minor proportion of those at risk. The cost effectiveness of ICD implantation was analyzed for two trials.[53,54] In MADIT the ICD treatment showed increased costs compared to the drug arm, mainly owing to initial costs (US$44 600 for ICD *v* US$18 900 for non-ICD). The cost of follow up was non-significantly higher for the non-ICD arm (US$1915 *v* US$1384). ICD therapy resulted in a cost of US$27 000 for every life year saved. In CIDS, the cost per year of life saved was much higher, at about US$130 000. The main reason for the difference in cost effectiveness between MADIT and CIDS was the estimates of efficacy, the costs being similar. The more modest estimate of ICD benefit in CIDS resulted in much lower cost effectiveness. In a subsequent analysis of CIDS for patients with LVEF <35% (in whom ICD implantation was associated with a greater survival benefit), the cost of 1 year of life gained was quite reasonable (between US$60 000 and US$ 90 000). Sheldon *et al.*[55] indicated that appropriate risk stratification by simple clinical risk factors (age ≥70, LVEF ≤35% and NYHA class III) in the CIDS population reduced the cost per year of life saved to about US$40 000.

Summary

Sudden death due to ventricular arrhythmia is an important health problem against which considerable progress has been made in the past 15 years. Both drugs and devices have been shown to reduce the risk of arrhythmic death. Patients with advanced coronary or myocardial disease are at high risk of arrhythmic death and should be treated with ACE inhibitors and β blockers. Those with symptomatic heart failure should receive spironolactone. The ICD clearly further reduces the risk of arrhythmic death in those at high risk, and should be used both in patients surviving sustained VT or VF and in those with very severe left ventricular dysfunction.

Summary of recommendations

Grade A Where antiarrhythmic drugs are to be used to prevent the recurrence of ventricular tachyarrhythmia, amiodarone and sotalol are superior to class I antiarrhythmic agents.

Grade A β Blockers are indicated in all patients with prior myocardial infarction or congestive heart failure.

Grade A ACE inhibitors and spironolactone should be used in patients with congestive heart failure.

Grade A Amiodarone is the antiarrhythmic drug of choice where there is an above average risk of proarrhythmia.

Grade A Class I antiarrhythmics should be avoided in patients with coronary artery disease or left ventricular dysfunction.

Grade A ICD is the treatment of choice for patients with cardiac arrest or sustained ventricular tachycardia.

Grade A The ICD is indicated for patients with coronary artery disease with LVEF≤30%.

Grade B The ICD may be considered for patients with LVEF≤40% and with inducible sustained VT.

References

1. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**:1473–82.
2. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;**117**:151–9.
3. Albert CM, Ruskin JN. Risk stratifiers for sudden cardiac death (SCD) in the community: primary prevention of SCD. *Cardiovasc Res* 2001;**50**:186–96.
4. Steinbeck G, Andresen D, Bach P *et al.* A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. *N Engl J Med* 1992;**327**:987–92.
5. Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. *N Engl J Med* 1993;**329**:452–8.
6. Mason JW. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. *N Engl J Med* 1993;**329**:445–51.
7. Greene HL. The CASCADE Study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. CASCADE Investigators. *Am J Cardiol* 1993;**72**:70F–4F.
8. International mexiletine and placebo antiarrhythmic coronary trial: I. Report on arrhythmia and other findings. Impact Research Group. *J Am Coll Cardiol* 1984;**4**:1148–63.
9. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406–12.
10. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 1993;**270**:1589–95.
11. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997;**349**:675–82.
12. Julian DG, Camm AJ, Frangin G *et al.* Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997;**349**:667–74.
13. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997;**350**:1417–24.
14. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999;**100**:2025–34.
15. Boutitie F, Boissel JP, Connolly SJ *et al.* Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. The EMIAT and CAMIAT Investigators. *Circulation* 1999;**99**: 2268–75.
16. Waldo AL, Camm AJ, deRuyter H *et al.* Effect of D-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral D-Sotalol. *Lancet* 1996; **348**:7–12.
17. Torp-Pedersen C, Moller M, Bloch-Thomsen PE *et al.* Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med* 1999;**341**:857–65.
18. Torp-Pedersen C, Moller M, Bloch-Thomsen PE *et al.* Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med* 1999;**341**:857–65.
19. Kober L, Bloch Thomsen PE, Moller M *et al.* Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet* 2000; **356**:2052–8.
20. Camm AJ. Azimilide Postinfarct Survival Evaluation (ALIVE): Azimilide does not affect mortality in post myocardial infarction patients. http://www. online.org/HTML_src/summarybyspec. asp? dd = Clinical styId = 3

21. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;**27**:335–71.
22. Carson P. Beta-blocker therapy in heart failure. *Cardiol Clin* 2001;**19**:267–78, vi.
23. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
24. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–7.
25. Cohn JN, Johnson G, Ziesche S *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**: 303–10.
26. Kober L, Torp-Pedersen C, Carlsen JE *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;**333**:1670–6.
27. Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. *Eur Heart J* 1997;**18**:41–51.
28. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1999;**33**:598–604.
29. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
30. Pitt B, Zannad F, Remme WJ *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–17.
31. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;**354**:447–55.
32. Strickberger SA, Hummel JD, Daoud E *et al.* Implantation by electrophysiologists of 100 consecutive cardioverter defibrillators with nonthoracotomy lead systems. *Circulation* 1994; **90**:868–72.
33. PCD Investigator Group. Clinical outcome of patients with malignant ventricular tachyarrhythmias and a multiprogrammable implantable cardioverter-defibrillator implanted with or without thoracotomy: an international multicenter study. *J Am Coll Cardiol* 1994;**23**:1521–30.
34. Shepard R, Epsten A. ICD infection avoidance: science, art, discipline. In: Kroll MW LM, ed. *Implantable cardioverter defibrillator therapy: the engineering–clinical interface*. Norwell, MA: Kluwer Academic Press, 1996.
35. Rosenqvist M. Pacing techniques to terminate ventricular tachycardia. *Pacing Clin Electrophysiol* 1995;**18**:592–8.
36. Wathen MS, Sweeney MO, DeGroot PJ *et al.* Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. *Circulation* 2001;**104**:796–801.
37. Wever EFD, Hauer RNW, van Capelle FJL *et al.* Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. *Circulation* 1995;**91**:2195–203.
38. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102**:748–54.
39. Connolly SJ, Gent M, Roberts RS *et al.* Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–302.
40. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**:1576–83.
41. Connolly SJ, Hallstrom AP, Cappato R *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; **21**:2071–8.
42. Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–40.
43. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882–90.
44. Buxton AE, Lee KL, DiCarlo L *et al.* Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 2000;**342**:1937–45.
45. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997;**337**:1569–75.
46. Moss AJ, Zareba W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
47. Bigger JT Jr, Whang W, Rottman JN *et al.* Mechanisms of death in the CABG Patch trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. *Circulation* 1999; **99**:1416–21.
48. Moss AJ, Cannom DS, Daubert JP *et al.* Multicenter Automatic Defibrillation Implantation Trial II (MADIT II): design and clinical protocol. *Ann Noninvas Electrocardiol* 1999;**4**:83–91.
49. Bardy GH, Lee KL, Mark DB. The Sudden Cardiac Death in Heart Failure Trial: pilot study [Abstract]. *PACE* 1997;**20**:1148.
50. Hohnloser SH, Connolly SJ, Kuck KH *et al.* The defibrillator in acute myocardial infarction trial (DINAMIT): study protocol. *Am Heart J* 2000;**140**:735–9.

51. Dorian P. Combination ICD and drug treatments – best options. *Resuscitation* 2000;**45**:S3–6.
52. Pacifico A, Hohnloser SH, Williams JH *et al.* Prevention of implantable-defibrillator shocks by treatment with sotalol. D,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 1999;**340**:1855–62.
53. Mushlin AI, Hall WJ, Zwanziger J *et al.* The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. *Circulation* 1998;**97**:2129–35.
54. O'Brien BJ, Goeree R, Bernard L, Rosner A, Williamson T. Cost-effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin: a Canadian perspective. *Clin Ther* 2001;**23**:2038–49.
55. Sheldon R, O'Brien BJ, Blackhouse G *et al.* Effect of clinical risk stratification on cost-effectiveness of the implantable cardioverter-defibrillator: the Canadian implantable defibrillator study. *Circulation* 2001;**104**:1622–6.

42 Impact of pacemakers: when and what kind?

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Introduction

The development and implementation of the first fully implantable cardiac pacemaker in 1958 transformed the outlook for patients with symptomatic bradycardia and Stokes–Adams attacks.[1] The first pacemaker recipient survived for over 43 years after receiving his initial implant. Since then, many millions of patients have benefitted from this dramatically effective form of treatment. Technological advances and innovation have enabled the development of increasingly sophisticated pacing systems, better able to simulate the normal cardiac activation sequence, and a wide variety of different pacing modes is now available.

Initially, pacemakers were only implanted for atrioventricular (AV) block, but their use was soon extended to the management of symptomatic bradycardia associated with sinus node disease. In recent years, improved understanding of pathophysiologic mechanisms has prompted the assessment of pacemaker therapy in a number of other conditions such as neurocardiogenic syncope, hypertrophic cardiomyopathy, dilated cardiomyopathy and paroxysmal atrial fibrillation. With the emergence of new indications for pacing and the availability of a vast array of different pacing modes and techniques, an evidence-based approach to the practice of cardiac pacing has become increasingly important.

Goals of cardiac pacing

The fundamental aims of cardiac pacing are to relieve symptoms, to improve the quality of life and, in some instances, to prolong survival. The achievement of these aims is mediated by improvements in hemodynamic function and functional capacity, reduction in cardiovascular morbidity, and prevention of sudden death. Any consideration of the indications for pacing and selection of the appropriate pacing mode must have regard to all of these factors and their interrelations, which are summarized in Figure 42.1. Hemodynamic differences between alternative pacing modes do not always translate into significant differences in clinical utility and a comprehensive assessment of outcome in clinical trials is therefore essential. It is important to note that inappropriate pacing or complications from pacing may result in new or worse symptoms and increased cardiovascular morbidity. This is perhaps best exemplified by the pacemaker syndrome, which is most often seen during ventricular pacing in the presence of retrograde ventriculoatrial conduction. The syndrome has aptly been described as an iatrogenic condition.[2]

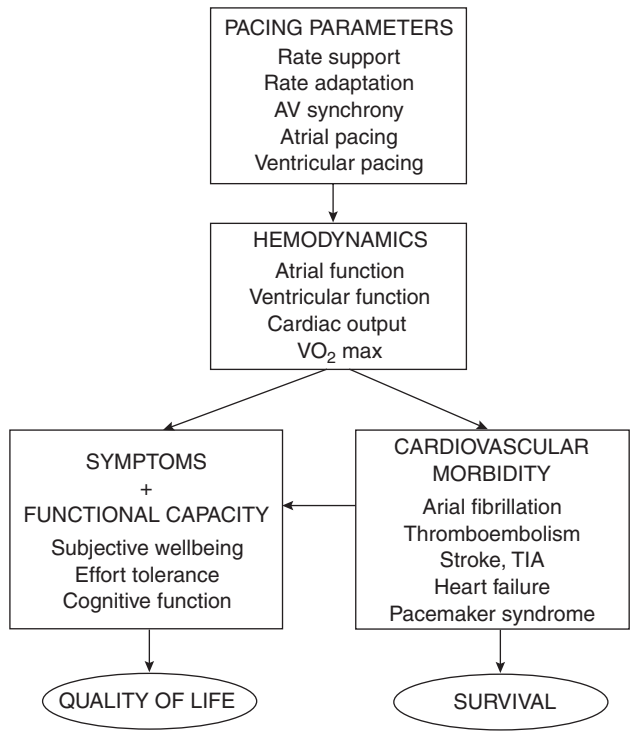

Figure 42.1 Relation of pacing parameters to clinical outcome

Current pacing practice

It is estimated that about 500 000 pacemakers per annum are implanted worldwide,[3–5] but there is considerable national and regional variation in the implant rate. In the United Kingdom, there are approximately 295 new implants per million population.[6] This is close to the median for European countries but the figure within Europe ranges from less than

100 per million (Russia) to 585 per million (Belgium).[4] The estimated new implant rate in the United States is 571 per million.[5] These variations may partly reflect differences in the age distribution and morbidity of the relevant populations but availability of resources and variations in standards of medical care and attitudes towards pacing may also be relevant. There has also been some suggestion, in the past, of inappropriate and excessive pacemaker implantation.[7]

In an effort to define appropriate pacing practice, a joint task force sub-committee of the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines for permanent pacemaker implantation in 1984.[8] These were updated and revised in 1991[9] and again in 1998[10] (Table 42.1). The guidelines follow an evidence-based approach and include grading of the evidence supporting each recommendation. With regard to the indications for pacing, the following classification is used:

- Class I – conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective
- Class II – conditions for which there is conflicting evidence and/or a divergence of opinion about the usefullness/efficacy of pacing
- Class III – conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.

Class II is subdivided into Class IIa – weight of evidence/opinion is in favor of usefullness/efficacy and Class IIb – usefullness/efficacy is less well established by evidence/opinion. It is recognized that, although applicable to the "average" patient, recommendations for specific conditions may require modification to take account of patient comorbidity, limited life expectancy, and other factors that only the implanting physician can evaluate appropriately.

A working party of the British Pacing and Electrophysiology Group (BPEG) also published recommendations for pacemaker prescription in 1991.[11] These advocated general principles to guide pacemaker mode selection and made specific recommendations for optimal and alternative pacing modes in various clinical settings (Table 42.2). The recommendations regarding mode selection have, however, been criticized and attention has been drawn to their reliance on observational data from retrospective studies rather than prospective randomized clinical trials.[12] Attention has also been drawn to the financial implications of the recommendations, implementation of which might increase pacing budgets by up to 75%.[13] For whatever reason, it is clear that the BPEG recommendations have not been universally adopted in the United Kingdom[14] and there is evidence of agism, with the preferential use of optimal pacing modes only in younger patients.[15]

General principles of pacemaker mode selection

- The ventricle should be paced if there is actual or threatened atrioventricular block.
- The atrium should be paced/sensed unless contraindicated.
- Rate response is not essential if the patient is inactive or has a normal chronotropic response.
- Rate hysteresis may be valuable if the bradycardia is intermittent.

Based on recommendations of a working party of the British Pacing and Electrophysiology Group[11]

Against this background, it is pertinent to review the evidence concerning the indications for pacing and pacemaker mode selection in order fully to comprehend the basis for rational, evidence-based pacing practice. It is important to note that there have been no randomized trials to assess the efficacy of pacing in the treatment of symptomatic AV block. The absence of any satisfactory alternative therapy and the overwhelming evidence of symptom relief from observational studies over four decades render such a trial unethical and unnecessary. In the assessment of new indications for pacing and alternative pacing modes, however, observational data require critical evaluation and, where inconclusive, should be supplemented by data from carefully designed clinical trials.

Conventional indications for pacing

The principal indication for cardiac pacing is to relieve or prevent symptoms associated with bradycardia. In high grade AV block, however, there is evidence that survival may also be improved by pacing, even in the absence of symptoms, and pacing should be considered on prognostic grounds alone.

The symptoms associated with bradycardia include manifestations of limited cardiac output (tiredness, exercise intolerance, breathlessness, edema or chest discomfort), relative cerebral ischemia (transient dizziness, light-headedness, presyncope or syncope), and uncoordinated cardiac contraction (palpitation, neck or abdominal pulsation). Where significant symptoms are clearly associated with documented bradycardia, the requirement for pacing will rarely be in doubt. In other contexts, the cause of symptoms may be unclear and it is important to note that the most common symptoms are non-specific and prevalent in the elderly population, even in the absence of bradycardia.

Remediable causes of bradycardia such as acute myocardial ischemia, electrolyte imbalance, hypothyroidism or drug toxicity should always be considered before proceeding to cardiac pacing. In some instances, drugs that depress sinus node function or AV conduction may be essential and pacing may be required to enable their continued use.

Table 42.1 ACC/AHA guidelines: indications for permanent cardiac pacing[10]

Condition	Class I	Class IIa	Class IIb	Class III
Acquired AV block (adults):				
First degree		First degree AV block with symptoms suggestive of "pacemaker syndrome" and alleviation of symptoms with temporary AV pacing **Grade B**	Marked first degree AV block (PR > 0·3 s) in patients with LV dysfunction and symptoms of CHF in whom a more physiologic AV interval results in hemodynamic improvement **Grade C**	Asymptomatic first degree AV block **Grade B**
Second degree	Second degree AV block (any type or level) with associated symptomatic bradycardia **Grade B**	Asymptomatic type I second degree block at intra- or infra-His levels found incidentally at EPS **Grade B** Asymptomatic type II second degree AV block **Grade B**		Asymptomatic type I second degree block at the supra-His (AV node) level **Grade B/C**
Third degree (CHB)	CHB associated with any of:	Asymptomatic CHB at any anatomic site, with average, awake, ventricular rates ≥40/min **Grade B/C**		AV block that is expected to resolve and is unlikely to recur (for example drug toxicity, Lyme disease) **Grade B**
	(a) Symptomatic bradycardia **Grade C** (b) Need for drugs causing symptomatic bradycardia **Grade C** (c) Documented asystole ≥3 s or escape rate <40/min in awake, symptom-free patients **Grade B/C** (d) Postablation of AV junction **Grade B/C** (e) Post operative AV block not expected to resolve **Grade C** (f) Neuromuscular disease (for example myotonic dystrophy) **Grade B**			
Chronic bifascicular or trifascicular block	Associated with intermittent CHB **Grade B**	Syncope not proven due to AV block when other likely causes, such as VT, have been excluded **Grade B**	None	Fascicular block with first degree AV block without symptoms **Grade B**
	Associated with type II second degree AV block **Grade B**	Incidental finding at EPS of markedly prolonged HV interval (<100 ms) in		Fascicular block without AV block or symptoms **Grade B**

Table 42.1 Continued

Condition	Class I	Class IIa	Class IIb	Class III
		asymptomatic patient **Grade B** Incidental finding at EPS of pacing induced infra-His block that is not physiologic **Grade B**		
AV block after the acute phase of myocardial infarction (MI)	Persistent second degree AV block in the His–Purkinje system with bilateral bundle branch block or third degree AV block within or below the His–Purkinje system after acute MI **Grade B** Transient advanced (second or third degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an EPS may be necessary **Grade B** Persistent and symptomatic second or third degree AV block **Grade C**	None	Persistent second or third degree AV block at the AV node level **Grade B**	Transient AV block in the absence of intraventricular conduction defects **Grade B** Transient AV block in the presence of isolated left anterior fascicular block **Grade B** Acquired left anterior fascicular block in the absence of AV block **Grade B** Persistent first degree AV block in the presence of bundle branch block that is old or age indeterminate **Grade B**
Sinus node dysfunction (SND)	SND with documented symptomatic bradycardia including frequent symptomatic sinus pauses (including iatrogenic bradycardia due to essential long term drug therapy with no acceptable alternative) **Grade C**	SND, occurring spontaneously or as a result of necessary drug therapy, with heart rates <40/min when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented **Grade C**	Chronic heart rates <30/min whilst awake, in minimally symptomatic patients **Grade C**	SND in asymptomatic patients, including those in whom substantial sinus bradycardia (<40/min) is due to long term drug treatment
Symptomatic chronotropic incompetence **Grade C**				SND in patients in whom symptoms suggestive of bradycardia are clearly documented not to be associated with a slow heart rate SND with symptomatic bradycardia due to non-essential drug therapy

Hypersensitive carotid sinus syndrome and neurally mediated syncope	Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3 s duration in the absence of any medication that depresses the sinus node or AV conduction **Grade C**	Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response **Grade C**	Neurally mediated syncope with significant bradycardia reproduced by head-up tilt with or without isoproterenol or other provocative maneuvers **Grade B**	Hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms
		Syncope of unexplained origin when major abnormalities of sinus node function or AV conduction are discovered or provoked at EPS		Vague symptoms, such as dizziness or light-headedness, or both, with a hyperactive cardioinhibitory response to carotid sinus stimulation Recurrent syncope, light-headedness or dizziness in the absence of cardioinhibitory response Situational vasovagal syncope in which avoidance behavior is effective
Tachycardia prevention	Sustained pause-dependent VT, with or without prolonged QT, in which the efficacy of pacing is thoroughly documented **Grade C**	High risk patients with congenital long QT syndrome **Grade C**	AV re-entrant or AV node re-entrant supraventricular tachycardia not responsive to medical or ablation therapy **Grade C** Prevention of symptomatic, drug refractory atrial fibrillation **Grade C**	Frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome Long QT syndrome due to reversible causes
Hypertrophic cardiomyopathy	Class I indications for sinus node dysfunction or AV block as above **Grade C**	None	Medically refractory, symptomatic hypertrophic cardiomyopathy patients with significant resting or provoked LV outflow obstruction **Grade C**	Asymptomatic or medically controlled patients
				Symptomatic patients without evidence of LV outflow obstruction
Dilated cardiomyopathy	Class I indications for sinus node dysfunction or AV block as above **Grade C**	None	Symptomatic, drug refractory dilated cardiomyopathy with prolonged PR interval when acute hemodynamic studies have demonstrated hemodynamic benefit **Grade C**	Asymptomatic dilated cardiomyopathy

Table 42.1 Continued

Condition	Class I	Class IIa	Class IIb	Class III
				Symptomatic dilated cardiomyopathy when patients are rendered asymptomatic by drug therapy
				Symptomatic ischemic cardiomyopathy
After cardiac transplantation	Symptomatic bradyarrhythmia or chronotropic incompetence that is not expected to resolve and meets other Class I indications for permanent pacing **Grade C**	None	Symptomatic bradyarrhythmia or chronotropic incompetence that, although transient, may persist for months and require intervention	Asymptomatic bradyarrhythmia postcardiac transplantation
Children and adolescents	Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia **Grade B**	Asymptomatic sinus bradycardia in a child with complex congenital heart disease where the resting heart rate is <35/min or ventricular pauses >3 s occur **Grade C** Bradycardia–tachycardia syndrome needing chronic antiarrhythmic therapy other than digitalis **Grade C**	Asymptomatic sinus bradycardia in an adolescent with congenital heart disease where the resting heart rate is <35/min or ventricular pauses >3 s occur **Grade C**	Asymptomatic sinus bradycardia in an adolescent where the longest R–R interval is <3 s and the minimum rate >40/min **Grade C**
	Advanced second or third degree AV block associated with symptomatic bradycardia, CHF or low cardiac output **Grade C**			Asymptomatic type I second degree AV block **Grade C**
	Congenital CHB with a wide QRS escape rhythm or ventricular dysfunction **Grade B**	Congenital CHB, beyond the first year of life, with an average heart rate <50/min, or with abrupt ventricular pauses two or three times the basic cycle length **Grade B**	Congenital CHB in an asymptomatic neonate, child or adolescent with an acceptable rate, narrow QRS complex and normal ventricular function **Grade B**	
	Congenital CHB in the infant with a ventricular rate <50–55/min or with congenital heart disease and a ventricular rate <70/min **Grade B/C**			

	Postoperative advanced second or third degree AV block that is not expected to resolve, or persists at least 7 days after cardiac surgery **Grade B/C**		Transient postoperative CHB that reverts to sinus rhythm with residual bifascicular block **Grade C**	Transient postoperative AV block with return of normal AV conduction within 7 days **Grade B**
		Long QT syndrome with 2:1 or third degree AV block **Grade B**		Asymptomatic postoperative bifascicular block, with or without first degree AV block **Grade C**
	Sustained pause-dependent VT, with or without prolonged QT, in which the efficacy of pacing is thoroughly documented **Grade B**			

Abbreviations: CHB, complete heart block; CHF, congestive heart failure; EPS, electrophysiology study; VT, ventricular tachycardia

Based on Gregoratos *et al.*[10]

Table 42.2 Recommended pacemaker modes

Diagnosis	Optimal	Alternative	Inappropriate
SND	AAIR	AAI	VVI/VDD
AVB	DDD	VDD	AAI/DDI
SND+AVB	DDDR/DDIR	DDD/DDI	AAI/VVI
Chronic AF+AVB	VVIR	VVI	AAI/DDD/VDD
CSS	DDI	DDD/VVI+hysteresis	AAI/VDD
MVVS	DDI	DDD	AAI/VVI/VDD

AF, atrial fibrillation; AVB, atrioventricular block; CSS, carotid sinus syndrome; MVVS, malignant vasovagal syndrome; SND, sinus node disease

Interpretation of mode acronyms:

First letter:	Chamber(s) paced	A, atrium; V, ventricle; D, atrium and ventricle
Second letter:	Chamber(s) sensed	A, atrium; V, ventricle; D, atrium and ventricle
Third letter:	Response to sensing	I, inhibition; T, triggering; D, inhibition and triggering
Fourth letter:	Additional functions	R, adaptive rate

Based on recommendations of the British Pacing and Electrophysiology Group[11]

The most common causes of bradycardia requiring pacing are impaired impulse formation, as in sinus node disease, or a disturbance of cardiac conduction, as in AV block. In the United Kingdom, sinus node disease accounts for about 45% of primary implants and AV block or other conduction disturbance for about 50%.[14] The remainder includes patients paced for a variety of conditions, including carotid sinus syndrome, cardio-inhibitory forms of neurocardiogenic syncope and others. The pattern is different in the United States, where sinus node disease accounts for about 50% of primary implants and AV block for about 38%.[5] The reasons for this disparity are unclear but it may reflect different perceptions regarding the indications for pacing.

Atrioventricular block

First degree AV block

Isolated prolongation of the PR interval may be seen as a normal variant in healthy young subjects. In this context, it is most likely due to autonomic influences and has no prognostic significance.[16] In older subjects, PR prolongation is more often associated with underlying pathology, such as conducting system fibrosis or coronary artery disease but it does not usually give rise to symptoms and pacing is not generally indicated.

Occasionally, however, symptoms may arise if the PR interval is markedly prolonged. Atrial systole may then closely follow delayed ventricular systole from the previous cycle, resulting in a comparable hemodynamic disturbance to that seen in the pacemaker syndrome caused by retrograde VA conduction during ventricular pacing. The phenomenon may be accentuated during exercise as the atrial rate increases and the PR interval fails to shorten appropriately. This has been referred to as the "pacemaker syndrome without a pacemaker"[17] or the "pseudo-pacemaker syndrome"[18] and a favorable response to dual chamber pacing has been reported.[19] In symptomatic patients with first degree AV block, the response to temporary dual chamber pacing should be assessed. If clinical and hemodynamic improvement can be demonstrated by restoration of a physiologic AV interval, permanent dual chamber pacing should be considered.[20,21] Symptomatic first degree AV block with a demonstrable improvement during temporary dual chamber pacing may reasonably be considered at least a Class II[20] and perhaps even a Class I[21] indication for pacing. **Grade B**

Second degree AV block

When second degree AV block of any type is associated with clearly attributable symptoms, pacing is indicated. In the absence of symptoms, the situation is more complex. Prognosis is thought to relate to the site of block, proximal block at the level of the AV node being more benign than distal block in the His–Purkinje system.[22] The ECG classification into Mobitz type I (Wenckebach), Mobitz type II or advanced (2:1, 3:1 or 4:1) second degree AV block is purely descriptive and the site of block cannot always be inferred although electrophysiologic studies have shown that type I block is most commonly proximal whereas type II block is almost always distal.[23] In the past, type I second degree AV block has often been regarded as benign but evidence from the Devon Heart Block and Bradycardia Survey in the United Kingdom[24] suggests that, even in asymptomatic patients, survival is significantly improved by pacing. Although this was a non-randomized, observational study, it constitutes the best available evidence and published opinion suggests that

pacing should be considered in asymptomatic type I second degree AV block, particularly in older patients with structural heart disease.[25,26] In young subjects, however, asymptomatic type I second degree AV block occurring during sleep or associated with athletic training is more likely to reflect high resting vagal tone and pacing is unnecessary.[27,28] **Grade B**

Complete AV block

In symptomatic complete AV block, pacing usually, although not invariably, improves the symptoms and should always be considered. Irrespective of symptoms, however, untreated acquired complete heart block is associated with significantly impaired survival. Overall mortality may exceed 50% at one year, the outlook being worst in older patients (>80 years) and those with associated non-rheumatic structural heart disease.[29] Male sex and a history of syncope have also been associated with a worse outlook in some studies[30] but there is conflicting evidence regarding syncope.[31] Transient AV block carries a more favorable prognosis, with a 1 year mortality of 36%, compared with 70% in patients with permanent AV block,[29] but a significant proportion of patients (38–39% over median follow up of 36–54 months) progress to permanent AV block and become pacemaker-dependent when paced.[32]

Observational studies of outcome in paced patients during the early days of cardiac pacing suggested that pacing in complete AV block could improve survival to approach that of a similar age- and sex-matched group.[30] Mortality was higher in those with a history of myocardial infarction but not influenced by pre-pacing QRS duration or morphology, ventricular rate (dichotomized about 40/min) or whether AV block was intermittent or constant.[33] In a more recent study of patients aged ≥65 years, paced for symptomatic, high grade AV block, overall survival was less than expected for an age- and sex-matched cohort.[34] However, in patients aged <80 years without structural heart disease, survival was normal. Congestive heart failure, chronic obstructive pulmonary disease, age, syncope, insulin-dependent diabetes and male gender emerged as independent predictors of increased mortality. There have been no prospective randomized trials to assess the impact of pacing on survival but the high mortality of untreated complete AV block, the prevalence of symptoms, and the strength of the data from observational studies suggest that such a trial is neither ethical nor necessary. The vast majority of patients with complete AV block should be paced, whether or not they have symptoms. **Grade B**

Congenital complete AV block

The natural history and management of congenital complete AV block in infancy and childhood is beyond the scope of this review. In patients surviving to adulthood, the prognosis has previously been regarded as benign, based largely on retrospective studies of small series of patients.[35] More recent data concerning long-term follow up (7–30 years) of 102 patients with isolated congenital complete AV block, who survived without symptoms to the age of 15 years, suggest a less favorable outlook.[36] Stokes–Adams attacks occurred in 27 patients, of whom eight died (six during the first attack) and six others required cardiac resuscitation. All survivors received pacemakers. A further eight patients had repeated fainting spells requiring pacing and 27 others were paced for other reasons (fatigue, effort dyspnea, dizziness, ectopics during exercise, mitral regurgitation or slow ventricular rates). Of 40 patients followed for 30 years, only four remained asymptomatic without pacing. The only significant predictor of risk was QTc prolongation, which was seen in seven patients, all of whom had Stokes–Adams attacks and three of whom died. In contrast to previous studies, low ventricular rates, widened QRS complexes, poor chronotropic response to exercise and ectopics were not predictive of future Stokes–Adams attacks or death. These data appear to support the authors' recommendation of prophylactic pacing in adolescents and adults with congenital complete AV block, even without symptoms, notwithstanding the fact that a number of questions remain unanswered.[37] **Grade B**

Fascicular block

In asymptomatic subjects with unifascicular block (right bundle branch block, left anterior hemiblock or left posterior hemiblock), the risk of progression to high grade AV block is remote[38] and pacing is not indicated. In asymptomatic bifascicular block (left bundle branch block or right bundle branch block with left anterior or posterior hemiblock), the risk of progression to high grade AV block is in the region of 2% per annum. Prognosis is principally determined by the presence or absence of underlying structural heart disease and prophylactic pacing is not routinely indicated.[39] Progression to high grade AV block is more commonly seen in patients with a history of syncope but should not be presumed to be the cause without further assessment. If high grade AV block is documented, pacing is mandatory. When the cause of syncope remains unclear, an electrophysiology study may help to identify patients likely to benefit from pacemaker implantation. A prolonged HV interval >100 ms and His–Purkinje block during atrial pacing have high specificity for prediction of subsequent progression to high grade AV block.[40,41] Unfortunately, these are rare findings and thus of low sensitivity. Less marked HV prolongation (>70 ms) is more common but its significance is uncertain.[42] Sensitivity for disclosure of latent high grade AV block may be markedly enhanced by the use of intravenous disopyramide during the study but this is not advised in patients with impaired left ventricular function.[43] The electrophysiology study may also be of value to identify inducible ventricular tachycardia, which is a relatively

common finding in patients with bundle branch block and a history of syncope.[44] This argues strongly against the empiric use of permanent pacing in this context. However, in patients with bifascicular block and a history of syncope for which no other cause is apparent despite thorough evaluation, including an electrophysiology study, empiric pacing may be the most expeditious course. This strategy is principally justified for relief of symptoms as pacing does not appear to influence mortality or the incidence of sudden death in this context.[39] **Grade B**

Atrioventricular and bundle branch block after myocardial infarction

Transient conduction disturbance is a relatively common complication of acute myocardial infarction. The acute management and indications for temporary cardiac pacing are beyond the scope of this review and will not be considered further. The long-term prognosis is principally determined by the extent of myocardial injury. When AV block complicates inferior myocardial infarction, it typically resolves within a few days and rarely persists beyond 2 or 3 weeks. In anterior infarction, however, AV block may reflect extensive septal necrosis and the prognosis is poor despite pacing.[45] Patients with high grade AV block persisting for more than 3 weeks after myocardial infarction should be considered for permanent pacing.

The occurrence of an intraventricular conduction disturbance (apart from isolated left anterior hemiblock) in patients with acute myocardial infarction identifies a group with poor short-term and long-term prognosis and an increased risk of sudden death.[46] The poor prognosis in this group, however, is mainly attributable to a high incidence of malignant ventricular arrhythmia, pump failure, and electromechanical dissociation, rather than progressive conduction disturbance. A prospective study of 50 patients randomized to pacing or control groups and followed for 5 years showed no significant difference in survival.[47] However, evidence from a retrospective multicenter study of patients with bundle branch block complicating myocardial infarction, indicates that transient high degree AV block during the acute phase is associated with a high incidence of recurrent AV block and sudden death that may be reduced by pacemaker implantation.[48,49] The risk appears to be particularly high in patients with right bundle branch block and left anterior hemiblock.[49,50] **Grade B**

Sino-atrial disease

Sino-atrial disease encompasses a wide spectrum of arrhythmia including sinus bradycardia, sinus arrest, sino-atrial block, sick sinus syndrome and the tachycardia–bradycardia syndrome in which paroxysmal atrial tachyarrhythmia alternates with bradycardia. The prognosis in sino-atrial disease is generally good unless myocardial ischemia, heart failure or systemic embolism are present.[51] Permanent pacing is indicated for the relief of symptoms that are due to bradycardia. Every effort should be made to establish a causal relationship by recording an ECG during symptoms although this may not always be possible. Occasionally, drugs needed to control tachyarrhythmia may cause or exacerbate bradycardia and pacing may be required to facilitate their continued use.

The first and only randomized trial to assess the efficacy of pacing in sick sinus syndrome has recently been reported.[52] One hundred and seven patients with symptomatic sick sinus syndrome were randomized to receive either no treatment, oral theophylline or permanent DDDR pacing. Patients were excluded in very severe cases, defined as symptomatic resting sinus rate <30/min, sinus pauses >3 s or heart failure refractory to treatment with ACE inhibitors and diuretics. During a mean follow up period of 19 months, both pacing and theophylline were associated with a lower incidence of heart failure compared with the untreated patients (3%, 3% and 17% respectively) but only pacing was associated with a significantly lower incidence of syncope (6%, 17% and 23% respectively). It is noteworthy that 14 of the 16 patients who were syncopal during follow up had a history of syncope at randomization. During follow up, 51% of patients in the control group and 42% in the theophylline group were withdrawn from the study due to syncope, overt heart failure, poorly tolerated paroxysmal tachyarrhythmia, patient wishes or drug side effects. There were no significant differences in NYHA class or symptom scores (fatigue, dizziness, and palpitation) between the groups either at baseline or after 3 months. The untreated controls showed subjective improvement, with a significant reduction of dizziness and a trend towards decreased fatigue. These findings were associated with significant increases in resting, mean and maximum heart rates, emphasizing the unpredictable natural history of the condition and the possibility of spontaneous improvement. Pacing remains the treatment of choice for patients with symptomatic sick sinus syndrome. In the absence of long-term follow up data to confirm efficacy and safety, theophylline or other pharmacologic means of chronotropic support cannot be recommended. **Grade A**

Pacing does not appear to improve survival in sino-atrial disease[53] and it is not generally indicated in asymptomatic patients. Such patients, however, should be followed closely to assess progression. Athletically trained subjects may have sinus rates as low as 30/min during sleep with pauses of almost 3 s.[54] These findings usually reflect high vagal tone and do not require pacing in the absence of symptoms. If lower rates or longer pauses are observed during sleep or if similar findings occur during the day, particularly if there is evidence of progression with time, prophylactic pacing may be justified on empiric grounds although there are no supportive data. **Grade B/C**

Mode selection in AV block and sinus node disease

AV block

The essential requirement in AV block is that the ventricle be paced. When sinus rhythm and chronotropic competence are preserved, dual chamber pacing with atrial tracking will ensure the maintenance of AV synchrony and physiologic rate adaptation. When sinus rhythm is absent or when chronotropic incompetence is present, an extrinsic sensor may be used to provide rate adaptation with either ventricular or dual chamber pacing, as appropriate.

Both dual chamber pacing[55–57] and adaptive rate single chamber pacing[58–60] have been shown to offer benefits in terms of improved hemodynamics, increased treadmill exercise tolerance and reduced symptoms when compared with single rate ventricular pacing in small randomized crossover trials. The mean patient age in most of these trials was younger than the typical paced population but similar benefits have recently been reported in patients aged 75 years or over.[61] Nonetheless, the long term clinical benefit of physiologic pacing in the elderly has been questioned.[12] Quality of life studies have yielded conflicting results although physiologic pacing does appear to offer advantages in terms of symptoms and there is considerable evidence of patient preference for physiologic modes.[62] Single chamber ventricular pacing is associated with an increased risk of pacemaker syndrome. The true incidence of this complication is unknown but estimated to be between 7 and 20%.[2] It has, however, been suggested that a subclinical form may be present in many apparently asymptomatic patients.[63] Data from a retrospective review of outcome in patients paced single or dual chamber has suggested that dual chamber pacing may confer a survival advantage in a subset of patients with congestive heart failure.[64] A more recent case–control study has confirmed this finding but showed no difference in overall survival.[65]

Sinus node disease

In isolated sino-atrial disease, rate support can be achieved by atrial, ventricular or dual chamber pacing. Small crossover studies comparing ventricular with dual chamber pacing have reported less favorable hemodynamics, worse symptomatology, and an increased risk of pacemaker syndrome.[62,66–68] Numerous retrospective studies also suggest that ventricular pacing is associated with an increased risk of atrial fibrillation, heart failure, and thromboembolism.[51,69] There is also evidence of increased mortality in ventricular paced patients.[70] Attention has been drawn to the confounding effect of selection bias on data derived almost exclusively from retrospective studies and the need for prospective randomized trials has been stressed.[71] A number of such trials have recently been completed and others are ongoing. These will be considered in the next section.

Randomized trials of pacemaker mode selection

The Danish Study

The first prospective randomized trial of pacemaker mode selection was reported from Denmark in 1994.[72] In this study, 225 patients with sick sinus syndrome were randomized to either AAI or VVI pacing and followed for a mean of 3·3 years. Neither the incidence of atrial fibrillation or stroke nor survival differed significantly between the two groups, although the incidence of a combined end point of stroke plus peripheral embolism was significantly lower in the atrial paced group. Only two of 115 patients in the VVI group required upgrade for severe pacemaker syndrome. Extended follow up of the same group of patients after a mean period of 5·5 years has subsequently been reported.[73] The previously identified benefits of atrial pacing were enhanced, with a significantly lower incidence of atrial fibrillation, thromboembolism and heart failure in the atrial paced group. All-cause mortality and mortality due to cardiovascular causes were also significantly lower in the atrial paced group. After adjustment for other pre-implant variables, there was a significant association between ventricular pacing and cardiovascular death but only a non-significant trend towards increased overall mortality. Only four of 110 patients in the atrial paced group developed second or third degree AV block, requiring pacemaker upgrade (0·6% per annum). Of these, two had right bundle branch block at the time of implant (as did four others in the atrial paced group who did not develop AV block). AV conduction, estimated as PQ interval and atrial stimulus-Q interval at atrial pacing rates of 100 and 120 min^{-1} remained stable during follow up.[74]

The Pacemaker Selection in the Elderly (PASE) Study

This trial randomized 407 patients, aged 65 or older (mean age 76 years), to ventricular or dual chamber pacing.[75] This was a *mode* randomization and all patients received DDDR pacing systems. The group included 175 patients with sinus node disease, 201 patients with AV block and 31 patients with other diagnoses. The study was powered to assess differences in health-related quality of life. As would be expected, there was marked improvement in quality of life (SF-36) after pacemaker implantation but there were no significant differences between groups in relation to pacing mode. Analysis of prespecified subgroups showed modest benefits in some quality of life domains and cardiovascular functional status (Specific Activity Scale) favoring dual chamber pacing in patients with sinus node disease. Similarly, there were trends of borderline statistical significance in clinical outcomes favoring dual chamber pacing in patients with sinus node disease but not in those with AV block (mean follow up 18 months). It is noteworthy that 26% of the patients randomized to ventricular pacing

crossed over to dual chamber pacing because of symptoms attributed to pacemaker syndrome. Whilst potentially significant in itself, the high crossover rate confounds interpretation of the data, particularly in respect of clinical outcomes. The investigators reviewed the clinical, hemodynamic and electrophysiological data in the group randomized to VVIR pacing, to determine what factors might predict intolerance of VVIR pacing sufficient to prompt crossover to the DDDR mode. In a multivariate analysis, a decrease in systolic blood pressure to <110 mmHg during ventricular pacing at the time of pacemaker implantation ($P=0{\cdot}001$), use of β blockers at the time of randomization ($P=0{\cdot}01$) and non-ischemic cardiomyopathy ($P=0{\cdot}04$) were the only variables that predicted crossover.[76]

The Canadian Trial of Physiologic Pacing (CTOPP)

In the largest trial reported to date, 2568 patients aged 18 years or older (mean age 73 years), with either AV block or sinus node disease, were randomized to receive either a ventricular (VVI/R) or a physiologic pacemaker.[77] In the physiologic arm, the investigator was allowed to choose either an atrial (AAI/R) or dual chamber (DDD/R) system. Adaptive rate pacing was used in both groups if chronotropic incompetence was evident and in patients with complete AV block randomized to receive ventricular pacing. Approximately 60% of patients had AV block and 40% had sinus node disease. Over a mean follow up of 3 years there was no significant difference in the primary outcome of cardiovascular death or stroke (VVI/R 5·5% per annum *v* physiologic 4·9% per annum; relative risk reduction *c* 9·4%; 95% CI 10–25·7; $P=0{\cdot}33$). Neither was there any significant difference in all-cause mortality or inhospital admission for heart failure. There was, however, a significant, albeit modest, reduction in atrial fibrillation (defined as an episode lasting more than 15 minutes) associated with physiologic pacing (VVI/R 6·6% per annum *v* physiologic 5·3% per annum; relative risk reduction 18·0%; 95% CI 0·3–32·6; $P = 0{\cdot}05$), the difference starting to emerge after 2 years' follow up. The difference was greater in respect of chronic atrial fibrillation, which was defined as AF still present 1 week after the index episode (VVI/R 3·84% per annum *v* physiologic 2·80% per annum; relative risk reduction 27·1%; 95% CI 5·5–43·6; $P = 0{\cdot}016$).[78] Perioperative complications were more common with physiologic pacing (VVI/R 3·8% *v* physiologic 9·0%; $P<0{\cdot}001$) mainly in relation to the pacing lead(s). There was no difference in functional capacity, assessed by a 6 minute walk test at 6 month follow up, even in those patients (*c* 37%) who were pacemaker dependent.[79] The investigators attempted to identify baseline characteristics that might predict benefit from physiologic pacing on the risk of stroke or death due to cardiovascular causes. There was a trend suggesting that younger patients (<74 years) might benefit from physiologic pacing.

Subgroup analysis of the CTOPP data suggests that the benefits of physiologic pacing may be influenced by pacemaker dependency.[80] This was assessed in 87% of the enrolled patients by recording the unpaced heart rate at the first follow up visit (2–8 months postimplant). In patients with unpaced heart rates $\leq 60\,\text{min}^{-1}$, the incidence of cardiovascular death or stroke was lower with physiologic pacing (VVI/R 6·4% per annum *v* physiologic 4·1% per annum; relative risk reduction 35·5%; 95% CI 12–53). By contrast, the treatment effect of physiologic pacing was slightly negative in patients with unpaced heart rates $>60\,\text{min}^{-1}$ (VVI/R 4·1% per annum *v* physiologic 4·3% per annum; relative risk reduction −1·9%; 95% CI 50–31). The difference in treatment effect between the two groups was of only borderline significance ($P=0{\cdot}058$) but the fact that the 95% confidence interval in the group with unpaced heart rates $\leq 60\ \text{min}^{-1}$ does not include zero, suggests a qualitative interaction between treatment effect and pacemaker dependency in respect of the primary outcome. Significant subgroup effects were also observed for the outcomes of cardiovascular death and total mortality but not for stroke/emboli or hospitalization for congestive heart failure. Although the reduction in relative risk of atrial fibrillation with physiologic pacing was larger in the group with unpaced heart rates $\leq 60\,\text{min}^{-1}$ than in the group with unpaced heart rates $>60\,\text{min}^{-1}$, the difference was not statistically significant ($P=0{\cdot}22$) due to a modest reduction in the latter group.

A quality of life substudy in 269 patients also showed the influence of pacemaker dependency.[81] Quality of life, assessed by a disease specific instrument, the Quality of Life Assessment Package (QLAP), and the generic SF-36, improved between implant and 6 month follow up. The improvement was similar in patients with ventricular and physiologic pacing when all subjects were considered. However, when only pacemaker-dependent subjects were considered, improvements were greater with physiologic than with ventricular pacing although the difference was only detected with the disease specific QLAP and not with the generic SF-36.

The Mode Selection Trial (MOST)

This large trial was designed to assess the benefits of rate adaptive, dual chamber pacing compared with rate adaptive, single chamber, ventricular pacing in patients with sick sinus syndrome.[82,83] Two thousand and ten patients aged ≥21 years were implanted with a DDDR pacing system and the pacing mode was randomized to VVIR or DDDR. The primary end point was death or non-fatal stroke. Secondary outcomes included health-related quality of life and cost effectiveness, atrial fibrillation and the development of pacemaker syndrome. During a median follow up of

33·1 months, there was no significant difference in the incidence of death (VVIR 21%; DDDR 20%) or stroke (VVIR 5%; DDDR 4%). However, the DDDR group did have a lower incidence of atrial fibrillation (VVIR 27%; DDDR 21%). Heart failure scores were also significantly improved but this did not result in a lower incidence of hospitalization for heart failure (VVIR 12%; DDDR 10%). Quality of life (assessed by the SF-36 questionnaire) was significantly better in the DDDR group. Crossover from VVIR to DDDR mode occurred in 31·4% (18·3% for pacemaker syndrome).

The Pacemaker Atrial Tachycardia (PAC-A-TACH) Trial

The Pacemaker Atrial Tachycardia (PAC-A-TACH) trial assessed the effect of pacing modality on atrial tachyarrhythmia recurrence in patients with the tachycardia–bradycardia syndrome.[84] This was a mode randomization study in 198 patients (median age 72 years), all of whom received dual chamber, rate adaptive pacemakers programmed to either VVIR or DDDR pacing. After a median of 23·7 months follow up, 44% of patients crossed over from VVIR to DDDR (due to pacemaker syndrome in 28% and atrial tachyarrhythmia in 13%) and 9% crossed over from DDDR to VVIR (due to recurrent atrial tachyarrhythmia in 7% and atrial lead problems in 2%). Intention-to-treat analysis showed no significant difference in atrial tachyarrhythmia recurrence rates at 1 year (VVIR 43%; DDDR 48%; $P = 0{\cdot}09$). Quality of life was assessed at randomization and at 6 month follow up using the Duke Activity Status Index and SF-36. Perhaps unsurprisingly, in view of the high crossover rate, there was no significant difference between the groups at 6 months in either intention-to-treat analysis or on-treatment analysis of those patients remaining in randomized mode.[85] Mortality, a secondary outcome, was noted to be significantly higher in the VVIR group and the trial was stopped after follow up of approximately 2 years in all patients. Cumulative mortality was 21% in the VVIR group and 5% in the DDDR group ($P < 0{\cdot}001$). Pacing mode (risk ratio 4·3; 95% CI 1·6–11·4; $P = 0{\cdot}004$) and prior history of MI (risk ratio 3·1; 95% CI 1·4–6·7; $P = 0{\cdot}006$) were identified as independent predictors of mortality.[86]

Ongoing trials

Three additional mode selection trials are ongoing. The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial aims to compare the clinical impact and cost utility of single and dual chamber pacing in elderly patients (≥70 years) with high-grade AV block.[87] Two thousand and twenty-one patients have been randomized to receive either single (randomly assigned to VVI or VVIR) or dual chamber pacemakers. The primary end point is all-cause mortality. Secondary outcomes include quality of life, exercise capacity, cardiovascular events and cost utility. Follow up is for a minimum of 3 years and will conclude in September 2002.

The Systematic Trial of Pacing to Prevent Atrial Fibrillation (STOP-AF) aims to assess the ability of physiologic pacing to prevent atrial fibrillation in patients aged ≥18 years with sick sinus syndrome.[88] All patients are implanted with a dual chamber pacemaker and randomized to programming in either atrial-based (AAI or DDD) or ventricular pacing modes Recruitment was closed after 227 patients had been enrolled.[89] The study, which uses sequential trial methodology to allow greater power with a limited sample size, includes an adaptive rate arm for patients with chronotropic incompetence. The primary end point is permanent atrial fibrillation resistant to DC cardioversion. Secondary outcomes include congestive heart failure, pacemaker syndrome, change of mode for lead problems, and death.

The DANPACE study aims to examine the relative merits of single lead atrial pacing (AAIR) and dual chamber pacing (DDDR) in 1900 patients aged ≥18 years with sick sinus syndrome with bradycardia (including tachycardia–bradycardia syndrome).[90] The primary outcome measure will be all-cause mortality. Secondary outcomes will include cardiovascular mortality, atrial fibrillation, thromboembolism, quality of life and economic evaluation. Recruitment is scheduled to be completed by December 2005, with follow up to December 2007.

Comment and recommendations

The results of the prospective randomized trials that have been reported to date, suggest that the clinical benefits of physiologic or dual chamber pacing may previously have been overstated. There is, however, consistent evidence of a modest but significant reduction in atrial fibrillation, particularly in its chronic form. It might be anticipated that this would translate, over time, into a lower incidence of stroke, thromboembolism and death. This was observed in the extended follow up of the Danish study but not in PASE, CTOPP or MOST. It may be relevant that significant differences in the occurrence of atrial fibrillation only occurred after 2 years in CTOPP, suggesting that the mean 3 year follow up may have been insufficient for differences in these other outcomes to emerge. For this reason, the CTOPP investigators embarked on an extended follow up for an additional 3 years, which concluded during 2001. The preliminary results show a persistent reduction of AF with physiologic pacing (20·1% relative risk reduction; $P = 0{\cdot}009$) but no difference in cardiovascular death, stroke or total mortality after a mean follow up of 6 years.[91]

When considering sinus node disease, it is important to note that the Danish study was the only one to use single-lead atrial pacing as the sole physiologic comparator. PASE

and MOST used exclusively dual chamber devices and in CTOPP only 5·2% of the patients randomized to physiologic pacing received an atrial pacemaker. Preservation of synchronized left and right ventricular activation with atrial pacing may confer benefits that are not assured with dual chamber pacing, even when careful attention is given to optimal programming.[92] The presence of a, generally redundant, ventricular lead with dual chamber pacing might also be deleterious. The DANPACE study should ultimately provide the necessary data to clarify the relative merits of atrial and dual chamber pacing in sinus node disease.

With regard to quality of life, the advantage of physiologic pacing appears modest, as assessed by standard measures. However, interpretation of the data is complicated by the divergent estimates of mode intolerance, as judged by the investigator, between those trials in which the mode randomization was achieved by software programming (PASE, PAC-A-TACH and MOST) and those in which it was achieved by implantation of different hardware (the Danish study and CTOPP). Each design has strengths and weaknesses[93] but software randomization trials are more vulnerable to the effect of investigator bias. In the software randomization trials, crossover rates ranged from 26% to 44%, whereas in the hardware randomization trials, they did not exceed 5%. The significance of these disparities is uncertain. Further data will be forthcoming from the UKPACE trial, which includes detailed assessment of quality of life and the incidence of the pacemaker syndrome.

The completed and ongoing trials include a cumulative total of over 7000 patients. In order to determine the true value of physiologic pacing and to identify patient sub-groups that may derive particular benefit, a meta-analysis of the pooled data is being planned. The data presented to date, suggest a modest benefit in favor of dual chamber pacing, which must be weighed against a higher perioperative complication rate. Cost utility will be a further consideration that may influence mode selection and relevant economic data from CTOPP, MOST and UKPACE are awaited. **Grade A**

Pending the outcome of the ongoing trials and further analysis of those that have already reported, continued adherence to current guidelines (see Table 42.2) is recommended. Current guidelines[11] recommend the avoidance of single chamber ventricular pacing. In AV block, dual chamber pacing is the preferred mode, with rate adaptation if there is evidence of chronotropic incompetence. In sino-atrial disease, atrial-based pacing, in some form, is preferable. When AV conduction is intact, single chamber adaptive rate atrial (AAIR) pacing is regarded as the optimal mode, as it preserves both atrioventricular synchrony and a normal ventricular activation pattern. Retrospective analysis of pooled data from 28 studies has shown a low risk of subsequent AV block (0·6% per annum)[94] and this is supported by data from the Danish study.[74] Dual chamber pacing may thus be unnecessary for many patients[95] although some physicians prefer to implant a DDDR pacing system with programming to AAIR mode, a mode conversion option or AV search hysteresis.[96] When a single chamber atrial pacing system is proposed, assessment of AV conduction at the time of implant to ensure preservation of 1:1 conduction during atrial pacing at 140/min is customary and prudent. When AV block coexists with sino-atrial disease, dual chamber pacing in DDDR mode is recommended. In patients with a history of paroxysmal atrial tachyarrhythmia, DDI pacing is preferable to avoid rapid ventricular tracking. The recent introduction of mode-switching pacemakers capable of switching from DDD/DDDR to DDI/DDIR mode on detection of atrial tachyarrhythmia has offered an attractive alternative.

New indications for pacing

Neurocardiogenic syncope

Neurocardiogenic syncope describes the clinical syndromes of syncope resulting from inappropriate autonomic responses, manifested as abnormalities in the control of peripheral vascular resistance and heart rate.[97] It is thought to account for the largest proportion of faints in clinical practice. The most common forms are carotid sinus syndrome and vasovagal syncope but other related syndromes include cough, deglutition, and micturition syncope. The pathophysiologic mechanisms are not fully understood but carotid sinus massage[98,99] and tilt-table testing[100] have emerged as useful diagnostic tools in carotid sinus syndrome and vasovagal syncope respectively, enabling abnormal reflex responses to be categorized as cardioinhibitory (asystole >3s, bradycardia or AV block), vasodepressor (fall in systolic blood pressure >50 mmHg) or mixed. This has invited assessment of the utility of cardiac pacing which might be expected to benefit patients with predominantly cardioinhibitory or mixed responses.

Carotid sinus syndrome

Early reports of pacing in carotid sinus syndrome confirmed its efficacy in some patients but persistent symptoms were seen in those in whom there was a significant vasodepressor response or hypotension during ventricular pacing.[101] The latter was improved by AV sequential pacing and it was suggested that this was the appropriate mode in patients with mixed responses. Attention has been drawn to the variable natural history of the condition, which may remit spontaneously, and the importance of a control group when evaluating therapy has been emphasized.[102] A prospective randomized trial of pacing in patients with severe carotid sinus syndrome has subsequently been reported.[103] Sixty patients were randomized to pacing (VVI in 18 and DDD in 14 patients) or no therapy (28 patients). During a mean follow up of 36 months, syncope recurred in 16 (57%) of the non-paced group and in only three (9%) of the paced

group. Nineteen patients (68%) in the non-paced group were eventually paced because of the severity of symptoms. Pacing is now the treatment of choice in all but the mildest forms of carotid sinus syndrome. Recent evidence suggests that carotid sinus syndrome is underdiagnosed and that comprehensive assessment of patients presenting with syncope, dizziness or falls may identify a significant number of otherwise unrecognized patients who may benefit from pacing.[104]

In the Syncope And Falls in the Elderly – Pacing And Carotid sinus Evaluation (SAFE PACE) trial, 24 264 patients with falls or syncope were identified from a total of 71 299 emergency room attendees aged ≥50 years during a 29 month period.[105] Patients with evident extrinsic or medical explanations for falling and those with cognitive impairment were excluded, leaving a residuum of 3384 non-accidental fallers. Of these, 1624 consented to and underwent carotid sinus massage, yielding 257 patients with cardioinhibitory or mixed carotid sinus hypersensitivity. One hundred and seventy five patients (mean age 73 years) were randomized to pacing or no pacing and followed for one year, to test the hypothesis that dual chamber pacing, with a rate-drop response algorithm, might reduce the frequency of further falls. Paced patients were significantly less likely to fall (odds ratio 0·42; 95% CI 0·23–0·75) than controls. Syncope and injurious events were also less frequent in the paced group.

SAFE-PACE 2[106] is a larger scale, multicenter, randomized controlled trial that is currently in progress, to further evaluate the preliminary observations from SAFE PACE in a wider cultural setting. Patients are eligible if they have had two or more unexplained falls (± up to one syncopal episode) and if they have a cardioinhibitory response to carotid sinus massage. Two hundred and twenty six patients will be randomized to receive either a pacemaker or an implantable loop recorder with long-term diagnostic capability, which will clarify the relationship between symptoms and arrhythmia in the non-paced patients. The primary outcome is the number of patients who fall during a 2 year follow up period. Secondary outcomes include frequency of falls, dizziness and presyncope, health and mental status (as perceived by the patient and the informant), injury rates, use of healthcare facilities, hospital admission, change in residential circumstances and cognitive function.

Comment and recommendations

Recurrent syncope caused by carotid sinus hypersensitivity is a class I indication for pacing and recurrent syncope without clear provocative events and with CICSH is a class IIa indication for pacing (see Table 42.1). Further data are required to clarify the role of pacing in patients with a history of recurrent falls (without clear evidence of syncope) and CICSH. For the time being, it should be regarded as experimental and its use should be restricted to the confines of randomized clinical trials. **Grade A/C**

Vasovagal syndrome

Pacing has also been evaluated in the so-called "malignant" form of vasovagal syndrome, characterized by recurrent syncope with only brief or absent prodromal symptoms. Evidence from several studies using temporary pacing during tilt-table testing indicates that pacing rarely prevents vasovagal syncope. The limited efficacy of pacing reflects the fact that hypotension precedes the onset of bradycardia in most patients. However, dual chamber pacing does attenuate the evolution of the final and most extreme degrees of hypotension and may thereby prolong the symptomatic presyncopal period in selected patients with a documented cardioinhibitory component.[107] A retrospective review of 37 patients receiving predominantly dual chamber pacemakers, followed for a mean of 50·2 months, reported symptomatic improvement in 89% with 62% remaining free of syncope and 27% being completely asymptomatic. The collective syncopal burden was reduced from 136 to 11 episodes per year.[108] This was an uncontrolled study but a number of multicenter prospective randomized trials have subsequently been initiated.

The North American Vasovagal Pacemaker Study[109,110] randomized patients with a history of frequent syncope (≥6 lifetime episodes) and a positive (cardioinhibitory) tilt test to receive either DDI pacing with a pacemaker incorporating a specialized rate-drop sensing algorithm, or no pacing. The rate-drop sensing algorithm is designed to detect the characteristic pattern of onset of bradycardia that is seen in vasovagal syndrome. The fall in heart rate is typically more marked than occurs with natural diurnal fluctuation yet less precipitous than that seen at the onset of complete AV block or asystole. On detection of a characteristic rate drop, pacing commences with a high initial intervention rate that gradually decreases.[111] It had been intended to enroll 284 patients, but the North American study was stopped towards the end of a 2 year pilot phase (May 1997) due to substantial benefit in the paced group. By that time, 54 patients had been enrolled and randomized, in equal numbers, to receive pacing or no pacing. Syncope recurred in 22% of patients who were paced compared with 70% of those who were not. This corresponds to a relative risk reduction of 85·4% (95% CI 59·7–94·7; $2P = 0{\cdot}000022$). Mean time to syncope was 112 days in the paced patients and 54 days in the non-paced patients. There was, however, no significant effect on presyncope, which was reported by 63% of paced patients and 74% of non-paced patients. The relatively small study size, resulting from early termination, resulted in some imbalance in important baseline characteristics. For example, the median number of previous syncopal episodes (lifetime experience) was lower in the paced group than in the non-paced group (14 *v* 35) as was the median number of episodes in the previous year (3 *v* 6). However, the authors report that the relative risk reduction was essentially unchanged when the analysis was adjusted for differences in baseline variables.

The Vasovagal International Study (VASIS) Group has subsequently reported a multicentre European trial of similar design.[112] Forty-two patients with at least three syncopal episodes in the preceding 2 years and a positive cardio inhibitory response to tilt testing were randomized to DDI pacing with rate hysteresis ($n = 19$) or no pacing ($n = 23$). Recruitment was slower than anticipated and there appears to have been a bias towards the inclusion of more severely affected patients. Syncope recurred in only one (5%) of the paced patients but in 14 (61%) of the unpaced patients ($P = 0{\cdot}0006$). The median time to first syncope in the unpaced group was 5 months.

The Syncope Diagnosis and Treatment (SYDIT) study assessed the relative efficacy of dual chamber pacing with a rate-drop sensing algorithm and pharmacologic therapy with atenolol.[113] Patients were eligible if they had at least three syncopal episodes in the preceding 2 years and a positive response to tilt testing (syncope with relative bradycardia). The study was terminated after 93 patients had been enrolled, as an interim analysis showed a significant effect in favor of pacing. Syncope recurred in only 4·3% of the paced group (after a median of 390 days) compared with 25·5% of the pharmacologically treated group (after a median of 135 days), giving an odds ratio of 0·133 (95% CI 0·028–0·632; $P = 0{\cdot}004$).

Less encouraging results have recently been presented from the second Vasovagal Pacemaker Study (VPS II).[114] The inclusion criteria were similar to those of the first VPS but in contrast to both that study and VASIS, it was double blinded. All patients received a pacemaker and were randomized to DDD pacing with a rate-drop response algorithm ($n = 48$) or no pacing (ODO mode) ($n = 52$). During a 6 month follow up, syncope recurred in 30% of the paced group, compared with 40% of the non-paced group. This equates to a relative risk reduction of 28·7% but the difference was not statistically significant (one-sided $P = 0{\cdot}153$). However, the event rate in the non-paced group was lower than expected and the study thus lacked sufficient power to draw a firm conclusion.

Comment and recommendations

The impressive results from the first VPS, VASIS and SYDIT studies require cautious interpretation. Enrolled patients had a substantial burden of previous syncope and a positive tilt-test with syncope (or presyncope) and relative bradycardia. There was, in addition, a suggestion of selection bias towards more severely affected and older patients. The applicability of the results to less severely affected patients and those of younger age is uncertain and these concerns are highlighted by the inconclusive results of VPS II. The accumulated data do, however, suggest that pacing should be considered in patients with severe symptoms refractory to conservative measures and drug therapy. The contrasting results of the second VPS raise the possibility of a placebo effect associated with the pacemaker implantation procedure in the earlier trials. Further clarification of the role of pacing may come from the Vasovagal Syncope and Pacing (SYNPACE) trial, in which every patient will receive a pacemaker and then be randomized to pacing "on" or "off" until the first recurrence of syncope or the end of follow up (at least 12 months).[115] Further data are also required to clarify the relative efficacy of pharmacologic therapy, such as β blockers, disopyramide, scopolamine, alpha agonists, selective serotonin reuptake inhibitors and others, which although largely disappointing, have been of benefit to some patients.[116] **Grade A**

Hypertrophic cardiomyopathy

The ability of pacing at the right ventricular apex to reduce the left ventricular outflow tract (LVOT) gradient in patients with hypertrophic obstructive cardiomyopathy has been recognized for over 30 years.[117] The benefits are thought to be due to eccentric or abnormal activation of the septum which may increase the LVOT diameter and decrease systolic anterior movement of the mitral valve during systole. A resurgence of interest was prompted by the development of sophisticated dual chamber pacemakers able to optimize ventricular filling by preservation of AV synchrony and maximize ventricular capture by the programming of a short AV delay. In some cases, drug therapy or ablation of the AV node may be required to prolong intrinsic AV conduction for maintenance of optimal LA-LV timing, whilst permitting maximal right ventricular pre-excitation by pacing.

Initial clinical studies showed encouraging results over the short and medium term with decreased symptoms and improved exercise capacity associated with reductions of LVOT gradient in the region of 60%.[118–121] An intriguing finding was the observation, in some series, of geometrical and functional changes, suggesting that left ventricular remodeling may occur after prolonged pacing. Decreased thickness of the anterior septum and the anterolateral wall of the left ventricle have been reported, with persistence of at least partial gradient reduction on pacemaker inhibition, for a period related to the duration of pacing.[122–124]

Three prospective randomized trials have subsequently been completed. All used a similar design with blinded crossover between active (DDD) and inactive (AAI backup at 30/min) pacing modes after 3 months.

A study performed at the Mayo Clinic[125] enrolled 21 patients with severe symptoms, refractory to drug therapy. The LVOT gradient decreased to a mean of 55 mmHg during DDD pacing, compared with 76 mmHg at baseline and 83 mmHg during the AAI phase. Quality of life scores and exercise duration during DDD pacing were significantly improved from baseline but not significantly different from those during the AAI phase. Overall, 63% of patients had symptomatic improvement during DDD pacing but 42% also improved during the AAI phase. In 5%, symptoms were worse during DDD pacing. The symptomatic improvement during the AAI

phase suggests that there is an important placebo effect associated with pacemaker implantation, underscoring the importance of randomized trials in assessing this form of treatment.

The European Pacing In Cardiomyopathy (PIC) study reported similar findings in a larger group of 83 similarly selected patients.[126] It was, however, a prerequisite for enrollment that patients had a reduction in peak pressure gradient of >30 mmHg during an acute trial of dual chamber pacing. LVOT gradient decreased to a mean of 30 mmHg during DDD pacing compared with 59 mmHg at baseline. Exercise duration was not significantly increased, except for a subgroup of patients with more severely limited exercise tolerance (<10 minutes of the Bruce protocol) during the inactive (AAI backup) phase. Dyspnea, angina and functional class improved during active pacing compared with the inactive phase and 95% of patients preferred pacing. A placebo effect was once again seen, with significant improvement in symptoms compared to baseline even during the inactive AAI backup phase.[126,127] Subsequent activation of pacing, however, resulted in significant improvement in symptoms and quality of life scores and, conversely, inactivation resulted in significant deterioration. Following the crossover phase, patients remained in their preferred mode for 6 months and were re-evaluated one year after the baseline assessment. Seventy-six patients opted for active pacing. The observed gradient reduction was sustained at 1 year, with further improvement in symptoms already favorably influenced and in some additional quality of life domains.[128,129]

The Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy (M-PATHY) randomized 44 patients (mean age 53 years) with severe refractory symptoms to 3 months each of active (DDD) and inactive (AAI backup at 30/min) pacing in a double-blind crossover study design.[130] After 6 months, all patients were offered an additional 6 months of active pacing in an uncontrolled and unblinded fashion. In the crossover phase, there were no significant differences in subjective or objective measures of symptoms or exercise capacity including NYHA functional class, quality of life, treadmill exercise time or peak oxygen consumption between active and inactive pacing. As in previous studies, however, many patients reported symptomatic improvement after pacemaker implantation suggesting a potent placebo effect. After 6 months of unblinded pacing, functional class and quality of life were improved compared with baseline ($P<0{\cdot}01$) but peak oxygen consumption was unchanged. Left ventricular outflow tract gradient decreased with active pacing from a mean of 82 mmHg to 48 mmHg ($P<0{\cdot}001$) but there was marked variability in response between patients. The gradient was decreased in 57% of patients but unchanged or increased in 43%. In contrast to reports from earlier studies, there was no evidence of remodeling as assessed by change in left ventricular wall thickness. Analysis of individual patient data showed that all of the six patients who completed the study and showed clinical benefit were aged 65 years or older.

Comment and recommendations

The role of dual chamber pacing in the management of patients with hypertrophic obstructive cardiomyopathy remains controversial. The accumulated data from the various studies suggest that pacing cannot be considered as primary or routine treatment. It may benefit some patients with significant symptoms refractory to drug therapy and obviate or delay the need for septal ablation or surgery but there is no evidence that it reduces the risk of sudden death or alters the long-term clinical course. A trial of pacing is certainly an option to consider in patients at high operative risk, particularly if elderly, before proceeding to surgery and in those for whom expert surgery is unavailable. Although some studies have shown a correlation of gradient reduction during temporary dual-chamber pacing with that observed during long-term follow up, the acute hemodynamic response is not a reliable predictor of symptomatic or functional improvement and temporary pacing studies are thus of little value in patient selection.[121,122,130] **Grade A**

Dilated cardiomyopathy

Conventional pacing

During the past decade, the use of dual chamber pacing in patients with heart failure but no bradyarrhythmic indication for pacing has been extensively explored. This was initially prompted by the suggestion that dual chamber pacing with a short AV delay might improve cardiac function in dilated cardiomyopathy by improving the relationship between atrial and ventricular systole, thereby decreasing presystolic, mitral and tricuspid regurgitation and increasing ventricular filling time.[131] Initial hemodynamic and clinical studies yielded encouraging results[132,133] but others failed to show any significant benefit.[134,135] It might be anticipated that patients with first-degree heart block would be most likely to benefit and this has been confirmed in hemodynamic[136] and short-term clinical studies.[137] Other criteria that may predict benefit from short AV delay pacing in this context include prolonged QRS duration, functional mitral regurgitation ≥450 ms, ventricular filling time <200 ms and early cessation of transmitral flow with concomitant diastolic mitral regurgitation on Doppler echocardiography.[138,139] During temporary pacing, responders will have an increase in systolic blood pressure and an increase in mitral regurgitation velocity (indicating a higher left ventricular systolic pressure and lower left atrial pressure), but despite these findings, the clinical outcome with pacing cannot be predicted with certainty.[139]

Alternative and multisite pacing

Recognition that pacing at the right ventricular apex is associated with an abnormal ventricular activation pattern that

might offset the advantage gained from the restoration of AV synchrony, prompted the assessment of alternative pacing sites within the right ventricle. Some investigators found acute hemodynamic benefit with pacing of the right side of the interventricular septum at an optimal AV delay,[140] whereas others, pacing the septal wall of the right ventricular outflow tract, did not.[141] A 3 month crossover trial in 16 patients with atrial fibrillation or flutter and AV block (post-ablation or spontaneous), showed no symptomatic or hemodynamic benefit from right ventricular outflow tract pacing compared with apical pacing.[142] The acute hemodynamic effect of combined pacing at two right ventricular sites (apex and outflow tract) has also been assessed.[143] No significant benefit was observed despite narrowing of the QRS. It has been suggested that individualized selection of the optimal septal pacing site (to minimize the QRS duration) might prove more effective.[144] Encouraging results have recently been reported with permanent His-bundle pacing. Significant improvement in hemodynamic function and NYHA class were observed during a mean 2 year follow up in a group of patients with chronic atrial fibrillation and severe dilated cardiomyopathy.[145] This technique requires further validation in a prospective controlled study.

Cardiac resynchronization therapy (CRT)

Recent interest has focused on the use of three or four chamber pacing with synchronized biventricular activation in an atrial tracking mode with optimized AV delay, particularly in patients with abnormalities of AV or intraventricular conduction. Biatrial synchronization may also be used in the presence of interatrial conduction delay. Up to 40% of patients with severe heart failure have intraventricular conduction delay.[146] This results in asynchronous contraction of the left and right ventricles, which may adversely affect hemodynamic function. CRT aims to reverse these changes by resynchronizing left and right ventricular activation and by ensuring AV synchrony with an optimal AV delay if sinus rhythm is preserved. The potential hemodynamic benefit of biventricular pacing was first described in 1983[147] but it was not until 1994 that the clinical application of the technique was reported in a patient with severe drug-refractory congestive heart failure.[148] Early case reports documented short-term clinical and hemodynamic improvement in patients with class III and IV heart failure using three or four chamber atriobiventricular pacing.[148–150] Acute hemodynamic studies have demonstrated decreased pulmonary capillary wedge pressure and increased peak LV dP/dt, systolic blood pressure and cardiac index during biventricular pacing.[150–154] Similar or greater improvements in some parameters were also reported with LV pacing alone.[151,153,154] The early studies of biventricular pacing used an epicardial pacing lead, implanted by limited thoracotomy or thoracoscopy, to pace the left ventricle, with a standard endocardial lead in the right ventricle. This approach has been superseded by the development of a technique for pacing the left ventricle by means of a lead introduced transvenously via the coronary sinus, with the tip located in one of the posterior or lateral cardiac veins overlying the left ventricular free wall.[155] A coronary sinus angiogram is often used to create an anatomical map to guide placement of the specialized leads that have been developed for this type of pacing.[156]

Non-randomized studies of CRT

Encouraging preliminary data regarding the clinical utility of CRT were reported from two non-randomized studies. The InSync study[157] was an uncontrolled safety and efficacy study of synchronized biventricular pacing using a purpose designed pacing system. The device used incorporated a Y-adaptor, offering pacing channels for the right atrium, the right ventricle and the left ventricle, the latter being paced transvenously via the coronary sinus and cardiac veins. The study included 81 patients (mean age 66 years) with symptomatic cardiac decompensation, NYHA class III ($n = 43$) or class IV ($n = 25$), refractory to medical therapy, QRS duration >150 ms, ejection fraction $<35\%$ and LV end-diastolic diameter (EDD) >60 mm. Implantation was technically successful in 84% of patients with a low requirement for re-intervention. There were significant improvements at 1 and 3 month follow up (compared with baseline) in NYHA functional class, quality of life (Minnesota Living with Heart Failure Score) and distance covered during a 6 minute walk. There were, however, seven deaths (including four sudden deaths) between 11 and 127 days post-implant. Follow up to 1 year has subsequently been reported and confirmed sustained clinical benefit in the survivors.[158]

The French pilot study experience (1994–1997) comprised a series of 50 patients (mean age 68 years) with refractory class III ($n = 26$) or class IV ($n = 34$) heart failure, EF$<35\%$, LV EDD >60 mm and QRS duration >150 ms.[159] Mean follow up was 15·4 months (range 1–48 months). There were 20 deaths in this series but with only two exceptions, these patients were in NYHA class IV at entry (one third of the total cohort were in a terminal phase, requiring permanent IV inotropic support). Deaths were classified as being due to progressive pump failure ($n = 11$), sudden cardiac death ($n = 6$) or non-cardiac cause ($n = 3$). Significant improvements during follow up were reported in functional status, exercise tolerance (in the 16 patients able to exercise at baseline) and ejection fraction.

Randomized trials of CRT

A number of randomized clinical trials have been initiated in Europe and the USA to assess further the efficacy of CRT in dilated cardiomyopathy.

The Pacing Therapy in Congestive Heart Failure (PATH-CHF) Trial – The PATH-CHF trial, was a single-blind randomized, crossover controlled trial designed to evaluate the effects of pacing on acute hemodynamic function and to assess chronic clinical benefit in patients with NYHA class III or IV congestive heart failure despite optimal medical therapy.[160] Patients were required to have a QRS duration ≥120 ms and a PR interval ≥150 ms. An epicardial lead was attached to the apex or midlateral segment of the left ventricle via a limited thoracotomy and endocardial leads were sited in the right atrial appendage and right ventricle. During the acute phase of the study, right and left univentricular pacing were compared with biventricular pacing, at a variety of pre-selected AV delays, using a randomized crossover design. Overall, biventricular and LV pacing increased LV dP/dt and pulse pressure more than right ventricular pacing. LV pacing increased LV dP/dt more than biventricular pacing.[153] Pacing site had a greater influence on hemodynamics than the AV delay. During the chronic phase of the study, 42 patients were randomized to either atriobiventricular pacing or the best atriouniventricular mode (determined during the acute phase) for a 4 week period. This was followed by a 4 week wash-out phase without pacing and a further 4 weeks in the alternate mode. Compared with baseline, active pacing showed significant benefits in terms of oxygen consumption at peak exercise and at anaerobic threshold and distance covered during a 6 minute walk (the primary end points).[161] Quality of life, assessed by the Minnesota Living with Heart Failure questionnaire, and NYHA functional class were also significantly improved. There was evidence of a placebo or carry-over effect, in that improvements during the first phase of active pacing were not eliminated during the subsequent wash-out period. There was, however, a further significant improvement during the second active pacing period, implying a genuine treatment effect. On completion of the crossover phase, patients were assigned to the best chronic pacing mode and followed for 1 year. During that time, the number of days spent in hospital for heart failure was significantly lower than in the year before implantation.[162]

The Multisite Stimulation In Cardiomyopathy (MUSTIC) Trial – The MUSTIC trial used a blinded crossover between active and inactive pacing (12 weeks in each mode) to assess biventricular pacing.[163] In this study, the left ventricular lead was introduced transvenously to a lateral or posterior cardiac vein. The initial implant success rate was 92%. Patients had severe but stable heart failure due to idiopathic or ischemic LV systolic dysfunction (NYHA class III) despite optimal medical therapy, ejection fraction <35%, LV EDD >60 mm, QRS duration >150 ms and no conventional indication for pacing. Sixty-seven patients in sinus rhythm were enrolled, of whom nine were withdrawn before randomization for various reasons (failed implantation, five; unstable heart failure, two; pre-existing indication for pacing, one; sudden death whilst the device was inactive, one). Ten patients failed to complete the two crossover periods. In the 48 patients who completed the study, the 6 minute walking distance (the primary end point) improved by 23% ($P<0{\cdot}001$) after 3 months biventricular pacing. Quality of life scores (Minnesota Living with Heart Failure questionnaire) improved by 32% ($P<0{\cdot}001$), peak oxygen uptake by 8% ($P<0{\cdot}03$) and hospitalizations were decreased by two thirds ($P<0{\cdot}05$). Active pacing was preferred by 85% of the patients ($P<0{\cdot}001$). At the end of the crossover phase, patients were programmed to their preferred mode and reassessed at 1 year. The clinical benefits were maintained.[164] The MUSTIC study had a separate limb for patients in atrial fibrillation and preliminary results from the 41 patients (of 64 enrolled) who completed the crossover phase have been presented.[165] Trends were observed in favor of biventricular pacing but the results did not achieve statistical significance. This contrasts with the findings in a non-randomized study in which patients with atrial fibrillation showed greater benefit than those in sinus rhythm.[166] In the latter study, the AV node was systematically ablated in the patients with AF, in order to provide complete and permanent biventricular capture. Some benefit may thus have been due to improved rate control. Conversely, patients in the MUSTIC AF study may have failed fully to benefit from CRT if rate control was inadequate and resynchronization only intermittent. The Optimal Pacing SITE (OPSITE) study will address this issue by sequentially comparing right ventricular pacing, first with LV and then with biventricular pacing, using a crossover design, in patients undergoing "ablate and pace" therapy for permanent atrial fibrillation, with and without impaired LV function.[167]

The Multicenter Insync Randomized Clinical Evaluation (MIRACLE) – MIRACLE is the largest trial of biventricular pacing reported to date.[168] This was a prospective, multicentre, double-blind, randomized controlled trial in patients with NYHA class III or IV chronic heart failure, ejection fraction ≤35%, LV EDD ≥55 mm, QRS duration ≥130 ms, on optimal and stable medical therapy. Preliminary results have been presented.[169] A total of 266 patients, successfully implanted with a transvenous CRT pacing system were randomized to active CRT ($n=134$) or control (VDD mode at 30/min; $n=132$) and followed for 6 months. The initial implant success rate was 93%. In the CRT group, there were eight deaths and one patient withdrawal. In the control group there were 10 deaths, two early crossovers and one other withdrawal. Amongst those who completed the study there were significant improvements in 6 minute walk distance with CRT (mean increase 39 m; $P=0{\cdot}033$). NYHA functional class improved by a mean of 0·8 in the CRT group, with 65% attaining class I or II, compared with 30% in the control group ($P<0{\cdot}001$). In the quality of life

assessment (Minnesota Living with Heart Failure questionnaire), there was evidence of a marked placebo effect with improvement in the control group also but the improvement in the CRT group (mean 19 points) was significantly greater ($P = 0{\cdot}013$). Treadmill exercise time was also significantly increased with CRT (*c* 2 mins) and there was a borderline significant increase in peak VO_2.

Further evidence of the efficacy of CRT is provided by the data reported on 1000 patients enrolled in the European CONTAK registry[170] and 190 patients enrolled in the Italian InSync registry.[171] These show similar outcomes to those in the other non-randomized studies and clinical trials.

In addition to the benefits of CRT described above, there is evidence that it may reduce norepinephrine levels[172] and sympathetic activity.[173] These effects may explain the apparent antiarrhythmic effect of CRT. In one crossover study, a diminished frequency of ventricular ectopy was noted during CRT, compared with that during sinus rhythm or right ventricular pacing.[174] Similarly, in the VENTAK-CHF study, CRT decreased the frequency of appropriate antitachycardia therapy delivery in patients with an implantable cardioverter defibrillator (ICD) with biventricular pacing capability.[175] A number of recently completed and ongoing trials will provide further evidence of the short-term clinical impact of CRT in patients with severe heart failure, some or all of whom are implanted with a biventricular ICD. These include CONTAK-CD, InSync ICD, MIRACLE ICD, PATH CHF-II and PACMAN.

Comment and recommendations

There is considerable evidence that CRT can improve hemodynamics, symptoms, quality of life and functional capacity in selected patients with advanced heart failure and intraventricular conduction delay. There is also some evidence that the need for hospitalization may be diminished. **Grade A**

To date, the evidence has come from relatively small and short-term studies in which all patients have received a device and outcomes have been compared pre- and post-implant or with the device alternately active and inactive. In order to define the true clinical utility of CRT, there is a pressing need for large-scale randomized trials comparing morbidity and mortality in patients receiving CRT (in addition to optimal medical therapy) and in patients receiving optimal medical therapy alone. Two such trials are ongoing. The Cardiac Resynchronization for Heart Failure (CARE-HF) trial in Europe will enrol 800 patients with stable class III or IV chronic heart failure due to LV systolic dysfunction, EF $\leq$ 35%, dilated LV (EDD $\geq$30 mm/m height) and either QRS duration $\geq$150 ms or QRS duration $\geq$120 ms with echocardiographic evidence of dysynchrony.[176] Patients will be randomized to optimal medical therapy alone or combined with CRT and followed for a minimum of 18 months. The primary end point is all-cause mortality or cardiovascular hospitalization. Secondary end points include all-cause mortality, hospitalization for heart failure, NYHA class at 90 days and quality of life at 90 days (including a generic measure, the EuroQol EQ-5D). Echocardiographic and neurohormonal parameters will also be assessed, as will cost effectiveness. The Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trial in the USA will enroll 2200 patients with stable class III or class IV heart failure, at least one hospitalization in the preceding year, EF $\leq$ 35%, LV EDD $\geq$ 60 mm, QRS duration $\geq$120 ms and PR interval $>$150 ms.[177] This is a three-limb study, in which patients will be randomized to optimal medical therapy alone or combined with CRT or combined with CRT and ICD backup (ratio 1:2:2). Minimum follow up will be 1 year. The primary end point is all-cause mortality and hospitalization. Secondary end points include cardiac morbidity, quality of life and peak VO_2. The results from these trials should be available by 2004. In the meantime, no firm recommendations can be made regarding the place of CRT in clinical practice. Further data are also required to clarify numerous unresolved issues regarding patient selection, the optimal LV pacing site, the relative merits of LV and biventricular pacing, the role of combined CRT and ICD therapy and cost utility. Technological developments are also needed to simplify LV lead placement and shorten the procedure time.

Atrial fibrillation

The influence of pacing mode selection on the incidence of atrial fibrillation (AF) in patients paced for sick sinus syndrome or AV block has been discussed above, as has the occasional need for pacing to permit antiarrhythmic drug therapy. The limited success of drug therapy in suppressing paroxysmal AF has prompted the assessment of various pacing strategies, even in patients with no other indication for pacemaker implantation. Possible mechanisms by which pacing might suppress AF in this context include reduction of bradycardia, overdrive suppression of atrial premature beats, elimination of compensatory pauses and reduction in interatrial or intra-atrial conduction delay and dispersion of refractoriness that might otherwise favor re-entry.

Atrial rate support

In selected patients with the vagally mediated, pause-dependent, form of atrial fibrillation, permanent atrial rate support has been shown to be of benefit although concomitant drug therapy may still be required.[178] In a broader context, the use of atrial-based pacing to prevent paroxysmal atrial fibrillation in patients selected for ablation of the AV

node was assessed in the Atrial Pacing Periablation for Prevention of Paroxysmal Atrial Fibrillation (PA^3) study.[179] The first phase of the study enrolled 97 patients with at least three episodes of paroxysmal AF in the previous year (the most recent within 3 months), all of whom were refractory to or intolerant of drug therapy and being considered for total AV node ablation. Patients were implanted with a DDDR pacemaker and randomized to atrial pacing (DDIR with lower rate 70/min) or no pacing (DDI 30/min). The use of the DDI mode in both groups activated the high-rate atrial diagnostic features of the pacemaker, which were used to determine the primary outcome. Diagnostic counters were reset after a 2 week run-in period, intended to permit stabilization of drug therapy and allow for short-term effects of lead placement on arrhythmia frequency. Patients and pacemaker diagnostics were reviewed 3 months post-implant and crossover from inactive to active pacing or progression to AV node ablation was permitted in the event of intolerable recurrent symptomatic AF. Time to first recurrence of AF (≥5 min) was similar in the two groups and the AF burden was lower in the non-paced group. The study suggests that rate-adaptive atrial pacing does not prevent recurrence of drug-refractory paroxysmal AF, in the short-term, in patients without symptomatic bradycardia. It is noteworthy that AV node ablation was deferred in 29% of patients in each group. Whilst the significance of this observation is unclear, it lends some support to the strategy of implanting a pacemaker and reviewing the patient before proceeding to planned ablation, rather than undertaking both procedures in one session.

The second phase of the PA^3 study considered the optimal pacing mode postablation and tested the hypothesis that DDDR pacing as compared with VDD pacing reduces the time to first recurrence, the frequency and the duration of paroxysmal AF postablation.[180] Sixty-seven patients were randomized to receive DDDR pacing (lower rate 70/min) with mode switch to DDIR, or VDD pacing (lower rate 60/min to favor preservation of AV synchrony) with mode switch to VVIR. There was a crossover at 6 months and total follow up of one year. Antiarrhythmic drugs were usually discontinued after pacemaker implantation. There was a progressive increase in the prevalence of persistent AF (approximately 30–35% at 6 months) and the AF burden with time but there were no statistically significant differences between the groups in time to recurrence, frequency or total burden of AF. By one year, 43% of patients had permanent AF. The study suggests that physiologic (DDDR) pacing, compared with ventricular pacing, does not prevent the recurrence of paroxysmal AF or progression to permanent AF after AV node ablation in patients with frequent paroxysmal AF. It is possible that the findings might be different if concomitant antiarrhythmic drug therapy were used, as there is evidence from randomized trials that "ablate and pace" therapy, although better than drug therapy for relief of symptoms, is associated with a higher incidence of permanent AF.[181,182] It is also possible that a higher pacing rate, to achieve more continuous overdrive, might have been more effective.

Atrial overdrive pacing

Overdrive pacing at higher rates in the right atrial appendage has been assessed in patients with paroxysmal AF and pacemakers implanted for conventional indications. In one study, 18 patients with DDDR mode-switching pacemakers, implanted for a variety of indications, were randomly assigned to pacing at 60, 75 and 90/min with crossover after intervals of 2 months.[183] The pacemaker Holter functions were used to assess the percentage of time spent in AF and/or the number of mode-switch episodes according to the device capability. When ranked according to the amount of AF, there was no significant difference in the amount of AF according to the pacing rate. Six patients were intolerant of pacing at 90/min and one other had increased angina. In another study, 27 patients with DDDR pacemakers, implanted for sick sinus syndrome, were randomized to two 3 month single-blinded crossover periods. In one, the pacemaker base rate was set to 60/min and in the other it was set to 10 beats/min above the mean heart rate (range 70–96/min; mean ± S.D. 75 ± 7/min). Pacemaker software recorded the number and duration of AF episodes, which were not significantly different between the two periods.[184] These findings contrast with an earlier report in which atrial overdrive was found to decrease the incidence of atrial arrhythmia in a study of 22 patients with frequent episodes and DDD pacemakers implanted for conventional indications.[185] However, even in that study, the sub-group with brady-tachy syndrome (all of whom had prior atrial tachyarrhythmia apparently not controlled by drug therapy) showed least benefit. Encouraging results have recently been reported from a randomized crossover study of medium (*c* 80/min) and high rate (*c* 90/min) right atrial overdrive pacing in 42 patients with paroxysmal AF but no conventional indication for pacing. Symptomatic (ECG verified) episodes of AF were less frequent during medium (1·42/week; $P = 0{\cdot}005$) and high rate (1·36/week; $P = 0{\cdot}006$) pacing than with no pacing (2·56/week).[186]

Rate-adaptive atrial pacing

The generally disappointing results in most studies of overdrive pacing may partly reflect a failure to achieve consistent or sustained overdrive. The mean or median percentage atrial pacing was below 75% in all of the studies described above. In this regard, the impact of sensor-driven rate adaptation has been examined in a prospective randomized crossover trial comparing DDD with DDDR pacing (3 months in each mode) in 78 patients with frequent symptomatic paroxysmal AF, brady-tachy syndrome and chronotropic

incompetence.[187] The percentage of atrial pacing was significantly higher in DDDR mode compared with DDD mode (81·1 ± 20·5 and 73·7 ± 20·0 respectively; $P < 0{\cdot}01$). There was a non-significant trend towards fewer symptomatic episodes in the DDDR mode. There were also fewer mode-switching episodes (91 ± 109·8 *v* 120 ± 120 over 3 months; $P < 0{\cdot}05$). However, no data were available regarding the duration of the episodes, so the AF burden is unknown. Rate-adaptive pacing would only be expected to confer an advantage during periods of increased activity, as is reflected in the relatively modest increase in the overall percentage of atrial pacing. A novel implementation of sensor-driven rate-adaptive pacing in this context is the use of fixed-rate overdrive pacing but with an Automatic Rest Rate function to allow overdrive pacing to continue but at a lower rate during periods of physical or mental inactivity. Preliminary results from a randomized crossover trial, comparing DDDR pacing with and without activation of the overdrive algorithm, in 78 patients show a reduction in the number and duration of mode switching episodes.[188]

Atrial pacing algorithms

A number of specific pacemaker algorithms have been developed to try and enhance the antiarrhythmic efficacy of atrial pacing. One example uses overdrive pacing, triggered by the occurrence of atrial premature beats, to eliminate post-extrasystolic pauses and suppress further ectopy.[189] Another uses dynamic atrial overdrive (DAO) to maintain a pacing rate just above the intrinsic sinus rate. Preliminary results from a randomized crossover study (ADOPT-A), comparing DDDR pacing with the algorithm "on" or "off" in 250 patients with paroxysmal AF and a conventional indication for pacing, have been presented.[190] There was a significant reduction in AF burden as assessed from symptomatic (ECG verified) episodes. The Consistent Atrial Pacing (CAP) algorithm also aims to achieve sustained overdrive pacing, whilst avoiding excessively high rates that might compromise patient tolerance, by continuously updating the atrial escape interval. In a randomized crossover study in 15 patients receiving DDDR pacing for sick sinus syndrome, the algorithm achieved 86 ± 28% atrial pacing, was well tolerated and decreased the number of premature atrial contractions. There was, however, no significant reduction in AF as assessed by the number of mode-switching episodes.[191] In a similar study of 61 patients receiving DDDR pacing for brady-tachy syndrome, the algorithm was well tolerated, decreased the number of premature atrial contractions and achieved 96 ± 7% atrial pacing but there was no significant reduction in symptomatic AF or mode-switching episodes.[192] In a sub-group of 31 patients who had less than 90% atrial pacing during standard DDDR pacing, the algorithm increased atrial pacing from 60 ± 26% to 97 ± 3% and mode-switch episodes decreased from 1·23 ± 1·27 to 0·75 ± 1·1 ($P < 0{\cdot}0001$). The CAP algorithm has subsequently been combined with two others (rate stabilization and post mode switching overdrive) in a device that also includes anti-tachycardia pacing capability. Preliminary clinical results in 31 patients with conventional pacing indications and atrial tachyarrhythmia, showed a reduction in the mean number of arrhythmia episodes but the total arrhythmia burden was unchanged.[193] Encouraging results have recently been presented from the Atrial Fibrillation Therapy (AFT) study, which assessed the efficacy of a device incorporating a combination of four preventive pacing algorithms.[194] The study included 372 patients with drug-refractory paroxysmal AF, with and without conventional indications for pacing. Conventional DDD pacing (at 40, 70 and 85/min) and DDDR pacing (at 70 and 85/min) did not significantly influence AF burden, mean duration of sinus rhythm or AF recurrence. In contrast, the AF preventive algorithm significantly improved all of these outcomes, when compared with DDD pacing at 70/min. Further studies in this area are ongoing.[195]

Biatrial pacing

It has been postulated that reduced dispersion of refractoriness might decrease the propensity to paroxysmal AF in susceptible patients and the efficacy of various multisite pacing techniques has been examined. Encouraging results were obtained with the use of biatrial synchronization in patients with advanced interatrial conduction delay and drug refractory atrial flutter and fibrillation.[196,197] Pacing leads were positioned in the right atrium and within the mid or distal coronary sinus to pace right and left atria simultaneously in triggered (AAT) mode. This strategy was subsequently evaluated in the Synchronized Biatrial Pacing (SYNBIAPACE) study.[198] This was a prospective randomized crossover study in which 42 patients (mean age 64 years) with a history (≥1 year) of recurrent drug-refractory AF and intra-atrial conduction delay (*P* wave duration ≥120 ms and interatrial conduction time ≥100 ms) spent 3 months in each of three pacing modes. Synchronous biatrial pacing at 70/min was compared with single site high right atrial DDD pacing at 70/min and the same at 40/min (the "inhibited" or control mode). Biatrial pacing was achieved using leads in the high right atrium and the mid or distal coronary sinus connected via a "Y"-bifurcated adapter to the atrial port of a bipolar DDDR pacemaker, incorporating a resynchronization algorithm to trigger atrial synchronous pacing after every sensed atrial event ("AAT" mode). There was no statistically significant difference between the three modes in either time to first arrhythmia recurrence (the primary end point) or time spent in atrial arrhythmia, although there was a trend favoring biatrial pacing. This was a relatively small study with short follow up in a highly selected group of patients and data from further studies are awaited to clarify the role of this pacing modality.

Dual site atrial pacing

An alternative approach that has been explored is the use of dual site atrial pacing, in DDDR mode, with leads in the high right atrium and at the coronary sinus os. Preliminary studies reported an increase in the arrhythmia-free interval and greater benefit than single site pacing at either site.[199] The same group subsequently reported on a series of 30 patients entered into a prospective but non-randomized, sequential, crossover comparison of single and dual site atrial pacing (3–6 month periods) with extended follow up (25–41 months) in the latter mode.[200] Arrhythmia free interval was significantly increased by dual site pacing as compared with single site pacing, either in the high right atrium or at the coronary sinus ostium, which was itself superior to a pre-implant control period. Single site pacing was of comparable efficacy at either site. Dual site pacing was achieved by connecting the high right atrial and coronary sinus ostial electrodes via a Y-connector to the atrial channel of a conventional DDDR pacemaker, the pacing rate being set to achieve overdrive with at least 80% of atrial events being paced. The technique has subsequently been evaluated in the Dual Site Atrial Pacing to Prevent AF (DAPPAF) study.[201] This was a randomized crossover comparison of dual site atrial pacing, single site high right atrial pacing and a support pacing control period (DDI 50/min or VDI), at 6 month intervals, in 120 patients with a history of paroxysmal AF and a bradyarrhythmic indication for pacing. Patient tolerance and adherence to the pacing mode was superior with dual site pacing compared with support pacing ($P < 0{\cdot}001$) and high right atrial pacing ($P = 0{\cdot}006$). There was a non-significant trend towards greater freedom from any symptomatic AF recurrence (the primary end point) with dual site pacing (hazard ratio 0·715, $P = 0{\cdot}07$) but not with high right atrial pacing ($P = 0{\cdot}19$), compared with support pacing. There was no significant difference between dual site and high right atrial pacing. Combined symptomatic and asymptomatic AF frequency, measured by device datalogs, was significantly reduced during dual site pacing, compared with high right atrial pacing ($P < 0{\cdot}01$). However, in antiarrhythmic drug treated patients, dual site pacing increased symptomatic AF free survival compared to support pacing ($P = 0{\cdot}011$) and high right atrial pacing (hazard ratio 0·669, $P = 0{\cdot}06$).[202]

Another prospective randomized trial, the New Indication for Pacing Prevention of AF (NIPP AF) study, examined whether dual site atrial pacing with atrial overdrive near the intrinsic rate, could reduce AF recurrence in patients with paroxysmal AF, refractory to a fixed regimen of sotalol, and no bradycardic indication for pacing.[203] Twenty-two patients were randomized in crossover fashion to 12 weeks of high right atrial pacing at 30/min or dual site pacing (high right atrium and coronary sinus os) with an overdrive algorithm. The time to the first clinical AF recurrence was prolonged (15 ± 17 to 50 ± 35 days, $P = 0{\cdot}006$) and total AF burden was reduced ($45 \pm 34\%$ *v* $22 \pm 29\%$, $P = 0{\cdot}04$) by dual site pacing with overdrive. However, there was no significant difference in symptoms or quality of life.

Alternative site atrial pacing

Encouraging preliminary results have recently been reported from studies of single site pacing of the interatrial septum. In an acute study comparing right atrial appendage pacing with dual site, septal or coronary sinus os pacing, the duration of atrial activation was found to be shorter and comparable at each of the latter sites.[204] This suggests that the benefits of dual site pacing might be attained without the added complexity of a second lead. Baillin *et al* randomized 120 patients with a conventional indication for pacing and a history of recurrent paroxysmal AF to pacing either the interatrial septum in the region of Bachmann's bundle or the right atrial appendage.[205] Septal pacing was associated with a shorter P wave duration and a higher rate of survival free from chronic AF at one year, compared with right atrial appendage pacing (75% *v* 47%; $P < 0{\cdot}05$). Padeletti *et al* randomized 46 patients with paroxysmal AF and sinus bradycardia to DDD(R) pacing with the atrial lead either on the interatrial septum at the triangle of Koch or in the right atrial appendage.[206] Within each group, a crossover comparison was made with a constant atrial pacing (CAP) algorithm "on" or "off". The number of paroxysmal AF episodes per month was lower in both groups with the CAP algorithm "on" but septal pacing was associated with a significantly lower frequency of AF episodes and AF burden with or without CAP. The same group have also reported success with the use of interatrial septal pacing to prevent early recurrence of AF after DC cardioversion in patients with a prior history of early recurrence (within 2–24 hours).[207]

Comment and recommendations

The use of pacing as a primary antiarrhythmic strategy in the management of AF is not yet justified by the available data. Interpretation of the data is confounded by heterogeneity of the pattern of the arrhythmia, the clinical characteristics of the patients and the end points and outcome measures in the various studies. In patients with conventional indications for pacing, the use of a device with preventive algorithms may be justified in selected cases. Similarly, multisite or alternative site atrial pacing may be worthy of consideration in some patients, such as those with evidence of intra- or interatrial conduction delay. These pacing modalities appear to be most effective when used as hybrid therapy with antiarrhythmic drugs. Indeed, it may be that much of the benefit in some of the studies is attributable to the facilitation of increased antiarrhythmic drug therapy by pacing. In the future, improved understanding and characterization of different

patterns and modes of onset of AF may facilitate a customized approach to treatment. For the time being, the value of device therapy in AF remains unproven. **Grade A**

Long QT syndrome

Patients with the long QT syndrome are at high risk of syncope and sudden death, usually due to polymorphic ventricular tachycardia. There are compelling data from observational studies[208,209] and from the International Long QT Syndrome Registry[210,211] indicating that cardiac pacing, with concomitant β blockade, may reduce the rate of recurrent syncope and sudden death. The registry data, from 124 patients who were paced for the long QT syndrome, indicate approximately a 50% reduction in the incidence of cardiac events. Interpretation of the data is confounded by the initiation or increase of β blockers at the time of pacing in some patients. However, 30 patients were identified in whom a pacemaker was implanted after failure of β blockers but without an increase in drug dosage. In this subset, there was a significant reduction in the incidence of syncope, confirming the independent benefit of pacing. It is important to note that pacing should not be implemented without concomitant β blocker therapy and that β blockers should not be stopped. Of the 10 registry patients in whom β blockers were withdrawn after pacemaker implantation, three died suddenly during 2 years' follow up. The benefit of pacing is thought to be due to the prevention of bradycardia and pauses together with rate-related shortening of the QT interval. Unfortunately, for pacing to be effective, relatively high rates (>80/min) may be required[212] with the attendant disadvantage of reduced battery life and the potential risk of tachycardia induced cardiomyopathy.[213]

Careful attention to pacemaker programming is essential.[214] Features that allow slowing of the heart rate below the programmed lower rate limit, such as hysteresis and sleep functions, should be programmed "off". Similarly, rate hysteresis search (a feature that extends the atrial escape interval periodically to search for intrinsic sinus activity) and algorithms that extend the postventricular atrial refractory period after ventricular premature beats, should be disabled, as they may favor the occurrence of pauses. Specific rate-smoothing algorithms that are capable of preventing post-extrasystolic pauses may be useful in this context.[215] There is some indirect experimental and clinical evidence to suggest that pacing might be of particular value in patients with the LQT3 genotype,[216–218] which is particularly associated with increased dispersion of repolarization during bradycardia and with arrhythmia occurring during sleep.[219] This has not been explored in clinical studies and it should not be inferred that other genotypes will not benefit from pacing. Further data are required to clarify the extent to which therapy in the long QT syndrome can be guided by genotype. Pacing should be considered as an adjuvant to β blockade in all patients with long QT syndrome and high grade AV block and whenever there is evidence of pause-dependent malignant arrhythmias. In selected patients, an implantable cardioverter defibrillator may also be indicated and the same device may be used for prophylactic pacing. **Grade B**

Post-cardiac transplantation

Bradycardia, usually due to transient sinus node dysfunction or AV block, may occur in almost two thirds of patients in the first few weeks following orthotopic cardiac transplantation.[220] Recovery from transient AV block usually occurs within 16 days but transient sinus node dysfunction may persist for several weeks and the optimal time for consideration of permanent pacemaker implantation is uncertain.[221] In some cases, temporary treatment with oral theophylline may avert the need for permanent pacing.[222] The proportion of transplant recipients receiving permanent pacing for persistent bradycardia ranges from 4% to 29% in different centres.[223] The variation may reflect differences in the incidence of bradycardia and the criteria for permanent pacing although differences in surgical technique may also be relevant.[224] In paced transplant recipients, bradycardia often resolves and pacemaker usage decreases during the first few months.[225] Deferring consideration of permanent pacing until 3 weeks after transplantation may mean that some patients with transient sinus node dysfunction are spared unnecessary pacemaker implantation. Deferral is also associated with a commensurate increase in pacemaker usage in those paced. However, even with this strategy, less than half of those using their pacemakers at 3 months continue to do so at 6 months and there are no clear predictive factors to guide patient selection.[226]

Following heterotopic cardiac transplantation, the donor and recipient hearts beat independently of one another, the denervated donor heart typically beating at a faster rate. Competitive contraction of the two hearts may be deleterious and left ventricular function in the recipient heart is improved when the two hearts beat out of phase. Acute studies have shown that paced linkage of the two hearts to produce consistent counterpulsation may result in significant functional improvement.[227] This technique has recently been evaluated in a chronic study using permanent dual chamber pacemakers with the atrial channel connected to the donor atrium and the "ventricular" channel connected to the recipient atrium.[228] Paced linkage was associated with significant improvements in symptoms, general health, energy, levels of activity and maximum cardiac output in the donor heart. **Grade A**

Sleep apnea

Sleep apnea with hypersomnolence is a relatively common disorder that is estimated to affect 2% to 4% of middle-aged adults, although asymptomatic forms with abnormal findings on polysomnography may be five times more frequent.[229]

The condition is associated with an increased risk of hypertension and cardiovascular disease, including bradyarrhythmia.[230] It has been noted that recognition and treatment of the condition in patients with transient but profound asymptomatic bradycardia, occurring only at night or whilst sleeping during the day, may reduce the need for pacemaker implantation, provided that advanced disease of the sinus node or AV conducting system have been excluded.[231]

Conversely, there have been anecdotal reports of improvements in sleep-disordered breathing following pacemaker implantation in patients with sinus node dysfunction and AV block.[232] Following similar observations in some patients receiving atrial overdrive pacing for the suppression of atrial tachyarrhythmia, the efficacy of atrial overdrive has been assessed in a randomized crossover trial.[233] A group of 152 patients with dual chamber pacemakers, implanted for conventional indications, was screened for symptoms of sleep-disordered breathing. Of 47 such patients that were identified, 26 underwent polysomnography and sleep apnea was confirmed in 15, all of whom had either sinus node disease or brady-tachy syndrome as their underlying diagnosis. Patients underwent polysomnographic studies on three consecutive nights. The first night provided a baseline evaluation to quantify the frequency and type of apnea or hypopnea. On the second night, the patients were randomly assigned to either backup ventricular pacing (40/min), to allow a predominantly spontaneous rhythm, or atrial overdrive pacing at a rate 15 beats/min faster than the baseline nocturnal heart rate. On the third night, the alternate mode was assessed. The mean sinus rate during spontaneous rhythm was 57 ± 5/min at baseline and the mean rate during atrial overdrive pacing was 72 ± 3/min. The hypopnea index (number of episodes divided by hours of sleep) was 9 ± 4 during spontaneous rhythm and 3 ± 3 during atrial overdrive ($P < 0{\cdot}001$). For both apnea and hypopnea, the index was 28 ± 22 during spontaneous rhythm and 11 ± 14 ($P < 0{\cdot}001$) during atrial overdrive.

The mechanism underlying the apparent improvement with pacing is unclear. The authors postulate that increased sympathetic activity during pacing might counteract sustained increases in vagal tone. Perhaps surprisingly, both obstructive and central forms of sleep apnea were improved, which may suggest a central mechanism affecting both respiratory rhythm and pharyngeal motor neuron activity.[234] It is noteworthy that 11 of the 15 patients had some degree of impairment of LV function but even the four patients with normal LV function showed more than a 50% reduction in the sleep apnea index. It remains unknown whether patients with sleep apnea but without conventional indications for pacing would show similar benefit and it would be premature to suggest a role for cardiac pacing in this condition. The study does, however, suggest that atrial overdrive might be of value in patients with sleep apnea who are already being paced for sinus node disease or brady-tachy syndrome.

Arrhythmia diagnosis

In recent years, the increasing sophistication and memory capacity of cardiac pacemakers has introduced the possibility of an important diagnostic role. In patients with syncope, the cause of which remains unknown after appropriate investigation, implantation of a pacemaker with diagnostic capabilities may enable the occurrence and cause of bradycardia to be identified whilst providing a therapeutic safety net.[235] Single chamber diagnostic devices capable of detecting the occurrence of bradycardia have been available for several years and dual chamber devices with diagnostic algorithms are now also available and enable the mechanism of bradycardia to be identified in many cases.[236]

In patients with known or suspected tachyarrhythmia, the Holter and telemetry functions of dual chamber pacemakers may be used to facilitate arrhythmia diagnosis. They also enable the frequency and natural history to be determined and the efficacy of antiarrhythmic therapy to be assessed.[237] In devices with the capability of switching from atrial tracking modes to non-tracking modes on detection of atrial tachyarrhythmia, mode-switch counters may serve a similar function, whilst the change in mode avoids the risk of rapid paced ventricular rates.

Conclusions

The role of cardiac pacing in symptomatic bradycardia is well established yet questions remain regarding appropriate mode selection in the conditions for which it is most often used, namely AV block and sino-atrial disease. Data from recent randomized trials have enriched the evidence base but further analysis and the results from ongoing trials must be awaited before the outstanding questions can be answered. Technological advances and innovation have greatly expanded the possibilities for sophisticated pacing with better emulation of normal physiology, yet for many of these developments, evidence of clinical utility is limited. In recent years, improved diagnostic techniques have increased understanding of the pathophysiology of other conditions, identifying many possible new roles for pacing as a therapeutic modality. The advent of large scale clinical trials to the field of cardiac pacing offers an opportunity both to test well-constructed hypotheses regarding established indications and to evaluate new ones, in order to provide a solid evidence base to guide future practice.

References

1. Elmqvist R, Senning A. An implantable pacemaker for the heart. In: Smith CN, ed. *Medical electronics* (Proceedings of the Second International Conference on Medical Electronics, Paris, 1959). London: Illiffe, 1960.

2. Travill CM, Sutton R. Pacemaker syndrome: an iatrogenic condition. *Br Heart J* 1992;**68**:163–6.
3. Mond HG. The world survey of cardiac pacing and cardioverter defibrillators: Calendar year 1997 – Asian Pacific, Middle East, South America, and Canada. *PACE* 2001;**24**: 856–62.
4. Ector H, Rickards AF, Kappenberger L *et al.* The world survey of cardiac pacing and implantable cardioverter defibrillators: Calendar year 1997 – Europe. *PACE* 2001;**24**:863–8.
5. Bernstein AD, Parsonnet V. Survey of cardiac pacing and implanted defibrillator practice patterns in the United States in 1997. *PACE* 2001;**24**:842–55.
6. Cunningham AD (National Pacemaker Database, 2001). Personal communication.
7. Greenspan AM, Kay HR, Berger BC *et al.* Incidence of unwarranted implantation of permanent cardiac pacemakers in a large medical population. *N Engl J Med* 1988;**318**:158–63.
8. Frye RL, Collins JJ, DeSanctis RW *et al.* Guidelines for permanent cardiac pacemaker implantation, May 1984: A report of the Joint American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Sub-committee on Pacemaker Implantation). *Circulation* 1984;**70**:331A–9A.
9. Dreifus LS, Fisch C, Griffin JC *et al.* Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Pacemaker Implantation). *Circulation* 1991;**84**:455–67.
10. Gregoratos G, Cheitlin MD, Conill A *et al.* ACC/AHA Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *J Am Coll Cardiol* 1998 (in press).
11. Clarke M, Sutton R, Ward D *et al.* Recommendations for pacemaker prescription for symptomatic bradycardia: report of a working party of the British Pacing and Electrophysiology Group. *Br Heart J* 1991;**66**:185–91.
12. Petch M. Who needs dual chamber pacing? *BMJ* 1993;**307**: 215–16.
13. de Belder MA, Linker NJ, Jones S, Camm AJ, Ward DE. Cost implications of the British Pacing and Electrophysiology Group's recommendations for pacing. *BMJ* 1992;**305**: 861–5.
14. National Pacemaker Database (United Kingdom and Republic of Ireland). *Annual Report* 2000. London: British Pacing and Electrophysiology Group.
15. Aggarwal RK, Ray SG, Connelly DT, Coulshed DS, Charles RG. Trends in pacemaker mode prescription 1984–1994: a single centre study of 3710 patients. *Heart* 1996;**75**:518–21.
16. Bexton RS, Camm AJ. First degree atrioventricular block. *Eur Heart J* 1984;**5**(Suppl. A):107–9.
17. Chirife R, Ortega DE, Salazar AL. "Pacemaker syndrome" without a pacemaker. Deleterious effects of first-degree AV block. *RBM* 1990;**12**:22.
18. Zornosa JP, Crossley GH, Haisty WK Jr *et al.* Pseudopacemaker syndrome: a complication of radiofrequency ablation of the AV junction. *PACE* 1992;**15**:590.
19. Mabo P, Varin C, Vauthier M. Deleterious hemodynamic consequences of isolated long PR intervals: correction by DDD pacing. *Eur Heart J* 1992;**13**:225.
20. Barold SS. Indications for permanent cardiac pacing in first-degree AV block: class I, II, or III? *PACE* 1996;**19**:747–51.
21. Wharton JM, Ellenbogen KA. Atrioventricular conduction system disease. In: Ellenbogen KA, Kay GN, Wilkoff BL, eds. *Clinical cardiac pacing*. Philadelphia: WB Saunders, 1995.
22. Dhingra RC, Denes P, Wu D *et al.* The significance of second degree atrioventricular block and bundle branch block. *Circulation* 1974;**49**:638–46.
23. Puech P, Grolleau R, Guimond C. Incidence of different types of AV-block and their localisation by His bundle recordings. In: Wellens HJJ, Lie KI, Janse MJ, eds. *The conduction system of the heart: structure, function and clinical implications*. Philadelphia: Lea & Febiger, 1976.
24. Shaw DB, Kekwick CA, Veale D, Gowers J, Whistance T. Survival in second degree atrioventricular block. *Br Heart J* 1985;**53**:587–93.
25. Campbell RWF. Chronic Mobitz type I second degree atrioventricular block: has its importance been underestimated? *Br Heart J* 1985;**53**:585–6.
26. Connelly DT, Steinhaus DM. Mobitz type I atrioventricular block: an indication for permanent pacing? *PACE* 1996; **19**:261–4.
27. Grossman M. Second degree heart block with Wenckebach phenomenon: its occurrence over a period of several years in a young healthy adult. *Am Heart J* 1958;**56**:607–10.
28. Meytes I, Kaplinsky E, Yahini JH, Hanne-Papara N, Neufeld HN. Wenckebach A-V block: a frequent feature following heavy physical training. *Am Heart J* 1975;**90**:426–30.
29. Johansson BW. Complete heart block. A clinical hemodynamic and pharmacological study in patients with and without an artificial pacemaker. *Acta Med Scand* 1966;**180**(Suppl. 451): 1–127.
30. Edhag O, Swahn Å. Prognosis of patients with complete heart block or arrhythmic syncope who were not treated with artificial pacemakers. *Acta Med Scand* 1976;**200**:457–63.
31. Rosenqvist M, Nordlander R. Survival in patients with permanent pacemakers. *Cardiol Clin* 1992;**10**:691–703.
32. Rosenqvist M, Edhag KO. Pacemaker dependence in transient high grade atrioventricular block. *PACE* 1984;**7**:63–70.
33. Ginks W, Leatham A, Siddons H. Prognosis of patients paced for chronic atrioventricular block. *Br Heart J* 1979;**41**: 633–6.
34. Shen WK, Hammill SC, Hayes DL *et al.* Long-term survival after pacemaker implantation for heart block in patients ≥65 years. *Am J Cardiol* 1984;**74**:560–4.
35. Campbell M, Emanuel R. Six cases of congenital heart block followed for 34–40 years. *Br Heart J* 1966;**59**:587–90.
36. Michaëlsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. *Circulation* 1995; **92**:442–9.
37. Friedman RA. Congenital AV block. Pace me now or pace me later? *Circulation* 1995;**92**:283–5.
38. Rowlands DJ. Left and right bundle branch block, left anterior and left posterior hemiblock. *Eur Heart J* 1984;**5**(Suppl. A): 99–105.

39.McAnulty JH, Rahimtoola SH, Murphy E *et al.* Natural history of "high-risk" bundle branch block. Final report of a prospective study. *N Engl J Med* 1982;**307**:137–43.

40.Scheinman MM, Peters RW, Sauvé MJ *et al.* Value of the H-Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol* 1982;**50**: 1316–22.

41.Dhingra RC, Wyndham C, Bauernfeind RA *et al.* Significance of block distal to His bundle induced by atrial pacing in patients with chronic bifascicular block. *Circulation* 1979; **60**:1455–64.

42.Ward DE, Camm AJ. Atrioventricular conduction delays and block. In: Ward DE, Camm AJ, eds. *Clinical electrophysiology of the heart.* London: Edward Arnold, 1987.

43.Englund A, Bergfeldt L, Rosenqvist M. Disopyramide stress test: a sensitive and specific tool for predicting impending high degree atrioventricular block in patients with bifascicular block. *Br Heart J* 1995;**74**:650–5.

44.Click RL, Gersch BJ, Sugrue DD *et al.* Role of electrophysiologic testing in patients with symptomatic bundle branch block. *Am J Cardiol* 1987;**59**:817–23.

45.Ginks WR, Sutton R, Oh W, Leatham A. Long-term prognosis after acute anterior infarction with atrioventricular block. *Br Heart J* 1977;**39**:186–9.

46.Col JJ, Weinberg SL. The incidence and mortality of intraventricular conduction defects in acute myocardial infarction. *Am J Cardiol* 1972;**29**:344–50.

47.Watson RDS, Glover DR, Page AJF *et al.* The Birmingham trial of permanent pacing in patients with intraventricular conduction disorders after acute myocardial infarction. *Am Heart J* 1984;**108**:496–501.

48.Hindman MC, Wagner GS, JaRo M *et al.* The clinical significance of bundle branch block complicating acute myocardial infarction. 1. Clinical characteristics, hospital mortality and one-year follow up. *Circulation* 1978;**58**:679–88.

49.Hindman MC, Wagner GS, JaRo M *et al.* The clinical significance of bundle branch block complicating acute myocardial infarction. 2. Indications for temporary and permanent pacemaker insertion. *Circulation* 1978;**58**:689–99.

50.Ritter WS, Atkins J, Blomqvist CG, Mullins CB. Permanent pacing in patients with transient trifascicular block during acute myocardial infarction. *Am J Cardiol* 1976;**38**:205–8.

51.Sutton R, Kenny RA. The natural history of sick sinus syndrome. *PACE* 1986;**9**:1110–14.

52.Alboni P, Menozzi C, Brignole M *et al.* Effects of permanent pacemaker and oral theophylline in sick sinus syndrome. The THEOPACE study: a randomized controlled trial. *Circulation* 1997;**96**:260–6.

53.Shaw DB, Holman RR, Gowers JI. Survival in sino-atrial disorder (sick-sinus syndrome). *BMJ* 1980;**280**:139–41.

54.Talan DA, Bauernfeind RA, Ashley WW, Kanakis C Jr, Rosen KM. Twenty-four hour continuous ECG recordings in long-distance runners. *Chest* 1982;**82**:19–24.

55.Kruse I, Arnman K, Conradson T-B, Rydén L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1982;**65**:846–55.

56.Perrins EJ, Morley CA, Chan SL, Sutton R. Randomized controlled trial of physiological and ventricular pacing. *Br Heart J* 1983;**50**:112–17.

57.Boon NA, Frew AJ, Johnston JA, Cobbe SM. A comparison of symptoms and intra-arterial ambulatory blood pressure during long term dual chamber atrioventricular synchronous (DDD) and ventricular demand (VVI) pacing. *Br Heart J* 1987;**58**:34–9.

58.Benditt DG, Mianulli M, Fetter J *et al.* Single-chamber cardiac pacing with activity-initiated chronotropic response: evaluation by cardiopulmonary exercise testing. *Circulation* 1987;**75**: 184–91.

59.Lipkin DP, Buller N, Frenneaux M *et al.* Randomized crossover trial of rate responsive Activitrax and conventional fixed rate ventricular pacing. *Br Heart J* 1987;**58**:613–16.

60.Smedgård P, Kristensson B-E, Kruse I, Rydén L. Rate-responsive pacing by means of activity sensing versus single rate ventricular pacing: a double-blind cross-over study. *PACE* 1987;**10**:902–15.

61.Hargreaves MR, Channon KM, Cripps TR, Gardner M, Ormerod OJM. Comparison of dual chamber and ventricular rate responsive pacing in patients over 75 with complete heart block. *Br Heart J* 1995;**74**:397–402.

62.Linde C. How to evaluate quality-of-life in pacemaker patients: problems and pitfalls. *PACE* 1996;**19**:391–7.

63.Sulke N, Dritsas A, Bostock J *et al.* "Subclinical" pacemaker syndrome: a randomized study of symptom free patients with ventricular demand (VVI) pacemakers upgraded to dual chamber devices. *Br Heart J* 1992;**67**:57–64.

64.Alpert MA, Curtis JJ, Sanfelippo JF *et al.* Comparative survival after permanent ventricular and dual chamber pacing for patients with chronic high degree atrioventricular block with and without pre-existent congestive heart failure. *J Am Coll Cardiol* 1986;**7**:925–32.

65.Linde-Edelstam C, Gullberg B, Norlander R *et al.* Longevity in patients with high degree atrioventricular block paced in the atrial synchronous or the fixed rate ventricular inhibited mode. *PACE* 1992;**15**:304–13.

66.Rediker DE, Eagle KA, Homma S, Gillam LD, Harthorne JW. Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. *Am J Cardiol* 1988;**61**:323–9.

67.Mitsuoka T, Kenny RA, Au Yeung T *et al.* Benefits of dual chamber pacing in sick sinus syndrome. *Br Heart J* 1988; **60**:338–47.

68.Hummel J, Barr E, Hanich R *et al.* DDDR pacing is better tolerated than VVIR in patients with sinus node disease. *PACE* 1990;**13**:504.

69.Camm AJ, Katritsis D. Pacing for sick sinus syndrome – a risky business? *PACE* 1990;**13**:695–9.

70.Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;**116**:16–22.

71.Lamas GA. Pacemaker mode selection and survival: a plea to apply the principles of evidence-based medicine to cardiac pacing practice. *Heart* 1997;**78**:218–20.

72.Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomized trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet* 1994;**344**:1523–8.

73.Andersen HR, Nielsen JC, Thomsen PEB *et al.* Long-term follow up of patients from a randomized trial of atrial versus ventricular pacing for sick sinus syndrome. *Lancet* 1997; **350**:1210–16.

74.Andersen HR, Nielsen JC, Bloch Thomsen PE *et al.* Atrioventricular conduction during long-term follow up of patients with sick sinus syndrome. *Circulation* 1998;**98**: 1315–21.
75.Lamas GA, Orav EJ, Stambler BS *et al.* Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. *N Engl J Med* 1998;**338**:1097–104.
76.Ellenbogen KA, Stambler BS, Orav EJ *et al.* Clinical characteristics of patients intolerant to VVIR pacing. *Am J Cardiol* 2000;**86**:59–63.
77.Connolly SJ, Kerr CR, Gent M *et al.* Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med* 2000;**342**:1385–91.
78.Skanes AC, Krahn AD, Yee R *et al.* Progression to chronic atrial fibrillation after pacing: The Canadian Trial of Physiologic Pacing. *J Am Coll Cardiol* 2001;**38**:167–72.
79.Connolly SJ, Talajic M, Roy D *et al.* The effect of pacemaker selection on functional capacity in the Canadian Trial of Physiologic Pacing (CTOPP). *Circulation* 1999;**100**(Suppl. I): I-465.
80.Tang ASL, Roberts RS, Kerr C *et al.* Relationship between pacemaker dependency and the effect of pacing mode on cardiovascular outcomes. *Circulation* 2001;**103**:3081–5.
81.Woodend K, Tang SI, Irvine J *et al.* Pacemaker dependency conditions the QoL benefits of physiological over VVI pacing: Canadian Trial of Physiologic Pacing (CTOPP). *Circulation* 1999;**100**(Suppl. I):I-20.
82.Lamas GA, Lee K, Sweeney M *et al.* The Mode Selection Trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. *Am Heart J* 2000;**140**:541–51.
83.Lamas GA, Lee KL, Sweeney MO *et al.* Ventricular pacing or dual chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;**346**:1854–62.
84.Wharton JM, Sorrentino RA, Campbell P *et al.* Effect of pacing modality on atrial tachyarrhythmia recurrence in the tachycardia-bradycardia syndrome: preliminary results of the Pacemaker Atrial Tachycardia Trial. *Circulation* 1998; **98**(Suppl. I):I-494.
85.Keating E, Grill C, Hafley G, Sorrentino RA, Lee KL, Wharton JM. Effect of pacing modality on quality of life in patients with the tachycardia-bradycardia syndrome. *J Am Coll Cardiol* 1999;**33**(Suppl. A):153A.
86.Wharton JM, Sorrentino RA, Criger D *et al.* Predictors of death in VVI-R and DDD-R paced patients with the tachycardia-bradycardia syndrome. *J Am Coll Cardiol* 1999;**33**(Suppl. A): 153A.
87.Toff WD, Skehan JD, de Bono DP, Camm AJ. The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial. *Heart* 1997;**78**:221–3.
88.Charles RG, McComb JM. Systematic trial of pacing to prevent atrial fibrillation (STOP-AF). *Heart* 1997;**78**:224–5.
89.Charles RG. Personal communication.
90.Andersen HR. Personal communication.
91.Kerr CR, Connolly SJ, Roberts RS *et al.* Effect of pacing mode on cardiovascular death and stroke. The Canadian Trial of Physiologic Pacing: long-term follow up. *PACE* 2002;**24**:553.
92.Andersen HR, Nielsen JC. Pacing in sick sinus syndrome – need for a prospective, randomized trial comparing atrial with dual chamber pacing. *PACE* 1998;**21**:1175–9.
93.Gribbin GM, McComb JM. Pacemaker trials: software or hardware randomization? *PACE* 1998;**21**:1503–7.
94.Rosenqvist M, Obel IWP. Atrial pacing and the risk for AV block: is there a time for change in attitude? *PACE* 1989; **12**:97–101.
95.Santini M, Ricci R. Is AAI or AAIR still a viable mode of pacing? *PACE* 2001;**24**:276–81.
96.Barold SS. Permanent single chamber atrial pacing is obsolete. *PACE* 2001;**24**:271–5.
97.Quan KJ, Carlson MD, Thames MD. Mechanisms of heart rate and arterial blood pressure control: implications for the pathophysiology of neurocardiogenic syncope. *PACE* 1997; **20**:764–74.
98.Morley CA, Sutton R. Carotid sinus syncope. *Int J Cardiol* 1984;**6**:287–93.
99.Brignole M, Menozzi C. Methods other than tilt testing for diagnosing neurocardiogenic (neurally mediated) syncope. *PACE* 1997;**20**:795–800.
100.Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986;**i**:1352–5.
101.Morley CA, Perrins EJ, Grant P *et al.* Carotid sinus syncope treated by pacing. Analysis of persistent symptoms and role of atrioventricular sequential pacing. *Br Heart J* 1982;**47**:411–18.
102.Sugrue DD, Gersh BJ, Holmes DR, Wood DL, Osborn MJ, Hammill SC. Symptomatic "isolated" carotid sinus hypersensitivity: natural history and results of treatment with anticholinergic drugs or pacemaker. *J Am Coll Cardiol* 1986;**7**: 158–62.
103.Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G. Long-term outcome of paced and nonpaced patients with severe carotid sinus syndrome. *Am J Cardiol* 1992;**69**:1039–43.
104.Dey AB, Bexton RS, Tynan MM, Charles RG, Kenny RA. The impact of a dedicated "syncope and falls" clinic on pacing practice in Northeastern England. *PACE* 1997;**20**:815–17.
105.Kenny RAM, Richardson DA, Steen N, Bexton RS, Shaw FE, Bond J. Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J Am Coll Cardiol* 2001;**38**:1491–6.
106.Kenny RA, for the SAFE PACE 2 study group. SAFE PACE 2: Syncope And Falls in the Elderly – Pacing And Carotid Sinus Evaluation. *Europace* 1999;**1**:69–72.
107.Petersen MEV, Sutton R. Cardiac pacing for vasovagal syncope: a reasonable therapeutic option? *PACE* 1997;**20**:824–6.
108.Petersen MEV, Chamberlain-Webber R, Fitzpatrick AP *et al.* Permanent pacing for cardioinhibitory malignant vasovagal syndrome. *Br Heart J* 1994;**71**:274–81.
109.Sheldon RS, Gent M, Roberts RS, Connolly SJ. North American Vasovagal Pacemaker Study: study design and organisation. *PACE* 1997;**20**:844–8.
110.Connolly SJ, Sheldon R, Roberts RS, Gent M on behalf of the Vasovagal Pacemaker Study Investigators. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999;**33**:16–20.
111.Sutton R, Petersen MEV. First steps towards a pacing algorithm for vasovagal syncope. *PACE* 1997;**20**:827–8.
112.Sutton R, Brignole M, Menozzi C *et al.* Dual-chamber pacing in the treatment of neurally mediated tilt-positive

cardioinhibitory syncope. Pacemaker versus no therapy: a multicenter randomized study. *Circulation* 2000;**102**: 294–9.
113.Ammirati F, Colivicchi F, Santini M for the Syncope Diagnosis and Treatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope. A multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52–7.
114.Presentation by S.J. Connolly. North American Society of Pacing and Electrophysiology, 23rd Annual Scientific Sessions, San Diego, USA, 11 May 2002.
115.Raviele A, Giada F, Sutton R *et al.* The Vasovagal Syncope and Pacing (Synpace) trial: rationale and study design. *Europace* 2001;**3**:336–41.
116.Raviele A, Themistoclakis S, Gasparini G. Drug treatment of vasovagal syncope. In: Blanc JJ, Benditt D, Sutton R, eds. *Neurally mediated syncope: pathophysiology, investigations, and treatment*. Armonk, NY: Futura, 1996.
117.Bourdarias JP, Lockhart A, Ourbak P *et al.* Hemodynamique des cardiomyopathies obstructives. *Arch Mal Coeur* 1964; **57**:737–8.
118.McDonald K, McWilliams E, O'Keefe B *et al.* Functional assessment of patients treated with permanent dual-chamber pacing as a primary treatment for hypertrophic cardiomyopathy. *Eur Heart J* 1988;**9**:893–8.
119.Fananapazir L, Cannon RO, Tripodi D, Panza JA. Impact of dual-chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and beta-adrenergic blocker therapy. *Circulation* 1992;**85**:2149–61.
120.Jeanrenaud X, Goy JJ, Kappenberger L. Effects of dual-chamber pacing in hypertrophic obstructive cardiomyopathy. *Lancet* 1992;**339**:1318–23.
121.Slade AKB, Sadoul N, Shapiro L *et al.* DDD pacing in hypertrophic cardiomyopathy: a multicentre clinical experience. *Heart* 1996;**75**:44–9.
122.Daubert JC. Pacing and hypertrophic cardiomyopathy. *PACE* 1996;**19**:1141–2.
123.Fananapazir L, Epstein ND, Curiel RV, Panza JA, Tripodi D, McAreavey D. Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy: evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. *Circulation* 1994;**90**:2731–42.
124.Pavin D, Gras D, De Place C, Leclercq C, Mabo P, Daubert C. Long-term effect of DDD pacing in patients with hypertrophic obstructive cardiomyopathy: is there a left ventricular remodelling? *PACE* 1996;**19**:680.
125.Nishimura RA, Trusty JM, Hayes DL *et al.* Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol* 1997;**29**: 435–41.
126.Kappenberger L, Linde C, Daubert C *et al.* Pacing in hypertrophic obstructive cardiomyopathy. A randomized crossover study. *Eur Heart J* 1997;**18**:1249–56.
127.Linde C, Gadler F, Kappenberger L, Ryden L, for the PIC Study Group. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 1999;**83**:903–7.
128.Kappenberger LJ, Linde C, Jeanrenaud X *et al.* Clinical progress after randomized on/off pacemaker treatment for hypertrophic obstructive cardiomyopathy. *Europace* 1999; **1**:77–84.
129.Gadler F, Linde C, Daubert C, McKenna WJ *et al.* Significant improvement of quality of life following atrioventricular synchronous pacing in patients with hypertrophic obstructive cardiomyopathy. Data from 1 year of follow up. *Eur Heart J* 1999;**20**:1044–50.
130.Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy: a randomized, double-blind, crossover study (M-PATHY). *Circulation* 1999;**99**:2927–33.
131.Brecker SJD, Xiao HB, Sparrow J, Gibson D. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *Lancet* 1992;**340**:1308–12.
132.Hochleitner M, Hörtnagl H, Fridrich L, Gschnitzer F. Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992;**70**:1320–5.
133.Auricchio A, Sommariva L, Salo RW, Scafuri A, Chiariello L. Improvement of cardiac function in patients with severe congestive heart failure and coronary artery disease by dual chamber pacing with shortened AV delay. *PACE* 1993; **16**:2034–43.
134.Linde C, Gadler F, Edner M *et al.* Results of atrioventricular synchronous pacing with optimized delay in patients with severe congestive heart failure. *Am J Cardiol* 1995;**75**: 919–23.
135.Gold MR, Feliciano Z, Gottlieb SS, Fisher ML. Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. *J Am Coll Cardiol* 1995;**26**: 967–73.
136.Nishimura RA, Hayes DL, Holmes DR Jr, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterisation hemodynamic study. *J Am Coll Cardiol* 1995; **25**:281–8.
137.Paul V, Cowell R, Morris-Thurgood J *et al.* First-degree heart block in heart failure: is this a class I indication for dual-chamber pacing? *PACE* 1995;**18**:906.
138.Brecker SJD, Gibson DG. What is the role of pacing in dilated cardiomyopathy? *Eur Heart J* 1996;**17**:819–24.
139.Glikson M, Hayes DL, Nishimura RA. Newer clinical applications of pacing. *J Cardiovasc Electrophysiol* 1997;**8**: 1190–203.
140.Cowell R, Morris-Thurgood J, Ilsley C, Paul V. Septal short atrioventricular delay pacing: additional hemodynamic improvements in heart failure. *PACE* 1994;**17**:1980–3.
141.Gold M, Shorofsky SR, Metcalf MD, Feliciano Z, Fisher ML, Gottlieb S. The acute hemodynamic effects of right ventricular septal pacing in patients with congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;**79**:679–81.
142.Victor F, Leclerq C, Mabo P *et al.* Optimal right ventricular pacing site in chronically implanted patients. *J Am Coll Cardiol* 1999;**33**:311–16.

143.Buckingham TA, Candinas R, Schläpfer J *et al.* Acute hemodynamic effects of atrioventricular pacing at differing sites in the right ventricle individually and simultaneously. *PACE* 1997;**20**:909–15.
144.Schwaab B, Fröhlig G, Alexander C *et al.* Influence of right ventricular stimulation site on left ventricular function in synchronous ventricular pacing. *J Am Coll Cardiol* 1999; **33**:317–23.
145.Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing. *Circulation* 2000; **101**:869–77.
146.Wilensky RL, Yudelman P, Cohen AI *et al.* Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. *Am J Cardiol* 1988;**62**:276–83.
147.de Teresa E, Chamorro JL, Pulpon LA *et al.* An even more physiological pacing. Changing the sequence of activation. In: Steinbech K, Glogar D, Laszkovics A *et al*, eds. *Cardiac pacing*. (Proceedings of the VIIth World Symposium on Cardiac Pacing). Darmstadt, Germany: Steinkopff Verlag, 1983.
148.Cazeau S, Ritter P, Bakdach S *et al.* Four chamber pacing in dilated cardiomyopathy. *PACE* 1994;**17**:1974–9.
149.Bakker PF, Meijburg H, de Jonge N *et al.* Beneficial effects of biventricular pacing in congestive heart failure. *PACE* 1994;**17**:820.
150.Cazeau S, Ritter P, Lazarus A *et al.* Multi-site pacing for end-stage heart failure. *PACE* 1996;**19**:1748–57.
151.Blanc JJ, Etienne Y, Gilard M *et al.* Evaluation of different ventricular pacing sites in patients with severe heart failure. *Circulation* 1997;**96**:3273–7.
152.Leclercq C, Cazeau S, Le Breton H *et al.* Acute hemody-namic effects of biventricular DDD pacing in patients with end-stage heart failure. *J Am Coll Cardiol* 1998;**32**: 1825–31.
153.Auricchio A, Stellbrink C, Block M *et al.* Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 1999;**99**:2993–3001.
154.Kass DA, Chen C-H, Curry C *et al.* Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;**99**:1567–73.
155.Daubert JC, Ritter P, Le Breton H *et al.* Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. *PACE* 1998;**21**:239–45.
156.Walker S, Levy T, Rex S, Brant S, Paul V. Initial United Kingdom experience with the use of permanent, biventricular pacemakers. Implantation procedure and technical considerations. *Europace* 2000;**2**:233–9.
157.Gras D, Mabo P, Tang T *et al.* Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync study. *PACE* 1998; **21**:2249–55.
158.Gras D, Ritter P, Lazarus A *et al.* Long-term outcome of advanced heart failure patients with cardiac resynchronisation therapy. *PACE* 2000;**23**:658.
159.Daubert JC, Cazeau S, Leclercq C. Do we have reasons to be enthusiastic about pacing to treat advanced heart failure? *Eur J Heart Failure* 1999;**1**:281–7.
160.Auricchio A, Stellbrink C, Sack S *et al.* The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study. *Am J Cardiol* 1999;**83**:130D–5D.
161.Auricchio A, Stellbrink C, Sack S *et al.* Long-term clinical effect of haemodynamically optimised cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:2026–33.
162.Auricchio A, Stellbrink C, Sack S *et al.* PATH CHF study: reduced hospitalization days due to heart failure. *Europace* 2001;**2**:B49.
163.Cazeau S, Leclercq C, Lavergne T *et al.* Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; **344**:873–80.
164.Linde C, Leclercq C, Rex S *et al.* Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation In Cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;**40**:111–18.
165.Daubert JC, Linde C, Cazeau S, Kappenberger L, Sutton R, Bailleul C. Clinical effects of biventricular pacing in patients with severe heart failure and chronic atrial fibrillation: results from the Multisite Stimulation in Cardiomyopathy – MUSTIC Study Group. *Circulation* 2000;**102**(Suppl. 2): II–693.
166.Leclercq C, Victor F, Alonso C *et al.* Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. *Am J Cardiol* 2000;**85**:1154–6.
167.Brignole M, Gammage M. An assessment of the optimal ventricular pacing site in patients undergoing "ablate and pace" therapy for permanent atrial fibrillation. *Europace* 2001; **3**:153–6.
168.Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J Cardiac Failure* 2000;**6**:369–80.
169.Abraham WT, Fisher WQ, Smith AL *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; **346**:1845–53.
170.Auricchio A, Pappone C, Schalij MJ, Neuzner J, Padeletti L, Maertens S. Sustained benefit of resynchronization therapy in large patient cohort. *Europace* 2001;**2**(Suppl. B):B48.
171.Zardini M, Tritto M, Bargiggia G *et al.* The InSync Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronization. *Eur Heart J* 2000;**2**(Suppl. J):J16–J22.
172.Saxon LA, DeMarco T, Chatterjee K, Kerwin WF, Boehmer J. Chronic biventricular pacing decreases serum norepinephrine in dilated heart failure patients with the greatest sympathetic activation at baseline. *PACE* 1999;**22**:830.
173.Hamdan MH, Zagrodyzky JD, Joglar JA *et al.* Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation* 2000;**102**:1027–32.
174.Walker S, Levy T, Rex S *et al.* Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure. *Am J Cardiol* 2000;**86**:231–3.

175.Higgins SL, Yong P, Scheck D *et al.* Biventricular pacing diminishes the need for implantable defibrillator therapy. *J Am Coll Cardiol* 2000;**36**:824–7.
176.Cleland JG, Daubert JC, Erdmann E *et al.* The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. *Eur J Heart Fail* 2001; **3**:481–9.
177.Bristow MR, Feldman AM, Saxon LA. *Heart* failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. *J Cardiac Failure* 2000;**6**:276–85.
178.Coumel P, Friocourt P, Mugica J, Attuel P, Leclerq JF. Long term prevention of vagal atrial arrhythmias by atrial pacing at 90/min: experience with 6 cases. *PACE* 1983; **6**:552–60.
179.Gillis AM, Wyse DG, Connolly S *et al.* Atrial pacing periablation for prevention of paroxysmal atrial fibrillation. *Circulation* 1999;**99**:2553–8.
180.Gillis AM, Connolly SJ, Lacombe P *et al.* Randomized crossover comparison of DDDR versus VDD pacing after atrioventricular junction ablation for prevention of atrial fibrillation. *Circulation* 2000;**102**:736–41.
181.Brignole M, Gianfranchi L, Menozzi C *et al.* Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. *Circulation* 1997;**96**:2617–24.
182.Marshall HJ, Harris ZI, Griffith MJ, Holder RL, Gammage MD. Prospective randomized study of ablation and pacing versus medical therapy for paroxysmal atrial fibrillation: effects of pacing mode and mode-switch algorithm. *Circulation* 1999;**99**:1587–92.
183.Ward KJ, Willett JE, Bucknall C, Gill JS, Kamalvand K. Atrial arrhythmia suppression by atrial overdrive pacing: pacemaker Holter assessment. *Europace* 2001;**3**:108–14.
184.Levy T, Walker S, Rex S, Paul V. Does atrial overdrive pacing prevent paroxysmal atrial fibrillation in paced patients? *Int J Cardiol* 2000;**75**:91–7.
185.Garrigue S, Barold SS, Cazeau S *et al.* Prevention of atrial arrhythmias during DDD pacing by atrial overdrive. *PACE* 1998;**21**:1751–9.
186.Wiberg S, Lonnerholm S, Jensen S *et al.* Effect of right atrial overdrive pacing on symptomatic attacks of atrial fibrillation: a multicenter randomized study. *PACE* 2001;**24**:554.
187.Bellocci F, Spampinato A, Ricci R *et al.* Antiarrhythmic benefits of dual chamber stimulation with rate-response in patients with paroxysmal atrial fibrillation and chronotropic incompetence. *Europace* 1999;**1**:220–5.
188.Funck RC, Adamec R, Lurje L *et al.* Atrial overdriving is beneficial in patients with atrial arrhythmias: first results of the PROVE study. *PACE* 2000;**23**:1891–3.
189.Murgatroyd FD, Nitzsché R, Slade AKB *et al.* A new pacing algorithm for overdrive suppression of atrial fibrillation. *PACE* 1994;**17**:1966–73.
190.Ip J, Beau S, Cameron D, for the ADOPT A Investigators. Early results of ADOPT A: Dynamic Atrial Overdrive™ pacing to treat paroxysmal atrial fibrillation. *PACE* 2001; **24**:615.
191.Lam CTF, Lau CP, Leung SK *et al.* Efficacy and tolerability of continuous overdrive atrial pacing in atrial fibrillation. *Europace* 2000;**2**:286–91.
192.Ricci R, Santini M, Puglisi A *et al.* Impact of consistent atrial pacing algorithm on premature atrial complex number and paroxysmal atrial fibrillation recurrences in brady-tachy syndrome: a randomized prospective cross over study. *J Intervent Cardiac Electrophysiol* 2001;**5**:33–44.
193.Israel CW, Lawo T, Lemke B, Grönefeld G, Hohnloser SH. Atrial pacing in the prevention of paroxysmal atrial fibrillation. *PACE* 2000;**23**:1888–90.
194.Presentation by A.J. Camm, on behalf of the AF Therapy study group. European Society of Cardiology, XXIII Congress, Stockholm, September 2001.
195.Anselme F, Saoudi N, Cribier A. Pacing in prevention of atrial fibrillation: the PIPAF studies. *J Intervent Cardiac Electrophysiol* 2000;**4**:177–84.
196.Daubert C, Mabo P, Berder V. Arrhythmia prevention by permanent atrial resynchronization in advanced interatrial block. *Eur Heart J* 1990;**11**:237.
197.Daubert C, Mabo P, Berder V *et al.* Permanent dual atrium pacing in major interatrial conduction block: a four years experience. *PACE* 1993;**16**:885.
198.Mabo P, Daubert JC, Bouhour A, on behalf of the SYNBIAPACE Study Group. Biatrial synchronous pacing for atrial arrhythmia prevention: the SYNBIAPACE study. *PACE* 1999;**22**:755.
199.Saksena S, Prakash, Hill M *et al.* Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. *J Am Coll Cardiol* 1996;**28**:687–94.
200.Delfaut P, Saksena S, Prakash A, Krol RB. Long-term outcome of patients with drug refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. *J Am Coll Cardiol* 1998;**32**:1900–8.
201.Fitts SM, Hill MR, Mehra R *et al.* Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. DAPPAF Phase 1 Investigators. *J Intervent Cardiac Electrophysiol* 1998;**2**:139–44.
202.Saksena S, Filipecki A. Atrial pacing to prevent atrial fibrillation: is there any evidence of its real efficacy? In: Raviele A, ed. *Cardiac arrhythmias 2001* (Proceedings of the 7th International Workshop on Cardiac Arrhythmias, Venice, 2001). Milan: Springer, 2001.
203.Lau CP, Tse HF, Yu CM *et al.* Dual-site atrial pacing for atrial fibrillation in patients without bradycardia. *Am J Cardiol* 2001;**88**:371–5.
204.Bennett DH. Comparison of the acute effects of pacing the atrial septum, right atrial appendage, coronary sinus os, and the latter two sites simultaneously on the duration of atrial activation. *Heart* 2000;**84**:193–6.
205.Baillin SJ, Adler S, Giudici M. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. *J Cardiovasc Electrophysiol* 2001;**12**:912–17.
206.Padeletti L, Pieragnoli P, Ciapetti C *et al.* Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. *Am Heart J* 2001;**142**:1047–55.

207.Padeletti L, Porciani MC, Michelucci A *et al.* Prevention of short term reversible chronic atrial fibrillation by permanent pacing at the triangle of Koch. *J Intervent Cardiac Electrophysiol* 2000;**4**:575–83.
208.Moss AJ, Liu JE, Gottlieb S *et al.* Efficacy of permanent pacing in the long QT syndrome. *Circulation* 1991;**84**:1524–9.
209.Eldar M, Griffin JC, Van Hare GF *et al.* Combined use of beta-adrenergic blocking agents and long-term cardiac pacing for patients with the long QT syndrome. *J Am Coll Cardiol* 1992;**20**:830–7.
210.Schwartz PJ. *The Long QT Syndrome*. New York: Futura, 1997.
211.Zareba W, Priori SG, Moss AJ *et al.* Permanent pacing in the long QT syndrome patients. *PACE* 1997;**20**:1097.
212.Viskin S, Alla SR, Baron HV *et al.* Mode of onset of torsade de pointes in congenital long QT syndrome. *J Am Coll Cardiol* 1996;**28**:1262–8.
213.Klein H, Levi A, Kaplinsky E, DiSegni E, David D. Congenital long-QT syndrome: deleterious effect of long-term high-rate ventricular pacing and definitive treatment by cardiac transplantation. *Am Heart J* 1996;**132**:1079–81.
214.Viskin S. Cardiac pacing in the long QT syndrome: review of available data and practical recommendations. *J Cardiovasc Electrophysiol* 2000;**11**:593–600.
215.Viskin S, Fish R, Roth A, Copperman Y. Prevention of torsade de pointes in the congenital long QT syndrome: use of a pause prevention pacing algorithm. *Heart* 1998;**79**:417–19.
216.Priori SG, Napolitano C, Cantù F, Brown AM, Schwartz PJ. Differential response to Na^+ channel blockade, α-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. *Circ Res* 1996;**78**:1009–15.
217.Schwartz PJ, Priori SG, Locati EH *et al.* Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na^+ channel blockade and to increases in heart rate. *Circulation* 1995;**92**:3381–6.
218.Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade des pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 1997;**96**:2038–47.
219.Schwartz PJ, Priori SG, Spazzolini C *et al.* Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; **103**:89–95.
220.Jacquet L, Ziady G, Stein K *et al.* Cardiac rhythm disturbances early after orthotopic heart transplantation: prevalence and importance of the observed abnormalities. *J Am Coll Cardiol* 1990;**16**:832–7.
221.Holt ND, Tynan MM, Scott CD, Parry G, Dark JH, McComb JM. Permanent pacemaker use after cardiac transplantation: completing the audit cycle. *Heart* 1996;**76**:435–8.
222.Bertolet BD, Eagle DA, Conti JB, Mills RM, Belardinelli L. Bradycardia after heart transplantation: reversal with theophylline. *J Am Coll Cardiol* 1996;**28**:396–9.
223.Miyamoto Y, Curtiss EI, Kormos RL, Armitage JM, Hardesty RL, Griffith BP. Bradyarrhythmias after heart transplantation. *Circulation* 1990;**82**(Suppl. IV):313–17.
224.DiBiase A, Tse TM, Schnittger I, Wexler L, Stinson EB, Valantine HA. Frequency and mechanism of bradycardia in cardiac transplant recipients and need for pacemakers. *Am J Coll Cardiol* 1991;**67**:1385–9.
225.Heinz G, Kratochwill C, Schmid S *et al.* Sinus node dysfunction after orthotopic heart transplantation: the Vienna experience 1987–1993. *PACE* 1994;**17**:2057–63.
226.Scott CD, Omar I, McComb JM, Dark JH, Bexton RS. Long-term pacing in heart transplant recipients is usually unnecessary. *PACE* 1991;**14**:1792–6.
227.Morris-Thurgood J, Cowell R, Paul V *et al.* Hemodynamic and metabolic effects of paced linkage following heterotopic cardiac transplantation. *Circulation* 1994;**90**:2342–7.
228.Morris-Thurgood J, Paul VE, Dyke C *et al.* Chronic linkage after heterotopic heart transplantation. *Transplant Proc* 1997;**29**:580.
229.Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;**328**:1230–5.
230.Stegman SS, Burroughs JM, Henthorn RW. Asymptomatic bradyarrhythmias as a marker for sleep apnea: appropriate recognition and treatment may reduce the need for pacemaker therapy. *PACE* 1996;**19**:899–904.
231.Grimm W, Koehler U, Fus E *et al.* Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. *Am J Cardiol* 2000; **86**:688–92.
232.Kato I, Shiomi T, Sasanabe R *et al.* Effects of physiological cardiac pacing on sleep-disordered breathing in patients with chronic bradydysrhythmias. *Psychiatry Clin Neurosci* 2001; **55**:257–8.
233.Garrigue S, Bordier P, Jaïs P *et al.* Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* 2002;**346**: 404–12.
234.Gottlieb DJ. Cardiac pacing – a novel therapy for sleep apnea? *N Engl J Med* 2002;**346**:444–5.
235.Murdock CJ, Klein GJ, Yee R, Leitch JW, Teo WS, Norris C. Feasibility of long-term electro-cardiographic monitoring with an implanted device for syncope diagnosis. *PACE* 1991;**13**: 1374–8.
236.Lascault G, Barnay C, Cazeau S, Frank R, Medvedowsky JL. Preliminary evaluation of a dual chamber pacemaker with bradycardia diagnostic functions. *PACE* 1995;**18**: 1636–43.
237.Cazeau S, Ritter P, Nitzsché R, Limousin M, Mugica J. Diagnosis of atrial arrhythmias using the Holter function of a new DDD pacemaker. *PACE* 1994;**17**:2106–13.

43 Syncope

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Introduction

Syncope is a symptom consisting of the sudden loss of both consciousness and postural tone, with subsequent spontaneous recovery. Syncopal episodes must be differentiated from other conditions in which real or apparent loss of consciousness may occur, such as seizures, sleep disturbances, accidents, and some psychiatric conditions. Establishing the basis for syncope is essential in order to ascertain prognosis and develop an effective treatment strategy.

Typically syncopal events are brief. Loss of consciousness rarely lasts longer than 10 or 20 seconds, and recovery is relatively prompt and usually unassociated with retrograde amnesia. Some forms of syncope are ushered in by a premonitory phase. This is especially the case with the vasovagal faint, in which lightheadedness, sweatiness, nausea and a feeling of being short of breath are not uncommon, especially in the younger fainter. Additionally, postsyncope recovery may be characterized by a prolonged period of fatigue and listlessness; this feature is once again most commonly associated with the vasovagal faint. As a result, depending upon the manner in which the medical history is elicited, the total duration of "syncope" is often reported to have been quite long. The latter is particularly the case in elderly individuals, in whom recollection of the events may be poor.

To date, with the exception of four recently completed pacing trials in patients with recurrent vasovagal faints, the evaluation and treatment of syncope has not been the subject of large-scale clinical study. Diagnostic strategies have been based largely on experience derived from multiple relatively small single-center non-randomized studies.

Certain syncope-related clinical issues have been subject to "expert task force" review and recommendation by professional and/or scientific societies. The American College of Cardiology task force report on tilt-table testing[1] and the recently published European Society Task Force on Syncope Evaluation[2] are examples of these processes. On the other hand, most current recommendations regarding evaluation and treatment of specific disorders associated with syncope (for example, sinus node dysfunction, AV block, ventricular arrhythmias) are based on compilations of uncontrolled and often retrospective experiences.

In several important clinical scenarios, such as acquired complete heart block, and syncope associated with life-threatening ventricular tachyarrhythmias, evidence of treatment efficacy (that is prevention of syncope recurrences) appears to be adequately substantiated despite the absence of randomized controlled trials. On the other hand, in conditions such as neurally mediated vasovagal syncope the efficacy of current pharmacologic treatments is less certain, and multicenter randomized studies are very much needed.

This chapter focuses on the diagnosis and treatment of the principal clinical conditions associated with syncope. The primary objectives are (1) to identify the most common causes of syncope, (2) to outline a practicable strategy for evaluation of the syncope patient, and (3) to define appropriate directions for treatment. Throughout, an attempt has been made to characterize the status of current clinical evidence related to each of these topics.

Epidemiologic considerations

Studies examining the population frequency of syncope have tended to comprise relatively small numbers of subjects in selected populations, such as the military or tertiary care medical centers or solitary medical practices. Consequently, the true incidence of syncope in the population as a whole remains uncertain. Nevertheless, a number of reports suggest that syncope accounts for approximately 1–3% of emergency room visits and from 1 to 6% of general hospital admissions in the United States,[3,4] and has a prevalence of 15–30% in selected young individuals such as military recruits.[2]

In terms of a broader population sample, the Framingham Study (in which biennial examinations were carried out over a 26 year period in 5209 free-living individuals) reported the occurrence of at least one syncopal event in approximately 3% of men and 3·5% of women.[5] The first occurred at an average age of 52 years (range 17–78 years) for men and 50 years (range 13–87 years) for women. Further, although syncope occurred at virtually all ages, its prevalence increased with advancing age, from eight per 1000 person-examinations in the 35–44 year old age group to approximately 40 per 1000 person-examinations in the ≥75 year age group. Indeed, among elderly patients

confined to long-term care institutions the annual incidence may be as high as 6%. Additionally, among patients who have experienced syncope the recurrence of symptoms was reported to be very common. Several reports provide solid estimates suggesting that recurrences are to be expected in about 30% of individuals.[5–7]

Classification of the causes of syncope

Box 43.1 provides a classification of causes of syncope based on the approximate frequency with which they may be expected to occur in a general internal medicine or family practice. However, the diagnostic problem is complicated by the fact that more than one cause often contributes to the clinical picture. For example, syncope in valvular aortic stenosis is not due solely to a narrowed orifice restricting cardiac output: inappropriate reflex vasodilation and/or primary cardiac arrhythmias often play an important role. Similarly, syncope in association with certain brady- and tachyarrhythmias depends in part on neural reflex factors. For example, the ability to initiate vasoconstriction in response to an arrhythmic stress seems to be an important factor in determining whether the affected individual is able to tolerate the stress or becomes lightheaded or syncopal.[8,9]

Box 43.1 Apparent transient loss of consciousness: diagnostic classification

Syncope

Neurally mediated reflex syncope
- Vasovagal faint
- Carotid sinus syncope
- Cough syncope and related disorders
- Gastrointestinal, pelvic or urologic origin

Orthostatic syncope
- Chronic blood/plasma loss (hemorrhage, diarrhea, Addison's disease, pheochromocytoma)
- Primary autonomic failure syndromes (for example, pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)
- Secondary autonomic failure syndromes (diabetic neuropathy, amyloid neuropathy)
- Drugs and alcohol

Primary cardiac arrhythmias
- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- AV conduction system disease
- Paroxysmal supraventricular and ventricular tachycardias
- Implanted device (pacemaker, ICD) malfunction

Structural cardiovascular or cardiopulmonary disease
- Cardiac valvular disease/ischemia
- Acute myocardial infarction
- Obstructive cardiomyopathy
- Subclavian steal syndrome
- Pericardial disease/tamponade
- Pulmonary embolus
- Pulmonary hypertension

Cerebrovascular
- Vascular steal syndromes
- Seizure disorders
- Panic attacks
- Hysteria

Miscellaneous conditions – not true syncope

Disorders resembling syncope
- Seizures
- Psychogenic 'syncope' (somatization disorders)

Disorders resembling syncope, but usually without complete loss of consciousness
- Hyperventilation (hypocapnia)
- Hypoglycemia
- Acute hypoxemia

In general terms, the classification of the causes of syncope leads to some reasonable conclusions regarding diagnostic testing strategies. It is apparent that attention should be focused on obtaining as detailed as possible medical history of the event(s), assessing the potential role of drugs in precipitating symptoms, and determining the presence or absence of structural heart disease. Neurologic studies (for example, EEG, MRI/CT) should be de-emphasized in the initial evaluation of the syncope patient in the absence of abnormal neurologic signs on physical examination or a clearcut history of seizure disorder.

Neurally mediated reflex syncope

In the various forms of neurally mediated reflex syncope (Box 43.2) systemic hypotension occurs primarily as a result of inappropriate neural reflex activity. In certain cases syncope is principally the result of parasympathetically induced bradycardia or asystole (so-called cardioinhibitory syncope) (Figure 43.1). In others, symptomatic hypotension is due primarily to inappropriate vasodilation (that is vasodepressor syncope). In most cases, however, both phenomena contribute;[1,2,8,10–12] in these latter cases the bradycardia is often modest but is none the less abnormal, given the severity of the hypotension (that is relative bradycardia).

Box 43.2 Neurally mediated reflex syncopal syndromes

Emotional syncope (common or "vasovagal" faint, "malignant" vasovagal faint)
Carotid sinus syncope
Cough, sneeze syncope
Exercise, postexercise variant
Gastrointestinal stimulation
  Swallow syncope, defecation syncope
Glossopharyngeal neuralgia
Postmicturition syncope
Raised intrathoracic pressure, airway stimulation
  Brass wind instrument-playing, weightlifting

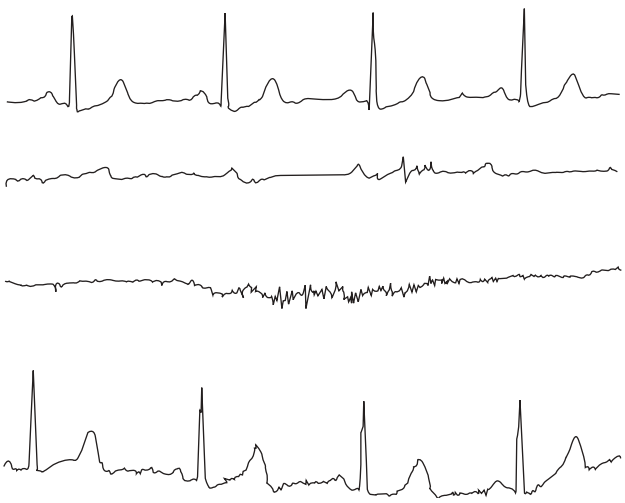

Figure 43.1 Continuous single-channel electrocardiographic recording during an episode of spontaneous vasovagal syncope. A characteristic finding is the presence of sinus bradycardia in conjunction with AV block, indicating the occurrence of concomitant cardioinhibition despite hypotension induced by bradycardia.

The vasovagal faint and carotid sinus syndrome are the most common forms of neurally mediated syncope. The vasovagal faint (also known as the "common faint") may be triggered by any of a variety of factors, including unpleasant sights, pain, extreme emotion and prolonged standing. Vasovagal syncope may often be suspected in the presence of a "typical" medical history, but often the history is not definitive. In such cases, tilt-table testing is the most important supportive diagnostic test.[1,8,10–12] Carotid sinus syndrome is probably the second most common form of the neurally mediated syncopal syndromes, but is often overlooked in clinical practice. Recent experience suggests that carotid sinus syndrome may be an important cause of nonaccidental "falls" in older individuals.[13] Consequently, this often overlooked diagnosis warrants careful consideration in all older patients who faint or present with falls and/or injuries that are not readily accounted for.

Despite the apparent "mixed" bradycardia–vasodilation picture observed during diagnostic evaluation (especially during tilt-table testing), substantial recent published clinical experience suggests that bradycardia might be more important than previously believed during spontaneous syncope epsiodes, especially in vasovagal fainters. In this regard, the VPS1 study utilized a relatively complex system to identify bradycardia.[14] The VASIS trial used a more intuitive classification scheme.[15,16] In both cases, randomized controlled trials versus conventional medical treatment at the time showed pacing to be highly effective in a subset of relatively symptomatic individuals with recurrent vasovagal faints. An additional pacemaker versus β adrenergic drug treatment trial[17] also ended in favor of pacing. Finally, in partial explanation of these observations, the recently reported ISSUE trial results indicated that tilt-table testing (for reasons as yet unknown) may overestimate the importance of the vasodilation component in vasovagal fainters.[18] Bradycardia was far more frequent than initially suspected, based on observations made using implantable loop recorders (Reveal®, Medtronic Inc., Minneapolis, MN, USA).

The occurrence of syncope (or unexplained "falls") without warning in older persons should lead to consideration of carotid sinus syndrome. The condition is probably present when symptoms are reproduced during firm linear carotid sinus massage (usually best undertaken with the patient in the upright position, carefully secured on a tilt-table) in conjunction with asystole, paroxysmal AV block, and/or a marked drop in systemic arterial pressure.[13] In the absence of symptom reproduction, a pause of 5 seconds or longer is probably sufficient to support the diagnosis (assuming other etiologies of syncope have been excluded to the extent that it is possible to do so).

Orthostatic syncope

The abrupt assumption of an upright posture often results in presyncopal symptoms (that is transient "gray-out") even in apparently healthy individuals, but frank syncope is thought to be uncommon. However, syncope may occur in some cases, especially in elderly or less physically fit individuals, or in patients who are volume depleted.

Iatrogenic factors such as excessive diuresis or the aggressive prescription of antihypertensive drugs are probably by far the most important contributors to the development of posturally related syncope. Less often, primary forms of autonomic nervous system dysfunction are the cause. Some of the more important of these include pure autonomic failure, multiple system atrophy, and Parkinson's disease with autonomic failure.[14] Although these conditions are rare, their recognition and study may provide valuable information of importance to a much larger group of patients who have disorders with less well defined defects, including neurally mediated hypotension and the postural tachycardia syndromes (POTS). Furthermore, as these often overlooked disturbances and their potentially subtle manifestations become more widely appreciated, they will be identified more often. For instance, Low *et al*[19] reviewed their experience in 155 patients referred for assessment of suspected orthostatic hypotension. Their findings revealed that among the most severely affected symptomatic patients ($n = 90$, mean age 64 years), pure autonomic failure accounted for 33%, multisystem atrophy for 26% and autonomic/diabetic neuropathy for 31%. Finally, secondary autonomic dysfunction due to neuropathies associated with chronic diseases (for example, diabetes mellitus), toxic agents (for example, alcohol) or infections (Guillain–Barré syndrome) are relatively

common and may also cause syncope in association with orthostatic hypotension.

Tilt-table testing facilities may be helpful in identifying patients susceptible to syncope associated with orthostatic hypotension. However, the diagnosis of the various forms of autonomic failure using tilt-table and other autonomic testing procedures[19–22] requires a level of experience which is currently not widely available.

Primary cardiac arrhythmias

Primary cardiac arrhythmias – that is, those rhythm disturbances arising as a result of cardiac conduction system disturbances, anomalous electrical connections or myocardial disease – are important causes of syncope. In general terms, the arrhythmias most often associated with syncope or near-syncope are the bradyarrhythmias accompanying sinus node dysfunction (also termed "sick sinus syndrome"[23,24]) or AV block, and the tachyarrhythmias of ventricular origin.

Sinus node dysfunction

Sinus node dysfunction comprises various sinus node and/or atrial arrhythmias that result in persistent or intermittent periods of inappropriately slow (sinus bradycardia, sinus pauses, sinoatrial exit block) or fast heart beating (most often atrial fibrillation or atrial flutter)[23–25] (Figure 43.2). In terms of syncope, the bradyarrhythmias appear to be the more important culprits. For example, among 56 patients with either severe bradyarrhythmias or bradycardia–tachycardia syndrome described by Rubenstein *et al*,[25] 25 (45%) presented with syncope and an additional 15 (27%) reported various presyncopal symptoms. In the vast majority of these cases (80%), bradyarrhythmias were considered to be the principal responsible rhythm disturbance.

In general terms, sinus node dysfunction may be considered as intrinsic or extrinsic in nature. Intrinsic sinus node dysfunction is, for the most part, closely associated with underderlying structural disturbances in the atria (for example, fibrosis, chamber enlargement). Atrial changes accompanying the aging process need also to be included in the intrinsic category. In the case of extrinsic sinus node dysfunction, autonomic nervous system influences, cardioactive drugs and/or metabolic disturbances may be the principal cause (perhaps acting in conjunction with some degree of intrinsic abnormality). Of the extrinsic contributors, drug-induced disturbances due to β adrenergic receptor blockers, calcium channel blockers, membrane-active antiarrhythmics (especially amiodarone, sotalol, flecainide and propafenone) and the antiepileptic drug carbamazepine (Tegretol®) have been recognized causes of bradycardia.[23,26,27] Extrinsic factors may also play a role in initiating or aggravating atrial tachyarrhythmias (for example, so-called vagally mediated atrial fibrillation, induction of atrial fibrillation following administration of adenosine), but their importance in terms of causing syncope in this manner is probably minor.

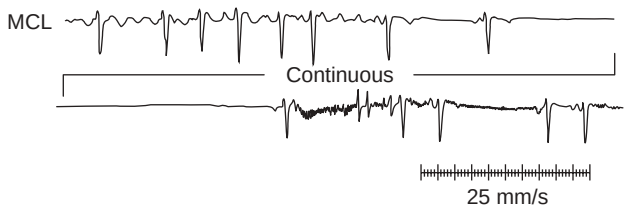

Figure 43.2 Electrocardiographic recording during a spontaneous "dizzy" spell. A prolonged pause following spontaneous termination of atrial fibrillation is a typical feature of sinus node dysfunction.

Disturbances of atrioventricular (AV) conduction

Disturbances of AV conduction range from prolongation of AV conduction time (first degree AV block) to intermittent failure of AV impulse transmission (second degree AV block) to complete conduction failure (third degree AV block). For practical purposes, isolated first degree AV block is not usually a cause of syncopal symptoms (pseudo-pacemaker syndrome accompanying fixed long PR intervals being a possible exception). However, first degree AV block in the presence of a wide QRS complex suggests more severe conduction system disease, and raises the possibility that higher grades of AV block may be occurring from time to time. Similarly, although isolated Mobitz type I second degree AV block is an unlikely cause of syncope, its presence in the setting of a wide QRS leads to the risk that periods of higher grade AV block may be occurring from time to time. As a rule, however, it is the more severe forms of acquired AV block (that is, Mobitz type II, "high grade" and complete AV block) that are most closely associated with syncopal symptoms. In these cases the cardiac rhythm may become dependent on often unreliable subsidiary pacemaker sites. Syncope (reported in 38–61%[28,29]) occurs because of the long delay before these pacemakers begin to "fire" consistently. In addition, these subsidiary pacemaker sites often have relatively slow rates (typically 25–40 beats/min) and are easily suppressed by drugs that patients may be taking (for example, β adrenergic blockers); consequently syncope or presyncope occurs as a result of a transient period of inadequate cerebral perfusion. In contrast to acquired forms of AV block, congenital complete AV block has generally been considered to be more benign and less often the cause of syncope. Recently, however, the benign nature of this condition has been questioned. Michaelson *et al*[30] suggest that syncope is more common and mortality greater in congenital AV block patients than had previously been suspected.

Syncope in patients with various forms of bundle branch block and fascicular block depends both on the risk of developing high grade or complete AV block, as well as on the

risk of occurrence of ventricular tachyarrhythmias. As a rule, in chronic infranodal conduction system disease, such as most forms of bifascicular block, progression to more severe AV block is slow. However, the risk increases the longer the duration of the HV interval (normal range 35–55 ms), and is particularly great for HV intervals >100 ms[31,32] (Figure 43.3). Nevertheless, despite clearcut evidence for severe conduction system disease, syncope in these patients may in fact be the result of ventricular tachycardia owing to the usual coexistence of conduction system disease with severe left ventricular dysfunction.[32] Invasive electrophysiologic testing is probably the most helpful way to address this latter concern in individual patients.

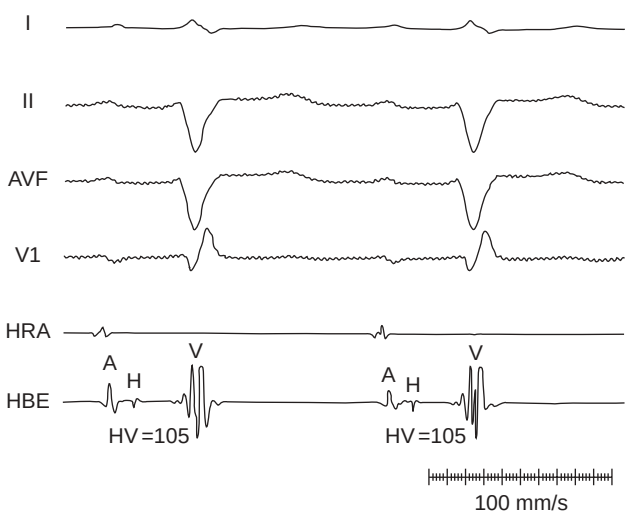

Figure 43.3 Electrocardiographic and intracardiac recordings illustrating first degree AV block and bifascicular block in conjunction with a prolonged HV interval. Syncope in this setting suggests an intermittent AV block origin. Proof requires further evaluation.

Ventricular tachyarrhythmias

Ventricular tachyarrhythmias have been reported to be responsible for syncope in up to 20% of patients referred for electrophysiologic assessment. Risk factors include underlying structural heart disease, evident conduction system disease, and congenital or drug-induced long QT syndrome (Figure 43.4). Tachycardia rate, status of left ventricular function, and the efficiency of peripheral vascular constriction determine whether the arrhythmia will induce syncopal symptoms.

Figure 43.4 Electrocardiographic recording illustrating polymorphic VT in a patient with recurrent syncope and presyncope. The arrhythmia morphology is suggestive of *torsade de pointes*.

Non-sustained ventricular tachycardia is a common finding during ambulatory electrocardiographic monitoring, especially in patients with structural heart disease. As a result, such a finding during the assessment of a syncope patient has not in the past been considered very helpful in the absence of documented concomitant symptoms. However, this conventional view is changing, especially in patients with severely diminished left ventricular function, given the recently reported MUSTT results.[33] Consequently, in the absence of other causes of syncope, the potential role of non-sustained ventricular tachycardia warrants additional testing, particularly electrophysiologic study with concomitant hemodynamic recordings. In fact, based on the combined findings of MUSTT and MADIT 2,[34] one may argue that an implantable defibrillator may be warranted independent of electrophysiologic study when severe left ventricular dysfunction is present (as assessed by an ejection fraction <35%).

A persisting perplexing problem is the appropriate approach to be taken when syncope occurs in patients with severe underlying left ventricular dysfunction (for example, dilated cardiomyopathy) in the absence of documented ventricular tachyarrhythmia. Recent evidence suggests that there is high risk for symptom recurrence and probably sudden death.[35,36] Prophylactic placement of an implantable cardioverter defibrillator (ICD) is becoming increasingly frequently recommended, although confirmation of the reasonableness of this strategy must await completion of the SCD-HEFT study.

Long QT syndrome (LQTS) presents a special form of ventricular tachycardia risk, known for its presentation as syncope. LQTS may not be among the most common causes of syncope, but must always be borne in mind. Syncope is primarily due to *torsade de pointes*, a form of polymorphic ventricular tachycardia characterized by an undulating ECG waveform produced by a shifting QRS axis in the setting of QT interval prolongation (acquired or congenital in origin). The acquired form of LQTS is by far the more common, and is most frequently the result of drugs that prolong the QT interval. *Torsade* in this setting is most often seen during periods of bradycardia (for example, sleep) or following pauses in the cardiac rhythm (for example, post PVC) which accentuate the QT interval. Some of the best-known offending drugs/agents are listed in Box 43.3. Congenital, idiopathic or familial LQTS is caused by mutations in cardiac ion channels that contribute to the action potential repolarization process. Congenital LQTS is a very infrequent cause of syncope, but its identification can be life saving. Affected individuals have QT prolongation and a high risk of recurrent syncope and sudden cardiac death due to *torsade de pointes*. An international registry for LQTS was established in 1979;[37] among 235 probands reported in a 1991 report, the annual rate of recurrent syncope and probable LQTS-related death was 5% and 0·9%, respectively.[38] Syncope and

sudden death in this setting is frequently associated with emotional or physical arousal, such as may be triggered by fear, loud noises or exertion.[37,38] Heterogeneity in clinical presentation exists, however, so that in other individuals *torsade de pointes* occurs because of bradycardia or during sleep in conjunction with rate-dependent QT interval prolongation.[39]

Box 43.3 Drugs/agents implicated in QT prolongation and *torsade de pointes*

Antiarrhythmic agents
Class IA
Quinidine
Procainamide
Disopyramide
Class III
Sotalol
Ibutilide
N-Acetylprocainamide (NAPA)
Dofetilide
Amiodarone (relatively low risk)

Antianginal agents
Bepridil (removed from market in USA)

Psychoactive agents
Phenothiazines
Thioridazine

Tricyclic antidepressants
Amitriptyline
Imipramine

Antibiotics
Erythromycin
Pentamidine
Fluconazole

Antiemetics
Droperidol

Non-sedating antihistamines
Terfenadine
Astemizole

Miscellaneous
Cisapride (removed from market in USA)
Arsenic

Supraventricular tachyarrhythmias

The supraventricular tachycardias are generally considered to be less frequent causes of syncope than are ventricular tachyarrhythmias. Supraventricular tachycardias are reported to be the cause of syncope in about 15% of patients referred for electrophysiologic evaluation.[40] The rate of the tachycardia, the volume status and posture of the patient at time of onset of the arrhythmia, the presence of associated structural cardiopulmonary disease, and the integrity of reflex peripheral vascular compensation are key factors determining whether hypotension of sufficient severity to cause syncope occurs.[9] As a rule, if symptoms of syncope or near-syncope do develop, it is at the onset of a paroxysmal tachycardia, before vascular compensation can evolve. However, syncope may also occur at the termination of tachycardia if a pause ensues prior to restoration of a stable atrial rhythm.

Structural cardiovascular or cardiopulmonary disease

Structural cardiac or cardiopulmonary disease is often present in syncope patients, particularly those in older age groups. However, in these cases it is the arrhythmias associated with structural disease that are more often the cause of the symptoms. In terms of syncope directly attributable to structural disease, probably the most common is that which occurs in conjunction with acute myocardial ischemia or infarction. Other relatively common acute medical conditions associated with syncope include pulmonary embolism and pericardial tamponade. The basis of syncope in these conditions is multifactorial, including both the hemodynamic impact of the specific lesion and neurally mediated reflex effects. The latter is especially important in the setting of acute ischemic events, exemplified by the bradycardia and hypotension often associated with inferior wall myocardial infarction.[8]

Syncope may also occur and be a presenting feature in conditions in which there is fixed or dynamic obstruction to left ventricular outflow (for example, aortic stenosis, hypertrophic obstructive cardiomyopathy).[8] In such cases symptoms are often provoked by physical exertion, but may also develop if an otherwise benign arrhythmia should occur (such as atrial fibrillation). The basis for the faint is partly inadequate blood flow owing to the mechanical obstruction. However, especially in the case of valvular aortic stenosis, ventricular mechanoreceptor mediated bradycardia and vasodilatation are thought to be important contributors.[8,41] In obstructive cardiomyopathy neural reflex mechanisms may also play a role, but the occurrence of atrial tachyarrhythmias (particularly atrial fibrillation) or ventricular tachycardia (even at relatively modest rates) is often a trigger for syncopal events.

On rare occasion subclavian "steal" syndrome or severe carotid artery disease may be the cause of syncope. Other even less common causes include left ventricular inflow obstruction in patients with mitral stenosis or atrial myxoma, right ventricular outflow obstruction, and right to left shunting secondary to pulmonic stenosis or pulmonary hypertension.

Cerebrovascular, neurologic and psychiatric disturbances

Cerebrovascular disease and neurologic disturbances (for example, seizure disorders) are rarely the cause of true syncope.[2,42] More often, these conditions result in a clinical

picture that may be mistaken for syncope but which can be distinguished by careful history taking and neurologic examination. On occasion certain seizure disorders (particularly of the temporal lobe) may so closely mimic (or induce) neurally mediated reflex bradycardia and hypotension that differentiation from "true" syncope is difficult. In such cases a diagnostic EEG is necessary (recognizing that not all forms of epilepsy will be detected by EEG). More often, a number of important features help differentiate seizures from true syncope:

- Seizures tend to be positionally independent, whereas syncope is most commonly associated with upright posture.
- Seizures are often preceded by an aura, whereas syncope is not.
- Seizures are often immediately accompanied by convulsive activity and incontinence, whereas in true syncope any abnormal motor activity is less severe and incontinence is unusual.[43,44]
- Seizures are typically followed by a confusional period, whereas true syncope is typically followed by prompt restoration of mental state (although fatigue may persist, especially in the case of vasovagal syncope).

Nevertheless, despite these diagnostic features the failure of "seizures" to respond to conventional treatment must result in reconsideration of a cardiac cause (particularly a cardiac arrhythmia).[43,44]

Transient disturbances of cerebrovascular blood flow may initiate a true syncopal spell. For example, cerebrovascular spasm (possibly as part of a migraine syndrome) may present with what appears to be a syncopal episode. In the latter case, other historical features of migraine and migraine susceptibility may suggest the diagnosis. On the other hand, it has recently been proposed that cerebrovascular spasm may be a cause of apparently "normotensive" syncope without migraine.[45,46] If this proves to be relatively common, then it will be necessary to reassess the nature of the diagnosis in many patients, particularly those where the syncope is currently considered to be psychogenic in origin.

Syncope may be mimicked by anxiety attacks, hysteria or other psychiatric disturbances. Anxiety attacks are frequently associated with hyperventilation and hypocapnia. Hysteria, however, tends to be characterized by its occurring in the presence of onlookers and being unassociated with marked alterations of heart rate, systemic pressure or skin color. Currently, however, despite the apparent frequency of these conditions in patients referred for evaluation of "syncope",[47] they must be considered only after other conditions have been carefully excluded.

Miscellaneous causes

Severe hyperventilation resulting in hypocapnia and transient alkalosis may be the most frequent "syncope-like" condition in this category. In these patients anxiety may be an important coexisting feature, but its presence alone is not sufficient to establish a diagnosis. The association of emotional upset or anxiety with syncope is also common in vasovagal fainters, and is a reasonable secondary event in any patient experiencing a syncopal episode.

Metabolic and endocrine disorders rarely cause true syncope. More often such conditions may be responsible for confusional states or behavioral disturbances. Nevertheless, making a clearcut distinction between such symptoms and syncope may not be possible by history alone. As a rule, though, unlike true syncope, conditions such as diabetic coma, or severe hypoxia or hypercapnia do not resolve in the absence of active therapeutic intervention.

Strategy for the diagnostic evaluation

The goal of diagnostic testing is to establish a sufficiently strong correlation between syncopal symptoms and detected abnormalities to permit both an assessment of prognosis and initiation of an appropriate treatment plan (Figure 43.5). To this end, the first step is to obtain a detailed medical history, including interviewing knowledgeable bystanders and relatives. Next, a physical examination along with certain basic tests (electrocardiogram (ECG) and echocardiogram) should be undertaken to ascertain whether there is evidence of underlying structural heart disease. Exercise testing may be included if syncope occurs with exertion, or if ischemic heart disease is suspected. Thereafter, the need for further specialized diagnostic testing will vary depending on a variety of factors, including the certainty of the initial clinical impression; findings during physical examination; the number and frequency of syncopal events reported; the occurrence of injury or accident; family history of syncope or sudden death; and the potential risks associated with the individual's occupation (for example, commercial vehicle driver, machine operator, professional athlete, sign painter, surgeon) or avocation (for example, skier, swimmer) that might be encountered if syncope recurred.

As a rule, if structural heart disease is deemed to be absent by initial evaluation, then tilt-table testing in conjunction with related assessment of autonomic nervous system function is the most useful diagnostic test, as neurally mediated vasovagal syncope and orthostatic hypotension are by far the most frequent causes of syncope in this setting. On the other hand, if abnormal cardiac findings are identified, their functional significance should be characterized by hemodynamic and/or angiographic assessment. Furthermore, because arrhythmias are a common cause of syncope in patients with structural cardiac disease, assessing the patient's susceptibility to tachy- and bradyarrhythmias by various non-invasive (for example, ambulatory electrocardiography, signal averaged electrocardiogram, SAECG) and invasive electrophysiologic

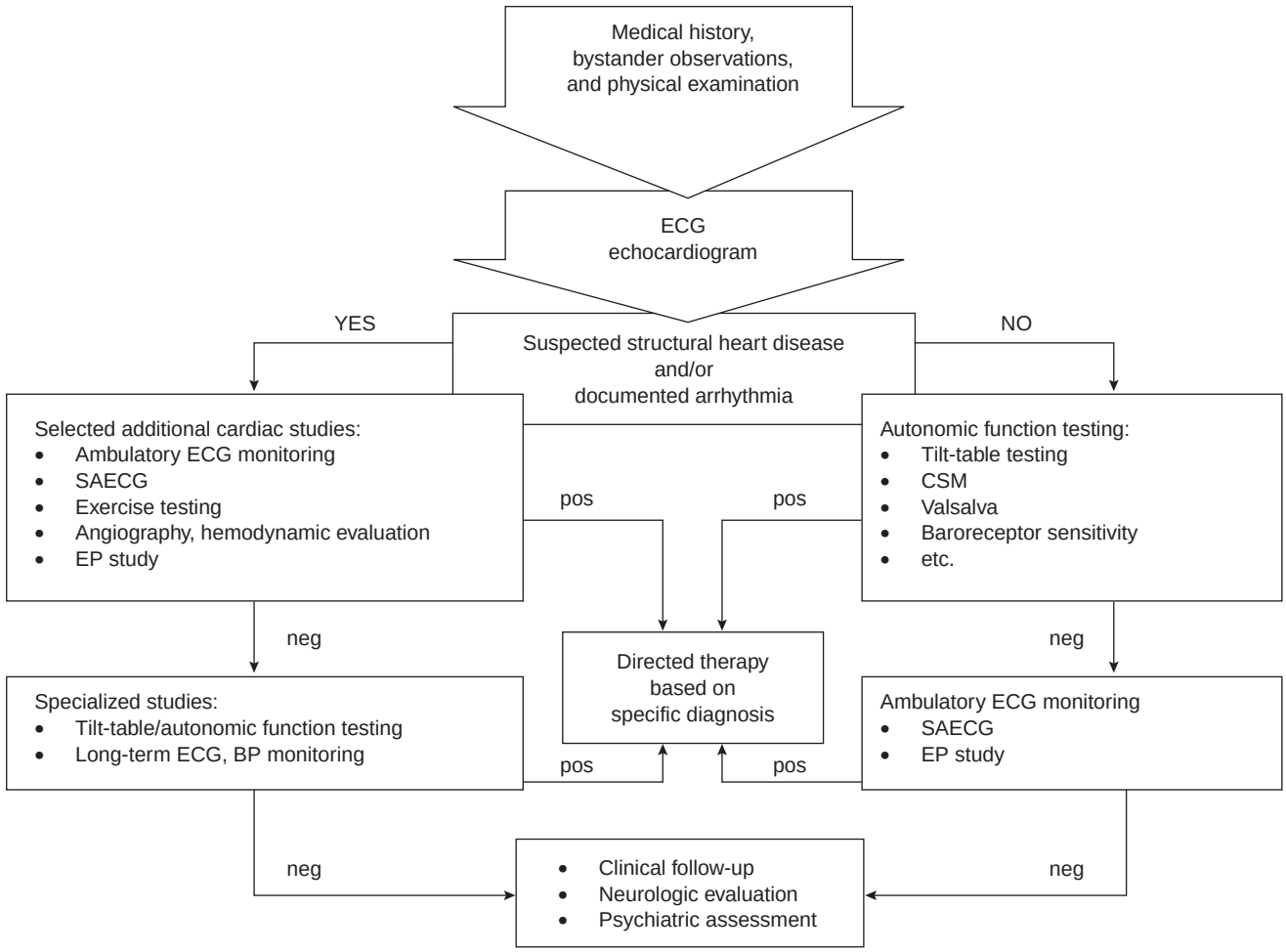

Figure 43.5 A practical strategy for the clinical evaluation of syncope

testing is warranted. Tilt-table testing would follow if the diagnosis remained in doubt.[1] Strong evidence supports the view that only infrequently should specialized neurologic studies be ordered early in the evaluation (for example, if the history were more suggestive of a seizure disorder).[1,42,43] In some cases the diagnosis can only be obtained by long-term ambulatory electrocardiographic monitoring, occasionally necessitating placement of an implantable loop recorder.[48–50]

Electrocardiographic recordings

Because cardiac arrhythmias are so frequently the cause of syncope, ECG documentation during a spontaneous syncopal event is highly desirable. In this regard, the 12-lead ECG is usually too brief to capture a specific cause. However, findings such as ventricular pre-excitation or QT interval prolongation may suggest a diagnosis. If it is feasible at all, obtaining ECG documentation during spontaneous symptoms often necessitates prolonged ambulatory monitoring by Holter or event recorders. Exercise testing is usually of limited utility unless the syncopal events are clearly exertionally related by history. However, in rare instances exercise testing may permit the detection of rate-dependent AV block, exertionally related tachyarrhythmias, or the exercise-associated variant of neurally mediated syncope.[8,51,52] Finally, although the signal averaged electrocardiogram (SAECG) cannot provide direct evidence for the cause of syncope, such testing may be helpful in patients with ischemic heart disease if "normal": a normal SAECG tends to exclude susceptibility to ventricular tachyarrhythmias.[53]

Imaging techniques

Echocardiography rarely provides a definitive basis for syncope. None the less, the echocardiogram is invaluable, given the importance of identifying underlying structural heart disease in patients with syncope. Further, in some cases the echocardiogram may provide direct clues to the cause if, for example, hypertrophic obstructive cardiomyopathy, severe

valvular aortic stenosis, intracardiac tumor (for example, myxoma) or anomalous origin of one or more coronary arteries are detected. Ultrasound techniques also are appropriately employed to assess vascular disturbances detected on physical examination. Thus, assessment of the carotid and/or subclavian system may be an appropriate step in selected individuals. Other imaging modalities, such as radionuclide imaging, are reserved for specific clinical indications.

Clinical electrophysiologic testing

Electrophysiologic testing for assessment of syncope has been the subject of many reports. Although there are no large randomized studies, there is reasonably strong evidence to indicate that electrophysiologic testing is most likely to be diagnostic in individuals with underlying structural heart disease[34,54–58]. **Grade B** For example, in a review by Camm and Lau,[40] testing was clearly more successful in patients with structural cardiac disease (71%) than in patients without (36%). However, care must be taken in interpreting the findings of electrophysiologic testing. Fujimura *et al*[59] summarized the outcomes of electrophysiologic testing in syncope patients in whom bradyarrhythmias were known to be the cause. Among 21 patients with known symptomatic AV block or sinus pauses, electrophysiologic testing only correctly identified 3 of 8 patients with documented sinus pauses (sensitivity 37·5%) and 2 of 13 patients with documented AV block (sensitivity 15·4%). On the other hand, although firm evidence is lacking, the induction of re-entry supraventricular or ventricular tachycardia in a syncope patient is highly likely to be significant. These arrhythmias are rarely inconsequential bystanders; however, demonstration of their hemodynamic significance in an individual patient may necessitate their induction with the patient in an appropriately secured upright tilt position.

Head-up tilt-table testing

So far, the head-up tilt table test is the only diagnostic tool to have been subjected to sufficient clinical scrutiny to assess its effectiveness in the evaluation of vasovagal syncope. The evidence supporting its utility in this setting is convincing, and an ACC expert task force has provided guidelines regarding indications for and the methodology of appropriate use of the tilt-table laboratory[1]. **Grade B** Such testing, especially when undertaken in the absence of drugs, appears to discriminate well between symptomatic patients and asymptomatic control subjects.[60–65] For example, de Mey and Enterling[60] reported only eight instances of hypotension bradycardia among 40 apparently normal subjects (20%). Similarly, during a 45 minute drug-free tilt at 60°, Raviele *et al*[62] noted that none of 35 control subjects developed syncope. In regard to the potential impact of provocative pharmacologic agents on the specificity of tilt testing, Natale *et al*[65] found that tilt-table testing at 60, 70 and 80° exhibited specificities of 92%, 92% and 80%, respectively, when low doses of isoproterenol were used. In summary, there is very strong evidence to suggest that tilt-table testing at angles of 60–70° in the absence of pharmacologic provocation exhibits a specificity of approximately 90%. In the presence of pharmacologic provocation test specificity may be reduced, but none the less remains in a range that permits the test to be clinically useful as a diagnostic procedure.

The combination of tilt-table testing and invasive electrophysiologic testing has substantially enhanced diagnostic capabilities in syncope patients. Sra *et al*[58] reported the results of electrophysiologic testing in conjunction with head-up tilt testing in 86 consecutive patients referred for evaluation of unexplained syncope. Electrophysiologic testing was abnormal in 29 (34%) of patients, with the majority of these (21 patients) being inducible sustained monomorphic ventricular tachycardia. Among the remaining patients, head-up tilt testing proved positive in 34 cases (40%), whereas 23 patients (26%) remained undiagnosed. In general, patients exhibiting positive electrophysiologic findings were older, more frequently male, and exhibited lower ventricular ejection fractions and higher frequency of evident heart disease than was the case in patients with positive head-up tilt tests or patients in whom no diagnosis was determined.

In a further evaluation of the combined use of electrophysiologic testing and head-up tilt testing in the assessment of syncope, Fitzpatrick *et al*[66] analyzed findings in 322 patients. Conventional electrophysiologic testing provided a basis for syncope in 229 of 322 cases (71%), with 93 patients having a normal electrophysiologic study. Among the patients with abnormal electrophysiologic findings, AV conduction disease was diagnosed in 34%, sinus node dysfunction in 21%, carotid sinus syndrome in 10% and an inducible sustained tachyarrhythmia in 6%. In the 93 patients with normal electrophysiologic studies, tilt-table testing was undertaken in 71 cases and reproduced syncope, consistent with a vasovagal faint, in 53 (75%).

Neurologic studies

Conventional neurologic laboratory studies (EEG, head CT and MRI) have had a relatively low yield in unselected syncope patients. For instance, among the 433 syncope evaluations reviewed by Kapoor[42] the EEG proved helpful in only three cases. Consequently, these studies should be restricted to those situations in which other clinical observations suggest organic nervous system disease (see discussion earlier). On the other hand, given the importance of orthostatic and dysautonomic causes of syncope, tilt-table testing and other tests of autonomic function have an increasingly important role to play (see earlier discussion). In regard to the latter, a wide range of disorders associated with orthostatic intolerance (see earlier) are now being recognized by virtue of

tilt-table testing and autonomic studies. These include postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension (of various etiologies), inappropriate sinus tachycardia, chronic fatigue syndrome, and the neurally mediated faints. Syncope has been associated with each of these disorders, although the mechanism of the faint is often unclear. It is reasonable to assume that the sophistication of this classification and the frequency with which these conditions are recognized will increase as further experience in their diagnosis and treatment is derived.

Treatment

Prevention of syncope recurrences depends critically on establishing an accurate etiologic diagnosis. Thereafter, the treatment strategy may encompass a wide range of approaches, including reassurance and education, as well as pharmacologic and device therapies. The effectiveness of treatment varies, however, depending upon the specific diagnosis. Thus, the evidence supporting the utility of cardiac pacing in carotid sinus syncope and acquired AV block is substantial. **Grade B** On the other hand, evidence favoring the effectiveness of pharmacologic management in vasovagal syncope is much more arguable (**Grade C**, with the possible exception of β adrenergic blockade and midodrine – **Grade B**), as large-scale randomized controlled treatment trials have yet to be undertaken.

In the case of neurally mediated syncopal syndromes, treatment initially comprises education regarding the avoidance of triggering events (for example, hot crowded environments, dehydration, effects of cough etc.), recognition of premonitory symptoms, and maneuvers to abort the episode (for example, a supine posture). Additionally, if possible, strategies should address trigger factors directly (for example, suppressing the cause of cough in cough syncope).

In vasovagal syncope, most patients require primarily reassurance and education. However, when symptoms are recurrent or severe, or threaten lifestyle or occupation, a more aggressive treatment strategy is needed. In some highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of enforced upright posture (so-called "tilt-training") or other physical maneuvers may be useful in reducing susceptibility.[67–69] For most symptomatic patients, however, pharmacologic approaches have been favored. "Volume expanders" (for example, electrolyte-containing "sports" drinks, fludrocortisone, salt tablets) are among the safest initial approaches (excluding patients with baseline hypertension), but have not been subjected to controlled study. **Grade C** β Adrenergic blocking drugs have been the subject of more detailed study and appear to be useful in younger fainters. **Grade B** Other potentially helpful agents include midodrine (a vasoconstrictor), disopyramide, and serotonin reuptake inhibitors. However, experience with any of these drugs is currently slight.[70–79] The few small controlled studies that have been reported (atenolol, cafedrine, disopyramide, scopolamine and etilefrine) all have methodologic problems. Midodrine may be an exception in that several single center studies, including a well designed controlled trial in which volume served as a control, tend to support its effectiveness[76–79]. **Grade B**

Cardiac pacing has proved highly successful in carotid sinus syndrome **Grade B** and is acknowledged to be the treatment of choice when bradycardia has been documented.[80] More recently, the role of pacing in vasovagal syncope has received increasing attention. In this regard, strong supportive evidence of efficacy of cardiac pacing in selected patients with vasovagal syncope has been provided in the report of the North American vasovagal pacemaker study,[14] the findings of the VASIS trial in Europe,[15] and in the study by Ammirati *et al*[17] A fourth study, VPS2, was recently reported (NASPE 2002). Although the full report is not available, pacing benefit appeared to have been less (about 30% syncope risk reduction at 6 months) than for the other studies. **Grade A**

Syncope patients qualified for inclusion in the North American study if they had both a positive head-up tilt test and either or both of (1) at least six syncopal episodes preceding the tilt test; or (2) at least one syncope recurrence within 6 months of a positive tilt test. Additionally, during the tilt test patients had to exhibit degrees of bradycardia exceeding certain pre-established thresholds. Syncope recurrence rate was substantially less in the pacemaker group than in control patients, resulting in an actuarial 1 year rate of recurrent syncope of approximately 18·5% for pacemaker patients and 59·7% for controls. However, the study was not without limitations, and a further follow up study addressing many of these limitations (particularly the potential placebo effect of a pacemaker implantation procedure) has been completed, but the results are not yet public. The results of the pacing arm of the VASIS trial[74] were similar to those of the North American Study. Finally, Ammirati *et al*[17] reported results in 93 patients (over 55 years of age) who had experienced three or more syncopal events over a 2 year period and who had positive tilt tests with evidence of bradycardia. Patients were randomized to either pacing (DDD mode with rate-drop algorithm, $n = 46$) or β adrenergic blocker therapy ($n = 47$). Paced patients had two syncope recurrences during a mean follow up of 390 days, whereas β blocker treated patients had 12 syncopal recurrences over a mean follow up of 135 days. Thus, cardiac pacing may play a useful role in severe cases with recurring periods of symptomatic cardioinhibition. **Grade A** In contrast, excluding carotid sinus syndrome, discussed above, experience with pacing in other forms of neurally mediated syncope has been too limited to permit comment.

The treatment of patients with orthostatic syncope is similar to that of the neurally mediated syncopal syndromes. However, greater emphasis must be given to modifying any potentially contributory drug treatments (for concomitant conditions). Further, physical maneuvers designed to ameliorate problems associated with upright posture seem to be helpful, although randomized controlled trials are not yet available. For instance, prescribed periods of upright posture (so-called "tilt-training"), antigravitational hose, and elevation of the bed head at night have a role to play in the treatment plan.[81] In terms of pharmacologic treatment, the mainstay has been attempted chronic expansion of central circulating volume. To this end, increased salt in the diet and/or use of salt retaining steroids (that is principally fludrocortisone) is usually the first step. **Grade C** Additional benefit has been reported with the use of agents such as erythropoietin in order to increase circulating blood volume. A further element in the strategy is reduction of the tendency for central volume to be displaced to the lower extremities with upright posture. To this end vasoconstrictors have been employed, although with limited success owing to the tendency for tachyphylaxis to develop. **Grade C** Of greatest current interest is midodrine.[76–79] Cardiac pacing at relatively rapid rates may prove valuable in certain very difficult cases, but this option has not been very wide accepted to date.

In the treatment of primary cardiac arrhythmias, especially the bradycardias and hypotensive tachyarrhythmias, strong clinical evidence supports the importance of treatment interventions for symptom prevention. The evidence unquestionably supports the importance of cardiac pacemaker therapy in patients with syncope due to bradyarrhythmias, whether due to sinus node dysfunction or to AV conduction disturbances.[82–87] **Grade B** In the case of paroxysmal supraventricular tachyarrhythmias (PSVT) there is little in the way of long-term follow up studies examining the efficacy of conventional antiarrhythmic drug treatment when the presenting feature was syncope. However, at present such patients are no longer usually treated in that fashion because of the frequency of drug-related side effects, issues of compliance, expense, and the availability of effective alternatives. Specifically, transcatheter ablation has become a very cost-effective treatment option[88] and, in PSVT associated with syncope, is probably the treatment of choice. **Grade B**

In the case of syncope due to ventricular tachycardia (VT), the almost ubiquitous presence of underlying left ventricular dysfunction increases the proarrhythmic risk associated with antiarrhythmic drug therapy (reported 5–15% incidence with Class 1 agents). Consequently, pharmacologic therapeutic strategies often involve early consideration of Class 3 agents (particularly amiodarone, given its proarrhythmia risk of 2% or less, and its generally well tolerated hemodynamic impact). However, given the difficulty of ensuring effective prophylaxis in this often high-risk patient population, the use of transcatheter ablation and implantable pacemaker cardioverter defibrillators (ICDs) is becoming increasingly important. Currently, ablation techniques are appropriate first choices in only a few forms of ventricular tachycardia, specifically symptomatic patients with right ventricular outflow tract tachycardia and bundle branch re-entry tachycardia. Although multicenter trials of this strategy have not been undertaken, the evidence is compelling for pursuing ablation in the former and reasonably strong in the latter (bundle branch re-entry, where an ICD may also be warranted in the setting of severe left ventricular dysfunction). **Grade B** In the future, ablation techniques may be used more extensively as mapping technology improves and energy delivery systems evolve. Nevertheless, it is probable that the frequent concomitant presence of poor left ventricular function may necessitate consideration of an ICD as well in these settings, despite successful ablation.

With regard to implantable devices for symptomatic ventricular tachyarrhythmias, several prospective treatment trials (MADIT, AVID, MUSTT and MADIT 2) provide evidence in favor of the efficacy of ICD compared to conventional pharmacologic approaches.[33,34,89,90] Although these studies did not directly target syncope patients, it is reasonable to extend the observations to those syncope patients in whom ventricular tachyarrhythmias and poor left ventricular function are identified. **Grade B** Furthermore, reports examining this issue retrospectively in fainters provide support for early ICD implantation. For instance, among patients with severe left ventricular dysfunction, Middlekauff *et al*[91,92] noted that the presence of a history of syncope was accompanied by both a significantly higher 1 year mortality (65% *v* 25% in comparable patients without syncope) and a greater tendency toward sudden death (45% of deaths *v* 12% in comparable patients).

In the subset of patients in whom structural cardiovascular or cardiopulmonary disease is the cause of syncope, treatment is best directed at amelioration of the specific structural lesion or its consequences. Thus, in syncope associated with myocardial ischemia, pharmacologic therapy and/or revascularization is clearly the appropriate strategy in most cases. Similarly, when syncope is closely associated with surgically addressable lesions (for example, valvular aortic stenosis, atrial myxoma, congenital cardiac anomaly), a direct corrective approach is often feasible. On the other hand, when syncope is caused by certain difficult to treat conditions, such as primary pulmonary hypertension or restrictive cardiomyopathy, it is often impossible to ameliorate the underlying problem adequately. Even modifying outflow gradients in hypertrophic obstructive cardiomyopathy (HOCM) is not readily achieved surgically. In the latter condition the effectiveness of standard pharmacologic therapies remains uncertain, and despite ongoing controversy recent success with cardiac pacing techniques offers considerable promise to symptomatic individuals.[93–95] **Grade C**

Cost effectiveness

Syncope occurs in all age groups. Further, syncope can masquerade as other things (for example, falls, unexplained injuries[13]), thereby causing considerable morbidity and lifestyle disturbance. Consequently, lost productivity, economic derangement and loss of vocation are important considerations and should be evaluated along with medical cost burden when assessing the manner in which syncope is to be evaluated and treated.

In 1982, Kapoor *et al*[96] identified a need for a more cost-effective approach to syncope evaluation. At that time, the average cost for evaluating syncope patients was estimated to be US$2600. However, as the actual etiology was determined in only relatively few cases, the real cost was far greater (approximately US$24 000 per specific diagnosis). Given inflation, and the more widespread proliferation of diagnostic imaging procedures, conventional electrophysiologic testing and tilt-table testing, it is reasonable to assume that the per patient expenditure has increased at least twofold in the past decade, an estimate approximately confirmed by Calkins *et al*[97] On the other hand, given the marked improvement in the frequency with which a specific diagnosis is now obtained, the cost per specific diagnosis is probably considerably lower now than was the case in 1982. Autonomic testing appears to have played an important role in improving both diagnostic capability and cost effectiveness.[98]

Summary

Syncope is a common medical problem with several potential causes and a tendency to a relatively high recurrence rate. Further, there is strong evidence for the view that prognosis is of particular concern among the subset of syncope patients with underlying organic cardiac or vascular disease. Consequently, assessment of each patient must be thorough, with particular attention being paid to the recognition and evaluation of structural cardiac and/or vascular disease. When structural disease is thought likely, hemodynamic and angiographic studies are needed. Syncope in the absence of structural heart or vascular disease is more often neurally mediated in origin, and autonomic function testing (particularly tilt-table testing) should be an early step in establishing the diagnosis. Specialized neurologic testing has proved useful in only a small minority of cases.

The treatment of syncope has been the subject of relatively few large-scale clinical trials. Nevertheless, when structural cardiovascular disturbances or primary cardiac arrhythmias are the cause of syncope, appropriately directed therapy (for example, valve replacement, pacemaker or ICD implantation) is essential and likely to be highly effective. On the other hand, documentation of pharmacologic treatment efficacy (with the possible exception of midodrine) in vasovagal faints, orthostatic hypotension and dysautonomic states, and the various neurologic and psychiatric conditions that can mimic syncope, is less well established. Pacemaker therapy, on the other hand, has been very thoroughly studied in vasovagal syncope and appears to be very effective in selected hard to treat patients (although controversy remains[99]), but patient acceptance is, not surprisingly, a significant hurdle among younger individuals.

Key points: the evaluation of the syncope patient

- The goals
  - Establish a correlation between symptoms and abnormalities
  - Assess prognosis
  - Initiate appropriate treatment plan
- Key steps
  - Obtain detailed medical history (including bystanders/relatives)
  - Identify underlying structural heart disease
- Factors determining need for further tests
  - Evidence for structural disease
  - Certainty of the initial clinical impression
  - Number and frequency of syncopal events
  - Occurrence of injury or accident
  - Family history of syncope or sudden death
  - Occupation, avocation

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References

1. Benditt DG, Ferguson DW, Grubb BP *et al.* Tilt-table testing for assessing syncope. An American College of Cardiology expert consensus document. *J Am Coll Cardiol* 1996;**28**:263–75.
2. Brignole M, Alboni P, Benditt D *et al.* Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;**22**:1256–306.
3. Gendelman HE, Linzer M, Gabelman M *et al.* Syncope in a general hospital population. *NY State J Med* 1983;**83**:116–65.
4. Wayne HH. Syncope: physiological considerations and an analysis of the clinical characteristics in 510 patient. *Am J Med* 1961;**30**:418–38.
5. Savage DD, Corwin L, McGee DL *et al.* Epidemiologic features of isolated syncope: The Framingham Study. *Stroke* 1985;**16**:626–9.
6. Kapoor WN, Karpf M, Wieand S *et al.* A prospective evaluation and follow-up of patients with syncope. *N Engl J Med* 1983;**309**:197–204.

7. Bass EB, Elson JJ, Fogoros RN, Peterson J, Arena VC, Kapoor WN. Long-term prognosis of patients undergoing electrophysiologic studies for syncope of unknown origin. *Am J Cardiol* 1988;**62**:1186–91.
8. Benditt DG, Goldstein MA, Adler S, Sakaguchi S, Lurie KG. Neurally mediated syncopal syndromes: pathophysiology and clinical evaluation. In: Mandel WJ, ed. *Cardiac Arrhythmias*, 3rd edn. Philadelphia: JB Lippincott, 1995.
9. Leitch JW, Klein GJ, Yee R *et al.* Syncope associated with supraventricular tachycardia: an expression of tachycardia or vasomotor response. *Circulation* 1992;**85**:1064–71.
10. Kenny RA, Bayliss J, Ingram A, Sutton R. Head up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986; **1**:1352–4.
11. Almquist A, Goldenberg IF, Milstein S *et al.* Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 1989;**320**:346–51.
12. Sutton R, Petersen M, Brignole M, Ravieli A, Menozzi C, Giani P. Proposed classification for tilt induced vasovagal syncope. *Eur J Cardiac Pacing Electrophysiol* 1992;**2**:180–3.
13. Kenny RAM, Richardson DA, Steen N *et al.* Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J Am Coll Cardiol* 2001;**38**:1491–6.
14. Connolly SJ, Sheldon R, Roberts RS, Gent M. Vasovagal pacemaker study investigators. The North American vasovagal pacemaker study (VPS): a randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999;**33**:16–20.
15. Sutton R, Brignole M, Menozzi C *et al.* for the VASIS investigators. Dual-chamber pacing is efficacious in treatment of neurally-mediated tilt-positive cardioinhibitory syncope. Pacemaker versus no therapy: a multicenter randomized study. *Circulation* 2000;**102**:294–9.
16. Brignole M, Menozzi C, Del Rosso A *et al.* New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. *Europace* 2000;**2**:66–76.
17. Ammirati F, Colivicchi F, Santini M *et al.* Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope. A multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52–6.
18. Moya A, Brignole M, Menozzi C *et al.* and ISSUE Investigators. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;**104**: 1261–7.
19. Low PA, Opfer-Gherking TL, McPhee BR *et al.* Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin Proc* 1995;**70**:617–22.
20. Bannister R. Chronic autonomic failure with postural hypotension. *Lancet* 1979;**ii**:404–6.
21. Low PA. Autonomic nervous system function. *J Clin Neurophysiol* 1993;**10**:14–27.
22. Weiling W, van Lieshout JJ. Investigation and treatment of autonomic circulatory failure. *Curr Opin Neurol Neurosurg* 1993;**6**:537–43.
23. Benditt DG, Sakaguchi S, Goldstein MA *et al.* Sinus node dysfunction: pathophysiology, clinical features, evaluation and treatment. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology. From Cell to Bedside*, 2nd edn. Philadelphia: WB Saunders, 1995.
24. Kaplan BM, Langendorf R, Lev M, Pick A. Tachycardia–bradycardia syndrome (so-called "sick sinus syndrome"). *Am J Cardiol* 1973;**26**:497–508.
25. Rubenstein JJ, Schulman CL, Yurchak PM *et al.* Clinical spectrum of the sick sinus syndrome. *Circulation* 1972;**6**:5–13.
26. Benditt DG, Benson DW Jr, Dunnigan A *et al.* Drug therapy in sinus node dysfunction. In: Rapaport E, ed. *Cardiology Update* 1984. New York: Elsevier, 1984.
27. Linker NJ, Camm AJ. Drug effects on the sinus node. A clinical perspective. *Cardiovasc Drugs Ther* 1988;**2**:165–70.
28. Rowe JC, White PD. Complete heart block: a follow-up study. *Ann Intern Med* 1958;**49**:260–70.
29. Penton GB, Miller H, Levine SA. Some clinical features of complete heart block. *Circulation* 1956;**13**:801–24.
30. Michaelsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. *Circulation* 1995;**92**:442–9.
31. Scheinman MM, Peters RW, Sauve MJ *et al.* Value of H-Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol* 1982;**50**:1316–22.
32. Dhingra RC, Denes P, Wu D *et al.* Syncope in patients with chronic bifascicular block. *Ann Intern Med* 1974;**81**:302–6.
33. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, for the Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882–90.
34. Moss AJ, Zareba W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**: 877–83.
35. Swerdlow CD, Winkle RA, Mason JW. Determinents of survival in patients with ventricular tachyarrhythmias. *N Engl J Med* 1983;**308**:1436–42.
36. Middelkauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol* 1993; **21**:110–16.
37. Moss AJ, Schwartz PJ, Crampton RS *et al.* The long QT syndrome: prospective longitudinal study of 328 families. *Circulation* 1991;**84**:1136–44.
38. Schwartz PJ *et al.* Stress and sudden death: the case of the long QT syndrome. *Circulation* 1991;**83**(Suppl II):71–80.
39. Tobe TJM *et al.* Late potentials in bradycardia-dependent long QT syndrome associated with sudden death during sleep. *J Am Coll Cardiol* 1992;**19**:541–9.
40. Camm AJ, Lau CP. Syncope of undetermined origin: diagnosis and management. *Prog Cardiol* 1988;**1**:139–56.
41. Johnson AM. Aortic stenosis, sudden death, and the left ventricular baroreceptors. *Br Heart J* 1971;**33**:1–5.
42. Kapoor W. Evaluation and outcome of patients with syncope. *Medicine* 1990;**69**:160–75.
43. Grubb BP, Gerard G, Rousch K *et al.* Differentiation of convulsive syncope and epilepsy with head up tilt table testing. *Ann Intern Med* 1991;**115**:871–6.
44. Zaidi A, Crampton S, Clough P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy – many seizure-like episodes have a cardiovascular cause. *PACE* 1999;**22**:814[Abstract].

45.Grubb BP, Gerard G, Roush K *et al.* Cerebral vasoconstriction during head-upright tilt induced vasovagal syncope: a paradoxic and unexpected response. *Circulation* 1991;**84**: 1157–64.
46.Njemanze PC. Cerebral circulation dysfunction and hemodynamic abnormalities in syncope during upright tilt test. *Can J Cardiol* 1993;**9**:238–42.
47.Linzer M, Varia I, Pontinen M *et al.* Medically unexplained syncope: relationship to psychiatric illness. *Am J Med* 1992; **92**:18–25.
48.Krahn AD, Klein GJ, Norris C, Yee R. The etiology of syncope in patients with a negative tilt table and electrophysiologic testing. *Circulation* 1995;**92**:1819–24.
49.Krahn A, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial. Conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;**104**: 46–51.
50.Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C, the Reveal Investigators. Use of an exended monitoring strategy in patients with problematic syncope. *Circulation* 1999;**99**: 406–10.
51.Sakaguchi S, Shultz J, Remole C, Adler S, Lurie K, Benditt D. Syncope associated with exercise, a manifestation of neurally-mediated syncope. *Am J Cardiol* 1995;**75**:476–81.
52.Calkins H, Seifert M, Morady F. Clinical presentation and long term follow up of athletes with exercise-induced vasodepressor syncope. *Am Heart J* 1995;**129**:1159–64.
53.Kuchar DL, Thorburn CW, Sammel NL. Signal-averaged electrocardiogram for evaluation of recurrent syncope. *Am J Cardiol* 1986;**58**:949–53.
54.DiMarco JB, Garan H, Hawthorne WJ *et al.* Intracardiac electrophysiologic techniques in recurrent syncope of unknown cause. *Ann Intern Med* 1981;**95**:542–8.
55.Akhtar M, Shenasa M, Denker S, Gilbert CJ, Rizwi N. Role of cardiac electrophysiologic studies in patients with unexplained recurrent syncope. *PACE* 1983;**6**:192–201.
56.Morady F, Shen E, Schwartz A *et al.* Long-term follow-up of patients with recurrent unexplained syncope evaluated by electrophysiologic testing. *J Am Coll Cardiol* 1983; **2**:1053–9.
57.Denes P, Ezri MD. The role of electrophysiologic studies in the management of patients with unexplained syncope. *PACE* 1985;**8**:424–35.
58.Sra JS, Anderson AJ, Sheikh SH *et al.* Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. *Ann Intern Med* 1991;**114**:1013–19.
59.Fujimura O, Yee R, Klein GJ *et al.* The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by bradycardia. *N Engl J Med* 1989;**321**:1703–7.
60.deMey C, Enterling D. Assessment of the hemodynamic responses to single passive head-up tilt by non-invasive methods in normotensive subjects. *Meth Find Exp Clin Pharmacol* 1986;**8**:449–57.
61.Fitzpatrick A, Theodorakis G, Vardas P *et al.* The incidence of malignant vasovagal syndrome in patients with recurrent syncope. *Eur Heart J* 1991;**12**:389–94.
62.Raviele A, Gasparini G, DiPede F, Delise P, Bonso A, Piccolo E. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. *Am J Cardiol* 1990;**65**:1322–7.
63.Grubb BP, Temesy-Armos P, Hahn H, Elliott L. Utility of upright tilt table testing in the evaluation and management of syncope of unknown origin. *Am J Med* 1991;**90**:6–10.
64.Grubb BP, Wolfe D, Samoil D *et al.* Recurrent unexplained syncope in the elderly: the use of head-upright tilt table testing in evaluation and management. *J Am Geriatr Soc* 1992; **40**:1123–8.
65.Natale A, Akhtar M, Jazayeri M *et al.* Provocation of hypotension during head-up tilt testing in subjects with no history of syncope or presyncope. *Circulation* 1995;**92**:54–8.
66.Fitzpatrick A, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. *J Am Coll Cardiol* 1991;**17**:125–30.
67.Ector H, Reybrouck T, Heidbuchel H, Gewillig M, Van de Werf F. Tilt training: a new treatment for recurrent neurocardiogenic syncope or severe orthostatic intolerance. *PACE* 1998; **21**:193–6.
68.Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for prevention of refractory neurocardiogenic syncope in adolescents. A controlled study. *Circulation* 1999;**100**:1798–1801.
69.Wieling W, Van Lieshout JJ, Van Leeuwen AM. Physical maneuvers that reduce postural hypotension in autonomic failure. *Clin Autonom Res* 1993;**3**:57–65.
70.Fitzpatrick AP, Ahmed R, Williams S *et al.* A randomized trial of medical therapy in malignant vasovagal syndrome or neurally-mediated bradycardia/hypotension syndrome. *Eur J Cardiac Pacing Electrophysiol* 1991;**1**:991–1202.
71.Brignole M, Menozzi C, Gianfranchi L *et al.* A controlled trial of acute and long-term medical therapy in tilt-induced neurally mediated syncope. *Am J Cardiol* 1992;**70**:339–42.
72.Morillo CA, Leitch JU, Yee R *et al.* A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993;**22**:1843–8.
73.Moya A, Permanyer-Miralda G, Sagrista-Sauleda J *et al.* Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo *J Am Coll Cardiol* 1995;**25**:65–9.
74.Mahanonda N, Bhuripanyo K, Kangkagate C *et al.* Randomized double-blind placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table results. *Am Heart J* 1995;**130**:1250–3.
75.Jankovic J, Gilden JL, Hiner BC, Brown DC, Rubin M. Neurogenic orthostatic hypotension: a double-blind placebo-controlled study with midodrine. *Am J Med* 1993; **95**:38–48.
76.Sra J, Maglio C, Biehl M *et al.* Efficacy of midodrine hydrochloride in neurocardiogenic syncope refractory to standard therapy. *J Cardiovasc Electrophysiol* 1997;**8**:42–6.
77.Samniah N, Sakaguchi S, Lurie KG, Iskos D, Benditt DG. Efficacy and safety of midodrine hydrochloride in patients with refractory vasovagal syncope. *Am J Cardiol* 2001;**88**: 80–3.
78.Perez-Lugones A, Schweikert R, Pavia S *et al.* Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. *J Cardiovasc Electrophysiol* 2001;**12**:935–8.

79.Ward CR, Gray JC, Gilroy JJ, Kenny RA. Midodrine: a role in the management of neurocardiogenic syncope. *Heart* 1998; **79**:45–9.
80.Benditt DG, Remole S, Asso A *et al.* Cardiac pacing for carotid sinus syndrome and vasovagal syncope. In: Barold SS, Mugica J, eds. *New Perspectives in Cardiac Pacing, 3.* Mount Kisco, NY: Futura, 1993.
81.Bannister R, Mathias C. Management of postural hypotension. In: Bannister R, ed. *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System.* Oxford: Oxford University Press, 1988.
82.Benditt DG, Peterson M, Lurie K *et al.* Cardiac pacing for prevention of recurrent vasovagal syncope. *Ann Intern Med* 1995;**122**:204–9.
83.Petersen MEV, Chamberlain-Webber R, Fitzpatrick AP *et al.* Permanent pacing for cardioinhibitory malignant vasovagal syndrome. *Br Heart J* 1994;**71**:274–81.
84.Perrins EJ, Astridge PS. Clinical trials and experience. In: Ellenbogen KA, Kay GN, Wilkoff BL, eds. *Clinical Cardiac Pacing.* Philadelphia: WB Saunders, 1995.
85.Stangl K, Wirtzfeld A, Seitz K *et al.* Atrial stimulation (AAI): long-term follow-up of 110 patients. In: Belhassen B, Feldman S, Copperman Y, eds. *Cardiac Pacing and Electrophysiology. Proceedings of the VIIIth World Symposium on Cardiac Pacing and Electrophysiology.* Jerusalem: R & L Creative Communications, 1987.
86.Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sick sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;**116**:16–22.
87.Andersen HR, Thuesen L, Bagger JP *et al.* Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet* 1994;**344**:1523–8.
88.Naccarelli GV, Dougherty AH, Jalal S, Shih H-T, Wolbrette D. Paroxysmal supraventricular tachycardia: comparative role of therapeutic methods – drugs, devices, and ablation. In: Saksena S, Luderitz B, eds. *Interventional Electrophysiology. A Textbook*, 2nd edn. Armonk, NY: Futura, 1996.
89.Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996; **335**:1933–40.
90.The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**:1576–83.
91.Middelkauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol* 1993; **21**:110–16.
92.Middelkauff HR, Stevenson WG, Saxon LA. Prognosis after syncope: impact of left ventricular function. *Am Heart J* 1993;**125**:121–7.
93.Fananpazir L, Epsterin ND, Curiel RV *et al.* Long-term results of dual-chamber (DDD) pacing in obstructive cardiomyopathy. Evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. *Circulation* 1994;**90**:2731–42.
94.Kappenberger L, Linde C, Daubert C *et al.* Pacing in hypertrophic obstructive cardiomyopathy. A randomized crossover trial. *Eur Heart J* 1997;**18**:1249–56.
95.Nishimura RA, Hayes DL, Ilstrup DM *et al.* Effects of dual-chamber pacing on systolic and diastolic function in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1996; **27**:421–30.
96.Kapoor W, Karpf M, Maher Y *et al.* Syncope of unknown origin: the need for a more cost-effective approach to its evaluation. *JAMA* 1982;**247**:2687–91.
97.Calkins H, Byrne M, El-Atassi R, Kalbfleisch S, Langberg JJ, Morady F. The economic burden of unrecognized vasodepressor syncope. *Am J Med* 1993;**95**:473–9.
98.Mathias CJ, Deguchi K, Schatz I. Autonomic-function investigations aid in the diagnosis of the cause of syncope and presyncope. *Lancet* 2001;**357**:348–53.
99.van Dijk N, Harms MP, Linzer M, Wieling W. Treatment of vasovagal syncope: pacemaker or crossing legs? *Clin Autonom Res* 2000;**10**:347–9.

44 Cardiopulmonary resuscitation

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Cardiopulmonary resuscitation interventions are used worldwide in attempts to restore spontaneous circulation in victims of sudden cardiac arrest. Healthcare providers frequently follow algorithmic advanced cardiac life support guidelines[1] in their approach to the four basic cardiac arrest rhythms: ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA), and asystole. Despite these guidelines, considerable clinical expertise and judgment are required in their application. This is partly because underlying causes for the arrest must always factor into clinical decisions, and may require deviations from the algorithms. The other concern is that definitive high quality evidence supporting specific interventions may be lacking and, therefore, alternatives may be acceptable. The reasons for this are many, but the key issue is that cardiac arrest outcomes are extremely difficult to study. They are relatively rare events, have many underlying causes, and issues of obtaining informed consent can make research difficult if not impossible. Some external evidence is available, though, and the practicing clinician should be aware of it. The focus of this chapter will be on the research evidence base for management of sudden cardiac death. An understanding and appraisal of this evidence will assist clinicians in deciding whether it applies to the individual patient and allow them to integrate it into resuscitation decisions most appropriately.

Monophasic *v* biphasic defibrillation

The termination of ventricular fibrillation by externally applied electricity was a major breakthrough in cardiac resuscitation. First described in 1956,[2] it has proved to be a remarkably effective treatment for an otherwise universally fatal arrhythmia. **Grade A** Multiple studies support the concept that the earlier the defibrillation is performed, the greater the probability of survival to hospital discharge.[3–5] **Grade A** As a result of this, a major focus in the past 10 years has been finding ways to improve access to early defibrillation, not only in the hospital, but in the community. The concept of public access defibrillation (defibrillation by trained non-medical personnel, including laypersons) has been strengthened by the development of automated external defibrillators (AEDs).[1] It has been recognized, however, that widespread dissemination of AED training and equipment will require devices that are small, light, inexpensive, easy to use, and capable of being stored for long periods without recharging.[6] This goal has motivated manufacturers to develop alternative waveforms with equal or greater efficacy in an effort to reduce defibrillator energy requirements and thus confer benefits in size, weight, cost, and battery life. One such advance is the introduction of lower energy biphasic waveforms, first commercially available in 1996 for external defibrillation.

The technology of defibrillation waveforms is complex. The classic monophasic waveform delivers current that flows in one direction. Two monophasic waveforms have been marketed and vary in the speed with which they return to the zero voltage point. The damped sinusoidal waveform (MDS) returns to baseline gradually, whereas the truncated exponential (MTE) returns instantaneously. Adequate research has not been done to determine if one type is superior. The recommended energy for monophasic defibrillation in the 2000 American Heart Association (AHA) guidelines is an escalating dose of 200 J, 200–300 J, then 360 J.[1]

Biphasic waveforms first deliver current in one direction and then the current is reversed and flows in the opposite direction for the duration of the discharge. As with monophasic waveforms, biphasic waveforms have different morphologies (Figures 44.1 and 44.2). Most deliver lower energy

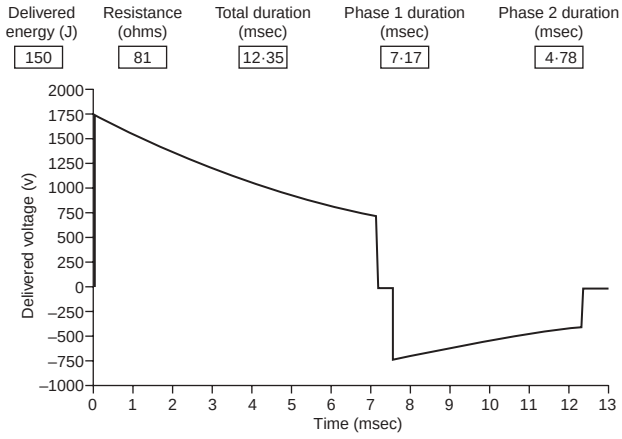

Figure 44.1 Biphasic truncated exponential waveform delivering non-escalating 150 J. Data from a patient event are included in the figure.

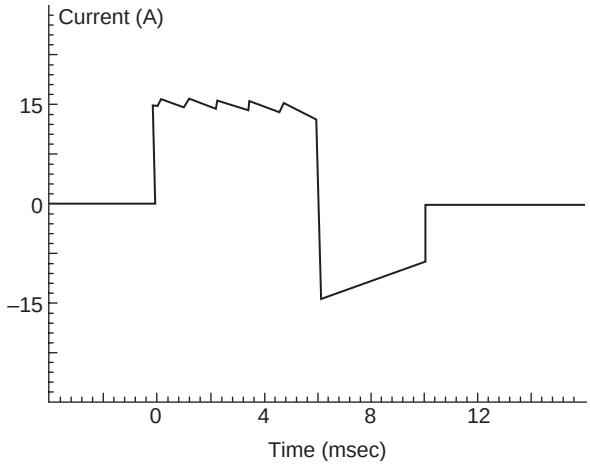

Figure 44.2 Rectilinear biphasic waveform delivering a relatively constant current during the first phase. The phasic durations are fixed at 6 and 4 msec. The figure depicts a 120 J shock delivered into a 50 ohm impedance.

defibrillation (usually 120–200 J) than their monophasic counterparts. The first device approved for clinical use employed a truncated exponential (BTE) waveform delivering non-escalating 150 J shocks, and most available data have been derived from experience with this waveform (Figure 44.1). Biphasic waveform defibrillators also incorporate an impedance compensation mechanism that alters waveform morphology based on impedance measurements during actual defibrillation. Evaluation of the evidence on biphasic waveforms is complicated further by the availability of a rectilinear biphasic waveform (120–200 J) (Figure 44.2) and traditional escalating high energy (200–360 J) BTE waveforms.

BTE waveforms have been shown to be superior to monophasic waveforms for internal defibrillation. Lower defibrillation thresholds and higher rates of defibrillation are well documented with these waveforms for internal defibrillations.[7,8] **Grade A** As a result, implantable cardioverter defibrillators (ICDs) are only available now with low energy biphasic waveforms.

Transthoracic biphasic waveforms have been developed and tested in patients undergoing electrophysiologic studies (EPS) and ICD implantation.[9–11] These multicenter, randomized, blinded, prospective studies were carried out by first inducing ventricular fibrillation, and then measuring the success rate of transthoracic "rescue" shocks. The accepted definition for defibrillation success is the termination of VF for a designated period (5–30 seconds, depending on the researchers). By this definition, a successful postshock rhythm can be any non-VF activity, including asystole. The energies tested included 115 and 130 J BTE shocks using impedance compensation and a 171 J Gurvich biphasic waveform. The BTE shocks were compared with 200 J and 360 J MDS waveforms,[10,11] and a 215 J MDS waveform was the comparison for the Gurvich waveform.[9] Evidence from these studies confirms that low energy biphasic shocks achieve at least the same defibrillation success rates on the first shock as 200–215 J monophasic shocks in VF of short duration (20–30 seconds). **Grade A** Furthermore, in a small subgroup of these patients, investigators looked at ECG abnormalities in the immediate postshock period.[12] They found that ECG ST-segment elevation was significantly greater with 200 J MDS waveform shocks than with either the 115 J or 130 J BTE shocks. **Grade A** This suggests that the lower energy shocks may cause less myocardial injury or ischemia.

These efficacy data are encouraging, but several factors make VF episodes outside of the EPS lab different. The etiology is clearly different, with ischemia a frequent cause of arrest. The duration of VF is invariably longer in the typical cardiopulmonary arrest. The higher levels of tissue hypoxia and acidosis that result could potentially make defibrillation more difficult. Also, laboratory evidence in a dog model suggests that the longer the duration of VF the more difficult it is to defibrillate.[13] A final concern is that the outcome most widely accepted to define resuscitation success – survival to hospital discharge[14,15] – may not be affected by the defibrillation success rate on the first shock in the EPS lab.

Unfortunately, minimal data evaluating biphasic defibrillation in settings outside the EPS lab are available at this time. A randomized, multicenter, non-concealed, non-blinded trial in Europe compared 150 J BTE shocks with 200–360 J monophasic escalating shocks in out-of-hospital cardiac arrest victims. In this study 115 out-of-hospital cardiac arrest patients presented with VF and were shocked with an AED. AEDs were prospectively randomized according to defibrillation waveform on a daily basis. The primary end point was the percentage of patients with VF as the initial monitored rhythm who were defibrillated in the first series of ≤3 shocks. In the biphasic waveform group 96% of 54 patients were defibrillated, whereas 59% of the 61 patients in the monophasic waveform group were defibrillated ($P < 0{\cdot}0001$; 95% CI 24–51). A higher percentage of patients (76%) achieved return of spontaneous circulation (ROSC) after biphasic defibrillation compared with monophasic defibrillation (54%, $P = 0{\cdot}01$). There was no difference in survival rate to admission or hospital discharge. However, due to the small size of the study, little can be concluded regarding these last two outcomes.[16] **Grade A** Also, 80% of the patients in the monophasic group were defibrillated with a monophasic truncated exponential waveform; there is some evidence that this waveform is less effective than the monophasic damped sine waveform.[17]

The evidence supporting biphasic waveforms in VF arrests is strengthened by data from multicenter out-of-hospital case series reports. These studies demonstrated that a single 150 J impedance compensating BTE shock defibrillated the initial VF episode in 86–89% of patients.[18,19] They

also reported that, of all VF episodes that received up to three shocks, 97–99% were terminated with three or fewer shocks. **Grade B** Termination of VF into an organized rhythm or asystole was the definition of success. These data compare favorably with the data from short duration VF in the EPS laboratory, where first shock defibrillation rates varied from 86% to 100% in three studies.[9–11]

In a recent evidence-based review by the AHA, it was noted that "research has not clearly established an expected success rate for out-of-hospital monophasic defibrillation".[20] A rough estimate can be derived, however, by reviewing what data are available. In 1996, Behr *et al* did a retrospective review of 86 patients treated for witnessed out-of-hospital VF who received one of two different monophasic waveforms. The first shock defibrillation rate for the 200J MTE waveform was reported to be 43% and for the 200J MDS waveform was 66%.[17] Although the first shock defibrillation rates were significantly different, survival to hospital discharge was not. In another prospective randomized trial by Weaver *et al*, first shock defibrillation rates for MDS waveforms at 175J and 320J were reported to be 61% for both energy levels.[21] Schneider *et al* reported a first shock defibrillation rate of 59% for the monophasic waveform arm in their prospective randomized study.[16]

The consistency of these rates across several studies suggests that biphasic waveforms have higher rates of defibrillation efficacy compared with monophasic waveforms. The real clinical question, however, is how do these results for initial defibrillation rates influence ultimate outcomes in terms of survival to hospital discharge. Clearly, good comparative out-of-hospital data on monophasic versus biphasic waveforms for management of VF do not exist to answer this question. However, patients who regain pulses with only defibrillation shocks have a very high survival rate when compared with patients who need advanced life support interventions (97% *v* 19%). **Grade B** These observations affirm the benefit of defibrillation as the definitive intervention in cardiac arrest caused by ventricular fibrillation.[22]

The present AHA guideline for the monophasic waveform energy sequence 200J to 300J to 360J has been acknowledged by the AHA to be "largely speculative and based on common-sense extrapolation from animal data and human case series".[20] At the present time, the AHA guidelines have designated initial low energy (150J) non-progressive impedance-adjusted biphasic waveform shocks a Class IIa recommendation (acceptable and useful; good to very good supporting evidence).[1] With the available evidence at this time, it is difficult to unequivocally state that biphasic waveforms are superior to monophasic, but they certainly appear to be at least equivalent. In fact, the question of superiority appears now to be moot, since only biphasic waveforms are being marketed for external defibrillators, following the experience with waveforms for ICDs. Both escalating and non-escalating biphasic energy defibrillators are now marketed, but few data exist comparing their efficacy.[1]

Drugs in cardiac arrest

On close review of the literature to date, there is little evidence that the administration of any drug improves survival to hospital discharge in cardiac arrest.[23] As a result, the International Guidelines for 2000 stress that during cardiac arrest "drug administration must be secondary to other interventions".[1] Once CPR, defibrillation, and proper airway management are established, certain drugs are considered by "standard practice" to be potentially useful. Recent research has gathered new information about some of these medications as well as some new medications that might be potentially useful. These drugs include epinephrine, vasopressin, amiodarone, and lidocaine.

Epinephrine

Historically, epinephrine has been used in resuscitation of all cardiac arrest rhythms.[1] Although considerable animal data exist supporting its use, no randomized, prospective, placebo-controlled trials have been done in humans to determine its efficacy. In a non-randomized cohort study over an 11 year period, Herlitz *et al* examined the use of epinephrine (adrenaline) in out-of-hospital VF.[24] During this observation period, some of the prehospital staff were authorized to give epinephrine and some were not. A total of 1203 cases were reviewed, with epinephrine administration in 417 (35%). In patients who experienced sustained VF, those who received epinephrine were hospitalized alive more frequently ($P < 0{\cdot}01$). However, survival to hospital discharge did not differ significantly. When the subgroup of patients who converted to asystole or PEA was reviewed, similar results were observed. Those who received epinephrine were more likely to be hospitalized alive ($P < 0{\cdot}001$). However, survival to discharge was not significantly different. **Grade B** Given the widespread acceptance of epinephrine as a "standard of care" in refractory VF, asystole and PEA, it is doubtful that better quality evidence of its efficacy will be available in the near future.

Despite the paucity of evidence supporting the use of epinephrine in cardiac arrest, considerable research has been done comparing high-dose epinephrine (0·07–0·20 mg/kg) with standard-dose epinephrine (1 mg every 3–5 minutes). A total of eight randomized trials have been done involving more than 9000 cardiac arrest patients.[25–32] The findings are consistently the same. High-dose protocols result in higher rates of return of spontaneous circulation during initial resuscitation. However, no difference can be found when survival to hospital discharge and final neurologic outcome are compared. **Grade A** The higher doses have not

clearly been shown to be harmful, but would likely confer added costs to healthcare systems by increasing hospitalization in hopeless situations.

Vasopressin

Vasopressin has been introduced in the 2000 guidelines as an acceptable alternative to epinephrine in refractory VF/pulseless VT.[1] It is a naturally occurring hormone that in high doses acts as a potent non-adrenergic vasoconstrictor. The theoretical advantage to vasopressin is that it lacks some of the potentially detrimental β adrenergic effects of epinephrine in the postresuscitation setting. In a human study, Rivers *et al* documented a dose-dependent impairment of systemic oxygen delivery and myocardial dysfunction from epinephrine.[33] Animal models have further demonstrated that these β adrenergic effects increase myocardial work and impair coronary perfusion.[34,35] In addition, Lindner *et al* have demonstrated that endogenous vasopressin levels were higher in patients who survived after CPR than in those with no ROSC.[36]

Adrenergic agents are believed to exert a beneficial effect during cardiac arrest by α receptor mediated increases in myocardial and cerebral blood flow.[37] Evidence from both animal and human studies demonstrates that a minimum coronary perfusion pressure (CPP) is required to achieve any ROSC.[38,39] In an animal cardiac arrest model, vasopressin has been shown to increase CPP during CPR.[40] From basic science research, then, it would appear to be a very promising agent for cardiac arrest.

Unfortunately, only two randomized trials exist that examined its efficacy in human cardiac arrest. Lindner *et al* prospectively randomized 40 out-of-hospital patients in VF to receive epinephrine (1 mg IV) or vasopressin (40 U IV) as the primary drug if initial defibrillation was unsuccessful. They reported four outcomes: successful resuscitation (ROSC and measurable blood pressure on admission to hospital), survival for at least 24 hours, survival to hospital discharge, and mean Glasgow Coma Score at hospital discharge. Only one of the four outcomes – survival for at least 24 hours – reached statistical significance ($P = 0{\cdot}02$). However, none of the other outcomes was significantly different, and no statistical correction was done for the multiple comparisons.[41] **Grade A**

A larger trial ($n = 200$) by Stiell *et al* randomized inhospital adult cardiac arrests to receive one dose of vasopressin (40 U IV) or epinephrine (1 mg IV) as the initial vasopressor. Initial rhythms were VF, pulseless VT, PEA, or asystole. When comparing vasopressin with epinephrine, survival did not differ for hospital discharge (12% *v* 14%, respectively; 95% CI for absolute increase in survival −11·8–7·8%) or 1 hour survival (39% *v* 35%, 95% CI 10·9–17) (Table 44.1).[42] It is important to at least note some differences in baseline characteristics of the two groups that might have affected the outcomes. More of the patients in the epinephrine group were in monitored settings (emergency department or intensive care) than in the vasopressin group (49% *v* 36%). Clearly this might favor outcomes in the epinephrine group. Also, only 42/200 presented with initial VF/VT, making the ultimate outcomes for the whole group less favorable and resulting in the likelihood of demonstrating less benefit. Despite these issues, the preliminary human evidence is disappointing, and has at this point failed to detect even a modest trend favoring vasopressin over epinephrine. **Grade A** The more fundamental clinical question, however, may be whether any drug actually improves survival. Given that

Table 44.1 Survival and adverse outcomes

Outcome measure	Vasopressin ($n = 104$)	Epinephrine ($n = 96$)	*P*	Percentage absolute difference (95% CI)
Primary survival measures				
1 hour	40 (39%)	34 (35%)	0·66	3·1 (−10·5–17·3)
Hospital discharge	12 (12%)	13 (14%)	0·67	−2·0 (−11·6–7·8)
Other survival measures				
Any return of pulse	62 (60%)	57 (59%)	0·97	0·2 (−14·0–14·5)
Pulse > 20 min	45 (43%)	38 (40%)	0·60	3·7 (−10·6–17·9)
24 hours	27 (26%)	23 (24%)	0·74	2·0 (−10·6–14·6)
30 days	13 (13%)	13 (14%)	0·83	−1·0 (−11·0–8·9)
Adverse outcomes				
Tachyarrhythmias	10 (10%)	8 (8%)	0·75	1·3 (−7·2–9·8)
Uncontrolled hypertension	0	0	–	–
Mesenteric infarction	0	0	–	–

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epinephrine has never been adequately studied, it is entirely possible that both drugs are equally ineffective (or possibly equally harmful) for improving survival in cardiac arrest.

Amiodarone and lidocaine

The use of lidocaine (lignocaine) for refractory VF/pulseless VT is largely based on historical use of the drug to prevent VF in acute MI.[43] Only one retrospective prehospital trial provides some supporting evidence for its use in VF/pulseless VT, demonstrating an improved survival to hospital admission rate.[44] Another retrospective study suggests that lidocaine has a detrimental effect on ROSC.[23] More recently, the prophylactic use of lidocaine in acute MI has been shown to be associated with increased morbidity and to cause more serious arrhythmias than it prevents.[45,46] Additionally, it has been established in experimental models that lidocaine increases energy requirements for defibrillation.[47–49] More study needs to be done to determine the role of lidocaine in cardiac arrest, and it should be recognized that current practice has no sound evidence base.

The ARREST trial is the only randomized, prospective, placebo-controlled trial that addresses the efficacy of an antiarrhythmic in cardiac arrest. Out-of-hospital cardiac arrest patients with VF (or pulseless VT) who had not responded after receiving three or more shocks and 1 mg of epinephrine, were randomly assigned to receive 300 mg of amiodarone or placebo ($n = 540$). The rate of admission to hospital with a perfusing rhythm was higher in the amiodarone group (44% *v* 34% of placebo; $P = 0{\cdot}03$). Among the patients who achieved ROSC, more in the amiodarone group experienced significant hypotension (59% *v* 48% of placebo; $P = 0{\cdot}04$) or bradycardia (41% *v* 25%; $P = 0{\cdot}004$). Ultimately there was no difference in survival rate to hospital discharge (13·4% of amiodarone *v* 13·2% of placebo).[50] **Grade A**

The most recent data comparing amiodarone and lidocaine in shock-resistant ventricular fibrillation were obtained in a randomized blinded trial in out-of-hospital cardiac arrest (ALIVE trial). In this study 348 patients were randomized to receive amiodarone (or placebo) or lidocaine (or placebo). The primary end point was survival to hospital admission. In the amiodarone group 22·7% of 179 patients survived to admission, whereas 11·0% of 165 patients in the lidocaine group survived ($P < 0{\cdot}0043$; odds ratio 2·37; 95% CI 1·30–4·33). In patients with VF as the initial rhythm, 25·2% of amiodarone versus 13·5% of lidocaine patients survived to admission ($P = 0{\cdot}02$). However, survival to discharge was not different between the two groups.[51]

The role of amiodarone in VF/pulseless VT has generated considerable controversy. It is cumbersome to dilute and administer, and in the ARREST trial required an average of 13 (and up to 21) minutes from the time of medic arrival to administration.[50] The drug cannot be provided in preloaded syringes because it adheres to plastic surfaces. Significant hypotension and bradycardia often accompany ROSC, complicating postresuscitation management. Finally, the cost of the drug is considerable, and can be prohibitive for prehospital services to stock. The consensus opinion by the most recent AHA guidelines is that the evidence for amiodarone, while better than any other antiarrhythmic, is only "fair".

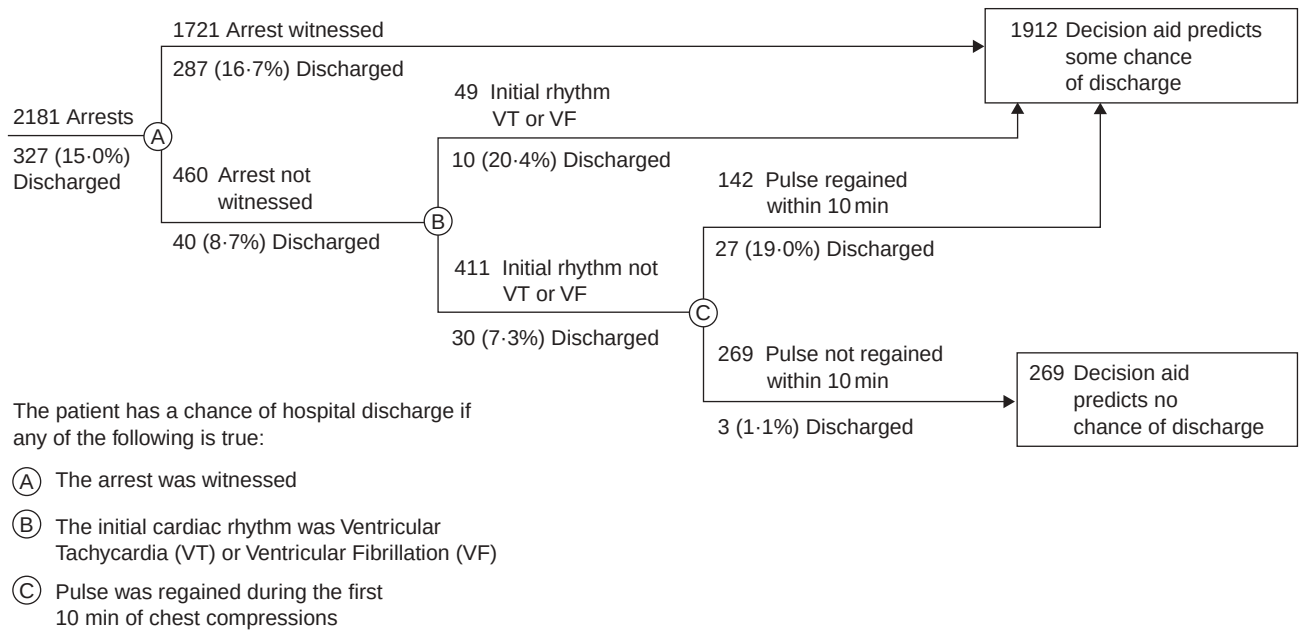

Figure 44.3 Utilization of a decision aid to the validation set of attempted resuscitations. (From van Walraven C, Forster AJ, Parish DC *et al* Validation of a clinical decision aid to discontinue in-hospital cardiac arrest resuscitations. *JAMA* 2001;**285**:1602–6)

They comment that "this practice decision (to use amiodarone), must be made with a clear awareness that the evidence – powerful in design – was weak in the conclusions".

Termination of resuscitation

Physicians involved in resuscitation invariably will be called upon to make the difficult decision of when to stop resuscitative efforts. Multiple factors come into play, with the ultimate decision involving a complex interaction of patient and physician variables. The most important single factor associated with poor outcomes is prolonged time of resuscitation. As time spent increases, chance of neurologically intact survival diminishes. A simple clinical decision aid has also been derived and recently validated for inhospital arrests. It involves assessing three simple parameters: whether the arrest was witnessed *or* the initial cardiac rhythm was either VF or VT *or* patients regained a pulse during the first 10 minutes of chest compressions. If none of these three variables was present, the aid predicts no chance of discharge.[52,53]

The validation was completed on data from 2181 inhospital cardiac arrest attempts over a 10 year period in a community hospital. Overall, 327 (15%) of patients survived to hospital discharge: 324 of these patients were predicted to survive (99·1%; 95% CI 97·1–99·8). In 269 (12·3%) resuscitations, patients were predicted not to survive. Only three of these patients (1·1%) were discharged and none was able to function independently. The negative likelihood ratio was 0·064 (Figure 44.3).[53] **Grade B** Ideally, prospective testing in another inhospital setting would further ensure its validity, but it does provide clinicians with some parameters to help them make complex decisions on individual cases.

References

1. International consensus on science, American Heart Association. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2000; **102**(Suppl. I):I60–165.
2. Zoll PM, Linenthal AJ, Gibson W, Paul MH, Normal LR. Termination of ventricular fibrillation in man by internally applied electric countershock. *N Engl J Med* 1956;**254**: 727–32.
3. Stiell IG, Wells GA, DeMaio VJ *et al.* Modifiable factors associated with improved cardiac arrest survival in a multicenter basic life support/defibrillation system: OPALS Study Phase I results. Ontario Prehospital Advanced Life Support. *Ann Emerg Med* 1999;**33**:44–50.
4. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: a graphic model. *Ann Emerg Med* 1993;**22**:1652–8.
5. Eisenberg MS, Copass MK, Hallstrom AP *et al.* Treatment of out-of-hospital cardiac arrest with rapid defibrillation by emergency medical technicians. *N Engl J Med* 1980;**302**:1379–83.
6. Weisfeldt ML, Kerber RE, McGoldrick RP *et al.* American Heart Association report on the Public Access Defibrillation Conference, December 8–10, 1994. Automatic External Defibrillation Task Force. *Circulation* 1995;**92**:2740–7.
7. Bardy GH, Ivey TD, Allen MD, Johnson G, Mehra R, Greene HL. A prospective randomized evaluation of biphasic versus monophasic waveform pulses on defibrillation efficacy in humans. *J Am Coll Cardiol* 1989;**14**:728–33.
8. Winkle RA, Mead RH, Ruder MA *et al.* Improved low energy defibrillation efficacy in man with the use of a biphasic truncated exponential waveform. *Am Heart J* 1989;**117**:122–7.
9. Greene HL, DiMarco JP, Kudenchuk PJ *et al.* Comparison of monophasic and biphasic defibrillating pulse waveforms for transthoracic cardioversion. *Am J Cardiol* 1995;**75**:1135–9.
10. Brady GH, Marchlinski FE, Sharma AD *et al.* Multicenter comparison of truncated biphasic shocks and standard damped sine wave monophasic shocks for transthoracic ventricular defibrillation. *Circulation* 1996;**94**:2507–14.
11. Bardy GH, Gliner BE, Kudenchuk PJ *et al.* Truncated biphasic pulses for transthoracic defibrillation. *Circulation* 1995;**91**: 1768–74.
12. Reddy RK, Gleva MJ, Gliner BE *et al.* Biphasic transthoracic defibrillation causes fewer ECG ST-segment changes after shock. *Ann Emerg Med* 1997;**30**:127–34.
13. Yakatis RW, Ewy GA, Otto CW, Taren DL, Moon TE. Influence of time and therapy on ventricular defibrillation in dogs. *Crit Care Med* 1980;**8**:157–63.
14. Cummins RO, Chamberlain D, Hazinski MF *et al.* Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital "utstein style". *Circulation* 1997;**95**:2213–39.
15. Cummins RO, Chamberlain DA, Abramson NS *et al.* Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the utstein style. *Circulation* 1991;**84**:960–75.
16. Schneider T, Martens PR, Paschen H *et al.* Multi-center, randomized, controlled trial of 150-J biphasic shocks compared with 200- to 360-J monophasic shocks in the resuscitation of out-of-hospital cardiac arrest victims. *Circulation* 2000;**102**: 1780–7.
17. Behr JC, Hartley LL, York DK, Brown DD, Kerber RE. Truncated exponential versus damped sinusoidal waveform shocks for transthoracic defibrillation. *Am J Cardiol* 1996;**78**: 1242–5.
18. Poole JE, White RD, Kanz KG *et al.* Low-energy impedance-compensating biphasic waveforms terminate ventricular fibrillation at high rates in victims of out-of-hospital cardiac arrest. *J Cardiovasc Electrophysiol* 1997;**8**:1373–85.
19. Gliner BE, Jorgenson DB, Poole JE *et al.* Treatment of out-of-hospital cardiac arrest with a low-energy impedance-compensating biphasic waveform automatic external defibrillator. *Biomed Instrument Technol* 1998;**32**:631–44.
20. Cummins RO, Hazinski MF, Kerber RE *et al.* Low-energy biphasic waveform defibrillation: evidence-based review applied to emergency cardiovascular care guidelines. *Circulation* 1998; **97**:1654–67.
21. Weaver W, Cobb L, Copass M *et al.* Ventricular defibrillation: a comparative trial using 175-J and 320-J shocks. *N Engl J Med* 1982;**307**:1101–6.

22.White RD, Hankins DG, Bugliosi TF. Seven years' experience with early defibrillation by police and paramedics in an emergency medical services system. *Resuscitation* 1998; **39**:145–51.
23.van Walraven C, Stiell IG, Wells GA, Herbert PC, Vandenheen K. The OTAC Study Group. Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest? *Ann Emerg Med* 1998;**32**:544–53.
24.Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Adrenaline in out-of-hospital ventricular fibrillation. Does it make a difference. *Resuscitation* 1995;**29**: 195–201.
25.Brown CG, Martin DR, Pepe PE *et al.* The Multicenter High-dose Epinephrine Study Group. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. *N Engl J Med* 1992;**327**:1051–5.
26.Stiell IG, Hebert PC, Weitzman BN *et al.* High-dose epinephrine in adult cardiac arrest. *N Engl J Med* 1992;**327**: 1045–50.
27.Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA* 1992;**268**:2667–72.
28.Lindner KH, Ahnefeld FW, Prengel AW. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. *Acta Anaesthesiol Scand* 1991;**35**:253–6.
29.Lipman J, Wilson W, Kobilski S *et al.* High-dose adrenaline in adult in-hospital asystolic cardiopulmonary resuscitation: a double-blind randomized trial. *Anaesth Intens Care* 1993; **21**:192–6.
30.Choux C, Gueugniaud PY, Barbieux A *et al.* Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. *Resuscitation* 1995;**29**:3–9.
31.Sherman BW, Munger MA, Foulke GE, Rutherford WF, Panacek EA. High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy. *Pharmacotherapy* 1997;**17**:242–7.
32.Gueugniaud PY, Mols P, Goldstein P *et al.* A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *N Engl J Med* 1998;**339**:1595–601.
33.Rivers E, Wortsman J, Rady M, Blake H, McGeorge F, Buderer N. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. *Chest* 1994;**106**:1499–507.
34.Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. *Circulation* 1988; **78**: 382–9.
35.Lindner KH, Ahnefeld F, Schuerman W, Bawdler IM. Epinephrine and norepinephrine in cardiopulmonary resuscitation – effects in myocardial oxygen delivery and consumption. *Chest* 1990;**97**:1458–62.
36.Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart* 1996;**75**:145–50.
37.Michael JR, Guerci AD, Koehler RC *et al.* Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;**69**:822–35.
38.Paradis NA, Martin GB, Rivers EP *et al.* Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990;**263**:1106–13.
39.Lindner KH, Ahnefeld FW, Bawdler IM. Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model. *Am J Emerg Med* 1991;**9**:27–31.
40.Barbar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. *Resuscitation* 1999;**41**:185–92.
41.Linder KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997;**349**:535–7.
42.Stiell IG, Hebert PC, Wells GA *et al.* Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomized controlled trial. *Lancet* 2001;**358**:105–9.
43.Lie KI, Wellens HJ, van Capelle FJ, Durrer D. Lidocaine in prevention of primary ventricular fibrillation: a double-blind, randomized study of 212 consecutive patients. *N Engl J Med* 1974;**291**:1324–6.
44.Herlitz J, Ekstrom L, Wennerblom B *et al.* Lidocaine in out-of-hospital ventricular fibrillation: does it improve survival? *Resuscitation* 1997;**33**:199–205.
45.Sadowski ZP, Alexander JH, Skrabucha B *et al.* Multicenter randomized trial and a systematic overview of lidocaine in acute myocardial infarction. *Am Heart J* 1999;**137**:792–8.
46.Alexander JH, Grayer CB, Sadowski Z *et al.* The GUSTO-I and GUSTO-IIb Investigators. Prophylactic lidocaine use in acute myocardial infarction: incidence and outcomes from two international trials. *Am Heart J* 1999;**137**:799–805.
47.Dorian P, Fain ES, Davy JM, Winkle RA. Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. *J Am Coll Cardiol* 1986;**8**:327–32.
48.Echt DS, Black JN, Barbey JT, Coxe DR, Cato E. Evaluation of anti-arrhythmic drugs in defibrillation energy requirements in dogs: sodium channel block and action potential prolongation. *Circulation* 1998;**79**:1106–17.
49.Babbs CF, Yim GK, Whistler SJ, Tacker WA, Geddes LA. Elevation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs. *Am Heart J* 1979;**98**:345–50.
50.Kudenchuk PJ, Cobb LA, Copass MK *et al.* Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;**341**:871–8.
51.Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;**346**:884–90.
52.van Walraven C, Forster AJ, Stiell IG. Derivation of a clinical decision rule for the discontinuation of in-hospital cardiac arrest resuscitations. *Arch Intern Med* 1998;**158**:129–34.
53.van Walraven C, Forster AJ, Parish DC *et al.* Validation of a clinical decision aid to discontinue in-hospital cardiac arrest resuscitations. *JAMA* 2001;**285**:1602–6.

Part IIIe

Specific cardiovascular disorders: Left ventricular dysfunction

Salim Yusuf, Editor

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

45 Prevention of congestive heart failure and treatment of asymptomatic left ventricular dysfunction

RS McKelvie, CR Benedict, Salim Yusuf

Epidemiology of heart failure

Over the past three decades, epidemiological studies have been increasingly used to identify the cause of major chronic degenerative diseases such as systemic hypertension and atherosclerosis.[1] Early studies on the prevalence and incidence of heart failure were drawn from private practice, hospital wards, and admissions to hospitals.[1] Also, data from survey studies were used to determine the prevalence rate of heart failure.[2] The prevalence of heart failure shows some disparity among the published studies, although generally the results are similar in demonstrating an increase with age.[3–7] Prevalence increases from approximately 0·7 cases/1000 persons in the younger age group (<50 years old) to approximately 27 cases/1000 in the older age group, (>65 years old) and approximately 63 cases/1000 in those over 75 years old.[8] The incidence is greater in men than in women and increases progressively with age.[5,6,9–11] The incidence in younger men (<50 years old) is approximately 1 case/1000 persons per year, increasing in the older age group (>65 years old) to 11/1000 per year, with an incidence of approximately 17/1000 persons per year in men 85 years or over.[12] In women the incidence increases in the younger age group (<50 years old) from 0·4/1000 persons per year to 5/1000 per year in older individuals (>65 years old), with an incidence of approximately 10/1000 persons per year in women 85 years or over.[12]

There are a number of reasons why some disparity has been observed among these studies examining incidence and prevalence in heart failure patients. The studies differ with regard to sampling methods (population based *v* cohort based), geography and demographics, case finding methods (medical record review versus systematic questionnaires and examinations), and diagnostic criteria.[13] Even though these differences are responsible for the disparities between studies, they also provide a more robust database and complementary information.

Once a diagnosis of heart failure has been made the prognosis has been uniformly observed to be relatively poor.[7,14–16] Croft *et al*[14] obtained Medicare hospital claims records from 1984 to 1986 and beneficiary enrollment data for 1986 to 1992 from the Health Care Financing Administration. The 1 year survival for black men (n = 6186) was 68%, for white men (n = 64 918) was 64%, for black women (n = 9097) was 71%, and for white women (n = 90 038) was 69%. Five year survival for black men was 24%, for white men 21%, for black women 30%, and for white women 29%. Mosterd *et al*[7] examined the prognosis for heart failure in the general population (n = 5255; 59·3% women) as part of the Rotterdam Study. In this study 1 year survival for men was 91% and for women was 87%, and survival at 5 years was 56% and 61%, respectively. Cowie *et al*[16] examined the survival of patients with a new diagnosis of heart failure. The total study population was 151 000 as of February 1996 (this was the midpoint of identification of cases, which ran from April 1995 to December 1996) and follow up for death was complete for all 220 cases to June 1997. One month survival for this group was 81%, 3 month survival was 75%, and 12 month survival was 62%.

Although there are some differences between these studies, and also clinical drug trials[17,18] in which 1 year mortality has been reported to be approximately 12%, there are several possible explanations for these discrepancies. Survival outcomes at 1 year will be related to whether the study is based on identifying patients with a new diagnosis (incidence) of heart failure or patients with a diagnosis of heart failure (prevalence) on entry into the study. Clinical drug trials usually take stable heart failure patients, and such patients would be considered "natural survivors" as they have survived the early high-risk period. This would also be true for any surveys of the general population that examined patients who on entry had a diagnosis of heart failure, such as the study by Mosterd *et al*[7] Also, clinical trials tend to recruit a select group of patients with a better prognosis than the general population of patients with heart failure. The typical age of patients in a drug trial is on average approximately 65 years, compared to the general population of heart failure patients with an average age of approximately 75 years.[19,20] Heart failure is often associated with considerable comorbidity, but patients with these types of

problems are less likely to be recruited into clinical drug studies. Thus these biases, seen especially in clinical drug trials, make the prognosis of heart failure appear much better than it actually is for most patients. These findings emphasize the imperative need to identify and aggressively treat patients with left ventricular dysfunction to prevent them developing heart failure.

Epidemiology of asymptomatic left ventricular dysfunction

Studies assessing the epidemiology of heart failure have largely identified symptomatic individuals because identification of these patients is based on clinical criteria and does not require measurement of left ventricular (LV) function.[13] Asymptomatic patients with LV dysfunction have therefore not been included in these studies. Consequently, the available data on the prevalence of patients with asymptomatic LV dysfunction are limited, even though treatment of these patients may be expected to significantly improve their outcome.[21] There have been several studies that screened the general population looking for the presence of asymptomatic LV dysfunction.[8,22–26]

In 1992 McDonagh *et al* measured the ejection fraction in 1467 people aged 25–74 years during a survey of coronary risk factors.[22] The mean ejection fraction in people defined as not having cardiovascular disease was 47%, and 34% was two standard deviations below the mean. Of the 2·9% with an ejection fraction of ≤30%, half had no symptoms. The frequency of both left ventricular systolic dysfunction and symptoms was greater in older age groups, increasing sharply up to the age of 45 and less sharply thereafter (Table 45.1). Of the 7·7% of individuals with an ejection fraction of 35%, 77% were asymptomatic. Of those with definite left ventricular systolic dysfunction (Table 45.1) the proportion with symptoms increased with age. The group with left ventricular systolic dysfunction had a greater prevalence of ischemic heart disease and hypertension than did the group with normal ventricular function (Table 45.2).

Mosterd *et al*[8] performed a population based cohort study examining the presence of symptomatic and asymptomatic left ventricular systolic dysfunction in the general population of individuals who were 55 years of age or older. A total of 2823 persons had M mode echocardiographic assessments and the echocardiograms of 556 participants were deemed inadequate to measure left ventricular dimensions reliably. The prevalence of left ventricular systolic dysfunction (fractional shortening ≤25%) in the 2267 persons with analyzable echocardiograms was 3·7% (95% CI 2·9–4·5). Overall, the prevalence in men ($n = 1028$) was 5·5% (95% CI 4·1–7·0) and in women ($n = 1239$) was 2·2% (95% CI 1·4–3·2). The age-adjusted prevalence of left ventricular dysfunction was approximately 2·5 times higher in men (OR 2·7, 95% CI 1·7–4·3). The relationship between left ventricular systolic function and symptoms/ signs of heart failure was examined in the 1698 individuals (771 men) in whom information on the presence of heart failure and echocardiographic data were available. Of the 35 individuals who had heart failure by symptoms and signs, only 10 (29%, 95% CI 15–46) had echocardiographic evidence of left ventricular systolic dysfunction. Interestingly, of the 60 individuals with left ventricular dysfunction by echocardiographic criteria only 24 (40%, 95% CI 28–53) were found to have at least one of the cardinal symptoms or signs of heart failure (shortness of breath, ankle edema or pulmonary edema): therefore 60% had asymptomatic left ventricular systolic dysfunction. Persons with left ventricular systolic dysfunction had more frequently sustained a myocardial infarction, undergone coronary artery bypass graft surgery or PTCA and were more likely to have angina pectoris.

Morgan *et al*[23] performed a cross-sectional survey to assess the prevalence and clinical characteristics of left ventricular systolic dysfunction among 817 elderly patients in a general practice setting. Echocardiography was used to

Table 45.1 Prevalence of definite left ventricular systolic dysfunction (EF ≤ 30%) by age according to the presence of symptoms (adapted with permission from McDonagh TA *et al.* Symptomatic and asymptomatic left ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829–33)

	Proportion with definite left ventricular systolic dysfunction (%) Age group (years)				
	25–34	**35–44**	**45–54**	**55–64**	**65–74**
Men	($n = 122$)	($n = 135$)	($n = 138$)	($n = 158$)	($n = 155$)
Symptomatic	0	0	1·4	2·5	3·2
Asymptomatic	0	0·7	4·4	3·2	3·2
Women	($n = 126$)	($n = 162$)	($n = 159$)	($n = 149$)	($n = 164$)
Symptomatic	0	0	1·2	2·0	3·6
Asymptomatic	0	0	1·2	0	1·3

Table 45.2 Risk factors for left ventricular systolic dysfunction in symptomatic and asymptomatic participants (adapted with permission from McDonagh TA *et al*). Symptomatic and asymptomatic left ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829–33)

Risk factor	Symptomatic % with RF (*n*)		OR (95% CI)	*P* value	Asymptomatic % with RF (*n*)		OR (95% CI)	*P* value
	LVSD present	LVSD absent			LVSD present	LVSD absent		
IHD								
All IHD	95% (21)	43% (197)	25 (3·6–100)	<0·001	71% (21)	17% (1138)	12·5 (4·5–33·3)	<0·001
MI	50% (22)	15% (20)	5·9 (2·3–14·3)	<0·001	14% (21)	2% (1167)	6·7 (1·8–25)	0·02
Angina	62% (21)	26% (206)	4·5 (1·8–11·1)	<0·001	43% (21)	6% (1155)	11·1 (4·5–25)	<0·001
ECG ischemia	77% (22)	25% (201)	10 (3·3–33·3)	<0·001	50% (20)	13% (1151)	6·7 (2·8–16·7)	<0·001
ECG abnormal	77% (22)	8% (201)	9·1 (3·1–25)	<0·001	60% (20)	18% (1151)	7·1 (2·8–16·7)	<0·001
Hypertension	80% (20)	53% (151)	3·1 (1·1–8·9)	0·02	67% (21)	36% (1227)	3·5 (1·4–8·5)	0·004
Valvular abnormality	25% (12)	6% (194)	5·5 (1·3–25)	<0·001	0% (14)	4% (1093)	–	0·99

Abbreviations: CI, confidence interval; IHD, ischemic heart disease; LVSD, definite left ventricular systolic dysfunction; MI, myocardial infarction; *n*, number in subgroups; OR, odds ratio; RF, risk factor

assess ventricular function in this group of patients aged 70–84 years. Left ventricular function was assessed qualitatively as normal, mild, moderate or severe dysfunction. In 667 (82%) of the patients a measurement of ejection fraction could be made. The mean ejection fraction for normal left ventricular function was 66·3% ± (SD) 13·5%, 47·7% ± 12·0% for mild dysfunction, 38·3% ± 8·1% for moderate dysfunction, and 26% ± 7·9% for severe dysfunction. The prevalence of left ventricular systolic dysfunction was higher in men (12·8%, 95% CI 9·6–16·6) than in to women (2·9%, 95% CI 1·8–5·0). The overall prevalence of all grades of left ventricular systolic dysfunction was 7·5% (95% CI 5·8–9·5). Prevalence was more than twice as great at age ≥ 80 years (men 20·5%, 95% CI 12·0–31·6; women 5·4%, 95% CI 1·8–12·2) than at ages 70–74 years (men 9·4%, 95% CI 5·5–14·7; women 2·2%, 95% CI 0·6–5·5), but the relative difference between men and women was preserved (20·5% *v* 5·4%; $P < 0·05$). At all ages the prevalence of left ventricular systolic dysfunction was much greater in men than in women (OR 5·1, 95% CI 2·6–10·1). About half (48%, 29/61 patients) of all patients with left ventricular systolic dysfunction had previous heart failure documented in their medical charts; thus 52% of the patients did not have documented heart failure and would have been considered to have asymptomatic left ventricular systolic dysfunction. Multivariate analysis demonstrated that the probability of having any grade of echocardiographically abnormal left ventricular function was increased by a previous history of heart failure, myocardial infarction, stroke, angina, age and male gender. Gardin *et al*[26] as part of the Cardiovascular Health Study, assessed cardiac function in 5201 people between the ages of 65 and 100 years old. Left ventricular systolic function was reported in a qualitative/semi-quantitative fashion, with cardiac function being assessed as normal or abnormal. The prevalence of abnormal cardiac function was greater ($P < 0·001$) in men (6·3%) than in women (1·8%); increased with age ($P < 0·001$) from 2·3% for ages 65–69 years to 5·5% for 80 years and older; and was greater ($P < 0·001$) in those with clinical coronary heart disease (10·5%) than in either those with only hypertension (1·7%) or those with neither clinical heart disease or hypertension (0·5%). In the Strong Heart Study left ventricular systolic function was assessed in 3184 adults who were middle-aged and older[25] (range 45–74 years, with a mean of 60 years). The prevalence of mild left ventricular systolic dysfunction (left ventricular ejection fraction <40%) was 2·9%, and 72% of these individuals had no evidence of heart failure.

Clearly the prevalence of asymptomatic left ventricular dysfunction in the general population is substantial, as it is similar to that found for symptomatic left ventricular systolic dysfunction. Furthermore, when patients are screened for

left ventricular systolic dysfunction, at least 50% of the cases are found in patients without a previous history of heart failure. These data are only recently being realized because most of the previous studies used signs and symptoms to identify patients with cardiac dysfunction, and there were no systematic evaluations of cardiac function performed. These studies further demonstrate that even in the elderly asymptomatic left ventricular dysfunction is high. The studies are consistent in demonstrating that those individuals with asymptomatic left ventricular dysfunction are more often men with a history of ischemic heart disease and hypertension.

Although the presence of asymptomatic LV systolic dysfunction is relatively common in the general population, a program of screening unselected individuals to identify such patients cannot currently be recommended. A more prudent approach would be to screen individuals who are at a greater risk of developing LV systolic dysfunction, such as those known to have ischemic heart disease or hypertension. Criteria that can be used to assess the risk of developing LV systolic dysfunction will be outlined below.

Left ventricular diastolic dysfunction

It is also very important to recognize that a great number of patients with symptoms and signs of heart failure do not have evidence of left ventricular systolic dysfunction. These findings highlight the possibility that many patients with typical symptoms of heart failure may have preserved left ventricular systolic function. Impaired LV diastolic function, whether by itself or in the presence of LV systolic dysfunction, is gaining more recognition as a potentially important contributor to the progression of LV systolic dysfunction and the development of symptomatic heart failure. The prevalence of normal ventricular systolic performance in patients with heart failure varies widely, from 13% to 74%, with the majority of studies reporting a value of 40–50%.[27–32] Normal ventricular systolic function with heart failure is more prevalent in patients over 65 years of age than those 65 or under, among hypertensive patients, and in women.[27–32] Studies report an annual mortality associated with diastolic heart failure of 3–9%, which is lower than that of patients with systolic heart failure.[27,29] However, other studies have demonstrated that the annual mortality for heart failure patients with associated preserved left ventricular systolic function is as great as in heart failure patients with impaired left ventricular systolic function.[28,30,33,34] In light of these studies to date, there is no doubt that left ventricular diastolic dysfunction represents a significant clinical problem, in terms of both prevalence and prognosis. A lack of consensus remains among physicians regarding what constitutes LV diastolic dysfunction measured by non-invasive techniques.[27] There is therefore a need to develop a consensus for diagnostic criteria of diastolic heart failure which could then be used to provide a better estimate of its prevalence and prognosis. There is also a need for randomized clinical trials to determine the appropriate treatment for patients with established LV diastolic dysfunction.

Factors that lead to the development of heart failure

Even though angiotensin-converting enzyme (ACE) inhibitors have been demonstrated to decrease the morbidity and mortality associated with heart failure the event rate for symptomatic heart failure remains very high, and other measures are required. The results from the Survival and Ventricular Enlargement (SAVE) trial[35] and the Prevention trial of the Studies of Left Ventricular Dysfunction (SOLVD)[21] demonstrate that the onset of heart failure can be prevented or delayed in patients with asymptomatic or minimally symptomatic LV systolic dysfunction with the use of ACE inhibitors (Figure 45.1). Recent data from the Heart Outcomes Prevention Evaluation study (HOPE) demonstrated a reduction in the incidence of heart failure in patients with no evidence of impaired left ventricular systolic

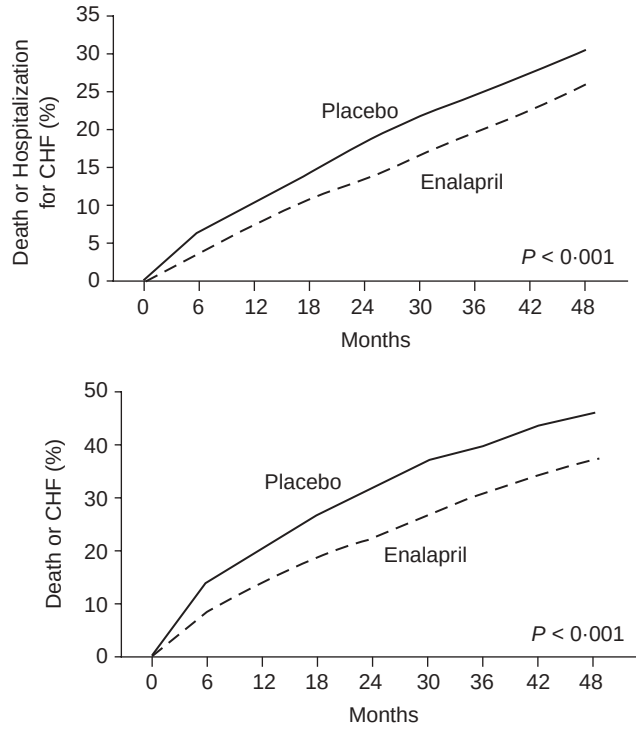

Figure 45.1 Death or hospitalization for heart failure and death or development of heart failure in the Prevention Trial from SOLVD. (From SOLVD Investigators, *N Engl J Med* 1993; **327**:685–91, with permission.)

function.[36] The combined findings from the ACE inhibitor studies suggest benefit for patients who are at high risk for heart failure, irrespective of the degree of left ventricular systolic dysfunction.[36,37] Aggressive treatment of the risk factors responsible for heart failure would also be potentially useful to prevent the development of left ventricular systolic dysfunction or the progression to symptomatic heart failure. Therefore, the most effective method to decrease mortality may be to identify patients who have asymptomatic LV dysfunction and treat them early to prevent the progression to symptomatic LV dysfunction. A number of factors have been identified which help predict whether an individual may have or develop LV dysfunction.

Hypertension

Hypertension has for many years been known to be an important risk factor for the development of heart failure.[5,9,11,38,39] In both men and women, hypertension is associated with a three- to fourfold increase in the risk of heart failure for individuals between 35 and 64 years, and approximately twofold increase for individuals over 65 years of age.[5,40] Although the relative risk is higher in the younger age group, the absolute excess risk is higher in the older age group, reflecting greater absolute risk differences.[40] Multivariate analyses have revealed that hypertension (systolic blood pressure of $\geq$140 mmHg or a diastolic of $\geq$90 mmHg, or current treatment of high blood pressure) is associated with a high population-attributable risk for coronary heart failure (CHF) accounting for 39% of cases in men and 59% in women.[39] Hypertension represents a continuous risk variable with no clear cut-off point below which CHF will not develop. Over four decades of observation there has been no significant change in the frequency of hypertension as an attributable cause of heart failure.[19] The results of more recent studies, such as the Heart Outcomes Prevention Evaluation (HOPE)[36] and the Perindopril Protection against Recurrent Stroke Study (PROGRESS)[41] studies, suggest that for high-risk patients it may be beneficial to lower blood pressure even if it is already within the "normal" range. Furthermore, a recent reanalysis of 20 years of blood-pressure data from the Framingham Heart Study suggests that the degree of benefit expected from a decrease in blood pressure may have been underestimated.[42] Therefore, hypertension remains an important risk factor for the development of heart failure.

Left ventricular hypertrophy

The presence of LV hypertrophy has been well documented as a risk factor for the development of heart failure, even after controlling for hypertension.[39] ECG evidence of LV hypertrophy criteria is associated with increased risk of CHF that is greater than the risk associated with cardiac enlargement on chest radiography. Data from Framingham demonstrate that the age-adjusted biennial rate of developing heart failure in men with ECG evidence of LV hypertrophy was 71/1000 patients aged 35–64 years and 102/1000 individuals aged 65–94 years, which was greater than that found when cardiac enlargement was present radiographically in men in the same age groups: 16/1000 individuals and 56/1000 individuals, respectively.[43] This suggests that the ECG findings reflect ischemia in addition to anatomical hypertrophy.[43] A recent report, based on a substudy from the Losartan Intervention For End (LIFE) point reduction in hypertension study, found that in hypertensive patients with clinical evidence of coronary artery disease (CAD) LV hypertrophy identifies those individuals with structural and functional cardiac abnormalities with a high risk for the development of heart failure.[44] Furthermore, in this study exceptionally high levels of myocardial oxygen demand were found in this group, and this may be additive to the ischemic effect in these patients. A recent study by Matthew *et al*[45] based on analysis of data from the HOPE study demonstrated the importance of LV hypertrophy as a predictor for the risk of developing heart failure. In this study of patients with normal or controlled blood pressure those with ECG evidence of LV hypertrophy had a much greater risk of developing heart failure (15·4% with ECG–LV hypertrophy versus 9·3% without ECG–LV hypertrophy; $P < 0{\cdot}0001$). LV hypertrophy is associated with a 15-fold increase in the incidence of heart failure in men 64 years of age or under and a fivefold increase in men 65 or older.[40] In women, LV hypertrophy is associated with a 13-fold increase in heart failure for the younger age group and a fivefold increase for the older age group.[40] Although the relative risk is higher in the younger age group, the absolute excess in risk is higher in the older age group, reflecting greater absolute risk differences.

Smoking

Cigarette smoking has been found in 42% of men and 24% of women who develop heart failure.[40] In men the relationship between cigarette smoking and the development of heart failure is greater in the younger age group than in the older age group.[5,40] Multivariate analyses have demonstrated smoking to be a strongly significant independent risk factor for the development of heart failure in men, even in the older age group.[5] The relationship between cigarette smoking and the risk of developing heart failure in women is inconsistent, although there has been a trend to an increase in relative risk in older women.[40] Therefore the data would suggest that smoking is a risk factor for the development of heart failure, and in fact the hazardous effects may be underestimated, as not all studies have taken into account changes in smoking habits over time, and this could lead to an underestimation of the number of smokers in the older age groups.[5]

Hyperlipidemia

There is some evidence to suggest a relationship between elevated triglyceride levels and the development of heart failure;[5] a high ratio of total cholesterol to high density lipoprotein (HDL) cholesterol is also associated with an increased incidence of heart failure.[40] The investigators in the Simvastatin Survival Study (4S) Group Trial found that patients in the simvastatin group had a significantly lower incidence (6·2%) of heart failure than those in the placebo group (8·5%).[46] Interestingly, a higher triglyceride concentration and a lower HDL concentration predicted the development of heart failure. These results further support the importance of lipid abnormalities as a factor responsible for the development of heart failure.

Diabetes mellitus

Diabetes mellitus is a well established risk factor for the development of coronary artery disease. Over the past 25 years, diabetes mellitus has been recognized as a factor responsible for the development of heart failure,[5,9,11,38,39] working through an independent mechanism rather than the simple acceleration of coronary atherosclerosis.[1] The presence of fibrosis in the hearts of patients with diabetes mellitus has been described and it is thought to be due to diabetic microangiopathy.[47] The prevalence of diabetes mellitus in heart failure patients has been reported to be approximately 22%.[48] The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study in 663 CHF patients found a 27% prevalence of documented diabetes, whereas 23% ($n=111$ patients) of non-diabetic patients had an elevated fasting glucose $\geq 6{\cdot}1$ mmol/l, and 11% ($n=53$ patients) of these had fasting glucose concentrations in the diabetic range (fasting glucose $\geq 7{\cdot}0$ mmol/l).[49] Therefore, approximately 44% of these patients had either known diabetes mellitus or abnormal fasting glucose levels. This suggests that most studies have underestimated the importance of glucose abnormalities in heart failure. Diabetes mellitus is more common in women than in men with heart failure,[40,50] and women with diabetes mellitus have a greater risk of developing heart failure than do men with diabetes mellitus.[40] Following a myocardial infarction, patients with diabetes mellitus who develop heart failure have more severe symptoms than those without diabetes mellitus who develop heart failure.[51] For any given level of infarct size, patients with diabetes mellitus had a lower ejection fraction than those without diabetes mellitus (Yusuf *et al*, unpublished data). In the SOLVD trial in patients with asymptomatic LV dysfunction, diabetes mellitus is an independent predictor of the development of heart failure and mortality.[52] Furthermore, the patients with diabetes mellitus treated with enalapril had a greater mortality than those without diabetes mellitus treated with enalapril, indicating that although ACE inhibitors benefit this subgroup of patients, diabetes mellitus still remains a significant predictor of outcome. However, in both cases patients on enalapril had lower rates of mortality than with placebo.

Therefore, these data indicate that abnormalities of glucose metabolism in CHF patients should be aggressively searched for and perhaps treated.

Microalbuminuria

In the Heart Outcomes Prevention Evaluation (HOPE) trial, microalbuminuria was found to be a predictor of heart failure and other cardiovascular events in patients with and without diabetes mellitus.[53] In this group at high risk of a cardiovascular event, microalbuminuria increased the adjusted relative risk of hospitalization for heart failure by 3·23-fold (95% CI 2·54–4·10).

Vital capacity

A low or a decrease in vital capacity over time has been found to be associated with an increased risk of developing heart failure.[43] The abnormality probably reflects the lungs, being congested with blood as a result of LV dysfunction. However, the relationship between vital capacity and the development of heart failure has not been a consistent finding in all studies.[5]

Heart rate

In hypertensive patients, resting heart rate was a predictor of the future development of heart failure.[54] The risk of heart failure increased with the heart rate in a continuous graded fashion, from an age-adjusted biennial rate of 14·6/1000 patients at heart rates less than 64 beats per minute (bpm) to a rate of 62·2/1000 patients at heart rates greater than 85 bpm. This may indicate asymptomatic LV dysfunction and subtle activation of the neuroendocrine system.

Obesity

Obesity has been reported to be an independent risk factor for the development of heart failure.[5,55] This finding would support efforts directed at dietary modification to promote weight loss and also help correct lipid abnormalities. A study by Schirmer *et al*[56] demonstrated that body mass index (BMI) was a very important variable for categorizing subjects as having LV hypertrophy: the odds of having LV hypertrophy increased in relation to the increase in BMI. These data further suggest that obesity may contribute to the development of heart failure.

Pathophysiologic abnormalities in asymptomatic LV dysfunction that predict the development of CHF

Neuroendocrine activation

Symptomatic heart failure is characterized by the activation of several neuroendocrine systems.[57–61] The well documented finding that ACE inhibitor therapy improves survival in patients with heart failure and reduces the rates of new heart failure in patients with asymptomatic LV dysfunction[21] further suggests that neurohormones play an important role in the pathogenesis of symptomatic heart failure.[17,62] A substudy of the SOLVD trial demonstrated that the median values for plasma norepinephrine, plasma atrial natriuretic factor (ANF), plasma arginine vasopressin (AVP) and plasma renin activity (PRA) were significantly higher in patients with asymptomatic LV dysfunction than in age and gender matched normal control individuals, with symptomatic patients having the highest neurohumoral values (Figure 45.2).[63] Plasma norepinephrine levels appear to increase early in the development of LV dysfunction, whereas the increase in PRA seems to occur only when the patients are taking diuretics. The degree of LV dysfunction is one of the mechanisms for activation of neurohormones, as patients with an ejection fraction greater than 0·45 and pulmonary congestion on chest radiography were found to have only minimal neurohormonal activation and a modest increase in AVP and PRA.[64]

In the SOLVD Prevention trial, plasma norepinephrine level was the strongest predictor of the future development of heart failure.[65] This finding was independent of LV ejection fraction, NYHA class, age, sex, cause of heart failure, treatment assignment to placebo or enalapril, or prerandomization ANF or PRA levels. Plasma norepinephrine levels above the median of 393 pg/ml were associated with

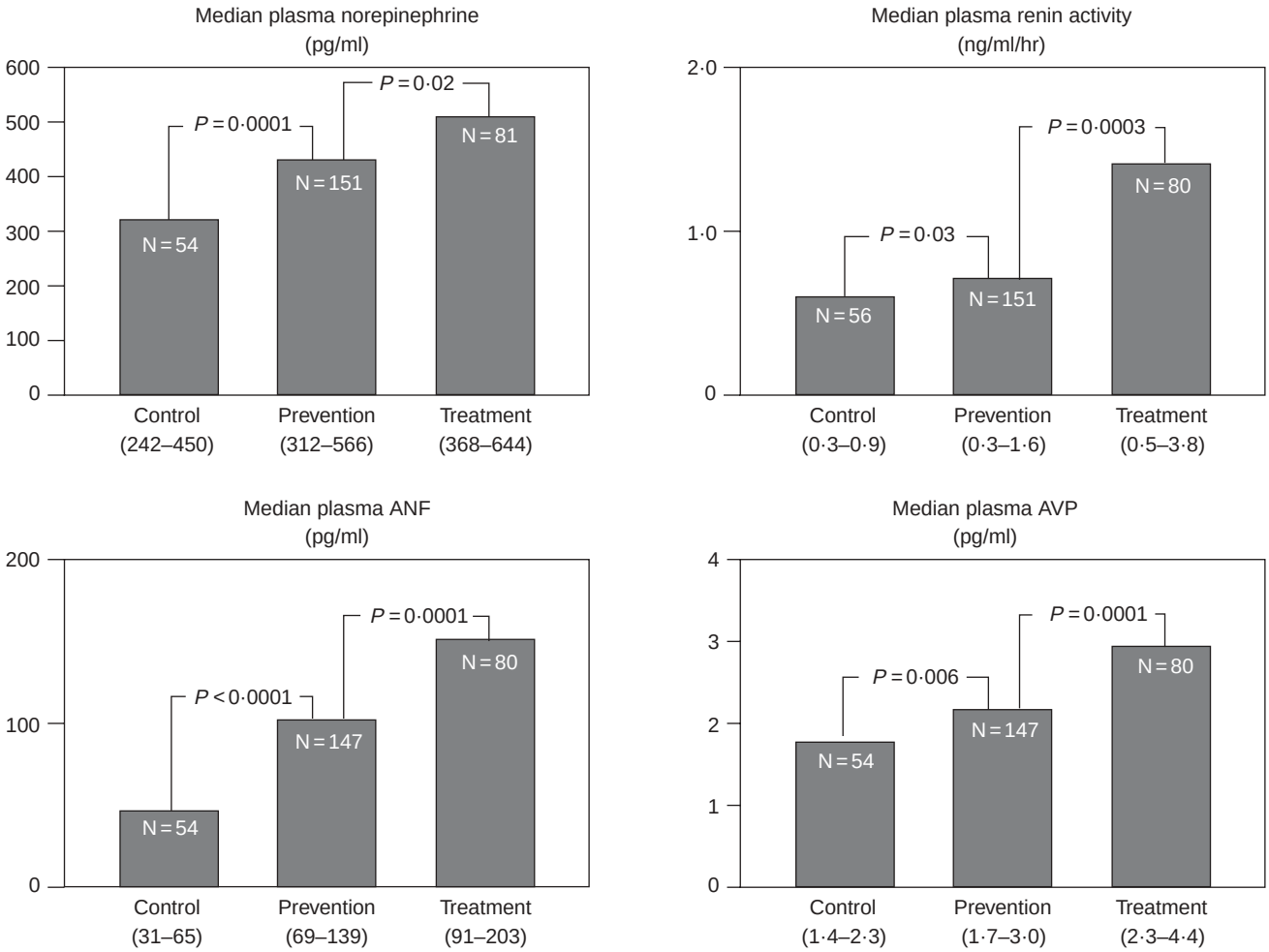

Figure 45.2 Comparison of norepinephrine, plasma renin activity, plasma atrial natriuretic factor (ANF) and plasma arginine vasopressin (AVP) in healthy control subjects, patients with asymptomatic left ventricular dysfunction and patients with symptomatic heart failure. (From Francis GS *et al*, *Circulation* 1990;**82**:1724–9, with permission.)

a relative risk of 2·59 ($P = 0·002$) for all-cause mortality, 2·55 ($P = 0·005$) for hospitalization for heart failure, 1·88 ($P = 0·002$) for the development of heart failure, 1·92 ($P = 0·001$) for ischemic events, and 2·59 ($P = 0·005$) for myocardial infarction (Figure 45.3). PRA and ANP were not as useful for predicting clinical outcome because although trends were observed for these hormones, they were not statistically significant. These data are very important because they suggest that modulating the release or effect of plasma norepinephrine early in patients with asymptomatic left ventricular dysfunction may improve prognosis and prevent heart failure and perhaps ischemic events.

A recent study examines the location of adrenergic activity in patients with early heart failure.[66] In this study a selective increase was found in cardiac adrenergic drive in patients with early heart failure. This preceded the augmented sympathetic outflow to the kidneys and skeletal muscle found in advanced heart failure. These data collectively indicate that activation of the sympathetic system in early heart failure is causally related to the syndrome and that drugs such as β blockers may be of value.

Recent data from the Australia–New Zealand Heart Failure Group has demonstrated that in patients with chronic ischemic LV dysfunction plasma N-terminal-brain natriuretic peptide (N-BNP) concentration is an independent predictor of mortality and heart failure events.[67] Other evidence suggests that natriuretic peptides may be of use to screen for and improve the ability to diagnose heart failure.[68–70]

Cardiac dilation and remodeling

The process of LV remodeling in the setting of a prior myocardial infarction leading to ventricular dilation has been well described.[71–76] Even several years after the initial cardiac insult, or remote from the precipitating cause of heart failure, this process continues progressively with continuing left ventricular dilation.[77–80] Among asymptomatic patients the rate of progression of ventricular dilation and systolic dysfunction is slower than in symptomatic patients.[77–80] It seems likely that asymptomatic and symptomatic patients represent a continuum of pathology, with the rate of progression of ventricular dilation accelerating

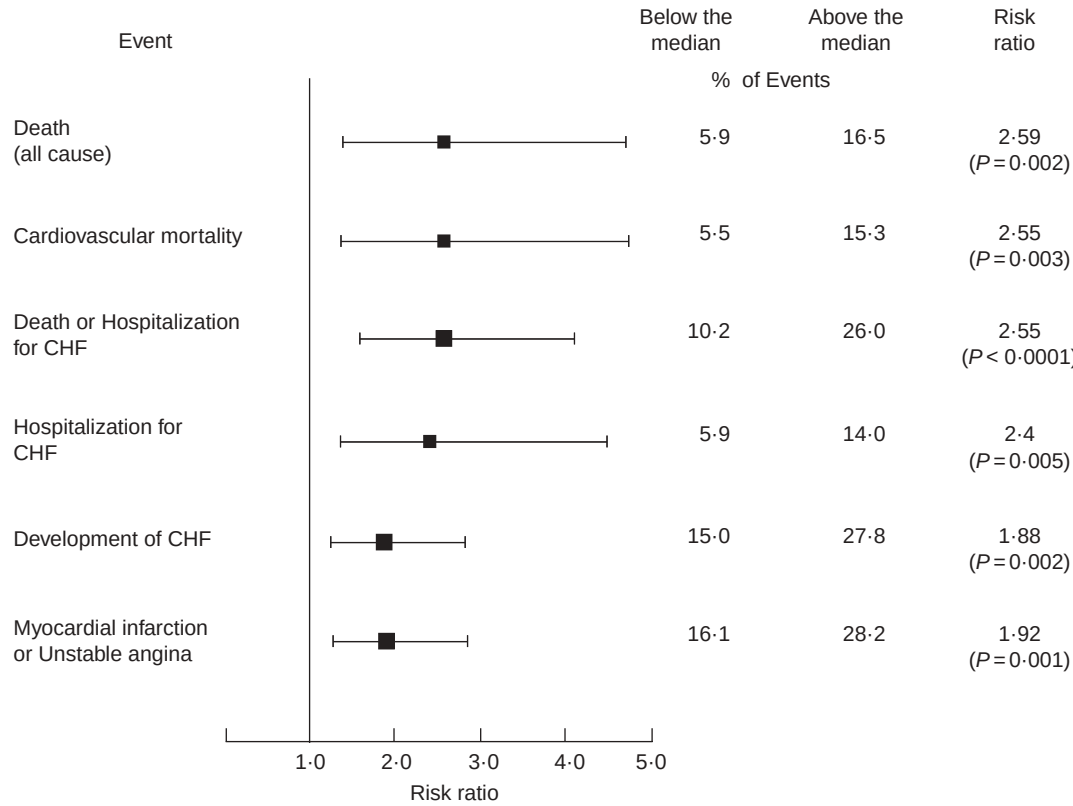

Figure 45.3 Effect of plasma norepinephrine level on all-cause mortality, cardiovascular mortality, development of heart failure, hospitalization for heart failure, and development of ischemic events. For each group, the increase in risk is shown as a percentage. Horizontal lines indicate the 95% CI. Size of each square is proportional to the number of events in that group. Vertical line corresponds to a finding of no effect. (From Bendict CR *et al*, *Circulation* 1996;**94**:690–7, with permission.)

at later stages. Although the exact stimuli affecting these changes in myocardial structure remain unknown, increased myocardial wall stress has been postulated to represent an initiating factor. Activation of the renin–angiotensin system appears to play an important role in the pathogenesis of ventricular remodeling by contributing to the increase in wall stress, and possibly by direct myocardial effects.[81–83]

The progression of LV dysfunction in asymptomatic patients can be insidious. When an initial insult causes the loss of large amounts of myocardium, the ejection fraction decreases and the end-diastolic volume increases (Figure 45.4). This increase in end-diastolic dimension is accompanied by relative thinning of the wall and an increase in wall stress.[84] As the compensatory remodeling process evolves the ventricle dilates further, but as hypertrophy develops, wall thickness increases and the ejection fraction may recover slightly. The degree of hypertrophy is never sufficient to normalize left ventricular wall stress. The results from SOLVD support this hypothesis, because in all patients studied the systolic and diastolic wall stresses were markedly augmented at baseline.[85] Neurohumoral systems are chronically activated in asymptomatic patients.[63] Because the mechanical and neurohumoral stimuli for hypertrophy continue to be activated, the remodeling process continues at a slow rate in asymptomatic patients with LV dysfunction. Furthermore, the ejection fraction may be maintained, probably because of new contractile units in the LV walls. Ventricular function is stable for a while until the rate of ventricular dilation increases and ejection fraction further declines. This is supported by data from the SOLVD treatment trial.[78] Hypertrophy is unable to keep pace with LV dilation, wall thickness decreases and wall stress increases, rapidly resulting in a decrease in ejection fraction despite further LV dilation. Therefore, even when the asymptomatic patient with LV dysfunction appears stable, there are significant changes taking place in the heart which ultimately result in the progression of LV dysfunction to symptomatic heart failure.

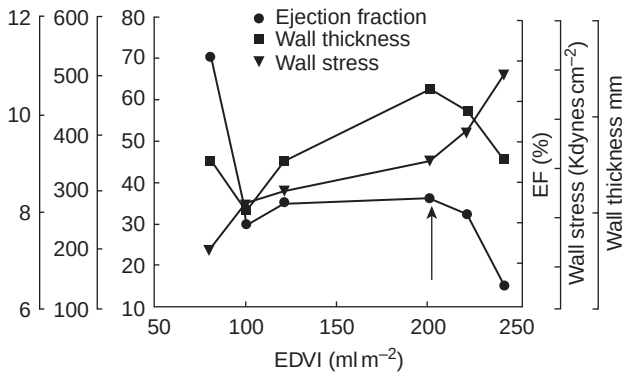

Figure 45.4 Hypothesis proposed to explain the changes in ejection fraction (EF), systolic wall stress, and wall thickness in relation to the progression of the myocardial insult. Under normal conditions, the EF is well above 50% and the wall stress is low. Immediately after the myocardial insult, EF and wall thickness decrease while wall stress increases. As the ventricle dilates, EF may recover slightly as a result of hypertrophy. The ventricle finally reaches a point that the rate and extent of dilation exceeds the capacity to hypertrophy, resulting in a rapid increase in wall stress (arrow). This would result in a decline in EF and a rapid deterioration of clinical status. (From Pouleur HG *et al*, *J Am Coll Cardiol* 1993;**22**(Suppl. A):43A–8A with permission.)

Clinical factors predicting the development of symptomatic heart failure in asymptomatic LV dysfunction

The SOLVD prevention trial was the first large study to examine the clinical outcome in 4228 patients with asymptomatic LV dysfunction, of whom 2117 with EF $\leq$ 35% were randomized to the placebo group (2111 to ACE inhibitors) and were followed for an average of 37·4 months (range 14·6–62 months). Of these 2117 patients 70% had an EF between 26 and 35%, 26·1% had an EF between 16 and 25%, and 3·9% had an EF $\leq$ 15%. By NYHA functional classification 67% of the patients were in class I and 33% were in class II. None were receiving treatment for heart failure.

During the follow-up period for this population, there were 334 (15.8%) deaths, 640 (30·2%) developed congestive heart failure and 273 (12·9%) had a first hospitalization for heart failure. Using the Cox multivariate model we examined the prognostic usefulness of several clinical, echocardiographic and neurohormonal parameters in predicting the subsequent clinical outcome in these patients. In a subset of these 2117 patients the prognostic usefulness of plasma neurohormones – plasma norepinephrine (PNE), ANF, AVP and PRA – and echocardiographic parameters – end-diastolic volume (EDV) and end-systolic volume (ESV) – were also examined. Key findings are summarized below.

Age

Increasing age was a significant risk factor for mortality in patients with asymptomatic LV dysfunction. For every 10 year increase in age the risk ratio for mortality was 1·2 (95% CI 1·08–1·32; $P < 0·0014$), for hospitalization for CHF was 1·24 (95% CI 1·10–1·38; $P < 0·0005$) and for the development of CHF was 1·20 (95% CI 1·10–1·27; $P < 0·0001$).

Sex

Unlike age, sex was not a prognostic variable for developing clinical end points. For example, the mortality rate in males was 16·06%, whereas in females it was 13·5%, which was

not significantly different. Similarly, hospitalization for CHF was 12·6% in males and 15·2% in females, and development of CHF was 28·9% in males and 30·4% in females, both of which were not significantly different. However, these results must be interpreted with caution because the SOLVD prevention trial consisted predominantly of males (~80%), which could have limited the ability to detect differences based on gender.

Ejection fraction

For a 5% lower EF, the risk ratio for mortality was 1·20 (95% CI 1·13–1·29; $P < 0·0001$), for hospitalization for CHF was 1·28 (95% CI 1·18–1·38; $P < 0·0001$), and for development of CHF was 1·20 (95% CI 1·13–1·26; $P < 0·0001$).

NYHA functional class

The NYHA functional class was not a risk factor for mortality but was a significant risk factor for risk of hospitalization for CHF (risk ratio 1·66; 95% CI 1·24–2·22; $P < 0·0007$) and the development of CHF symptoms (risk ratio 1·48; 95% CI 1·16–1·89; $P < 0·0016$).

Etiology of heart failure

Patients with an ischemic or non-ischemic etiology for asymptomatic LV dysfunction had similar outcomes with respect to mortality (15% *v* 13·2%), hospitalization for heart failure (11·5% *v* 13·9%) and development of heart failure (37% *v* 40·3%). Hypertension was not a significant contributor for the development of clinical events. In contrast, the presence or absence of diabetes mellitus was a major risk factor for mortality (risk ratio 1·89; 95% CI 1·27–2·24; $P = 0·0003$), hospitalization for heart failure (risk ratio 1·98; 95% CI 1·46–2·69; $P = 0·0001$) and for the development of heart failure (risk ratio 2·06; 95% CI 1·58–2·59; $P < 0·0001$). A current (but not past) history of smoking increased the risk of death (risk ratio 1·21; 95% CI 1·10–1·32; $P < 0·001$) but had only a weak and non-significant impact on the development of heart failure.

Cardiothoracic ratio

Increased cardiothoracic ratio (>0·50) was a univariate risk factor for the development of clinical end points, but in the multivariate model it failed to reach statistical significance, most probably owing to the impact of ejection fraction in this model.

Neurohormonal predictors

Previous studies in patients with symptomatic LV dysfunction have indicated that several neurohormones, including PNE, PRA and ANF, are increased, and both PNE and ANF may be useful for predicting clinical outcomes, including mortality, in these patients. However, it is important to note that these studies have not determined whether the neurohormonal activation present is a cause or consequence of heart failure in these patients. In contrast, examination of the prognostic usefulness of neurohormones in patients with asymptomatic LV dysfunction may help us to determine whether the neurohormonal system could possibly play a role in the progression of the heart failure syndrome. In a subset of 514 patients with asymptomatic LV dysfunction from the SOLVD prevention trial, PNE, but not PRA, ANF or AVP, was found to be significantly associated with heart failure events and predicted the development of subsequent ischemic events (see Figure 45.3).[65] It is important to note that development of an interim ischemic event has previously been shown to worsen clinical outcome in this population.[60] Unlike PNE, the other neurohormones failed to predict the occurrence of subsequent clinical events in patients with asymptomatic LV dysfunction, which suggests that adrenergic activation in patients with LV dysfunction may be an early event.

Echocardiographic predictors

Over 40 years ago Linzbach[86] described structural dilation of the LV as the morphological basis for the development of congestive heart failure. More recent studies on ventricular remodeling support this concept.

Greenberg *et al*[79] have examined the changes in echocardiographic parameters in patients with LV dysfunction in a subset of the SOLVD trial. In the placebo treated group there was a significant increase in the end-diastolic volume from baseline after 4 months (200 ± 42 ml *v* 208 ± 43 ml; $P = 0·025$) and after 1 year of follow up (200 ± 42 ml *v* 210 ± 46 ml; $P = 0·003$). The end-systolic volume increased significantly from baseline after 4 months (148 ± 38 ml *v* 155 ± 43 ml, $P = 0·028$) and 1 year of follow-up (148 ± 38 ml *v* 156 ± 42 ml, $P = 0·014$). Vasan *et al*[87] reported from the Framingham study database that in asymptomatic individuals increases in LV internal dimension (both end-systolic and end-diastolic volumes) were important predictors for subsequent development of congestive heart failure.

In summary, there are a number of factors that increase the risk of developing LV dysfunction, whereas the variables of LV size, ejection fraction, increased PNE, age, and the etiology of LV dysfunction (diabetes mellitus), are important independent risk factors for the development of clinical heart failure events (Box 45.1).

Prevention of symptomatic heart failure

Although a number of clinical trials have documented that pharmacologic therapy reduces mortality in patients with

Box 45.1 Factors related to the development and prognosis of asymptomatic left ventricular dysfunction

- Ischemic heart disease
- Hypertension
- Left ventricular hypertrophy
- Smoking
- Hyperlipidemia
- Diabetes mellitus
- Microalbuminuria
- Low or decreased vital capacity over time
- Elevated resting heart rate
- Obesity
- Age
- Ejection fraction
- Plasma norepinephrine
- Cardiac dilatation

symptomatic heart failure, the prognosis of this condition remains poor.[6,17,19,35,62,88–90] These results suggest that the greatest opportunity for reducing the incidence and excess mortality of heart failure is through preventive strategies.

Treatment of hypertension

Grade A1a The development of heart failure in the setting of hypertension could be due to a number of reasons, including activation of the renin–angiotensin–aldosterone system, acute or chronic subendocardial ischemia, inappropriately high wall stress, and alterations in the peripheral circulation.[91] A number of studies have demonstrated that the treatment of hypertension substantially reduces the risk for the development of heart failure.[11,92–96] A meta-analysis by Psaty *et al*[97] demonstrated that CHF was effectively prevented with low-dose diuretic therapy (relative risk 0·58; 95% CI 0·44–0·76), high-dose diuretic therapy (relative risk 0·17; 95% CI 0·07–0·41), and β-blocker therapy (relative risk 0·58; 95% CI 0·40–0·84). More recently the Blood Pressure Lowering Treatment Trialists Collaboration[98] performed a prespecified overview of 15 trials comparing active treatment regimens with placebo, trials comparing more intensive versus less intensive blood pressure lowering strategies, and trials comparing treatment regimens based on different drug classes. The pooled data from these studies demonstrated that ACE inhibitors, calcium antagonists and other blood pressure lowering drugs significantly reduced cardiovascular death and major cardiovascular events. There was a trend to a reduced incidence of heart failure with ACE inhibitor therapy (RR 0·84, 95% CI 0·68–1·04), calcium antagonists (RR 0·72, 95% CI 0·48–1·07), and when more intensive blood pressure strategies were compared to less intensive strategies (RR 0·78, 95% CI 0·53–1·15). Although there was no clear evidence of a reduction in the risk of heart failure as defined, the 95% CI did not exclude possible benefits of moderate magnitude among the assigned therapies. The small number of heart failure events would have limited the ability to detect any true benefits of these therapies. In the case of ACE inhibitors several other randomized trials have provided clear evidence that heart failure is prevented in other high-risk situations,[37] and in a large trial of high-risk patients there was a benefit of ACE inhibitors when a wider definition was used for heart failure.[36] The findings that calcium antagonists may not be as effective to prevent heart failure as other antihypertensive agents (such as diuretics, β blockers, ACE inhibitors or clonidine) despite similar blood pressure control was reported in a meta-analysis by Pahor *et al*[99] of nine eligible trials comprising 27 743 participants, in which those individuals assigned to calcium antagonists had a significantly higher risk of developing heart failure (RR 1·25, 95% CI 1·07–1·46, P 0·005) than those assigned to other drug therapy. Interestingly, in this overview analysis calcium antagonists were found to be potentially less effective than a diuretic or β blocker (RR 1·12, 95% CI 0·95–1·33), and ACE inhibitors were found to be potentially more effective than a calcium antagonist (RR 0·82, 95% CI 0·67–1·00) for preventing heart failure. Therefore, aggressive management of hypertension will help reduce the risk of developing heart failure. However, the data would suggest that hypertensive patients should be treated either alone or in combination with diuretic, β blocker or ACE inhibitor to most effectively reduce the risk of developing heart failure.

Lipid lowering therapy to prevent congestive heart failure

Grade A1d It has been clearly demonstrated that lipid lowering therapy significantly reduces mortality in patients with coronary artery disease.[100] A recent report from the 4S Study Group suggests that lipid lowering treatment with simvastatin ($n = 2223$) compared to placebo ($n = 2221$) prevents the onset of heart failure.[46] In this study, 189 patients (8·5%) in the placebo group were diagnosed with CHF during follow up, compared to 147 (6·2%) in the simvastatin group, resulting in a 27% ($P < 0·003$) reduction in the incidence of CHF for the simvastatin group. Further studies are required to determine whether this reduction is related to the effect of lipid lowering on coronary artery disease, or is exerted through another independent mechanism.

Prevention of myocardial ischemia

Grade A1a Treatment strategies should also be directed at preventing ischemia in patients with heart failure. In heart failure patients it has been demonstrated that the occurrence of a new myocardial infarction increases the risk of subsequent death by up to eight times, and that one third of

all deaths are preceded by a major ischemic event.[101] Similar data have been reported by Rutherford *et al*[102] from the SAVE trial. These data emphasize that reductions in ischemic events should be an integral part of the management of patients with LV dysfunction. Although not formally examined in patients with asymptomatic LV dysfunction, β blockers may be very useful to reduce the development of symptomatic heart failure. β Blockers are commonly used to treat patients with findings of myocardial ischemia. Studies of β-blocker therapy in patients with symptomatic heart failure have demonstrated improvements in LV ejection fraction and decreases in cardiac dilatation.[103–105] Studies in patients following myocardial infarction have demonstrated that β blockers reduce mortality and morbidity when initiated relatively earlier following an acute myocardial infarction.[106,107] Furthermore, the relative benefit on mortality after a myocardial infarction is similar in the presence or absence of heart failure, although the absolute benefit may be greater in the former because of the higher event rate.[107] Retrospective analyses of the SAVE database in postmyocardial infarction patients[108] and the SOLVD trial involving patients mainly from the prevention trial (Exner *et al* 1999) demonstrated that the beneficial effects of β-blocker therapy were additional to those of ACE inhibitor therapy. The recently published Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study has further prospectively demonstrated that the β blocker carvedilol used in patients following myocardial infarction complicated by LV dysfunction reduces the frequency of all-cause and cardiovascular mortality, and recurrent non-fatal myocardial infarctions.[109] These beneficial effects were additional to those of evidenced-based treatments for acute myocardial infarction, including ACE inhibitors. In trials of patients with symptomatic heart failure β blockers have been shown to reduce mortality and reduce the incidence of repeat episodes of heart failure or hospitalizations for heart failure.[90] Based on these data it may be advisable to use β-blocker therapy in patients found to have asymptomatic LV dysfunction, with the expectation that progression to symptomatic LV dysfunction should be significantly reduced. Prospective randomized trials are required to assess whether β-blocker therapy would be beneficial to reduce the risk of developing symptomatic heart failure in patients with asymptomatic LV dysfunction or those with other markers of high cardiovascular risk.

ACE inhibitors in asymptomatic LV dysfunction or other markers of high risk

Grade A1a There have been a number of trials demonstrating the effects of ACE inhibitors to reduce mortality and morbidity in patients with heart failure.[37,110] Therapy with ACE inhibitors in patients with asymptomatic LV dysfunction[21] has been shown to significantly reduce the total number of deaths or cases of CHF (risk reduction 29%; 95% CI 21–36), and also to reduce the total number of deaths or hospitalizations for CHF (risk reduction 20%; 95% CI 9–30). The recently published HOPE data further define which patients would benefit from ACE inhibitor therapy.[36] In patients at high risk for a cardiovascular event who did not have LV dysfunction or heart failure on admission to the study, ramipril decreased the incidence of heart failure (ramipril 417 *v* placebo 535; RR 0·77, 95% CI 0·67–0·87; $P < 0{\cdot}001$). Therefore, an ACE inhibitor should be routinely administered to any patient with LV dysfunction (ejection fraction $< 0{\cdot}40$) and to those patients meeting the HOPE study criteria who do not have a contraindication to this form of therapy.

Conclusions

The population incidence and prevalence of CHF are relatively high. CHF is associated with significant mortality, morbidity and poor quality of life for the patient. This is a progressive disorder, and at present there are relatively few therapies that slow or prevent its progression. Asymptomatic LV dysfunction occurs in 1–5% of the population, depending on the prevalence of other cardiovascular risk factors. Although routine screening of the general population cannot be justified, screening of high-risk individuals may be of value. Risk factors for the development of CHF have been identified, and these could be used to determine those who are at greatest risk for the development of LV dysfunction and ultimately symptomatic CHF.

Suggested approach to identify and treat patients with asymptomatic left ventricular dysfunction

1. Determine those at greatest risk of developing left ventricular dysfunction:
   - Hypertension
   - Left ventricular hypertrophy
   - Diabetes mellitus and/or impaired glucose tolerance
   - Hyperlipidemia (hypertriglyceridemia and low HDL)
   - Previous extensive myocardial infarction
   - Age
   - Smoking
   - Obesity
2. Assess cardiac function using radionuclide ventriculography or quantitative echocardiography.
3. If ejection fraction $< 40\%$ then start ACE inhibitors in all tolerant patients. Modify other risk factors (for example, diabetes, hypertension, dyslipidemia) and treat symptoms of myocardial ischemia.

4. If ejection fraction ≥ 40% then counsel patients, modify risk factors (for example, diabetes, hypertension etc.), treat symptoms of myocardial ischemia, and treat those meeting the HOPE study criteria with an ACE inhibitor.

These individuals should receive appropriate counseling, lifestyle advice and therapy to alter risk factors for cardiovascular disease and CHF. The fact that the prognosis from CHF remains so poor makes it clear that the greatest opportunity to reduce its incidence and the attendant high mortality is through strategies directed towards preventing its development.

References

1. Smith WM. Epidemiology of congestive heart failure. *Am J Cardiol* 1985;**55**:3A–8A.
2. Gibson TC, White KL, Klainer LM. The prevalence of congestive heart failure in two rural communities. *J Chronic Dis* 1966;**19**:141–52.
3. Parameshwar J, Shackell MM, Richardson A, Poole-Wilson PA, Sutton GC. Prevalence of heart failure in three general practices in north west London. *Br J Gen Pract* 1992; **42**:287–9.
4. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;**20**:301–6.
5. Eriksson H, Svärdsudd K, Larsson B *et al.* Risk factors for heart failure in the general population: the study of men born in 1913. *Eur Heart J* 1989;**10**:647–56.
6. Rodeheffer RJ, Jacobsen SJ, Gersh BJ *et al.* The incidence and prevalence of congestive heart failure in Rochester, Minnesota. *Mayo Clin Proc* 1993;**68**:1143–50.
7. Mosterd A, Cost B, Hoes AW *et al.* The prognosis of heart failure in the general population: The Rotterdam Study. *Eur Heart J* 2001;**22**:1318–27.
8. Mosterd A, Hoes AW, Bruijne de MC *et al.* Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999; **20**:447–55.
9. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971;**285**:1441–6.
10. Remes J, Reunanen A, Aromaa A, Pyörälä K. Incidence of heart failure in eastern Finland: a population-based surveillance study. *Eur Heart J* 1992;**13**:588–93.
11. Yusuf S, Thom T, Abbott RD. Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension* 1989;**13**(Suppl. I):I-74–9.
12. Cowie MR, Wood DA, Coats AJS *et al.* Incidence and aetiology of heart failure. *Eur Heart J* 1999;**20**:421–8.
13. Yamani M, Massie BM. Congestive heart failure: insights from epidemiology, implications for treatment. *Mayo Clin Proc* 1993;**68**:1214–18.
14. Croft JB, Giles WH, Pollard RA *et al.* Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the medicare population. *Arch Intern Med* 1999;**159**:505–10.
15. Senni M, Tribouilloy CM, Rodeheffer RJ *et al.* Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999; **159**: 29–34.
16. Cowie MR, Wood DA, Coats AJS *et al.* Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;**83**:505–10.
17. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
18. CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomized trial. *Lancet* 1999;**353**:9–13.
19. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993; **88**:107–15.
20. Cowie MR, Mosterd A, Wood DA *et al.* The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208–25.
21. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685–91.
22. McDonagh TA, Morrison CE, Lawrence A *et al.* Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;**350**:829–33.
23. Morgan S, Smith H, Simpson I *et al.* Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;**318**:368–72.
24. Petrie M, McMurray J. Changes in notions about heart failure. *Lancet* 2001;**358**:432–4.
25. Devereux RR, Roman MJ, Paranicas M *et al.* A population-based assessment of left ventricular systolic dysfunction in middle-aged and older adults: the Strong Heart Study. *Am Heart J* 2001;**141**:439–46.
26. Gardin JM, Siscovick D, Anton-Culver H *et al.* Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. *Circulation* 1995;**91**:1739–48.
27. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features, and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;**26**:1565–74.
28. McAlister FA, Teo KK, Taher M *et al.* Insights into the contemporary epidemiology and outpatient management of congestive heart failure. *Am Heart J* 1999;**138**:87–94.
29. Vasan RS, Larson MG, Benjamin EJ *et al.* Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;**33**:1948–55.
30. Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol* 2001;**88**:530–3.
31. Ritzman DW, Gardin JM, Gottdiener JS *et al.* Importance of heart failure with preserved systolic function in patients ⩽65 years of age. *Am J Cardiol* 2001;**87**:413–9.
32. Dauterman KW, Go AS, Rowell R *et al.* Congestive heart failure with preserved systolic function in a statewide sample of community hospitals. *J Cardiac Failure* 2001;**7**:221–8.

33. McDermott MM, Feinglass J, Lee PI *et al.* Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997; **134**:728–36.
34. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community. Trends in medicine and survival in a 10 year period. *Arch Intern Med* 1999;**159**:29–34.
35. Pfeffer MA, Braunwald E, Moyé LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med* 1992; **327**:669–77.
36. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
37. Flather MD, Yusuf S, Kober L *et al.* for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;**355**:1575–81.
38. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure: the Framingham Study. *N Engl J Med* 1972;**287**:781–7.
39. Levy D, Larson MG, Ramachandran S *et al.* The progression from hypertension to congestive heart failure. *JAMA* 1996;**275**:1557–62.
40. Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;**22**(Suppl. A):6A–13A.
41. PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033–41.
42. Clarke R, Shipley M, Lewington S *et al.* Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150**: 341–53.
43. Kannel WB. Epidemiological aspects of heart failure. *Cardiol Clin* 1989;**7**:1–9.
44. Zabalgoitia M, Berning J, Koren MJ *et al.* for the LIFE Study Investigators. Impact of coronary artery disease on left ventricular systolic function and geometry in hypertensive patients with left ventricular hypertrophy (The LIFE Study). *Am J Cardiol* 2001;**88**:646–50.
45. Matthew J, Sleight P, Lonn E *et al.* for the Heart Outcomes Prevention Evaluation (HOPE) Investigators. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation* 2001; **104**:1615–21.
46. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyörälä K on behalf of the 4S Study Group. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Cardiac Failure* 1997;**3**:249–54.
47. van Hoeven KH, Factor SM. A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease. *Circulation* 1990;**82**:848–55.
48. Bangdiwala SI, Weiner DH, Bourassa MG *et al.* for the SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD) registry: rationale, design, methods and description of baseline characteristics. *Am J Cardiol* 1992;**70**:347–53.
49. Suskin N, McKelvie RS, Burns RJ *et al.* Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. *Eur Heart J* 2000;**21**:1368–75.
50. Johnstone D, Limacher M, Rousseau M *et al.* for the SOLVD Investigators. Clinical characteristics of patients in studies of left ventricular dysfunction (SOLVD). *Am J Cardiol* 1992; **70**:894–900.
51. Herlitz J, Malmberg K, Karlson BW, Rydén L, Hjalmarson Å. Mortality and morbidity during a five-year follow-up of diabetics with myocardial infarction. *Acta Med Scand* 1988; **224**:31–8.
52. Shindler DM, Kostis JB, Yusuf S *et al.* for the SOLVD Investigators. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996;**77**: 1017–20.
53. Gerstein H, Mann JFE, Yi Q *et al.* for the HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and non-diabetic individuals. *JAMA* 2001;**286**:421–6.
54. Kannel WB. Epidemiology of heart failure in the United States. In: Poole-Wilson PA, Colucci WS, Massie BM, Chatterjee K, Coats AJS, eds. *Heart failure. Scientific principles and clinical practice*. New York: Churchill Livingstone, 1997.
55. Sorlie P, Gordon T, Kannel WB. Body build and mortality: the Framingham Study. *JAMA* 1980;**243**:1828–31.
56. Schirmer H, Lunde P. Rasmussen K. Prevalence of left ventricular hypertrophy in a general population. The Tromsø Study. *Eur Heart J* 1999;**20**:429–38.
57. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Intern Med* 1984;**101**:370–7.
58. Cohn JN, Levine TB, Olivari MT *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;**311**:819–23.
59. Gottlieb SS, Kukin ML, Ahern D, Packer M. Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. *J Am Coll Cardiol* 1989;**13**:1534–9.
60. Levine TB, Francis GS, Goldsmith SR, Simon A, Cohn JN. Activity of the sympathetic nervous system and renin–angiotensin system assessed by plasma hormone levels and their relationship to hemodynamic abnormalities. *Am J Cardiol* 1982;**49**:1659–66.
61. Curtiss C, Cohn JN, Vrobel T, Franciosa JA. Role of renin–angiotensin system in systemic vasoconstriction of chronic congestive heart failure. *Circulation* 1978;**58**: 763–70.
62. The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;**316**:1429–35.
63. Francis GS, Benedict C, Johnstone DE *et al.* for the SOLVD Investigators. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990;**82**: 1724–9.

64.Benedict CR, Weiner DH, Johnstone DE *et al.* for the SOLVD Investigators. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. *J Am Coll Cardiol* 1993;**22**(Suppl. A): 146A–53A.
65.Benedict CR, Shelton B, Johnstone DE *et al.* for the SOLVD Investigators. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. *Circulation* 1996;**94**:690–7.
66.Rundqvist R, Elam M, Bergmann-Sverrisdottir Y, Eisenhofer G, Friberg P. Increased cardiac adrenergic drive precedes generalized sympathetic activation in human heart failure. *Circulation* 1997;**95**:169–75.
67.Richards AM, Doughty R, Nicholls MG *et al.* for the Australia–New Zealand Heart Failure Group. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia–New Zealand Heart Failure Group. *J Am Coll Cardiol* 2001; **37**: 1781–7.
68.Smith JA, Bruusgaard D, Bodd E, Hall C. Relations between medical history, clinical findings and plasma N-terminal proatrial natriuretic peptide in patients in primary health care. *Eur J Heart Failure* 2001;**3**:307–13.
69.Kelly R, Struthers AD. Are natriuretic peptides clinically useful as markers of heart failure? *Ann Clin Biochem* 2001;**38**:94–102.
70.Sagnella GA. Measurement and importance of plasma brain natriuretic peptide and related peptides. *Ann Clin Biochem* 2001;**38**:83–93.
71.Eaton LW, Weiss JL, Bulkley RH, Garrison JB, Weisfeldt ML. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. *N Engl J Med* 1979;**300**:57–62.
72.Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. Left ventricular diastolic pressure–volume relations in rats with healed myocardial infarctions: effects on systolic function. *Circ Res* 1981;**49**:618–26.
73.Erlebacher JA, Weiss JL, Easton LW, Kallman C, Weisfeldt ML, Bulkley BH. Late effects of acute infarct dilatation on heart size: a two dimensional echocardiographic study. *Am J Cardiol* 1982;**49**:1120–6.
74.Roberts CS, MacLean D, Maroko P, Kloner RA. Early and late remodelling of the left ventricle after acute myocardial infarction. *Am J Cardiol* 1984;**54**:407–10.
75.McKay RG, Pfeffer MA, Pasternak RC *et al.* Left ventricular remodelling after myocardial infarction. A corollary to infarction expansion. *Circulation* 1986;**74**:693–702.
76.Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1988;**i**:255–9.
77.Konstam MA, Kronenberg MW, Rousseau MF *et al.* for the SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. *Circulation* 1993;**88**:2277–83.
78.Konstam MA, Rousseau MF, Kronenberg MW *et al.* for the SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation* 1992;**86**:431–8.
79.Greenberg B, Quiñones MA, Koilpillai C *et al.* for the SOLVD Investigators. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. *Circulation* 1995;**91**:2573–81.
80.Koilpillai C, Quiñones MA, Greenberg B *et al.* for the SOLVD Investigators. Relation of ventricular size and function to heart failure status and ventricular dysrhythmia in patients with severe left ventricular dysfunction. *Am J Cardiol* 1996; **77**:606–11.
81.Litwin SE, Litwin CM, Raya TE, Warner AL, Goldman S. Contractility and stiffness of non-infarcted myocardium after coronary ligation in rats: effects of chronic angiotensin converting enzyme inhibition. *Circulation* 1991;**83**:1028–37.
82.Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res* 1985;**57**:84–95.
83.Jugdutt BI, Schwarz-Michorowski BL, Khan M. Effect of long-term captopril therapy on left ventricular remodelling and function during healing of canine myocardial infarction. *J Am Coll Cardiol* 1992;**19**:713–21.
84.Pouleur HG, Konstam MA, Udelson JE, Rousseau MF for the SOLVD Investigators. Changes in ventricular volume, wall thickness and wall stress during progression of left ventricular dysfunction. *J Am Coll Cardiol* 1993;**22**(Suppl. A):43A–8A.
85.Pouleur H, Rousseau MF, van Eyll C *et al.* for the SOLVD Investigators. Cardiac mechanics during development of heart failure. *Circulation* 1993;**87**(Suppl. IV):IV-14–20.
86.Linzbach AJ. Heart failure from the point of view of quantitative anatomy. *Am J Cardiol* 1960;**5**:370–82.
87.Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997; **336**:1350–5.
88.Cohn JN, Archibald DG, Ziesche S *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–52.
89.Cohn JN, Johnson G, Ziesche S *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325**:303–10.
90.Brophy JM, Joseph L, Rouleau JL. β-Blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med* 2001;**134**:550–60.
91.Litwin SE, Grossman W. Mechanisms leading to the development of heart failure in pressure-overload hypertrophy. *Heart Failure* 1992;April/May:48–54.
92.Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on mortality in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *JAMA* 1967; **202**: 1028–34.
93.Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension, II: results in patients with diastolic blood

pressure averaging 90 through 114 mmHg. *JAMA* 1970; **213**:1143–51.
94. Furberg CD, Yusuf S. Effect of drug therapy on survival in chronic heart failure. *Adv Cardiol* 1986;**34**:124–30.
95. The Systolic Hypertension in the Elderly Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;**265**:3255–64.
96. Cutler JA, Psaty BM, MacMahon S, Furberg CD. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BH, eds. *Hypertension: Pathophysiology, diagnosis and management*. New York: Raven Press, 1995.
97. Psaty BM, Smith NL, Siscovick DS *et al.* Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; **277**:739–45.
98. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of ACE-inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 2000;**355**:1955–64.
99. Pahor M, Psaty BM, Alderman MH *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. *Lancet* 2000;**356**:1949–54.
100. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (45). *Lancet* 1994;**344**:1383–9.
101. Yusuf S, Pepine CJ, Garces C *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;**340**:1173–8.
102. Rutherford JD, Pfeffer MA, Moyé LA *et al.* Effects of captopril on ischemic events after myocardial infarction. *Circulation* 1994;**90**:1731–8.
103. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy. The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study. *Circulation* 2000;**101**:378–84.
104. Australia–New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator–β blocker, in patients with congestive heart failure due to ischemic heart disease. *Circulation* 1995;**92**:212–18.
105. Kukin ML, Kalman J, Charney RH *et al.* Prospective, randomized comparison of effect on long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Circulation* 1999; **99**:2645–51.
106. Held P. Effects of beta-blockers on ventricular dysfunction after myocardial infarction. Tolerability and survival effects. *Am J Cardiol* 1993;**71**:39C.
107. Houghton T, Freemantle N, Cleland JGF. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomized trials. *Eur J Heart Failure* 2000;**2**:333–40.
108. Vantrimpont P, Rouleau JL, Wun CC *et al.* for the SAVE Investigators. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the survival and ventricular enlargement (SAVE) study. *J Am Coll Cardiol* 1997;**29**:229–36.
109. Exner DV, Dries DL, Waclawia MA *et al.* Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post-hoc analysis of the studies of left ventricular dysfunction. *J Am Coll Cardiol* 1999;**33**:916–23.
110. The CARPRICORN Investigators. Effect of carvedilol on outcome after mycoardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
111. McKelvie RS, Yusuf S. Large trials and meta-analyses. In: Poole-Wilson PA, Colucci WS, Massie BM, Chatterjee K, Coats AJS, eds. *Heart failure. Scientific principles and clinical practice*. New York: Churchill Livingstone, 1997.

46 Management of overt heart failure

Bert Andersson, Karl Swedberg

The cardiac muscle may be exposed to various ischemic, hemodynamic, metabolic, or toxic conditions that eventually lead to the clinical syndrome of congestive heart failure (CHF). Given a certain severity, any cardiac disorder will ultimately lead to heart failure. Further, many non-cardiac disorders will result in heart failure, alone or in combination with cardiovascular conditions. Last, but not least, progressive deterioration of cardiac function with age further increases the susceptibility to develop heart failure. Taken together, the aforementioned circumstances, in a continuously aging population, may explain why CHF is one of the most common, and most costly, diseases in Western society.

CHF is a potentially lethal condition. It has been evident during the past decade that whilst we are in possession of some drugs that may improve cardiac function and symptoms as well as survival, other agents are simultaneously capable of impairing long-term survival. Furthermore, as with other treatment traditions, we lack modern documentation about the oldest drugs, such as diuretics. In this chapter we intend to cover the present knowledge regarding evidence-based medical therapies in CHF.

Cardiac glycosides

Digitalis is the oldest of the drugs used in the treatment of CHF today. It has been used for at least 200 years. Although all internists, general practitioners, and cardiologists have profound experience with this drug, the mode of action is still partly unknown. The main action of the drug is thought to be exerted by action on the plasma membrane Na^+/K^+-ATPase, increasing intracellular concentrations of Na^+ and Ca^+. A variety of autonomic effects have been shown in acute experimental studies.

Acute effects in CHF

Older uncontrolled studies have suggested that digitalis produced beneficial hemodynamic effects in patients with decompensated heart failure, expressed as a decrease in pulmonary capillary wedge pressure, an increase in cardiac output, and a fall in heart rate.[1,2] It appears that the effect of digitalis on hemodynamics is dependent on the hemodynamic state of the patient. Whereas positive effects have been observed in decompensated heart failure, the effects in normal subjects are largely negligible.[3,4] Although the slowing of heart rate would be of benefit in diastolic heart failure without systolic dysfunction, there are no data to support the use of digoxin in diastolic heart failure. On the contrary, on a theoretical basis, the increase in intracellular Ca^+ and increase in contractility may be harmful to the hypertrophic heart. Although digoxin has been found to act synergistically in combination with different vasodilators, no such effects were seen in combination with dobutamin. Ferguson showed that acute administration of digitalis restored baroreceptor function and caused a decrease in sympathetic activity.[5,6] Goldsmith *et al* were not able to reproduce these results with regard to norepinephrine kinetics or baroreceptor function.[7] Both increase and decrease in neurohormonal activity has been reported following acute digoxin administration.

Chronic digitalis therapy

The first double-blind placebo-controlled trial with chronic digoxin treatment was published in 1977.[8] In a crossover design, 46 patients were randomized; about one third were in atrial fibrillation. Sixteen patients deteriorated while on placebo, eight of whom improved after being switched over to digoxin. In a 3 month trial, Fleg *et al* could not show any superior effect of digitalis treatment over placebo, although the majority of patients on digitalis deteriorated after discontinuation of the drug.[9] Improvement of myocardial function in patients with mild heart failure was demonstrated by Taggart *et al*[10] Other studies have shown positive effects of digoxin on clinical heart failure symptoms, echocardiographic findings, and exercise capacity, in particular in patients with more advanced left ventricular dysfunction.[11–13]

The trials mentioned above were small, and the first large study was the Captopril-Digoxin Multicenter Research Group trial.[14] In this study 300 patients with relatively mild heart failure were compared using captopril, digoxin, or placebo. Digoxin and captopril were equally effective in preventing hospitalization or an increase in diuretic dosages. Although digoxin-treated patients showed a significant increase in ejection fraction, in contrast to the captopril group, digoxin did not improve exercise capacity as much as captopril. In another study with 433 patients with mild heart failure, the German and Austrian Xamoterol Study Group investigated the effect of digoxin together with

xamoterol and placebo. Digoxin improved clinical indices of heart failure but not exercise capacity.[15]

Several trials have used a withdrawal design for the placebo-treated patients. Di Bianco *et al* compared digoxin with milrinone in a 3 month multicenter trial in 230 patients with moderate to severe heart failure.[16] The digoxin-treated patients showed a significant improvement in left ventricular function and exercise capacity compared with the placebo group. Furthermore, digoxin was significantly less prone to induce arrhythmias compared with milrinone.

In the PROVED trial a randomized double-blind withdrawal of digoxin was investigated in 88 patients with NYHA class II–III.[17] More placebo patients had worsening heart failure with an increase in the need for diuretics and hospitalization, and an impairment in exercise capacity and LV function. In a similar study – the RADIANCE trial – 178 patients with CHF were investigated during digoxin withdrawal compared with maintained digoxin therapy.[18] The results were also similar to those of the PROVED trial, with placebo patients showing a statistically significant deterioration in cardiac function, hospitalization, quality of life and exercise capacity.

It should be noted that the withdrawal study design is inferior compared with prospective treatment studies. Because of the selection of responders and exclusion of non-responders who have suffered from deterioration or even lethal arrhythmias during digoxin treatment, the study design will result in different answers.

The Digitalis Investigators Group (DIG) study is the largest study in CHF. It is the only survival study of digoxin. The effect of digoxin was studied in a multicenter, prospective, randomized, placebo-controlled, double-blind trial in 7788 patients with mild to moderate heart failure and sinus rhythm.[19] Among the investigated patients, 6800 had signs of systolic dysfunction expressed as ejection fraction of $<45\%$. The remaining 998 patients might be considered to have diastolic dysfunction. There was no effect on the primary end point of all-cause mortality (odds ratio 1·0). Digoxin significantly reduced the number of hospitalizations from worsening heart failure.

Documented value of digoxin

Proven indication: always acceptable **Grade A**

- Symptomatic left ventricular systolic heart failure and sinus rhythm. Symptomatic improvement, improved exercise capacity and decreased hospitalization for heart failure
- CHF with atrial fibrillation. Heart rate control

Acceptable indication but of uncertain efficacy and may be controversial **Grade A**

- Symptomatic heart failure due to diastolic dysfunction

Not proven: potentially harmful (contraindicated) **Grade A**

- Bradycardia and atrioventricular block
- Significant ventricular arrhythmias
- Renal dysfunction
- Electrolyte disturbances, hypokalemia in particular

Taken together, present data on digoxin suggest that this drug induces small but beneficial effects on cardiac function, morbidity, and symptoms. There is a neutral effect on all-cause mortality, with a possibly lower incidence of deaths from worsening heart failure, balanced by an increase in arrhythmic and myocardial infarction deaths. However, the therapeutic window is narrow, and the potential risk for serious arrhythmias cannot be ignored.

Diuretics

Fluid retention is a consistent finding in almost every patient with CHF. The need for reduction of blood volume in patients with edema was recognized several hundred years ago. Drugs with mild diuretic effects, such as mercury salts, carbonic anhydrase inhibitors, and thiazides, have all been used. A more substantial way of inducing diuresis was achieved when the loop-diuretics were introduced, and this class of drugs has since been the cornerstone of heart failure treatment.[20] The compensatory fluid retention, as a response to lower cardiac output and reduced kidney perfusion,[21] might be of some benefit in restoring optimal preload in the earlier states of CHF. A further increase in intracavitary pressure increases wall stress in the myocardium with a parallel increase in oxygen consumption and energy expenditure. The elevation of venous pressure shifts the hydrostatic balance across the capillary wall toward a net filtration of fluid to the extracellular space, and finally to the formation of edema. The edema impairs the transportation of oxygen, nutritive substances, and waste products, which ultimately leads to organ failure. In the case of pulmonary edema, the decrease in oxygen uptake affects all organs in the body. The decrease in renal blood flow stimulates the renin system, which leads to secretion of angiotensin and aldosterone. Other neurohormones that promote retention of sodium and water include vasopressin, norepinephrine, and prostaglandins.[22] Sodium excretion is promoted by atrial natriuretic factor, dopamine, and prostacyclin.

Acute neuroendocrine and hemodynamic effects

In patients with pulmonary edema, intravenous furosemide is normally followed by a prompt response and relief of symptoms. There have not been consistent findings regarding the mode of action of loop-diuretics in the acute phase of decompensated heart failure. The reduction in filling pressures occurs even before diuresis is initiated,[23–25] and has been attributed to vasodilation. However, arterial vasoconstriction has also been found, alone or in combination with venodilation.[26–28] Regarding cardiac output, an increase, no change, or a decrease has been reported. Although furosemide is the most thoroughly tested loop-diuretic, there are others available, including bumetanide,[29] ethacrynic acid,[30] piretanide,[31]

and toresemide.[32] There is little information about the acute neuroendocrine effects of diuretics. The effects on vascular tone suggest signs of neuroendocrine modulation. Venodilation may be due to the release of renal vasodilator prostaglandins.[33]

Chronic neuroendocrine and hemodynamic effects

Most long-term studies have involved a small number of patients and used a variety of drugs and doses. The first study to give information with oral diuretics was performed in a small number of patients with valvular heart disease.[24] Hydrochlorthiazide was administered and resulted in a reduction in weight, pulmonary artery pressure, arterial pressure, heart rate, and cardiac output at rest as well as during exercise. Results from other studies have yielded similar results, with different diuretics, including furosemide,[34] piretanide,[35] torasemide,[36] and amiloride.[37] Chronic neuroendocrine effects are less well studied. Oral furosemide treatment has been associated with a reduction in norepinephrine concentration and a profound increase in plasma renin activity, angiotensin, and plasma aldosterone concentration.[38,39]

Effects on survival

No study has been performed examining the effect of diuretics on long-term survival. There has been some concern raised regarding the potential neurohormonal activation by diuretics. However, any long-term neuroendocrine activation has not been demonstrated. Further, it should be kept in mind that studies showing positive survival effects in heart failure – with ACE inhibitors, β blockers or vasodilators – have all used diuretics as background treatment.

Documented value of diuretics

Proven indication: always acceptable **Grade A**

- Symptomatic improvement in case of congestion. Improvement of exercise capacity

Acceptable indication but of uncertain efficacy and may be controversial **Grade B**

- Long-term treatment in conjunction with other drugs for heart failure, such as ACE inhibitors, vasodilators and β blockers

Not proven: potentially harmful (contraindicated) **Grade C**

- Heart failure without congestion or edema
- Severe decompensated hypokalemia or hyperuricemia

Clinical management

It is clear that diuretics reduce symptoms in CHF. The effect on symptoms has been formally tested in trials with furosemide and torasemide.[40,41] Further, it has been observed that the effects of ACE inhibitors may require the coadministration of diuretics.[42,43] Diuretics are also more effective in relieving edema and congestive symptoms than ACE inhibitors when given as single therapy.[44] Through an increase in urinary excretion of electrolytes, diuretics are prone to induce hypokalemia, hyponatremia, hypocalcemia, hypomagnesemia, and metabolic alkalosis.[45] The need for potassium supplements might be diminished by using potassium-sparing diuretics, such as amiloride or aldosterone. ACE inhibitors act synergistically with potassium-sparing diuretics, which may produce hyperkalemia. The addition of a potassium-sparing diuretic to a loop-diuretic will further increase diuresis. Additionally, the diuretic effect of a loop-diuretic is boosted by other diuretics acting at different sites in the nephron. Therefore, the combination of a loop-diuretic with a thiazide enhances the diuretic effect.

It is difficult to foresee a future situation when diuretics are no longer needed in the treatment arsenal of CHF. Further, the obvious need for relief of edema and fluid retention will prevent the launching of any long-term survival study. With reference to the multiple side effects produced by electrolyte disturbances it is advisable to keep the diuretic dosages as low as possible, and aim for combination therapies in which dosages are minimized.

Aldosterone receptor blockers

Aldosterone plays an important role in the pathophysiology of heart failure, facilitating sodium retention and potassium loss. Further, it activates the sympathetic nervous system and stimulates myocardial and vascular fibrosis, and is a component of the circulating renin–angiotensin–aldosterone system.[46–49]

Although aldosterone antagonists have diuretic effects they differ from other diuretic agents in that they are neuroendocrine antagonists, and thereby have a potential to be effective in the long-term treatment of patients with CHF. Spironolactone is an old drug that has been used for decades as a potassium-sparing agent. However, the long-term clinical effects in the treatment of CHF was not tested until recently. The concept of aldosterone antagonism was studied in the RALES study where 1663 patients in NYHA class III or IV were randomized to spironolactone or placebo.[50] Spironolactone was initiated with 25 mg/day with adjustments to 12·5 or 50 mg depending on serum potassium. Ninety five per cent of the patients were on ACE inhibitors while only 11% had a background therapy of β blockers. The trial was discontinued early after a mean follow up period of 24 months because of beneficial effect of spironolactone. There were 386 (46%) deaths in the placebo group and 284 (35%) in the spironolactine group; RR 0·70 (95% CI 0·60–0·82), $P < 0·001$. The lower risk was attributed to both a lower risk from progressive heart failure and sudden death from cardiac causes. The RALES trial demonstrates

that improved antagonism of the renin–angiotensin system by spironolactone reduces the risk of both morbidity and mortality in CHF. To reduce endocrine side effects by spironolactone, a selective aldosterone receptor blocker (eplerenone) is now tested in patients with CHF.

Documented value of spironolactone

Proven indication: always acceptable **Grade A**

- Improvement of survival in severe CHF
- Reduction of morbidity in severe heart failure

Acceptable indication but of uncertain efficacy and may be controversial **Grade B**

- Reduction of morbidity in mild to moderate heart failure
- Reduction of mortality in mild to moderate heart failure

Not proven: potentially harmful (contraindicated) **Grade C**

- Hyperkalemia

Vasodilators

Vasodilation reduces left ventricular afterload and preload, and these beneficial effects were observed in 1956,[51,52] but it was not until the 1970s that the concept was widely accepted.[53,54] The first drugs used were pure vasodilators, such as nitroprusside, nitroglycerin, and phentolamine. Later, agents with combined effects were developed. Examples of combination therapies are the inotropic drugs with simultaneous vasodilation, such as dobutamine, and ACE inhibitors, which are reviewed in another section of this chapter.

Reduction of afterload and preload in CHF improves the left ventricular performance according to the Frank–Starling relation with less myocardial oxygen demand and increased cardiac output.[55,56] Further, vasodilation might reduce valvular regurgitation by means of afterload reduction. Vasodilation may improve organ dysfunction by acting directly on selected vascular beds, such as the coronary and the renal vasculature.

Acute vasodilator therapy

Nitroglycerin and nitroprusside are the drugs most commonly used for acute short-term vasodilation therapy in heart failure.

Nitroglycerin

Nitroglycerin causes smooth muscle cell relaxation and vasodilation of arterial and venous vessels through action on guanylate cyclase and the generation of cyclic guanosine monophosphate.[57] Nitrates can be used as sublingual tablet, lingual–buccal spray, or as intravenous infusion. Administration causes reduction in left ventricular filling pressures within 3–5 minutes, mainly by venodilation and lowering of preload.[58–63] Further, nitroglycerin reduces systemic vascular resistance and afterload, with ensuing improvement in cardiac output. Although the effect of nitroglycerin on coronary blood flow has not been studied in CHF, it is conceivable that nitrate therapy favorably affects myocardial perfusion and oxygen supply/demand ratio.[64,65] Acute nitrate administration appears to be especially useful in cases of elevated filling pressures and ischemic conditions, such as in ischemic cardiomyopathy and myocardial infarction.

Nitroprusside

Nitroprusside generates nitric oxide and nitrosothiols, which stimulate guanylate cyclase to increase intracellular cGMP. The smooth muscle cell relaxation is rapidly induced after administration. Sodium nitroprusside is converted to cyanide and is metabolized to thiocyanate. Thiocyanate may accumulate and lead to thiocyanate toxicity during prolonged nitroprusside therapy. As compared to nitroglycerin, nitroprusside is far more potent and causes a more pronounced arterial vasodilation.[61] The most prominent effect of nitroprusside is the arterial vasodilation with afterload reduction. There are minor effects on renal and hepatosplanchnic vasculature.[61] In contrast to nitroglycerin, nitroprusside may induce a coronary steal phenomenon.[66] Nitroprusside is best employed in cases of acute heart failure after cardiac surgery or myocardial infarction, or in patients waiting for a more definitive intervention, such as valvular surgery. Further, nitroprusside has been used to stabilize patients with chronic heart failure and to determine their optimal level of vasodilation.[67] Owing to its potent vasodilation property, nitroprusside may cause adverse hypotension, especially in cases of inadequate filling pressure. Thiocyanate and cyanide toxicity is rare during short term administration ($\leq$3 micrograms/kg/min for less than 72 hours).

Hemodynamic effects of long-term vasodilator therapy

Nitrates and hydralazine

Oral nitroglycerin and hydralazine have been studied, either alone or in combination therapy. The effects on left ventricular function and hemodynamics are similar to the acute effects of vasodilators described above.[68–71]

Hydralazine was available as an antihypertensive agent when vasodilator therapy was adopted as a therapeutic strategy in CHF. Hydralazine acts as a dominant arterial vasodilator, but has probably also mild inotropic properties, which might be due to a reflex activation of sympathetic activity.[72,73] This inotropic action might be responsible for a less

favorable effect on myocardial oxygen consumption counteracting the unloading effects of vasodilation.[74,75]

The addition of a nitrate to hydralazine causes a greater effect on the reduction in filling pressures than can be achieved by hydralazine alone.[76] In view of the beneficial action of nitrates on coronary dynamics, a nitrate should be added to hydralazine therapy in patients with significant coronary artery disease.[77] Although hydralazine–nitrate therapy was marginally superior to ACE inhibitor in improving exercise capacity, this combination displayed worse tolerability.[78]

Calcium-channel blockers

Besides its vasodilatory effect, the first generation calcium-channel blocker nifedipine possesses negative inotropic effects. Deleterious effects with regard to hemodynamics, neurohormonal activation, and disease progression have been demonstrated in several trials.[79] Diltiazem has been associated with deterioration, no change, or improvement in hemodynamic function. In a postinfarction study, patients with heart failure did not benefit from verapamil treatment, in contrast to patients without heart failure.[80] Furthermore, the effects of diltiazem were unfavorable in patients with CHF in conjunction with myocardial infarction in a large placebo-controlled trial in 1237 patients.[81] Second generation calcium-channel blockers have not been extensively studied in patients with heart failure, but there are indications of a risk for clinical deterioration with drugs such as nisoldipine and nicardipine.[82,83] The second generation calcium-channel blocker felodipine caused vasodilation and an increase in cardiac output during 8 weeks of treatment in a placebo-controlled trial.[84]

Other vasodilators

Other potent vasodilators, such as prazosin, minoxidil, and epoprosternol, are discussed in the next section regarding survival. These drugs are currently not used in the long-term management of CHF.

Effects on survival

Hydralazine and isosorbide dinitrate

The V-HeFT I was the first placebo-controlled clinical trial to study the effect of a vasodilator on survival in patients with chronic heart failure. The study recruited 642 patients with mild to moderate heart failure, and randomized to receive placebo, prazosin hydrochloride, or the combination of hydralazine hydrochloride and isosorbide dinitrate. Two years after randomization, the survival in the hydralazine-isosorbide treated group was significantly better than the placebo group ($P < 0{\cdot}028$). For the entire follow up, the difference was not significant ($P = 0{\cdot}093$). The mortality rate in the prazosin group was not different from the placebo group.[85]

The second V-HeFT study examined the efficacy of hydralazine and isosorbide with that of enalapril. There were 804 patients, randomized to the two treatment strategies. Two years after randomization, the all-cause mortality was 18% in the enalapril group as compared with 25% in the hydralazine-isosorbide group ($P = 0{\cdot}016$). For the total follow up, the difference was not significant ($P = 0{\cdot}08$).

Calcium-channel blockers

Felodipine was studied in the V-HeFT III study, in which the effect on survival was neutral.[86] Amlodipine, a third generation calcium-channel blocker, was investigated in the PRAISE trial.[87] A total of 1153 patients with NYHA class III–IV were randomized, including 421 patients with non-ischemic dilated cardiomyopathy. The overall effect on mortality as well as on the combined end point mortality and hospitalization was neutral. Whereas the mortality was unchanged in the subgroup with ischemic heart failure, there were significantly fewer end points in the non-ischemic group treated with amlodipine as compared to patients on placebo (22% *v* 35%, $P < 0{\cdot}001$). However, this was not expected prior to the conduct of the study and the hypothesis was assessed in the PRAISE-2 trial among patients with non-ischemic CHF.[88] Patients with non-ischemic etiology of CHF in NYHA class IIIb or IV ($n = 1652$) were randomized to placebo or amlodipine 10 mg/day. There was no significant difference in all-cause or cardiac mortality and cardiac event rates between the two groups. Combining the data of PRAISE-1 and PRAISE-2 suggest a complete prognostic neutrality. However, based on these trials amlodipine and felodipine may be safely used to treat angina or hypertension in patients with CHF, if other proven drugs such as ACE inhibitors and β blockers are ineffective or not tolerated.

Other vasodilators

Flosequinan is a vasodilator with a combined venous and arterial effect, with a possible positive inotropic and chronotropic effect. A large multicenter trial (PROFILE) was launched to study the effects on survival in heart failure patients. However, this study had to be stopped prematurely, because of an increase in mortality in the flosequinan-treated patients.[89] Additionally, the prostacyclin epoprostenol might improve hemodynamics, but has been shown to have an adverse effect on mortality in severe heart failure.[90]

Documented value of vasodilators

Proven indication: always acceptable **Grade A**

- Short-term reduction of afterload in cases with acute heart failure
- The combination hydralazine-isosorbide dinitrate can be used for long-term treatment in patients who do not tolerate ACE inhibitors

Acceptable indication but of uncertain efficacy and may be controversial **Grade B**

- Third generation calcium-channel blockers may be used for symptomatic treatment of conditions such as angina pectoris or hypertension

Not proven: potentially harmful (contraindicated) **Grade C**

- Vasodilators other than hydralazine-isosorbide dinitrate and third generation calcium-channel blockers may increase mortality during long-term treatment
- Treatment of patients with concomitant significant aortic or mitral stenosis

Most vasodilators can improve hemodynamics on a short-term basis. Besides the combination of hydralazine and isosorbide dinatrate, the long-term effects of different vasodilators are either neutral or detrimental. The majority of studies have shown harmful effects with calcium-channel blockers in CHF, with the exception for felodipine and amlodipine where the effects on survival have been neutral. It is therefore suggested that vasodilators other than ACE inhibitors may be used to relieve symptoms and to acutely improve the hemodynamic condition. The effects on survival are less favorable as compared with ACE inhibitors, but hydralazine-isosorbide dinitrate may be used in patients who do not tolerate ACE inhibitors.

Drugs affecting the renin–angiotensin system

Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors have been introduced for the treatment of heart failure within the past decade. Their potential value was suggested by studies showing improved symptomatology,[91] hemodynamics[92,93] and survival.[94] It was hypothesized that ACE inhibitors might attenuate left ventricular remodeling after myocardial infarction[95,96] and thus possibly prevent the progression to symptomatic heart failure. Neuroendocrine activation has been shown to be of prognostic importance[97] and ACE inhibitors have the potential of modulating this activation.[98] Several studies have reported results on the effects of ACE inhibitors on survival in patients with clinical heart failure, following acute myocardial infarction generally and following myocardial infarction with left ventricular dysfunction or heart failure.

Survival trials

CONSENSUS included 253 patients in NYHA class IV randomized to placebo or enalapril. After a follow up of 6 months (primary objective), the overall mortality was reduced by 27% ($P=0{\cdot}003$). Number of days for hospital care was reduced and NYHA classification significantly improved with enalapril.[94]

In the largest study, the Studies of Left Ventricular Treatment (SOLVD) trial, 2569 patients with symptomatic heart failure NYHA class II–III received placebo or enalapril besides conventional heart failure therapy.[99] The average follow up was 41.4 months. Mortality was significantly reduced from 40% to 35% ($P=0{\cdot}0036$). Hospitalizations for heart failure were also reduced. The largest reduction in mortality occurred among deaths attributed significantly to progressive heart failure. Symptoms and quality of life assessed by questionnaire were improved.[100]

In the Survival and Ventricular Enlargement (SAVE) trial, 2231 patients with ejection fraction of 40% or less, but without overt heart failure or symptoms of myocardial ischemia, were randomly assigned treatment with captopril or placebo.[101] Mortality from all causes was 20% in the captopril group and 25% in the placebo group (RR 19%, $P=0{\cdot}019$).

In the TRACE study 1749 patients with left ventricular dysfunction were randomly assigned treatment with placebo or the ACE inhibitor trandolapril.[102] Treatment was initiated 3–7 days from the onset of myocardial infarction. All-cause mortality in the placebo group was 42·3% and 34·7% in the trandolapril group, a 22% relative reduction of mortality ($P=0{\cdot}00065$).

In the AIRE study, 2006 patients with clinical evidence of heart failure any time after the index infarction, were randomly allocated to treatment with ramipril or placebo on day 3–10 from the onset of infarction.[103] Clinical evidence of heart failure was defined as at least one of the following: signs of left ventricular failure on chest radiograph, bilateral auscultatory crackles extending at least one third of the way up the lung fields in the absence of chronic pulmonary disease, or auscultatory evidence of a third heart sound with persistent tachycardia. The average follow up was 15 months with a minimum of 6 months. Mortality from all causes at the end of the study was 17% in the ramipril group and 23% in the placebo group (RR 27%, $P=0{\cdot}002$).

Improved blockade of the renin–angiotensin system was tested in the ATLAS trial. Patients with CHF ($n=3164$) and ejection fraction $<30\%$ were randomized to a low dose of lisinopril (2.5–5·0 mg/day) or a high dose (32.5–35 mg/day) for a median of 45·7 months.[104] There were 717 deaths in the low-dose group versus 666 in the high-dose group (hazard ratio 0·92; $P=0{\cdot}128$) for the high dose. The combined end point of all-cause mortality or hospitalization for any reason showed a hazard ratio of 0·88 (95% CI 0·82–0·96),

($P=0{\cdot}002$). The side effects and tolerability were similar in the two groups.

These findings indicate that patients with heart failure should generally not be maintained on very low doses of an ACE inhibitor, and suggest that a difference in efficacy between intermediate and high doses of an ACE inhibitor is likely to be very small. Thus, patients should be titrated to dose levels observed in trials, that is lisinopril or enalapril at least 16–18 mg/day. The value of additional dose levels such as >20 mg/day lisinopril is uncertain but supported by the results of the ATLAS trial.

A recent meta-combined analysis of individual patients from five large randomized studies with ACE inhibitors was presented by Flather and coworkers. Three of these studies were postinfarction trials, enrolling 5966 patients, in a total of 12 763 cases. The risk of death was significantly lower in the ACE inhibitor-treated group (23% *v* 27%; odds ratio 0·80, 95% CI 0·74–0·87), as was the risk of re-infarctions (8·9% *v* 11%; odds ratio 0·79, 95% CI 0·70–0·89). The treatment benefits were independent of age, sex, and baseline treatment.[105]

Trials on exercise capacity

There are many trials that have focused on this objective. An extensive review of these trials has recently been published[106] and indicated that these agents improve exercise capacity, as well as symptoms in patients with chronic CHF. Changes in exercise capacity are consistent with changes in symptoms.

Trials on hemodynamics

ACE inhibitors were documented in early studies to induce beneficial hemodynamic responses. These effects included a vasodilatory effect and an increased cardiac output, increased stroke volume, and reduced pulmonary wedge pressure.[92,93]

Trials on prevention

A reduced incidence of heart failure by ACE inhibitors has been demonstrated in several trials. In the prevention arm of the SOLVD study,[99] the incidence of heart failure and the number of hospitalizations were reduced and similar findings were reported in SAVE.[101] In an overview of ACE inhibitor trials,[107] the preventive potential of ACE inhibitors is clearly demonstrated.

The potential antiatherosclerotic effect of ACE inhibitors, suggested from experimental animal studies, is supported by observations from the SOLVD[108] and SAVE[101] studies, in which the incidence of myocardial infarction and unstable angina were reduced. The HOPE trial tested the hypothesis that the ACE inhibitor ramipril might favorably influence survival in patients with different atherosclerotic conditions and in patients with high-risk diabetes mellitus ($n=9297$).[109] These patients were considered not to have CHF at inclusion. The primary composite end point of myocardial infarction, stroke, or death from cardiovascular causes was significantly reduced in the treatment group (651 *v* 826 end points; RR 0·78; 95% CI 0·70–0·86, $P<0{\cdot}001$). Ramipril also reduced the risk of heart failure (9·1% *v* 11·6%; RR 0·77, $P<0{\cdot}001$). Thus, even though this was not a study on CHF patients, ramipril appeared to protect high-risk atherosclerotic and diabetic patients from future development of CHF and other cardiovascular complications.

Cost effectiveness

Enalapril therapy for patients with heart failure (SOLVD) was cost effective and justified by added benefits compared to other vasodilator therapy.[110] In asymptomatic patients with left ventricular dysfunction after an acute myocardial infarction (SAVE), captopril was cost effective in patients aged 50–80 years compared to other interventions.[111] Ramipril therapy for patients with clinical heart failure after acute myocardial infarction appears highly cost effective when assessed using data from the AIRE study.[112] ACE inhibitor treatment was considered cost effective in an evaluation of five independent studies regarding economic analysis.[113]

Documented value of ACE inhibitors

Proven indication: always acceptable **Grade A**

- Symptomatic chronic heart failure and documented systolic myocardial dysfunction. Improved survival and reduced morbidity have been demonstrated. Symptoms will be attenuated and exercise capacity improved
- Following acute myocardial infarction with clinical signs of heart failure or significant systolic dysfunction (ejection fraction <40%). Improved survival and reduced morbidity have been demonstrated
- Prevention of cardiovascular events, including heart failure, in patients with atherosclerotic disease, or in patients with diabetes mellitus and additional risk factors

Acceptable indication but of uncertain efficacy and may be controversial **Grade C**

- Heart failure from diastolic dysfunction

Not proven: potentially harmful (contraindicated) **Grade C**

- Treatment of patients with significant aortic or mitral stenosis
- Treatment of patients with hypotension (systolic blood pressure <80 mmHg)
- Treatment of patients with pronounced renal dysfunction

Clinical perspective

All patients with documented left ventricular systolic dysfunction (ejection fraction < 35–40%) should be considered for treatment with an ACE inhibitor. In symptomatic

patients this should be considered first-line therapy in addition to a diuretic agent. Treatment should be continued long term. Patients with clinical CHF should be maintained on ACE inhibitor treatment in combination with a diuretic.

Contraindications to ACE inhibitors include hypotension (in general systolic blood pressure < 80 mmHg), pronounced renal dysfunction (serum creatinine > 250 micromol/1), history of angioneurotic edema, and important valve stenosis.

The dosage to be used should be titrated from a low dose and increased to the moderate high levels employed in clinical trials. If no hypotension or renal dysfunction develops, titration up to enalapril 10 mg 2×/day, captopril 50 mg 2×/day ramipril 10 mg/day, trandolapril 4 mg 4×/day, quinapril 10 mg 2×/day will be most effective.

Angiotensin II receptor (AT_1) antagonists

As ACE inhibition does not provide complete blockade from the synthesis of angiotensin II, a more effective blockade has been postulated by a specific antagonism at the receptor (AT_1) level. Hemodynamic effects of losartan have been similar to the effects of enalapril in comparative trials.[114] In a pilot trial, ELITE, patients with heart failure were randomized to losartan 50 mg/day or captopril 50 mg 3×/day for 48 weeks.[115] The primary end point was renal dysfunction. The effect on serum creatinine did not differ between the two groups. The secondary end point, death and/or hospitalization for heart failure, was 9·4% in the losartan group and 13·2% in the captopril group ($P = 0·075$). The difference was entirely due to a 46% decrease in total mortality among losartan-treated patients, 8·7% and 4·8% respectively ($P = 0·035$).

In an attempt to confirm the findings from the ELITE study, ELITE-II was conducted in 3152 class II–IV patients with ejection fractions (EF) of <40%, randomized to losartan 50 mg/day or captopril 50 mg 3×/day.[116] There was no significant difference in all-cause mortality or sudden death (hazard ratio 1·13; 95% CI 0·95–1·35, $P = 0·16$). Significantly fewer patients in the losartan group discontinued study treatment because of adverse effects (9·7 *v* 14·7%; $P < 0·001$).

In RESOLVD, there were no differences between groups receiving candesartan and enalapril in exercise tolerance, ventricular function, or symptomatic status over 43 weeks.[117] However, combined therapy with candesartan plus enalapril markedly reduced ventricular volumes and improved ejection fraction over 43 weeks compared to either candesartan or enalapril alone. There was greater inhibition of aldosterone levels with the combination at 20 weeks, but this difference narrowed at 43 weeks. The study was too small to examine the impact of clinical outcomes.

In the Val-HeFT study 5010 patients in class II–IV and EF of <40% were randomized to placebo or valsartan.[7] Dose levels were increased to 160 mg 2×/day. Background therapy with an ACE inhibitor was present in 93%. There was no effect on all-cause mortality (484 in the placebo group *v* 495 in the valsartan group; RR 1·02, 95% CI 0·90–1·15, $P = 0·8$). In the other primary end point, mortality or hospitalizations, there was a significant reduction from 801 (32.1%) to 723 (28·8%) (RR 0·87, 95% CI 0·79–0·96, $P = 0·009$). In a subgroup analysis patients on a background therapy with a β blocker were found to have an increased risk when given valsartan. A similar observation was observed in ELITE-II. On the other hand, patients in the RESOLVD study had an improvement in left ventricular function when metoprolol was added to enalapril or candesartan or the combination. Therefore, these apparant subgroup interactions should be viewed with considerable caution.

The newer trials with angiotensin receptor blocker (ARBs) are suggestive, but do not offer definitive proof that ARBs can be used for symptomatic treatment of patients with heart failure who do not tolerate ACE inhibitors. As yet, the documentation regarding survival benefits is not as good as for ACE inhibitors.

Documented value of AT_1-receptor antagonists

Proven indication: always acceptable **Grade A**

- Symptomatic treatment of patients with heart failure who do not tolerate ACE inhibitors

Acceptable indication but of uncertain efficacy and may be controversial **Grade C**

- Symptomatic treatment in patients who do not tolerate β blockers

Not proven and potentially harmful **Grade C**

- Treatment of patients with a background therapy of both an ACE inhibitor and a β blocker

Non-digitalis inotropic drugs

In CHF it is often apparent that the heart suffers from inotropic failure. It is therefore not surprising that vast efforts have been invested in order to develop drugs that might increase contractility or the state of inotropy. Although several drugs with inotropic activity are available today, it has become increasingly evident that these drugs are associated with important negative effects.

There are inotropic agents in different classes according to their mode of action.[118] Cardiac glycosides affect sarcolemmal ions through the effects on ion channels or ion pumps. These drugs are covered in another section of this chapter. Other drugs increase the intracellular level of cyclic adenosine monophosphate (cAMP), either by receptor stimulation (β adrenergic agonists), or by decreasing cAMP breakdown (phosphodiesterase inhibitors). One class of agents affects intracellular calcium mechanisms by release of sarcoplasmic reticulum calcium, or by increasing the

sensitivity of contractile proteins to calcium. Further, there are inotropic drugs with multiple mechanisms of action.

β Agonist drugs

Dobutamine

Drugs with β receptor agonist properties induce an increase in intracellular cAMP activity by stimulation of cellular receptors. Already during the 1960s patients with cardiogenic shock were treated with β receptor agonists isoproterenol and norepinephrine.[119] It was realized that both drugs had potential negative effects, such as an increased risk for arrhythmias or – in the case of norepinephrine – an untoward vasoconstriction. The development of dobutamine, a drug that is a modification of the isoproterenol molecule, resulted in an agent with β_1, β_2 and α_1 adrenergic activity.[120] Dobutamine induces vasodilation in combination with an increase in contractility, leading to an increase in stroke volume and cardiac output.[121–123] An enhancement of contractility is usually associated with an increase in myocardial oxygen consumption.[124] Side effects, such as arrhythmias or an unfavorable blood pressure response, are usually modest. Dobutamine can only be administered intravenously, in doses from 2 micrograms/kg/min up to 20–25 micrograms/kg/min.[125] It has been noticed that dobutamine may decrease β receptor sensitivity,[126,127] and prolonged infusion over 96 hours has been associated with a decrease in the hemodynamic effect by as much as 50%.[128] Beneficial short-term action encouraged investigators to use the drug in patients with chronic heart failure on an outpatient basis. Intermittent therapy was found to increase quality of life and hemodynamics.[129] However, a clinical trial had to be stopped prematurely because of an increase in mortality in the dobutamine-treated group.[130]

Dopamine

Dopamine (DA) is an adrenergic agonist with predominantly β_1 receptor activity.[131,132] This drug increases contractility with minor effects on heart rate or blood pressure. At low doses (0·5–2.0 micrograms/kg/min), DA acts on DA receptors, while at doses above 5·0 micrograms/kg/min it has effects through β_1 receptors, and at higher doses also through α receptors. Infusion at low doses causes dilation of smooth muscles in renal, mesenteric, and coronary arteries, leading to an increase in diuresis.[133,134]

Ibopamine

Ibopamine is an orally active dopaminergic agonist, with the active metabolite epinine *N*-methyldopamine acting on DA_1 and DA_2 receptors. This agent had positive hemodynamic effects in terms of an increase in cardiac output, a reduction in systemic vascular resistance, and no effect on heart rate.[135,136] In a study with digoxin and ibopamine in 161 patients with mild to moderate chronic heart failure, it was observed that ibopamine had some positive effects in patients with less ventricular dysfunction, and no effects on mortality.[137] To evaluate the long-term effects of ibopamine, a study (PRIME-II) was initiated in 1906 patients with NYHA class III–IV heart failure. However, the study was terminated prematurely because of an increase in mortality in the ibopamine group: 25% (232 of 953) in the ibopamine group died versus 20% (193 of 953) in the placebo group (RR 1·26, 95% CI 1·04–1·53, $P = 0{\cdot}017$).[138]

Xamoterol

Xamoterol is a drug with β adrenergic blocking effects and high partial agonist activity, and long-term effects are similar to those of other inotropic agents. A multicenter trial had to be discontinued because of an increase in mortality in the active treatment group: 32 of 352 (9·1%) patients in the xamoterol group and 6 of 164 (3·7%) patients in the placebo group died ($P = 0{\cdot}02$).[139]

Phosphodiesterase inhibitors

Through inhibition of cAMP breakdown, the phosphodiesterase inhibitors bypass the β receptor pathway. The first phosphodiesterase inhibitor was amrinone, a drug with inotropic and vasodilatory effects. During infusion, amrinone induced afterload reduction, a decrease in filling pressures, increase in cardiac index, and also an increased rate of contractility and relaxation.[140–142] The major side effect is thrombocytopenia. Similarily, the related agent milrinone has been found to enhance myocardial contractility, besides having potent vasodilatory effects,[143–145] but without thrombocytopenia.[146] The short-term effects of another agent – enoximone – have been similar to those of other phosphodiesterase inhibitors.[147–149] As phosphodiesterase inhibitors elicit intracellular effects through other pathways than β adrenergic drugs, it has been hypothesized that the combination of these two classes of drugs would enhance myocardial performance. Results from clinical trials have supported this concept.[150,151]

Whereas short-term administration may improve myocardial performance and clinical condition in CHF,[145,152] the long-term effects of phosphodiesterase inhibitors have been discouraging. Oral phosphodiesterase administration has been tested in several trials for chronic heart failure, all of which have demonstrated no beneficial effect or a substantial increase in mortality in patients receiving the investigated drug.[16,153–155] In the PROMISE trial 1088 class III–IV patients were given milrinone or placebo. There was a 28% increase in mortality in patients treated with milrinone (95% CI 1–61%, $P=0{\cdot}038$).[153]

Calcium-sensitizing drugs

Pimobendan is the most thoroughly studied drug in this class of inotropics. The effect is mediated by an increase in the affinity of troponin C for intracellular calcium.[156,157] Pimobendan inhibits phosphodiesterase and thereby has effects similar to those of milrinone.[156,158] In clinical trials pimobendan has been shown to exert improvement in cardiac index, exercise performance, and quality of life.[159,160] However, treatment effects did not show congruity among different doses, and there was also a tendency toward increased mortality in a large 24 week trial.[161]

Vesnarinone is a drug with muliple actions. It is a synthetic quinolinone derivative that in part inhibits phosphodiesterase, with simultaneous effects on transmembrane ion transports. This drug seemed to have effects on contractility without increasing the heart rate,[162,163] which made it an interesting candidate for long-term therapy in heart failure. Furthermore, it was demonstrated that vesnarinone might inhibit the production of cytokines, including tumor necrosis factor (TNF-α).[164] A moderate size trial with two doses of vesnarinone was started in 1989. Whereas the 120 mg treatment arm had to be stopped prematurely because of a significant increase in mortality in the active treatment group (16 deaths *v* three deaths in the 60 mg arm and six deaths in the placebo group), the 60 mg group continued. Unexpectedly, on completion of the study it was shown that 60 mg of vesnarinone was associated with a reduction in the combinded end point mortality or cardiovascular morbidity (26 of 239 *v* 50 of 238; RR 50%, 95% CI 20–69, $P = 0{\cdot}003$).[165] This study was followed by a larger placebo-controlled trial (VEST), with 3800 patients. However, the study was stopped early because of a 26% increase in mortality in patients treated with 60 mg of vesnarinone.[166]

Levosimendan is a new calcium-sensitizing agent with properties similar to pimobendan. This drug has, so far, been tested in short-term studies, and no long-term survival studies have been presented. Levosimendan was compared with dobutamine in 151 patients. A 10 minute bolus was followed by a 24 hour infusion of 0·05–0·6 micrograms/kg/min. Dobutamine was given as an open-label infusion (6 micrograms/kg/min). The primary efficacy variable was the proportion of patients showing an increase in stroke volume, a decrease in pulmonary capillary wedge pressure, or an increase in cardiac output. The response rate to levosimendan ranged from 50% at the lowest dose to 88% at the highest dose (compared with placebo 14% and dobutamine 70%).[167] In another study, levosimendan was compared with placebo in 146 patients in NYHA class III–IV. The dose range was 0·1–0·4 micrograms/kg/min. Treatment caused dose-dependent decreases in right and left ventricular filling pressures and mean arterial pressure. There were minor increases in heart rate at higher doses and symptoms improved as compared with placebo.[168] Thus, short-term infusion (up to 24 hours) of levosimendan (0·05–0·2 micrograms/kg/min) is well tolerated and leads to favorable hemodynamic effects. Further, there are unpublished data suggesting that levosimendan might have long-term favorable effects in patients with myocardial infarction and heart failure.

The clinical effects appear to be similar to those of phosphodiesterase inhibitors, although experimental data suggest that no adverse effects on myocardial metabolism occur with levosimendan. No comparable studies have been conducted between levosimendan and a phosphodiesterase inhibitor, and long-term data are still required before the clinical value can be established.

Documented value of inotropic drugs

Proven indication: always acceptable

- Short-term improvement of symptoms in patients with severe heart failure **Grade A**
- Bridging towards more definitive surgical treatment, such as cardiac transplantation **Grade C**

Acceptable indication but of uncertain efficacy and may be controversial **Grade C**

- Intermittent short-term treatment in chronic heart failure

Not proven: potentially harmful (contraindicated) **Grade A**

- Long-term treatment in chronic heart failure. These drugs increase the risk of mortality.

It should be obvious from the summary above that different inotropic drugs, with a wide variety of modes of action, may improve symptoms and cardiac function on a short-term basis. However, inotropic drugs increase the risk of mortality. Whether these detrimental long-term effects could be abolished in the development of any other compound is unclear.

Anti-adrenergic agents

β Adrenergic blockade

Clinicians have generally been cautious in using β blockers in patients with CHF, even though investigators in the early 1970s were already proposing a possible beneficial effect of β blockers in such cases.[169,170] However, data have been gathered during recent years indicating that this class of drugs may have a significant contribution to make in the heart failure treatment armamentarium of the near future.

Early case reports suggested that β blockers had a potential to elicit overt heart failure in some cases.[171,172] However, although the possibility of such an adverse reaction has been of concern, there are no placebo-controlled trials that have proven that β blockers are detrimental in congestive heart failure. On the contrary, analysis of several myocardial infarction studies has shown that patients with signs of CHF showed a similar or better response to β blockers than did patients without heart failure.[173–175]

Hemodynamic effects

The short-term effects of β adrenergic blockade differs markedly from the long-term effects, which might be one explanation for the difficulties in understanding the mode of action during long-term therapy. After IV administration, there is a rapid reduction in heart rate, contractility, and blood pressure, with ensuing fall in cardiac output.[176–179] However, intraventricular volumes, stroke volume, and ejection fraction are unaffected.[177,178] β Blockers with vasodilating properties cause an acute reduction in afterload with reduction in filling pressures.[176–179] During 1–3 months of treatment, positive diastolic effects have been observed and these effects probably precede full effects on cardiac systolic function.[178,180]

During long-term treatment (3–12 months), β blockers induce myocardial improvement, as expressed by an increase in ejection fraction, cardiac output, and exercise capacity.[181–185] Similar to ACE inhibitors, β blockers attenuate left ventricular remodeling.[186–188] In the RESOLVD trial, metoprolol CR/XL was compared with placebo over 24 weeks in 426 patients receiving either an ARB (candesartan) or an ACE inhibitor (enalapril) or the combination. There was a significant improvement in measures of LV function in the β blocker treated group with an attenuation in the increase in LV dimensions.[189]

Effects of neurohormones

Acute administration of metoprolol causes a reflex increase in peripheral catecholamines without alteration of the transmyocardial gradient.[178] With radioactive labeling of norepinephrine, the non-selective β blocker propranolol was shown to reduce myocardial norepinephrine spillover as compared to the β_1 selective blocker metoprolol.[190] There are sparse data on the long-term effects of β adrenergic blockade on neurohormonal activation, but some studies suggest a beneficial reduction in peripheral norepinephrine level.[191–195] A decrease in renin–angiotensin activity has been noted, while the levels of atrial natriuretic peptides might increase on a short-term basis.[189]

Effects on quality of life and hospitalizations

A reduction of the need for hospitalizations has been demonstrated in studies with bisoprolol,[196] metoprolol,[197] and carvedilol.[198] Quality of life was improved in the Metoprolol in Dilated Cardiomyopathy (MDC) trial.[199] Whereas both patient and physician global assessments of heart failure symptoms improved, quality of life scores were not improved in the US carvedilol studies or in the MERIT-HF study.[200–202] In the Australian–New Zealand study, there was a tendency towards worse symptoms.[187] Further, carvedilol has been shown to reduce the progression towards overt heart failure.[187]

Effects on survival

One of the first studies of β blockers in congestive heart failure showed a reduced mortality in patients treated by β blockade as compared with historical controls.[169] Not until 1993, when the MDC trial was published, did additional information on clinical outcome become available. This study showed a trend towards a 34% reduction in the combined end point deaths and need for heart transplantation ($P=0{\cdot}058$) in 383 patients with idiopathic dilated cardiomyopathy, treated with placebo or metoprolol.[199] A late follow up of this study has recently demonstrated that this trend was also maintained, or possibly reinforced, regarding all-cause mortality and actual cardiac transplantations 3 years after randomization.[203] In the CIBIS study, bisoprolol was used in a placebo-controlled trial in 641 patients. Overall there was a non-significant reduction in mortality (RR 0·80, 95% CI 0·56–1·15, $P= 0{\cdot}22$).[204] Four studies in the USA, investigating different effects of carvedilol, were combined in a total of 1094 patients with varying degrees of heart failure, and demonstrated a lower mortality in the carvedilol group (22 of 696 [3·2%] *v* 31 of 398 [7·8%] deaths; RR 65%, 95% CI 39–80, $P< 0{\cdot}01$).[205] However, there was no statistically beneficial effect of carvedilol regarding survival in the Australia–New Zealand trial of 415 patients with chronic heart failure of varying etiology.[206] None of the aforementioned trials was designed to specifically study mortality, and the number of events in each trial was relatively modest.

The first study designed to test the potential survival benefits of long-term β blockade was the CIBIS-II study. The β_1 selective antagonist bisoprolol was tested versus placebo in 2647 patients in NYHA III–IV and with an ejection fraction of ≤35.[196] Study drug was initiated with 1·25 mg/day being progressively increased to 10 mg/day over 3 months. The study was stopped by the safety committee after a mean follow up of 1·3 years. All-cause mortality was significantly lower with bisoprolol than with placebo (156 [11·8%] *v* 228 [17·3%]; hazard ratio 0·66, 95% CI 0·54–0·81, $P<0{\cdot}0001$. There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (3·6% *v* 6·3%; hazard ratio 0·56, $P=0{\cdot}001$).

In the MERIT-HF trial metropolol controlled release/extended release (CR/XL) was compared in 3991 patients with chronic heart failure in NYHA class II–IV and an ejection fraction of <0·40· Background therapy including an ACE inhibitor or an ARB was present in 95% of the patients. Treatment was initiated with metoprolol CR/XL 12.5–25 mg/day and titrated for 6–8 weeks up to target dose of 200 mg/day. The study was also stopped early on the recommendation of the independent safety committee. Mean follow up time was 1 year. All-cause mortality was lower in the metoprolol group than in the placebo group: 145 (7·2% per patient-year of follow up) versus 217 deaths

(11·0%) (RR 0·66, 95% CI 0·53–0·81, $P=0·0009$). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 *v* 132; RR 0·59, $P=0·0002$) and fewer deaths from worsening heart failure (30 *v* 58; RR 0·51, $P=0·0023$).[197]

In the BEST trial the effects of the non-selective β blocker bucindolol was compared with placebo in 2708 patients with CHF in NYHA class III–IV.[207] Bucindolol was initiated with 3 mg 2×/day and titrated up over 6–8 weeks to 50–100 mg 2×/day. The study was prematurely terminated by the safety committee. Mortality was reduced from 447 deaths to 409 deaths (RR 0·91, 95% CI 0·88–1·02, $P=0·12$). In a subgroup analysis there was a heterogeneous response among groups analyzed. Patients with NYHA class IV or ejection fraction below 20% did not appear to benefit. Furthermore, in a subgroup of African-Americans there was a 17% excess mortality suggesting a lack of benefit among these patients. However, these were post hoc analyses and not prespecified end points.

The recently reported COPERNICUS trial was performed in 2289 patients with symptomatic chronic heart failure with symptoms at rest or at minimal exertion.[198] Carvedilol was initiated with 3·125 mg ×2/day and titrated to 25 mg ×2/day. There was a significant reduction in all-cause mortality from 190 (18·5% per patient-year) to 130 (11·4%) with a hazard ratio of 0·65 (95% CI 0·52–0·81); $P=0·0001$. The effect was consistent among a number of prespecified subgroups.

In a post hoc subgroup analysis of patients in the MERIT-HF study with similar characteristics as the patients in the COPERNICUS trial, with an EF of <0·25 and NYHA class III–IV, there was a comparable reduction in all-cause mortality (45 [11%] *v* 72 [18%] deaths; hazard ratio 0·61, 95% CI 0·11–0·58, $P=0·0086$).[208]

All three large β blocker studies (CIBIS-II, MERIT-HF, COPERNICUS) had been stopped early because of clear evidence of benefit and therefore resulted in limited long-term experience with this treatment. Nevertheless, these trials have extended the documentation for survival benefit with β adrenergic blockers to more than 15 000 patients. Overall experience from these trials is that treatment has been possible to initiate with high tolerability during the titration phase. As the BEST trial showed somewhat different results than the other three trials and also compared with the meta-analysis by Doughty *et al*[209] there is a suggestion that these agents differ in their effect. Several smaller trials have been published comparing metoprolol and carvedilol. A recent crossover study suggested that there are differences with respect to receptor effects, while long-term clinical effects were comparable.[210] This is further explored in the COMET trial where carvedilol and metoprolol are compared in 3042 patients. The trial finishes its follow up in October 2002, and results are expected by the end of 2002. The effects of β blockers in the elderly are currently being studied in the SENIORS trial where nebivalol is being compared with placebo in patients above 70 years of age and with chronic heart failure.

In the situation of heart failure secondary to acute myocardial infarction, there are data from several older large post myocardial infarction trials that β blockers would be beneficial also when symptoms of heart failure are present.[173–175] These findings were first tested prospectively in the CAPRICORN study, in which carvedilol or placebo was given to 1959 patients with a recent myocardial infarction and signs of left ventricular dysfunction (EF ≤40%).[211] There was no effect on the primary end point mortality or cardiovascular hospitalization (hazard ratio 0·92, 95% CI 0·80–1·07), but there was a statistically significant reduction in all-cause mortality, 166 (15%) versus 151 (12%) deaths (hazard ratio 0·77, 95% CI 0·60–0·98, $P=0·03$). The risk reduction was of similar magnitude as previous post myocardial infarction trials with β blockers.

Documented value of β blockers

Proven indication: always acceptable **Grade A**

- To improve long-term survival in patients with mild to severe heart failure
- To improve cardiac function and symptoms in patients with symptomatic chronic heart failure, already on conventional treatment with ACE inhibitors (or an ARB), diuretics or digitalis
- To improve outcome in patients with acute myocardial infarction and left ventricular dysfunction with or without symptomatic heart failure
- Symptomatic treatment of patients with heart failure who do not tolerate ACE inhibitors

Acceptable indication but of uncertain efficacy and may be controversial **Grade C**

- Symptomatic heart failure from diastolic dysfunction

Not proven: potentially harmful (contraindicated) **Grade C**

- Acute decompensated heart failure
- CHF with pronounced hypotension and/or bradycardia

Clinical perspective

Drug titration and intolerance

Due to initial negative inotropic effects, treatment with β blockers requires a slow titration procedure. Parallel to myocardial recovery, β blocker dosages can usually safely be increased. It has been noticed that patients with simultaneous marked hypotension and tachycardia, expressing severe decompensation, may not tolerate β blockers. Nevertheless, figures of intolerance have been low in randomized trials, comparable to those of ACE inhibitors. Starting doses with different β blockers have been: bisoprolol 1·25 mg/day; carvedilol 3·125–6.25 mg 2×/day; metoprolol

12.5–25 mg/day. Doses are increased every 1–2 weeks, when doses are doubled, until maintenance doses of full conventional β blockade are achieved.

Although a reduction in heart rate probably is important, it has not been possible to adequately identify responders from non-responders to β blocker therapy. In cases with significant obstructive pulmonary disease, β blockers should be used with caution, and a selective β blocker would be preferred.

Central nervous system modulators

Moxonidine

Reduction of the sympathetic nervous system activity can also be achieved by stimulating receptors within the central nervous system. Studies in this area has been performed with clonidine[212] and moxonidine. Moxonidine has been documented in several phase II and III trials. In a study over 12 weeks in 97 patients, Swedberg and coworkers demonstrated a significant attenuation of plasma norepinephrine levels.[213] With a sustained release preparation of moxonidine, a more prolonged and effective reduction of plasma norepinephrine was obtained in 265 subjects.[214] The reduction was 40–50%, achieved within 3 weeks from initiation. However, in a large phase III trial with moxonidine sustained release (MOXCON) an early increase in death rate and adverse events in the moxonidine SR group led to premature termination of the trial because of safety concerns after 1934 patients had been entered. Final analysis revealed 54 deaths (5·5%) in the moxonidine SR group and 32 deaths (3·1%) in the placebo group. Survival curves revealed a significantly ($P = 0{\cdot}005$) worse outcome in the moxonidine SR group. Hospitalization for heart failure, acute myocardial infarction, and adverse events were also more frequent in the moxonidine SR group.[215] This trial terminated the efforts to explore whether CNS inhibition of adrenergic activation could be an alternative to β adrenergic blockade in heart failure.

Antiarrhythmic drugs in heart failure

Although progressive pump dysfunction is a common cause of death in heart failure, sudden death is probably the most common reason, and has been considered responsible in 25–50% of all deaths.[216–219] Besides a few cases of primary asystole, the majority of sudden deaths are due to ventricular arrhythmias.[220] The issue of antiarrhythmic therapy in heart failure patients has therefore been of major interest. Internal cardioversion defibrillators are now used for prevention of sudden death from ventricular arrhythmias, and the use of these therapeutic devices is dealt with elsewhere in this book.

Most antiarrhythmics cause a depression of left ventricular function. Although frequent and complex ventricular arrhythmias may be predictive of sudden death, left ventricular dysfunction is a more powerful predictor.[221] Furthermore, these drugs may have a proarrhythmic effect, especially in cases of left ventricular dysfunction. In the CAST study the efficacy of antiarrhythmic drugs in patients with left ventricular dysfunction after myocardial infarction and with complex ventricular arrhythmias was evaluated. Patients who responded with attenuation of arrhythmias after drug testing were randomized to encainide, flecainide, or moricizine. The results showed an increase in mortality in patients treated with these agents.[222] Amiodarone is a class III antiarrhythmic drug with no or little negative inotropic effect. Previous promising smaller trials encouraged larger trials, such as the GESICA study. In this study, 516 patients with heart failure on conventional treatment were randomized to open label amiodarone treatment ($n = 260$) or conventional treatment ($n = 256$). Both sudden deaths and deaths due to heart failure were reduced, comprising in total 87 deaths in patients on amiodorone and 106 in the placebo group ($P = 0{\cdot}02$).[223] However, these results were not reproduced in another study in patients with CHF and asymptomatic ventricular arrhythmias.[224] In this study 674 patients were investigated, but amiodarone treatment was not associated with reduction of overall mortality or mortality from sudden death. Two other parallel studies have recently been finished, in which amiodarone was used in patients with a recent myocardial infarction and left ventricular dysfunction.[225,226] In addition, patients in the CAMIAT study had complex ventricular arrhythmias. Although all-cause mortality was not significantly lower in the treatment groups, both studies showed a reduction in arrhythmic deaths. A meta-analysis of 13 amiodarone trials demonstrated a significant reduction in total mortality (10·9 *v* 12.3% per year; OR 0·87 [95% CI 0·78–0·99], $P = 0{\cdot}03$) and in arrhythmic deaths (4·0 *v* 5·7% per year; OR 0·71 [95% CI 0·59–0·85], $P = 0{\cdot}0003$).[227,228]

Sotalol, a β blocker with class III antiarrhythmic properties, has not been found to reduce deaths from ventricular arrhythmias. On the contrary, a study with the non-β blocker isoform *d*-sotalol in postmyocardial patients had to be terminated in advance because of an increased mortality in the sotalol group.[229]

ACE inhibitors reduce the risk of progressive heart failure deaths. The possibility of ACE inhibitors to affect arrhythmias has been reviewed.[230] In some of the heart failure trials there has also been a reduction in the rate of sudden deaths.[78,231] However, these findings were not confirmed in the SOLVD trial.[232] The most impressive effects on sudden deaths have been found in the large survival studies with β blockers. Consistent effects were found with all three agents, bisoprolol, metoprolol, and carvedilol.[196–198]

Documented value of antiarrhythmic therapy in heart failure

Proven indication: always acceptable **Grade A**

- β Adrenergic blockade in patients with congestive heart failure

Acceptable indication but of uncertain efficacy and may be controversial **Grade B**

- Prevention of arrhythmic deaths in patients with ventricular arrhythmias

Not proven: potentially harmful (contraindicated) **Grade A**

- Class I antiarrhythmic drugs in patients with asymptomatic ventricular arrhythmias and heart failure
- Class III antiarrhythmic drugs, besides amiodarone

Mechanical devices and pacing

Different kinds of left ventricular mechanical assist devices (LVADs) have been studied for several years and they have been in clinical use since at least early 1990s.[233] Long-term effects have been unclear. A randomized trial has been presented in this context. In REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure), 129 patients with advanced heart failure in NYHA class IV were randomized to optimal medical management or LVAD (HeartMate).[234] No patient was eligible for heart transplantation. The objectives were to assess effects on survival and quality of life. The mean age was 67 years and the average ejection fraction 17%.

Kaplan–Meier survival analysis showed a reduction of 48% in the risk of death from any cause in the group that received left ventricular assist devices as compared with the medical therapy group (RR 0.52, 95% CI 0.34–0.78, $P = 0.001$). The rates of survival at 1 year were 52% in the device group and 25% in the medical therapy group ($P = 0.002$), and the rates at 2 years were 23% and 8% ($P = 0.09$), respectively. The frequency of serious adverse events in the device group was 2.35 times (95% CI 1·86–2.95) that in the medical therapy group, with a predominance of infection, bleeding, and malfunction of the device. The quality of life was significantly improved at 1 year in the device group assessed as SF-36 and Beck Depression Inventory. There was also a non-significant improvement in Minnesota Living with Heart Failure.

The study shows that LVADs can prolong life and improve quality of life in severe heart failure. The treatment effect is

Table 46.1 Key recommendations

Aim of treatment	Class of drug	Level of evidence
Symptomatic improvement of congestion, improvement of exercise capacity	Diuretics	**Grade A**
Reduction of mortality in mild to moderate heart failure	Angiotensin converting enzyme inhibitors	**Grade A**
	β Adrenergic blockers	**Grade A**
Reduction of mortality in severe heart failure	Angiotensin converting enzyme inhibitors	**Grade A**
	β Adrenergic blockers	**Grade A**
	Spironolactone	**Grade A**
Reduction of mortality in patients not tolerating an ACE inhibitor	Angiotensin-II receptor 1 blockers	**Grade B**
Reduction of morbidity and symptoms in mild–severe heart failure	Angiotensin converting enzyme inhibitors	**Grade A**
	β Adrenergic blockers	**Grade A**
	Angiotensin-II receptor 1 blockers	**Grade A**
	Spironolactone	**Grade A**
	Digitalis	**Grade A**
Short-term improvement of symptoms in patients with severe CHF. Bridging towards more definitive surgical treatment, such as cardiac transplantation	Non-digitalis inotropic drugs	**Grade A**
Prevention of arrhythmic deaths in patients with symptomatic ventricular arrhythmias	Amiodarone	**Grade B**
Bridging towards heart transplantation in terminal heart failure	Left ventricular assist device	**Grade B**

limited in time and there was no significant improvement after 2 years. The important question is to evaluate the cost effectiveness of this expensive therapy in relation to other treatments. The published information suggests that the treatment costs were considerable. **Grade B**

There are several surgical approaches to heart failure including revascularization, left ventricular reconstruction, cardiomyoplasty and mitral valvular repair. However, the clinical studies have not been controlled, and yet the partial left ventricular ventriculotomy (Batista) and cardiomyoplasty have even been classified as not recommended. **Grade C**

Besides conventional indication for antibradycardia pacing, other pacing modalities have been tried for patients with CHF. A dual chamber pacing with shortening of the atrioventricular conduction has been investigated in a small series. More recently, so called resynchronization therapy using pacing of both the right and the left ventricles has been introduced. There are promising results from smaller studies showing improved left ventricular function and symptomatology.[237–239] Larger randomized studies are now in progress testing this concept on clinical outcomes.

Concluding remarks

In the treatment of CHF there are two main classes of drugs – ACE inhibitors and β blockers – with solid and consistent documentation for reduction of morbidity and mortality. Furthermore, spironolactone has recently been accepted by the scientific community to be of value in this respect. The ARBs have not sufficient documentation to be placed on an equal status with ACE inhibitors. However, the ARBs are widely accepted as a substitute when patients are not tolerating an ACE inhibitor (Table 46.1). The concept of neurohormonal blockade is also evaluated in studies on endothelin receptor blockers and vasopeptidase inhibitors. Some of these trials are imminent. The development of devices and surgical methods are today somewhat more uncertain.

References

1. Ribner B, Plucinski DA, Hsieh AM *et al.* Acute effects of digoxin on total systemic vascular resistance in congestive heart failure due to dilated cardiomyopathy. *Am J Cardiol* 1985;**56**:896.
2. Gheorghiade M, St Clair J, St Clair C, Beller GA. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. *J Am Coll Cardiol* 1987;**9**:849.
3. Cohn K, Selzer A, Kersh ES *et al.* Variability of hemodynamic response to acute digitalization in chronic cardiac failure due to cardiomyopathy and coronary artery disease. *Am J Cardiol* 1975;**31**:461.
4. Braunwald E. Effects of digitalis on the normal and the failing heart. *J Am Coll Cardiol* 1985;**5**:51A.
5. Ferguson DW, Berg WJ, Sanders JS *et al.* Sympathoinhibitory responses to digitalis glycosides in heart failure patients. *Circulation* 1989;**80**:65–77.
6. Ferguson DW. Baroreflex-mediated circulatory control in human heart failure. *Heart Failure* 1990;**6**:3.
7. Goldsmith SR, Simon AB, Miller E. Effect of digitalis on norepinephrine kinetics in congestive heart failure. *J Am Coll Cardiol* 1992;**20**:858–63.
8. Dobbs SN, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure. Placebo controlled trial in outpatients. *BMJ* 1977;**1**:749.
9. Fleg L, Gottlieb SH, Lakatta EG. Is digoxin really important in compensated heart failure? *Am J Med* 1982;**73**:244.
10. Taggart AJ, Johnston GD, McDevitt DG. Digoxin withdrawal after cardiac failure in patients with sinus rhythm. *J Cardiovasc Pharmacol* 1983;**5**:229.
11. Lee DCS, Johnston RA, Bingham JB *et al.* Heart failure in outpatients. A randomized trial of digoxin versus placebo. *N Engl J Med* 1982;**306**:699.
12. Guyatt GH, Sullivan MJJ, Fallen EL *et al.* A controlled trial of digoxin in congestive heart failure. *Am J Cardiol* 1988; **61**:371.
13. Haerer W, Bauer U, Hetzel M, Fehske J. Long-term effects of digoxin and diuretics in congestive heart failure. Results of a placebo-controlled randomized double-blind study. *Circulation* 1988;**78**:53.
14. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild moderate heart failure. *JAMA* 1988; **259**:539–44.
15. German and Austrian Xamoterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. *Lancet* 1988;**i**:489.
16. DiBianco R, Shabetai R, Kostuk W *et al.* A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989;**320**: 677–83.
17. Uretsky BF, Young JB, Shahidi FE *et al.* Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. *J Am Coll Cardiol* 1993;**22**:955–62.
18. Packer M, Gheorghiade M, Young JB *et al.* Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med* 1993;**329**:1–7.
19. Perry G, Brown E, Thornton R *et al.* The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–33.
20. Stason WR, Cannon PJ, Heinemann HO, Laragh JH. Furosemide: a clinical evaluation of diuretic action. *Circulation* 1966;**34**:910–20.
21. Cody RJ, Ljungman S, Covit AB *et al.* Regulation of glomerular filtration rate in chronic congestive heart failure patients. *Kidney Int* 1988;**34**:361–7.
22. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Intern Med* 1984;**101**:370–7.

23. Lal S, Murtagw JG, Pollock AM, Fletcher E, Binnion PF. Acute hemodynamic effects of furosemide in patients with normal and raised left atrial pressures. *Br Heart J* 1969;**31**: 711–17.
24. Stampfer M, Epstein SE, Beiser D, Braunwald E. Haemodynamic effects of diuresis at rest and during intense uprights exercise in patients with impaired cardiac function. *Circulation* 1968;**37**:900–11.
25. Magrini F, Niarchos AP. Hemodynamic effects of massive peripheral edema. *Am Heart J* 1983;**105**:90–4.
26. Francis GS, Siegel RM, Goldsmith SR *et al.* Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Intern Med* 1985; **103**:1–6.
27. Dikshit K, Vyden JK, Forrester JS *et al.* Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after myocardial infarction. *N Engl J Med* 1973;**288**: 1087–90.
28. Nelson GIC, Ahuja RC, Silke B, Taylor SH. Haemodynamic effects of furosemide and its influence on repetitive rapid volume loading in acute myocardial infarction. *Eur Heart J* 1983;**4**:706–11.
29. Verma SP, Silke B, Reynolds G *et al.* Immediate effects of bumetanide on systemic haemodynamics and left ventricular volume in acute and chronic heart failure. *Br J Clin Pharmacol* 1987;**24**:21–32.
30. Ramirez A, Abelman WH. Haemodynamic effects of diuresis by ethacrynic acid. *Ann Intern Med* 1968;**121**:320–7.
31. Valette H, Hebert JL, Apoil E. Acute haemodynamic effects of a single intravenous dose of piretanide in congestive heart failure. *Eur J Clin Pharmacol* 1983;**24**:163–7.
32. Fiehring H, Achhammer I. Influence of 10 mg torasemide iv and 20 mg furosemide iv on the intracardiac pressures in patients with heart failure at rest and during exercise. *Prog Pharmacol Clin Pharmacol* 1990;**8**:87–104.
33. Mackay IG, Muir AL, Watson ML. Contribution of prostaglandins to the systemic and renal vascular response to frusemide in normal man. *Br J Clin Pharmacol* 1984;**17**: 513–19.
34. Ikram H, Chan W, Espiner EA, Nicholls ME. Haemodynamic and humoral responses to acute and chronic frusemide therapy in congestive heart failure. *Clin Sci* 1980;**59**:443–9.
35. Haerer W, Bauer U, Sultan N. Acute and chronic effects of a diuretic monotherapy with piretanide in congestive heart failure – a placebo controlled trial. *Cardiovasc Drugs Ther* 1990;**4**:515–22.
36. Podszus T, Piesche L. Effect of torasemide on pulmonary and cardiac haemodynamics after oral treatment of chronic heart failure. *Prog Pharmacol Clin Pharmacol* 1990;**8**:157–66.
37. Cheitlin MD, Byrd R, Benowitz N. Amiloride improves haemodynamics in patients with chronic congestive heart failure treated with chronic digoxin and diuretics. *Cardiovasc Drugs Ther* 1991;**5**:719–26.
38. Francis GS, Benedict C, Johnstone DE *et al.* Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. *Circulation* 1990;**82**:1724–9.
39. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987;**57**:17–22.
40. Achhammer I. Long-term efficacy and tolerance of torasemide in congestive heart failure. *Prog Pharmacol Clin Pharmacol* 1990;**8**:127–36.
41. Dusing R, Piesche L. Second-line therapy of congestive heart failure with torasemide. *Prog Pharmacol Clin Pharmacol* 1990;**8**:105–20.
42. Odemuyiwa O, Gilmartin J, Kenny D, Hall RJC. Captopril and the diuretic requirements in moderate and severe chronic heart failure. *Eur Heart J* 1989;**10**:586.
43. Anand IS, Kalra GS, Ferrari R *et al.* Enalapril as initial and sole treatment in severe chronic heart failure with sodium retention. *Int J Cardiol* 1990;**28**:341.
44. Richardson A, Bayliss J, Scriven AJ *et al.* Double-blind comparison of captopril alone against furosemide plus amiloride in mild heart failure. *Lancet* 1987;**ii**:709.
45. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. *Arch Intern Med* 1994;**154**:1905–14.
46. Laragh JH. Hormones in the pathogenesis of congestive heart failure: vasopressin, aldosterone, angiotensin II. *Circulation* 1962;**25**:1015–23.
47. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS trial study group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* 1990;**82**:1730–6.
48. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;**83**:1849–65.
49. Young M, Fullerton M, Dilley R, Funder J. Mineralocorticoids, hypertension, and cardiac fibrosis. *J Clin Invest* 1994;**93**: 2578–83.
50. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A *et al.* The effect of spironolactone on morbidity and mortality in patients with severe failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**: 709–17.
51. Eichna LW, Sobel BJ, Kessler RH. Hemodynamic and renal effects produced in congestive heart failure by the intravenous administration of a ganglionic blocking agent. *Trans Assoc Am Phys* 1956;**69**:207–13.
52. Burch GE. Evidence for increased venous tone in chronic heart failure. *Arch Intern Med* 1956;**98**:750–66.
53. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest* 1968;**47**:960–70.
54. Majid PA, Sharma B, Taylor SH. Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 1971;**ii**:719–24.
55. Franciosa JA, Guiha NH, Limas CJ, Rodriguera E, Cohn JN. Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet* 1972;**i**:650–4.
56. Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. *N Engl J Med* 1977;**297**:27–31.
57. Tsai SC, Adamik R, Manganiello VC, Moss J. Effects of nitroprusside and nitroglycerin on cGMP content and PGI2 formation in aorta and vena cava. *Biochem Pharmacol* 1989; **38**:61–5.
58. Lavine SJ, Campbell CA, Held AC, Johnson V. Effect of nitroglycerin-induced reduction of left ventricular filling pressure

on diastolic filling in acute dilated heart failure. *J Am Coll Cardiol* 1989;**14**:233–41.
59. Mason DT, Braunwald E. The effects of nitroglycerin and amyl nitrate on arteriolar and venous tone in the human forearm. *Circulation* 1965;**32**:755–65.
60. Armstrong PW, Armstrong JA, Marks GS. Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive heart failure. *Circulation* 1980;**62**:160–6.
61. Leier CV, Bambach D, Thompson MJ *et al.* Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin, and nitroprusside in patients with congestive heart failure. *Am J Cardiol* 1981;**48**:1115–23.
62. Flaherty JT, Reid PR, Kelly DT *et al.* Intravenous nitroglycerin in acute myocardial infarction. *Circulation* 1975;**51**:132–9.
63. Ludbrook PR, Byrne JD, Kurnik PB, McKnight RC. Influence of reduction of preload and afterload by nitroglycerin on left ventricular diastolic pressure-volume relation and relaxation in man. *Circulation* 1977;**56**:937–43.
64. DeMarco T, Chatterjee K, Rouleau JL, Parmley WW. Abnormal coronary hemodynamics and myocardial energetics in patients with chronic heart failure caused by ischemic heart disease and dilated cardiomyopathy. *Am Heart J* 1988; **115**:809–15.
65. Unverferth DV, Magorien RD, Lewis RP, Leier CV. The role of subendocardial ischemia in perpetuating myocardial failure in patients with nonischemic congestive cardiomyopathy. *Am Heart J* 1983;**105**:176–9.
66. Chiariello M, Gold HK, Leinbach RC, David MA, Maroko PR. Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. *Circulation* 1976;**54**:766–73.
67. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. *Am J Cardiol* 1989;**63**:461–4.
68. Chatterjee K, Ports TA, Brundage BH *et al.* Oral hydralazine in chronic heart failure: sustained beneficial hemodynamic effects. *Ann Intern Med* 1980;**92**:600–4.
69. Franciosa JA, Nordstrom LA, Cohn JN. Nitrate therapy for congestive heart failure. *JAMA* 1978;**240**:443–6.
70. Miller RR, Awan NA, Maxwell KS, Mason DT. Sustained reduction of cardiac impedance and preload in congestive heart failure with the antihypertensive vasodilator prazosin. *N Engl J Med* 1977;**297**:303–7.
71. Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. *Circulation* 1984;**70**:63–8.
72. Leier CV, Desch CE, Magorien RD *et al.* Positive inotropic effects of hydralazine in human subjects. Comparison with prazosin in the setting of congestive heart failure. *Am J Cardiol* 1980;**46**:1039–44.
73. Rouleau JL, Chatterjee K, Benge W, Parmley WW, Hiramatsu B. Alterations in left ventricular function and coronary hemodynamics with captopril, hydralazine, and prazosin in chronic ischemic heart failure, a comparative study. *Circulation* 1982;**65**:671–8.
74. Daly P, Rouleau JL, Cousineau D, Burgess JH, Chatterjee K. Effects of captopril and a combination of hydralazine and isosorbide dinitrate on myocardial sympathetic tone in patients with severe congestive heart failure. *Br Heart J* 1986; **56**:152–7.
75. Magorien RD, Unverferth DV, Brown GP, Leier CV. Dobutamine and hydralazine. Comparative influences of positive inotropy and vasodilation on coronary blood flow and myocardial energetics in nonischemic congestive heart failure. *J Am Coll Cardiol* 1983;**1**:499–505.
76. Massie B, Chatterjee K, Werner J *et al.* Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally in the vasodilator therapy of chronic heart failure. *Am J Cardiol* 1977;**40**:794–801.
77. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Provocation of myocardial ischemia events during initiation of vasodilator therapy for severe chronic heart failure. Clinical and hemodynamic evaluation of 52 consecutive patients with ischemic cardiomyopathy. *Am J Cardiol* 1981;**48**:939–46.
78. Cohn JN, Johnson G, Ziesche S *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**:303–10.
79. Elkayam U, Amin J, Mehra A *et al.* A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;**82**:1954–61.
80. Danish Study Group on Verapamil in Myocardial Infarction. Secondary prevention with verapamil after myocardial infarction. *Am J Cardiol* 1990;**66**:331–401.
81. Iida K, Matsuda M, Ajisaka R *et al.* Effects of nifedipine on left ventricular systolic and diastolic function in patients with ischemic heart disease. *Japan Heart J* 1987;**28**:495–506.
82. Barjon JN, Rouleau JL, Bichet D, Juneau C, De Champlain J. Chronic renal and neurohumoral effects of the calcium-entry blocker nisoldipine in patients with congestive heart failure. *J Am Coll Cardiol* 1987;**9**:622–30.
83. Gheorghiade M, Hall V, Goldberg D, Levine TB, Goldstein S. Long-term clinical and neurohormonal effects of nicardipine in patients with severe heart failure on maintenance therapy with angiotensin converting enzyme inhibitors. *J Am Coll Cardiol* 1991;**17**:274A.
84. Dunselman PHJM, Kuntze CEE, Van Bruggen A *et al.* Efficacy of felodipine in congestive heart failure. *Eur Heart J* 1989;**10**: 354–64.
85. Cohn JN, Archibald DG, Ziesche S *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;**314**:1547–52.
86. Cohn JN, Ziesche SM, Smith R *et al.* Effect of the calcium antagonist felodipine has supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. *Circulation* 1997;**96**:856–63.
87. Packer M, O'Connor CM, Ghali JK *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;**335**:1107–14.
88. Thackray S, Witte K, Clark AL, Cleland JG. Clinical trials update: OPTIME-CHF, PRAISE-2, ALL-HAT. *Eur J Heart Fail* 2000;**2**:209–12.
89. Packer M, Rouleau J, Swedberg K *et al.* Effect of flosequinan on survival in chronic heart failure. *Circulation* 1993;**88**:301.

90.McKenna WJ, Swedberg K, Zannad F *et al.* Experience of chronic intravenous epoprostenol infusion in end-stage cardiac failure:results of FIRST. *Eur Heart J* 1994;**15**:I-36.
91.Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation* 1984;**70**:271–8.
92.DiCarlo L, Chatterjee K, Parmley WW *et al.* Enalapril A new angiotensin converting inhibitor in chronic heart failure:acute and chronic hemodynamic evaluations. *J Am Coll Cardiol* 1983;**2**:865–71.
93.Packer M, Medina N, Yushak M, Lee WH. Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure. Experience in 100 consecutive patients. *Br Heart J* 1985;**54**:298–304.
94.The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;**316**:1429–35.
95.Sharpe N, Murphy J, Heather S, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1988;**i**:255–9.
96.Pfeffer JM, Pfeffer MA. Angiotensin converting enzyme inhibition and ventricular remodeling in heart failure. *Am J Med* 1988;**84**:37–44.
97.Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* 1990;**82**: 1730–6.
98.Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 1992;**20**:248–54.
99.The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685–91.
100.Rogers WJ, Johnstone DE, Yusuf S *et al.* Quality of life among 5025 patients with left ventricular dysfunction randomized between placebo and enalapril: the studies of left ventricular dysfunction. *J Am Coll Cardiol* 1994;**23**:393–400.
101.Pfeffer MA, Braunwald E, Moyé LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;**327**:669–77.
102.Kober L, Torp-Pedersen C, Carlsen JE *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**:1670–6.
103.The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–8.
104.Packer M, Poole-Wilson PA, Armstrong PW *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999; **100**:2312–18.
105.Flather MD, Yusuf S, Kober L *et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–81.
106.Narang R, Swedberg K, Cleland JG. What is the ideal study design for evaluation of treatment for heart failure? Insights from trials assessing the effect of ACE inhibitors on exercise capacity. *Eur Heart J* 1996;**17**:120–34.
107.Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;**273**: 1450–6.
108.Yusuf S, Pepine CJ, Garces C *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;**340**:1173–8.
109.Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
110.Paul SD, Kuntz KM, Eagle KA, Weinstein MC. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. *Arch Intern Med* 1994;**154**:1143–9.
111.Tsevat J, Duke D, Goldman L *et al.* Cost effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol* 1995;**26**:914–19.
112.Martinez C, Ball SG. Cost effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction. *Br J Clin Pract* 1995;**78**(Suppl.): 26–32.
113.McMurray J, Davie A. The pharmacoeconomics of ACE inhibitors in chronic heart failure. *Pharmacoeconomics* 1996;**9**:188–97.
114.Dickstein K, Chang P, Willenheimer *et al.* Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. *J Am Coll Cardiol* 1995;**26**:438–45.
115.Pitt B, Segal R, Martinez FA *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of losartan in the elderly study, ELITE). *Lancet* 1997;**349**:747–52.
116.Pitt B, Poole-Wilson PA, Segal R *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;**355**:1582–7.
117.McKelvie RS, Yusuf S, Pericak D *et al.* Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;**100**:1056–64.
118.Feldman AM. Classification of positive inotropic agents. *J Am Coll Cardiol* 1993;**22**:1233–7.
119.Smith JH, Oriol A, Morch J *et al.* Hemodynamic studies in cardiogenic shock. Treatment with isoproterenol and metaraminol. *Circulation* 1967;**35**:1084–91.
120.Tuttle RR, Mills J. Dobutamine. Development of a new catecholamine to selectively increase cardiac contractility. *Circ Res* 1975;**36**:185–96.
121.Meyer SL, Curry GC, Donsky MS *et al.* Influence of dobutamine on hemodynamics and coronary blood flow in patients

with and without coronary artery disease. *Am J Cardiol* 1976;**38**:103–8.
122. Akhtar N, Midulic E, Cohn JN, Chaudry MH. Hemodynamic effect of dobutamine in patients with severe heart failure. *Am J Cardiol* 1975;**36**:202–5.
123. Leier CV, Webel J, Buch CA. The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. *Circulation* 1977;**56**:468–72.
124. Pozen RG, DiBianco R, Katz RJ *et al.* Myocardial metabolic and hemodynamic effects of dobutamine in heart failure complicating coronary artery disease. *Circulation* 1981;**63**: 1279–85.
125. Leier CV, Unverferth DV, Kates RE. The relationship between plasma dobutamine concentrations and cardiovascular responses in cardiac failure. *Am J Med* 1979;**66**:238–42.
126. Colucci WS, Denniss AR, Leatherman GF. Intracoronary infusion of dobutamine to patients with and without severe congestive heart failure. *J Clin Invest* 1988;**81**:1103–10.
127. Bristow MR, Port JD, Hershberger RE, Gilbert EM, Feldman AM. The β-adrenergic receptor-adenylate cyclase complex as a target for therapeutic intervention in heart failure. *Eur Heart J* 1989;**10**:45–54.
128. Unverferth DV, Blanford M, Kates RE, Leier VI. Tolerance to dobutamine after a 72-hour continuous infusion. *Am J Med* 1980;**69**:262–6.
129. Applefeld MM, Newman KA, Grove WR *et al.* Intermittent continuous outpatient dobutamine infusion in the management of congestive heart failure. *Am J Cardiol* 1983;**51**: 455–8.
130. Dies F, Krell MJ, Whitlow P *et al.* Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986;**74**:II-38–II-38.
131. Goldberg LI. Cardiovascular and renal actions of dopamine. Potential clinical application. *Pharmacol Rev* 1972;**241**: 1–29.
132. Goldberg LI, Volkman PH, Kohli JD. A comparison of the vascular dopamine receptor with other dopamine receptors. *Annu Rev Pharmacol Toxicol* 1978;**18**:57–79.
133. Rajfer SI, Goldberg LI. Dopamine in the treatment of heart failure. *Eur Heart J* 1982;**3**:103–6.
134. Lockhandwala MF, Barrett RJ. Cardiovascular dopamine receptors. Physiological pharmaceutical and therapeutic implications. *J Auton Pharmacol* 1982;**2**:189–215.
135. Caponetto S, Terrachini V, Canale C *et al.* Long-term treatment of congestive heart failure with oral ibopamine: effects of rhythm disorders and neurohormonal alterations. *Cardiology* 1990;**77**:43–8.
136. Itoh H, Taniguchi K, Tsajibayashi R, Koike A, Sato Y. Hemodynamic effects and pharmacokinetics of long-term therapy with ibopamine in patients with chronic heart failure. *Cardiology* 1992;**80**:356–60.
137. van Veldhuisen DJ, Man in't Veld AJ, Dunselman PHJM *et al.* Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). *J Am Coll Cardiol* 1993;**22**:1564–73.
138. Hampton JR, van Veldhuisen DJ, Kleber FX *et al.* Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997;**349**:971–7.
139. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;**336**:1–6.
140. Alousi AA, Farah AE, Lesher GY, Opalka CJJ. Cardiotonic activity of amrinone-WIN 40680 [5-amino-3,4′bipyridin-6(1H)-one]. *Circ Res* 1979;**45**:666–77.
141. Millard RW, Dube G, Grupp G *et al.* Direct vasodilator and positive inotropic actions of amrinone. *J Mol Cell Cardiol* 1980;**12**:647–52.
142. Firth B, Ratner AV, Grassman ED *et al.* Assessment of the inotropic and vasodilator effects of amrinone versus isoproterenol. *Am J Cardiol* 1984;**54**:1331–6.
143. Rettig GF, Schieffer HJ. Acute effects of intravenous milrinone in heart failure. *Eur Heart J* 1989;**10**:39–43.
144. Baim DS, McDowell AV, Cherniles J *et al.* Evaluation of a new bipyridine inotropic agent – milrinone – in patients with severe congestive heart failure. *N Engl J Med* 1983;**309**:748–56.
145. Klocke RK, Mager G, Kux A *et al.* Effects of a twenty-four hour milrinone infusion in patients with severe heart failure and cardiogenic shock as a function of the hemodynamic initial condition. *Am Heart J* 1991;**121**:1965–73.
146. Kinney EL, Ballard JO, Carlin B, Zelis R. Amrinone-mediated thrombocytopenia. *Scand J Haematol* 1983;**31**:376–80.
147. Cowley AJ, Stainer K, Fullwood L, Muller AF, Hampton JR. Effects of enoximone in patients with heart failure uncontrolled by captopril and diuretics. *Int J Cardiol* 1990;**28**: S45–S53.
148. Bristow MR, Renlund DG, Gilbert EM, O'Connell JB. Enoximone in severe heart failure: clinical results and effects on β-adrenergic receptors. *Int J Cardiol* 1990;**28**:S21.
149. Herrmann HC, Ruddy TD, Dec GW *et al.* Diastolic function in patients with severe heart failure: comparison of the effects of enoximone and nitroprusside. *Circulation* 1987; **75**:1214–21.
150. Gage J, Rutman H, Lucido D, LeJemtel TH. Additive effects of dobutamine and amrinone on myocardial contractility and ventricular performance in patients with severe heart failure. *Circulation* 1986;**74**:367–73.
151. Uretsky BF, Lawless CE, Verbalis JG *et al.* Combined therapy with dobutamine and amrinone in severe heart failure. *Chest* 1987;**92**:657–62.
152. Anderson JL. Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure. Results of a multicenter study in the United States. *Am Heart J* 1991; **121**:1956–64.
153. Packer M, Carver JR, Rodeheffer RJ *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;**325**:1468–75.
154. Uretsky BF, Jessup M, Konstam MA *et al.* Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. *Circulation* 1990;**82**:774–80.
155. DiBianco R, Shebetai R, Silverman BD *et al.* Oral amrinone for the treatment of chronic congestive heart failure. Results of a multicenter randomized double-blind and placebo-controlled withdrawal study. *J Am Coll Cardiol* 1984;**4**:855–66.
156. Hagemeijer F. Calcium sensitization with pimobendan. Pharmacology, haemodynamic improvement, and sudden death in patients with chronic congestive heart failure. *Eur Heart J* 1993;**14**:551–66.

157.Fujino K, Sperelakis N, Solaro RJ. Sensitization of dog and guinea pig heart myofilaments to calcium activation and the inotropic effect of pimobendan. Comparison with milrinone. *Circ Res* 1988;**63**:911–22.
158.Böhm M, Morano I, Pieske B *et al.* Contribution of cAMP-phosphodiesterase inhibition and sensitization of the conctractile proteins for calcium to the inotropic effects of pimobendan in the failing human heart. *Circ Res* 1991;**68**: 689–701.
159.Katz SD, Kubo SH, Jessup M *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of pimobendan, a new cardiotonic and vasodilator agent, in patients with severe congestive heart failure. *Am Heart J* 1992;**123**: 95–103.
160.Kubo SH, Gollub S, Bourge R *et al.* Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure. *Circulation* 1992;**85**:942–9.
161.Just H, Hjalmarson Å, Remme WJ *et al.* pimobendan in congestive heart failure. Results of the PICO trial. *Circulation* 1995;**92**:722.
162.Schwartz A, Wallick ET, Lee SW *et al.* Studies on the mechanism of action of 3,4-dihydro-6-4-(3,4-dimethoxybenzoyl)-1-piperazinyl-2(1H)-quinolinone (OPC-8212), a new positive inotropic drug. *Arzneimittelforschung* 1984;**34**:384–9.
163.Yamashita S, Hosokawa T, Kojima M *et al. In vitro* and *in vivo* studies of 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone on myocardial oxygen consumption in dogs with ischemic heart failure. *Japan Circ J* 1986;**50**:659–66.
164.Matsumori A, Shioi T, Yamada T, Matsui S, Sasayama S. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. *Circulation* 1994;**89**:955–8.
165.Feldman AM, Bristow MR, Parmley WW *et al.* Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993;**329**:149–55.
166.Otsuka America, PNC. Letter to VEST Investigators, 29 July 1996.
167.Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V *et al.* Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *J Am Coll Cardiol* 2000;**36**: 1903–12.
168.Slawsky MT, Colucci WS, Gottlieb SS *et al.* Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. *Circulation* 2000; **102**:2222–7.
169.Swedberg K, Waagstein F, Hjalmarson Å, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet* 1979;**i**:1375–6.
170.Waagstein F, Hjalmarson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975;**37**:1022–36.
171.Sloand EM, Thompson BT. Propranolol-induced pulmonary edema and shock in a patient with pheochromocytoma. *Arch Intern Med* 1984;**144**:173–4.
172.Greenblatt DJ, Koch-Weser J. Adverse reactions to propranolol in hospitalized patients. *Am Heart J* 1973;**86**: 478–84.
173.Herlitz J, Hjalmarson Å, Holmberg S *et al.* Development of congestive heart failure after treatment with metoprolol in acute myocardial infarction. *Br Heart J* 1984;**51**:539–44.
174.Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;**73**:503–10.
175.Olsson G, Rehnqvist N. Effect of metoprolol in postinfarction patients with increased heart size. *Eur Heart J* 1986;**7**: 468–74.
176.Gilbert EM, Anderson JL, Deitchman D *et al.* Long-term β-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo. *Am J Med* 1990;**88**: 223–9.
177.DasGupta P, Lahiri A. Can intravenous beta blockade predict long-term haemodynamic benefit in chronic congestive heart failure secondary to ischaemic heart disease? *Clin Invest* 1992;**70**:S98–S104.
178.Andersson B, Lomsky M, Waagstein F. The link between acute haemodynamic adrenergic beta-blockade and long-term effects in patients with heart failure. *Eur Heart J* 1993;**14**: 1375–85.
179.Haber HL, Simek CL, Gimple LW *et al.* Why do patients with congestive heart failure tolerate the initiation of beta-blocker therapy. *Circulation* 1993;**88**:1610–19.
180.Andersson B, Caidahl K, Di Lenarda A *et al.* Changes in early and late diastolic filling patterns induced by long-term adrenergic beta-blockade in patients with idiopathic dilated cardiomyopathy. *Circulation* 1996;**94**:673–82.
181.Woodley SL, Gilbert EM, Anderson JL *et al.* β-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation* 1991;**84**:2426–41.
182.Eichhorn EJ, Bedotto JB, Malloy CR *et al.* Effect of β-adrenergic blockade on myocardial function and energetics in congestive heart failure. *Circulation* 1990;**82**:473–83.
183.Bristow MR, O'Connell JB, Gilbert EM *et al.* Dose-response of chronic β-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. *Circulation* 1994;**89**:1632–42.
184.Eichhorn EJ, Heesch CM, Risser RC, Marcoux L, Hatfield B. Predictors of systolic and diastolic improvement in patients with dilated cardiomyopathy treated with metoprolol. *J Am Coll Cardiol* 1995;**25**:154–62.
185.Metra M, Nardi M, Giubbini R, Cas LC. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic vaiables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1995;**24**:1678–87.
186.Hall SA, Cigarroa CG, Marcoux L *et al.* Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol* 1995;**25**:1154–61.
187.Australia-New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator-β-blocker, in patients with congestive heart failure due to ischemic heart disease. *Circulation* 1995;**92**:212–18.
188.Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the

treatment of chronic heart failure. *J Am Coll Cardiol* 2000; **36**:2072–80.
189. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation* 2000;**101**:378–84.
190. Newton GE, Parker JD. Acute effects of β_1-selective and nonselective β-adrenergic receptor blockade on cardiac sympathetic activity in congestive heart failure. *Circulation* 1996;**94**:353–8.
191. Andersson B, Blomström-Lundqvist C, Hedner T, Waagstein F. Exercise hemodynamics and myocardial metabolism during long-term beta-adrenergic blockade in severe heart failure. *J Am Coll Cardiol* 1991;**18**:1059–66.
192. Nemanich JW, Veith RC, Abrass IB, Stratton JR. Effects of metoprolol on rest and exercise cardiac function and plasma catecholamines in chronic congestive heart failure secondary to ischemic or idiopathic cardiomyopathy. *Am J Cardiol* 1990;**66**:843–8.
193. Eichhorn EJ, McGhie AI, Bedotto JB *et al.* Effects of bucindolol on neurohormonal activation in congestive heart failure. *Am J Cardiol* 1991;**67**:67–73.
194. Andersson B, Hamm C, Persson S *et al.* Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol* 1994;**23**: 1397–404.
195. Yoshikawa T, Handa S, Anzai T *et al.* Early reduction of neurohumoral factors plays a key role in mediating the efficacy of beta-blocker therapy for congestive heart failure. *Am Heart J* 1996;**131**:329–36.
196. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
197. The MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–7.
198. Packer M, Coats AJ, Fowler MB *et al.* Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344**:1651–8.
199. Waagstein F, Bristow MR, Swedberg K *et al.* Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;**342**:1441–6.
200. Colucci WS, Packer M, Bristow MR *et al.* Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation* 1996;**94**:2800–6.
201. Packer M, Colucci WS, Sackner-Bernstein JD *et al.* Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. *Circulation* 1996;**94**:2793–9.
202. Hjalmarson A, Goldstein S, Fagerberg B *et al.* Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure:the Metoprolol CR/XL. Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000; **283**:1295–302.
203. Andersson B, for the MDC Study Group. 3-year follow-up of patients randomised in the Metoprolol in Dilated Cardiomyopathy trial. *Lancet* 1998;**351**:1180–1.
204. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;**90**:1765–73.
205. Packer M, Bristow MR, Cohn JN *et al.* The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;**334**:1349–55.
206. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;**349**:375–80.
207. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;**344**: 1659–67.
208. Goldstein S, Fagerberg B, Hjalmarson Å *et al.* Metoprolol controlled release/extended release in patients with severe heart failure: Analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol* 2001;**38**:932–8.
209. Doughty RN, MacMahon S, Sharpe N. Beta-blockers in heart failure:promising or proved? *J Am Coll Cardiol* 1994;**23**: 814–21.
210. Maack C, Elter T, Nickenig G *et al.* Prospective crossover comparison of carvedilol and metoprolol in patients with chronic heart failure. *J Am Coll Cardiol* 2001;**38**:939–46.
211. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
212. Manolis AJ, Olympios C, Sifaki M *et al.* Suppressing sympathetic activation in congestive heart failure. A new therapeutic strategy. *Hypertension* 1995;**26**: 719–24.
213. Swedberg K, Bergh CH, Dickstein K, McNay J, Steinberg M. The effects of moxonidine, a novel imidazoline, on plasma norepinephrine in patients with congestive heart failure. Moxonidine Investigators. *J Am Coll Cardiol* 2000;**35**: 398–404.
214. Swedberg K, Bristow MR, Cohn JN *et al.* The effects of moxonidine SR, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002 (in press).
215. Jones CG, Cleland JGF. Meeting report – the LIDO, HOPE, MOXCON and WASH studies. *Eur J Heart Fail* 1999;**1**: 425–31.
216. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham study. *Am Heart J* 1988;**115**: 869–75.
217. Kjekshus J. Arrhythmias and mortality in congestive heart failure. *Am J Cardiol* 1990;**64**:42I–48I.
218. Andersson B, Waagstein F. Spectrum and outcome of congestive heart failure in a hospitalized population. *Am Heart J* 1993;**126**:632–40.
219. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;**72**: 681–5.
220. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation* 1993;**88**:2593–61.
221. Bigger TJJ, Fleiss JL, Kleiger R *et al.* The relationship between ventricular arrhythmias, left ventricular dysfunction and mortality in the two years after myocardial infarction. *Circulation* 1984;**69**:250–8.

222.Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report. Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406–10.
223.Doval HC, Nul DR, Grancelli HO *et al.* Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;**344**:493–8.
224.Singh SN, Fletcher RD, Fisher SG *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;**333**:77–82.
225.Julian DG. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;**349**:667–74.
226.Cairns JA. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. *Lancet* 1997;**349**:675–82.
227.Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. *Lancet* 1997; **350**:1417–24.
228.Connolly SJ. Meta-analysis of antiarrhythmic drug trials. *Am J Cardiol* 1999;**84**:90R–3R.
229.Waldo AL, Camm AJ, deRuyter H *et al.* Effect of D-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348**: 7–12.
230.Pahor M, Gambassi G, Carbonin P. Antiarrhythmic effects of ACE inhibitors. A matter of faith or reality? *Cardiovasc Res* 1994;**28**:7–12.
231.Newman TJ, Maskin CS, Dennick LG *et al.* Effects of captopril on survival in patients with heart failure. *Am J Med* 1988;**84**:140–4.
232.The SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
233.McCarthy PM, Smedira NO, Vargo RL *et al.* One hundred patients with the HeartMate left ventricular assist device: evolving concepts and technology. *J Thorac Cardiovasc Surg* 1998;**115**:904–12.
234.Louis AA, Manousos IR, Coletta AP, Clark AL, Cleland JG. Clinical trials update: The Heart Protection Study, IONA, CARISA, ENRICHD, ACUTE, ALIVE, MADIT II and REMATCH. *Eur J Heart Fail* 2002;**4**:111–16.
235.Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**: 1527–60.
236.Iskandrian AS, Mintz GS. Pacemaker therapy in congestive heart failure: a new concept based on excessive utilization of the Frank-Starling mechanism. *Am Heart J* 1986;**112**: 867–70.
237.Auricchio A, Stellbrink C, Block M *et al.* Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 1999;**99**:2993–3001.
238.Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–40.
239.Cazeau S, Leclercq C, Lavergne T *et al.* Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**: 873–80.

47 Acute myocarditis and dilated cardiomyopathy

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Definition of myocarditis

"Myocarditis is an inflammatory disease of the myocardium which is diagnosed by established histological, immunological and immunochemical criteria." It is an inflammatory cardiomyopathy associated with cardiac dysfunction.[1] There are a variety of etiologic causes of myocarditis and the exact pathophysiologic mechanism remains to be elucidated.

Immunopathogenesis of myocarditis

A broad spectrum of infectious and non-infectious agents have been associated with myocarditis (Boxes 47.1–47.3). The application of virologic, serologic, and, most recently, molecular biologic methods has substantiated epidemiologic observations of an infectious cause in many cases. While there are limited clinical data, there has been significant animal research into the etiology and pathophysiology of myocarditis. Coxsackie A and B viruses have been the most frequently implicated infectious agents in myocarditis. However, serologic studies suggestive of recent infection with Coxsackie virus are found in only about 40% of cases.[2] Similarly, it is uncommon to recover virus in culture from myocardial tissue obtained during or after acute myocarditis despite serologic evidence suggestive of viral infection.[3,4] Molecular genetic methods have continued to provide evidence for antecedent viral infection in some cases of myocarditis. Bowles *et al*[6] using Northern hybridization identified Coxsackie B-specific RNA in nucleic acid extracts of myocardial tissue from nine of 17 patients with histologically proven myocarditis or inflammatory cardiomyopathy.

The use of the polymerase chain reaction (PCR) has produced variable results. Although some studies have found Coxsackie B or other enteroviral sequences in myocardial tissue from cases of cardiomyopathy or myocarditis by PCR,[7] others have failed to find any evidence of persistent Coxsackie B RNA in similar specimens[8] or have found a high frequency of enteroviral RNA in control specimens.[9] In a comparison of 34 children with myocarditis and 17 controls with congenital heart disease, 68% of 38 myocardial specimens had viral genome detected with PCR. There was a predominance of adenovirus when compared with adults.

Box 47.1 Common etiologies of myocarditis

Infectious
- Adenovirus
- Coxsackie virus
- Cytomegalovirus
- Epstein–Barr virus
- HIV-1
- Borrelia (Lyme's disease)
- Toxoplasmosis

Drug induced
- Amphetamines
- Anthracyclines (especially doxorubicin)
- Catecholamines
- Cocaine
- Cyclophosphamide
- Interleukin 2

Systemic diseases
- Crohn's disease
- Kawasaki disease
- Sarcoidosis
- Systemic lupus erythematosus
- Ulcerative colitis
- Cardiac rejection
- Giant cell myocarditis
- Peripartum myocarditis

Hypersensitivity
- Hydrochlorothiazide
- Methyldopa
- Penicillins
- Sulfadiazine
- Sulfamethoxazole

All control specimens and blood specimens were negative.[10] In a group of 40 postorthotopic heart transplant patients, 32% (41 samples) of 129 specimens obtained as a routine surveillance screen to rule out rejection had viral amplification with PCR. Of these, 16 were positive for CMV, 14 for adenovirus, six for enterovirus, three for parvovirus, and two for herpes simplex. In 13 of 21 patients with positive PCR, histologic scores also were consistent with moderate to severe rejection.[11] Matsumori[12] compared 36 patients with heart muscle disease and 40 consecutive patients who underwent cardiac catheterization. In six patients (16·7%)

Box 47.2 Uncommon infectious etiologies of myocarditis

Viral
- Arbovirus (dengue fever, yellow fever)
- Arenavirus (Lassa fever)
- Coronavirus
- Echovirus
- Encephalomyocarditis virus
- Hepatitis B
- Herpes virus
- Influenza virus
- Junin virus
- Mumps virus
- Poliomyelitis virus
- Rabies
- Respiratory syncytial virus
- Rubella virus
- Rubeola virus
- Vaccinia virus
- Varicella virus
- Variola virus

Bacterial
- Brucellosis
- *Campylobacter jejuni*
- *Chlamydia trachomatis*
- Clostridia
- Diphtheria
- Franciscella (Tularemia)
- Gonococcus
- Hemophilus
- Legionella
- Listeria
- Meningococcus
- *Mycobacteria* (*tuberculosis, avium-intercellulare, leprae*)
- Mycoplasma
- Pneumococcus
- Psittacosis
- Salmonella
- Staphylococcus
- Streptococcus
- *Tropheryma whippelii* (Whipple's disease)

Fungal
- Aspergillus
- Actinomycetes
- Blastomyces
- Candida
- Coccidioides
- Cryptococcus
- *Fusarium oxysporum*
- Histoplasma
- Mucormycosis
- Norcardia
- Sporothrix

Rickettsial
- *Rickettsia rickettsii* (Rocky Mountain spotted fever)
- *Coxiella burnetii* (Q fever)
- Scrub typhus
- Typhus

Spirochetal
- Leptospira
- Syphilis

Helminthic
- Cysticercus
- Echinococcus
- Schistosoma
- Toxocara (visceral larva migrans)
- Trichinella

Protozoal
- Entamoeba
- Leishmania

with dilated cardiomyopathy versus one patient (2·5%) with ischemic heart disease, hepatitis C was detected. Of these six patients, three had hepatitis C RNA identified on endomyocardial biopsy by the competitive nested PCR technique. The initial presentation in two patients was 'flu-like syndrome followed by heart failure (endomyocardial biopsy positive for myocarditis in one patient). The third patient presented with chronic heart failure. Thus, the accumulating evidence strongly implicates an antecedent or perhaps persistent or latent viral infection in the pathogenesis of myocarditis. However, the inability to convincingly establish one or a few etiologic agents in all cases suggests that other factors, such as immunologic and/or genetic, are contributory.

The difficulty in recovering infectious agents or even evidence of an ongoing infection in cases of lymphocytic myocarditis has prompted the speculation that this is at least partly autoimmune in etiology. Perhaps the best evidence for an autoimmune component in the progression of the disease comes from murine models of Coxsackie B3-induced myocarditis in susceptible animal strains. This experimental disease shows histologic resemblance to human disease[13–19] and has been useful in examining the immunologic and genetic elements of myocarditis. Original studies of this model showed a biphasic illness in which early (5–7 days postinfection) viral myocyte damage was supplanted later (9–45 days) by mononuclear interstitial infiltration and chronic inflammation.[19,20] During the early phase, infectious virus was readily recovered from the myocardium; during the postinfectious phase, infectious virus was not recoverable. It is noteworthy that genetic factors dictated the susceptibility to the development of the late phase disease[19,20] as well as the susceptibility to the initial viral infection. This animal model closely resembles the currently held model for clinical disease in humans.

The nature of the antigen(s) that initiate and perpetuate the immune response in myocarditis is not known with certainty. The hypothesis of molecular mimicry is frequently invoked to explain the occurrence of autoimmune disease following an infection. Within the framework of this hypothesis, an immune response to a dominant epitope

Box 47.3 Uncommon non-infectious causes of myocarditis

Drug-induced

Toxic myocarditis

- Amphetamines
- Arsenic
- Chloroquine
- Ephedrine[5]
- Emetine
- 5-Fluorouracil
- Interferon α
- Lithium
- Paracetamol
- Thyroid hormone

Hypersensitivity myocarditis

- Acetazolamide
- Allopurinol
- Amphotericin B
- Carbamazepine
- Cephalothin
- Chlorthalidone
- Colchicine
- Diclofenac
- Diphenhydramine
- Furosemide
- Indomethacin
- Isoniazid
- Lidocaine
- Methysergide
- Oxphenbutazone
- Para-aminosalicylic acid
- Phenindione
- Phenylbutazone
- Phenytoin
- Procainamide
- Pyribenzamine
- Ranitidine
- Reserpine
- Spironolactone
- Streptomycin
- Tetracycline
- Trimethaprim

Toxins

- Arsenic
- Carbon monoxide
- Copper
- Iron
- Lead
- Mercury
- Phosphorus
- Scorpion stings
- Snake venom
- Spider bites
- Wasp stings

Systemic diseases

- Arteritis (giant cell, Takayasu)
- β thalassemia major
- Churg–Strauss vasculitis
- Cryoglobulinemia
- Dermatomyositis
- Diabetes mellitus
- Hashimoto's thyroiditis
- Mixed connective tissue disease
- Myasthenia gravis
- Periarteritis nodosa
- Pernicious anemia
- Pheochromocytoma
- Polymyositis
- Rheumatoid arthritis
- Scleroderma
- Sjögren's syndrome
- Thymoma
- Wegener's granulomatosis

Other

- Eosinophilic myocarditis
- Genetic
- Granulomatous myocarditis
- Head trauma
- Hypothermia
- Hyperpyrexia
- Ionizing radiation
- Mononuclear myocarditis

expressed by an infectious agent could induce disease following infection. In the event that a similar or cross-reacting epitope is also present on host cells, tissue damage might result.[21] Coxsackie B3 antibodies that cross-react with myosin have been described.[22] In addition, antibodies against myosin are frequently found in experimental myocarditis.[23,24] An alternative hypothesis is that immune reactivity to self antigens results from the aberrant expression of normally sequestered epitopes or upregulation of epitopes normally expressed at a density that favors tolerance.[25] Thus, an autoimmune component of disease pathology appears to be involved in the experimental model of the disease and, in all likelihood, is etiologic in clinical disease as well. However, the same etiologic pathway may not be followed in all cases of myocarditis. This may explain the failure to identify a consistent underlying immunopathologic picture in most cases of clinical myocarditis.

It appears, therefore, that the etiology of myocarditis is heterogeneous; likewise, a variety of immune effector mechanisms have been identified in myocarditis, further underscoring the heterogeneity of the disease. The earliest potential effector mechanism to be described in myocarditis was the production of autoantibodies to normal cellular antigens. A broad variety of tissue antigens have been identified as targets for autoantibodies. Among these are the β adrenergic receptor,[26] the adenine nucleotide translocator,[27] laminin,[28] branched chain ketoacid dehydrogenase,[29] heat shock protein-60 (HSP-60),[30] and sarcolemmal

epitopes.[31] Although antibodies to these antigens are frequently identified in association with myocarditis, their significance is not known. They may function in the pathogenesis of the disease or they may be epiphenomena arising in conjunction with the principal pathogenic process. Perhaps these antibodies do not initiate myocyte damage/dysfunction, but contribute to pathology at later stages of the disease.

Dilated cardiomyopathy: background and pathogenesis

Idiopathic dilated cardiomyopathy (IDC) is characterized by dilation and impaired contraction of the left ventricle or both ventricles.[1] Dilated cardiomyopathy has been postulated to occur in some cases as a result of recognized or unrecognized myocarditis. Dec and colleagues[13–19] reported that endomyocardial biopsy examination revealed myocarditis in 66% of patients with acute dilated cardiomyopathy (of <6 months duration). In the Myocarditis Treatment Trial, only 10% of those screened with heart failure of less than 2 years duration had biopsy-proven myocarditis.[32] Nonetheless, in a substantial number of cases of IDC no identifiable etiologic process can be ascribed. Viral infections have been frequently implicated in IDC, as in myocarditis. Several serologic studies have found increased prevalence or levels of antibodies to Coxsackie B in cases of IDC.[33–36] Recent investigations have used the very sensitive PCR to search for persistent enteroviral RNA in IDC cases with equivocal results. Among the various studies, a wide percentage range of IDC cases with demonstrable enteroviral RNA has been reported (0–32%); in comparison, 0–38% of biopsies from non-IDC cases also have been reported positive for enteroviral RNA.[7,37] Thus, the finding of persistent virus or viral RNA in IDC does not appear to be specific for the disease, although the overall consensus continues to favor an inciting infection in many cases.

A great deal of evidence is suggestive of autoimmune or autoimmune-like mechanisms in the pathogenesis of IDC. A spectrum of autoantibodies against similar cellular components as were identified for acute myocarditis has been found among cases of IDC. The principal cellular components reactive with antiheart antibodies associated with IDC are the adenine nucleotide translocator,[37] β adrenoceptors,[26] myosin,[38] laminin,[28] actin, tropomyosin, and heat shock protein-60 (HSP-60).[30] However, antibodies reactive with tissue antigens are often present in the circulation of asymptomatic individuals.[39] Thus, the source and significance of these antibodies relative to the pathology of IDC remain a mystery.

One of the most frequently examined aspects of IDC is the proposed linkage between disease frequency and the genes of the major histocompatibility complex (MHC). Such evidence would strengthen the argument for an immunologic component in IDC and establish a genetic component as well. The most frequently described linkage between IDC and MHC genes in Caucasian populations has been with class II alleles. Four of five independent studies identified a positive association of IDC with HLA DR4.[40] An association between HLA DR4 and anti-β receptor antibodies also has been noted.[24] Linkage with other class II alleles has been described in other ethnic groups,[41] underscoring possible ethnic differences. These studies strongly implicate genetically controlled immunologic factors with possible immune reactivity to tissue antigens in the pathogenesis of IDC. The specific predisposing HLA-related locus/loci, however, may depend on the genetic background (ethnicity) as well as the specific vector (viral strain) involved. Conflicting findings regarding the association of HLA DR4 with familial cardiomyopathy have been reported. One study observed an association of DR4 with familial disease,[42] whereas a separate study found no such association.[43]

Despite inconclusive findings implicating HLA DR4 or any HLA allele in IDC, the genetic contribution to familial disease is incontrovertible. The possibility exists that a proportion of sporadic cases may, indeed, represent familial disease of incomplete penetrance (that is, not all gene carriers exhibit the characteristic phenotype of the disease) and that disease expression may be modified by other factors either genetic or environmental. Consistent with this hypothesis, some overlap between familial and sporadic disease has been noted. A central role for dysfunctional cytoskeletal elements in the pathogenesis of dilated cardiomyopathy is emerging. Mutations in the genes for cardiac actin,[44] dystrophin,[45] desmin,[46] and lamin A/C[47] have been found to cosegregate with disease in affected families. A mutated *δ-sacroglycan* gene, the product of which associates with the dystrophin complex, has been identified in both familial and sporadic cases of dilated cardiomyopathy. Additionally, exon 8 C/T polymorphism of endothelin type A gene has been implicated in sporadic cases of dilated cardiomyopathy.[48] In aggregate, these observations have led to a proposed "common pathway" for the development of cardiomyopathy (both familial and sporadic) that involves cytoskeletal elements.[49] The association of *δ-sacroglycan* gene mutations with both sporadic and familial cases supports the notion of a degree of etiologic overlap between these diseases involving functional alterations in cytoskeletal elements. This notion is further supported by the finding that variations in the gene encoding the actin-binding region of the nebulette protein, a Z-disc protein is significantly increased in non-familial dilated cardiomyopathy.[50]

Cytoskeletal dysfunction in the pathogenesis of cardiomyopathy is not inconsistent with either immune-mediated or infectious etiologies. As stated above, IDC is frequently associated with antibodies to cytoskeletal elements – for example, laminin,[28] myosin,[38] actin, tropomyosin,[30] and

other sarcolemmal epitopes[31] – and immunization with cardiac myosin induces disease in animal models.[51,52] The cytoskeletal common pathway hypothesis also incorporates reported enteroviral associations with the disease. Enteroviral protease 2A was demonstrated to directly cleave dystrophin producing postinfectious cardiomyopathy in a mouse model.[53] Thus, the common pathway concept unifies much of the experimental, genetic and epidemiologic information surrounding myocarditis and cardiomyopathy further substantiating a relationship between these disease entities.

Epidemiology and natural history of myocarditis and IDC

The true incidence of myocarditis is unknown. In 12 747 autopsies performed in Sweden from 1975 to 1984, an incidence of 1·06% was found.[54] However, autopsies of children and young adults presenting with sudden death report an incidence as high as 17–21%.[2] In the Myocarditis Treatment Trial, 9·6% of 2333 patients with recent onset of heart failure (onset within 2 years of study enrollment) met pathologic criteria for myocarditis.[32] Of 3055 patients enrolled in the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) with suspected myocarditis, 526 (17·2%) had either histologic or immunologic evidence of acute or chronic myocarditis. However, only 74 patients met criteria for acute myocarditis.[55] There is both a seasonal variation and a male predominance. Of 136 patients with biopsy-proven myocarditis, 63% presented between December and April.[56] A 'flu-like illness within 3 months of presentation was reported by 57%.[56] Only 41% reported a similar illness within 1 month of presentation.[56] Blacks and males were noted to have a 2·5-fold increased risk.[56] Patients with acute myocarditis tend to present at a somewhat younger age (43 ± 16 years) when compared to patients with IDC (50 ± 17 years).[56]

Of the more than three million people in the United States with heart failure, 25% of cases are secondary to IDC.[57] From 1975 to 1984, Codd and colleagues[58] detected 45 cases of dilated cardiomyopathy based on echocardiography, angiography, endomyocardial biopsy, and autopsy results. The median age at the time of diagnosis was 54 years, although presentation may be in childhood, adulthood, or old age. Forty-one cases (91%) were diagnosed during life. Of these, 36 patients (88%) were symptomatic prior to diagnosis, with dyspnea being the most common symptom (75% were New York Heart Association [NYHA] functional class III–IV). Five patients (14%) had a syncopal event; 27 patients (75%) had clinical heart failure, and nine (25%) had angina. Five of the 41 patients (12%) were identified during a routine medical evaluation and were asymptomatic. Four cases (9%) were diagnosed at autopsy although all had been symptomatic. The overall age- and sex-adjusted incidence was noted to increase from 3·9/100 000 person-years in 1975–1979 to 7·9/100 000 person-years in 1980–1984. The age- and sex-adjusted prevalence was 36·5/100 000 population. The prevalence of dilated cardiomyopathy in patients less than 55 years old was 17·9/100 000. Within this group, over one third were NYHA functional class III or IV at the time of diagnosis. The annual incidence is 5–8 cases per 100 000.[57] More recently, Felker[59] *et al* reported 51% of 1278 patients referred for symptomatic heart failure were classified as idiopathic. A histologic diagnosis was made in 16% of patients (myocarditis, $n=117$; amyloidosis, $n=41$; doxorubicin toxicity, $n=16$; hemochromatosis, $n=9$; endomyocardial fibroelastosis, $n=1$, rheumatic carditis, $n=1$, thrombotic thrombocytopenic purpura, $n=1$; and interferon-induced cardiomyopathy $n=1$). Endomyocardial biopsy in IDC yielded non-specific findings, including myocyte hypertrophy or interstitial fibrosis.

A random echocardiographic survey of 1640 patients in North Glasgow, reported a prevalence of 2·9% left ventricular dysfunction (defined as ejection fraction [EF] $\leq 30\%$ with the Simpson's biplane rule method). Slightly less then half of the patients were asymptomatic, resulting in a population prevalence of 1·4%. There was no significant difference in mortality rate between symptomatic and asymptomatic patients.[60] The Rotterdam study reported a heart failure prevalence of 3·7% in patients 55–94 years. However, 5·5% men and 2·2% women (prevalence 2·5 times higher in men) were noted to have impaired left ventricular function fractional shortening (FS) $\leq 25\%$; 60% with impaired left ventricular function were asymptomatic (population prevalence 2·2%).[61] However, both studies included patients with multiple etiologies of heart failure.

Approximately 20–25% of dilated cardiomyopathy cases are classified as familial. If liberal criteria are used for the diagnosis (history of unexplained heart failure or depressed left ventricular function in a first-degree relative), up to 35% of cases may be inherited. Those with familial cardiomyopathy versus sporadic cases, are younger ($51{\cdot}21 \pm 12{\cdot}72$ *v* $54{\cdot}34 \pm 11{\cdot}98$; $P < 0{\cdot}03$). They more frequently have ST segment and T waves abnormalities on ECG. However, these are non-specific findings.[62] Twenty-nine per cent of asymptomatic relatives may have abnormalities on echocardiogram, including left ventricular enlargement (LVE) ($\geq 112\%$ predicted), depressed fractional shortening (dFS) ($\leq 25\%$), or frank dilated cardiomyopathy. When compared to normal relatives, those with LVE or dFS are more likely to have an abnormal exercise stress test, with a maximal oxygen consumption (V_{O_2} max) of $<80\%$. Relatives with an abnormal V_{O_2} max have a lower absolute V_{O_2} max (30 ± 8 *v* 43 ± 9 cc/kg/min) than normal relatives. The occurrence of LVE with a dFS is associated with QRS duration prolongation

on signal averaged ECG. At mean follow up of 39 months, 27% of those with LVE developed symptomatic dilated cardiomyopathy.[63]

An increased incidence of IDC is noted in blacks.[64,65] The cumulative survival in blacks at 12 and 24 months is 71·5% and 63·6% respectively, compared with 92% and 86·3% among whites. One year survival is adversely affected by an ejection fraction (EF) <25% or ventricular arrhythmias (<60% in both instances). Patients 60 years of age or greater had a threefold increased risk of death among both blacks and whites.[65]

Males have an increased incidence of IDC.[64,65] The male:female ratio is 3·4:1· The incidence rate for men is greater than for women within all age groups.[58] In a multicenter registry of IDC, DeMaria *et al*[66] enrolled 65 women and 238 men (male:female ratio 3·66). Patients referred for cardiac transplant were excluded. Of the various clinical characteristics evaluated, 10 variables were significantly different between men and women. Men more frequently had a history of ethanol abuse and cigarette smoking. However, subgroup analysis revealed no influence of these variables on gender-related differences. Symptoms of heart failure were more frequently detected in women and were indicative of more advanced heart failure (NYHA class III–IV in 48%). Left bundle branch block (LBBB) was detected more frequently in women, while left anterior hemiblock (LAHB) was noted to be more common in men. There was more pronounced left ventricular dilation in women, with a slightly but not significantly higher mean myocardial thickness. Exercise tolerance was poorer in women. The median survival was 16 months for women and 19 months for men. Seven women (11%) and 17 men (7%) underwent cardiac transplantation, while 16% of women and 11% of men died from cardiac causes.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as the development of heart failure in the last month of pregnancy or within 5 months of delivery, in the absence of an identifiable cause for cardiac failure and the absence of recognizable heart disease prior to the last month of pregnancy. Additionally, left ventricular dysfunction is demonstrable by echocardiographic criteria.[67] Risk factors include age over 30, African descent, obesity, multiparity, twin gestation (7–10%), pre-eclamsia and gestational hypertension.[68,69] The incidence varies from 1 in 15 000 to 1 in 100 live births.[70] PPCM is a distinct entity, rather then clinically silent cardiomyopathy, which becomes manifest owing to the hemodynamic stress of pregnancy. The incidence and natural history of the disease differs from IDC. Myocarditis has been reported in 8–76% of patients with PPCM.[68,71–73] The variability is likely due to sampling error and timing of endomyocardial biopsy, geographic variation in incidence and inclusion criteria for the diagnosis.

Other factors implicated in PPCM include abnormal immune responses to pregnancy, maladaptive responses to the stress of pregnancy, stress-activated cytokines (TNFα or interleukin-1), abnormalities of relaxin, selenium deficiency, and prolonged tocolytic therapy.[48,67] As there have been reports of familial PPCM,[74] strong consideration should be given to screening family members of patients with PPCM.

The safety of subsequent pregnancies must be carefully considered. Witlin[75] noted that of 28 patients with PPCM, five died (18% mortality), three (11%) had cardiac transplant, 18 (64%) had continued functional impairment, and two (7%) had regression of cardiomyopathy. Six women had subsequent pregnancies. Of these, four deteriorated clinically, one remained well compensated on therapy, and one had no recurrence. Elkayam[76] identified 44 women (23 white, 16 black, five Hispanic; aged 19–39 years) with PPCM who had subsequent pregnancies. Cardiomyopathy was diagnosed prior to delivery in seven women; in the first month post delivery in 28 women, and between 2 and 6 months post delivery in nine women. The mean time from index pregnancy and subsequent pregnancy was 27 ± 18 months. The mean EF increased significantly from 32 ± 11% to 49 ± 12% ($P< 0·001$) prior to the subsequent pregnancies. However, during the subsequent pregnancy mean EF decreased to 42 ± 13% ($P< 0·001$). Twenty-eight patients had normalization of EF (>50%) prior to the subsequent pregnancy, although 21% developed heart failure during the subsequent pregnancy. Of 16 women with persistent left ventricular dysfunction, 44% developed heart failure with the subsequent pregnancy. Three women died during or after subsequent pregnancies, all with residual left ventricular dysfunction. Premature delivery (<37 weeks gestation) occurred in 13% of those who normalized the EF versus 50% in those who did not.

Women who have recovered from PPCM have a lower contractile reserve upon dobutamine challenge when compared to normal controls, despite similar baseline ventricular size and function.[70] This may explain recurrent symptoms with subsequent pregnancies and may be helpful in determining which patients will tolerate future pregnancy. Women whose left ventricular size and function do not return to normal, should be strongly advised against subsequent pregnancies.[48,67]

Mortality varies from 7% to 50%, with almost half of the deaths secondary to heart failure, arrhythmias, or thromboembolic events.[68,77] Almost half of the deaths occur within the first 3 months post partum. Mortality secondary to thromboembolic events is as high as 30%. Approximately 50% of patients who regain normal cardiac function do so within 6 months of initial diagnosis. Non-survivors have greater hemodynamic compromise and LV dysfunction. LV stroke work index is significantly associated with adverse events (death or transplantation; $P= 0·02$).[73]

ACE inhibitors are the mainstay of treatment post partum. They are contraindicated during pregnancy due to

teratogenicity. Hydralazine and nitrates are safe alternatives during pregnancy.[67] In patients with an EF < 35%, the use of heparin during pregnancy and warfarin post partum should be considered. While the use of β blockers is not contraindicated during pregnancy, there are no data evaluating their use during pregnancy. Use of a β blocker should be considered in patients with persistent symptoms and echocardiographic evidence of left ventricular dysfunction more than 2 weeks post partum.[67] In addition, cautious use of diuretics may be necessary when sodium and fluid restriction fails. Exercise may help improve symptoms.

Midei[71] reported on the use of immunosuppressants in 18 women with PPCM. Fourteen (78%) had biopsy evidence of myocarditis. Ten patients were treated with prednisone/azathioprine and four were untreated. One patient died, despite treatment. Four patients with myocarditis improved clinically without therapy. Follow up biopsy showed near complete resolution in two. Four patients without myocarditis were not treated. Two improved and two required transplantation. After completion of treatment, biopsy, left ventricular stroke work index, and pulmonary capillary wedge pressure returned to normal in 12 (not repeated in two patients).

Bozkurt compared the use of immune globulin, 1 g/kg on 2 consecutive days in six women (NYHA II–IV; EF < 40%) with a retrospective control group of 11 patients with PPCM. Only one of 11 biopsied, had evidence of myocarditis. Four control patients had an improvement of >10% in EF, although only two were left an EF >50%; four died or had residual severe left ventricular dysfunction. Within the treatment group, all had a significantly greater improvement in EF than with conventional therapy alone($P < 0{\cdot}042$); three normalized their EF.[78]

Clinical presentations

Myocarditis

The presenting symptoms and physical examination are often non-specific in both myocarditis and IDC. A history of a 'flu-like syndrome may be present in up to 90% of patients with myocarditis, although only approximately 40% report a viral syndrome within the prior month.[2] The initial presentation may be one of acute or chronic heart failure or cardiogenic shock, or may mimic an acute myocardial infarction.[79,80] Of the 3055 patients in the ESETCID study, 69% had a normal or mildly reduced EF (>45%). Dyspnea was present in 71·7%. While 31·9% had chest pain and 17·9% had arrhythmic events, 78·3% of those with an EF > 45% and 100% of those with an EF <45% had subjective clinical symptoms.[81]

The Dallas Criteria[82] (Box 47.4) were developed in order to standardize the histologic criteria for diagnosis of myocarditis (Figure 47.1), facilitating a multicenter treatment study. However, a negative biopsy does not rule out myocarditis owing to interobserver variability, sampling error, and the temporal evolution (transient presence) of pathologic features.

Box 47.4 Dallas criteria classification of myocarditis[82]

Initial biopsy

- *Myocarditis*: myocyte necrosis, degeneration or both in the absence of significant CAD with adjacent inflammatory infiltrate +/− fibrosis
- *Borderline myocarditis*: inflammatory infiltrate too sparse or myocyte damage not apparent
- *No myocarditis*

Subsequent biopsy

- Ongoing (persistent) myocarditis +/− fibrosis
- Resolving (healing) myocarditis +/− fibrosis
- Resolved (healed) myocarditis +/− fibrosis

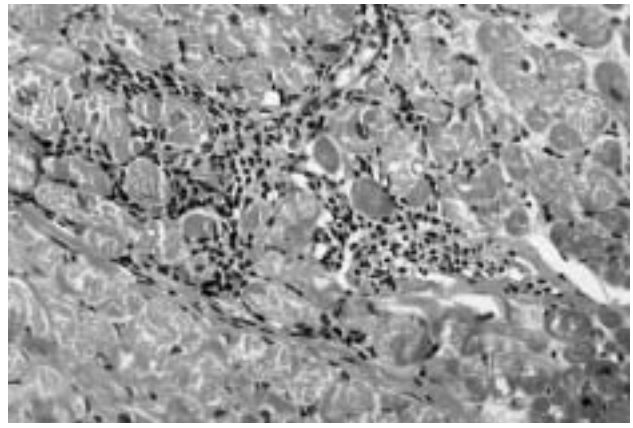


Figure 47.1 Acute myocarditis. Lymphocytic infiltrate of the myocardium with associated myocyte damage. (Hematoxylin & eosin; slide courtesy of Robert Yowell MD.)

Lieberman *et al*[83] proposed a clinicopathologic description of myocarditis, based on the initial manifestations, endomyocardial biopsy, and recovery (fulminant, acute, chronic active, or chronic persistent myocarditis). Patients with fulminant myocarditis had severe hemodynamic compromise, requiring vasopressors or left ventricular assist device. In addition, distinct onsets of symptoms that could be dated – fever, or viral illness within 2 weeks of hospitalization – were present (two of three criteria required). Patients were younger (aged 35 ± 16 *v* 43 ± 13; $P = 0{\cdot}05$), had higher resting heart rates (100 ± 20 *v* 88 ± 21; $P = 0{\cdot}04$), and higher right atrial pressures ($9{\cdot}9 \pm 8$ mmHg *v* $6{\cdot}2 \pm 5$ mmHg; $P = 0{\cdot}02$), but lower mean arterial pressures (80 ± 18 mmHg *v* 92 ± 16 mmHg; $P = 0{\cdot}005$). Patients with acute myocarditis had an indistinct onset of symptoms, were hemodynamically stable or required low doses of vasopressors and were afebrile. Of 147 patients fulfilling Dallas Criteria, 15 met clinical criteria for fulminant myocarditis and 132 met criteria for acute myocarditis.

At 1 year, 93% with fulminant myocarditis survived without transplant compared to 85% with acute myocarditis. At 11 years, 93% with fulminant myocarditis survived without transplant, while 45% with acute myocarditis were alive without transplant.[84]

IDC

IDC is initially manifest by heart failure in 75–85% of patients. Ninety per cent of patients referred to a tertiary care center are NYHA functional class III–IV at presentation.[64,65] Other potential manifestations include asymptomatic cardiomegaly or left ventricular dysfunction on routine evaluation, arrhythmias or even cardiogenic shock, as in myocarditis. Patients with left bundle branch block (LBBB) have been noted to have a greater left ventricular diastolic dimension normalized for body surface area. The presence of LBBB on ECG may precede the development of cardiomyopathy in 40% of patients. LBBB may be noted on ECG for years prior to the onset of heart failure. At rest and when exercised, these patients may have a higher mean pulmonary artery pressure, although left ventricular end-diastolic volume remains normal, by comparison with normal patients.[85] Laboratory, *x* ray, and other diagnostic tests are helpful but may be equally non-specific, while myocyte hypertrophy, degeneration of myocytes, interstitial fibrosis, and small clusters of lymphocytes (>5 per high power field) have been noted histologically (Figure 47.2).[64,65]

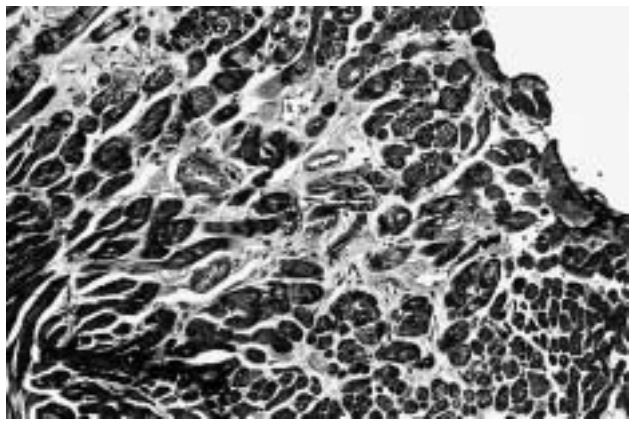


Figure 47.2 Idiopathic dilated cardiomyopathy. Myocyte hypertrophy with mild nuclear enlargement and increased interstitial collagen. (Trichrome stain; slide courtesy of Robert Yowell MD.)

Prognosis

Myocarditis

In patients with myocarditis, ECG abnormalities associated with a longer duration of illness (>1 month) include left ventricular hypertrophy (LVH), left atrial enlargement (LAE), LBBB, and atrial fibrillation (AF). The presence of an abnormal QRS complex on ECG correlates with severity of left ventricular damage and is an independent predictor of survival. LAE, AF, and LBBB also are associated with an increased mortality.[86] Higher baseline left ventricular ejection fraction (LVEF) is positively associated with survival, while intensity of conventional therapy at baseline is negatively associated with survival.[32] The presence of right ventricular (RV) dysfunction, as evidenced by abnormal RV descent on echocardiogram, was shown to be the most important predictor of death or need for cardiac transplantation in a group of 23 patients with biopsy-proven myocarditis who were followed long term.[87] In addition, a net increase in LVEF (between initial and final EF) was associated with improved survival, whereas baseline EF was not predictive of outcome. The presence and degree of left ventricular regional wall motion abnormalities did not predict the clinical course.[87]

Light microscopic findings on biopsy have not been shown to predict outcome in myocarditis. Less than 10% of biopsies repeated at 28 weeks and 52 weeks continue to show evidence of ongoing or recurrent myocarditis, regardless of therapy. However, higher baseline serum antibodies to cardiac immune globulin (Ig) G by indirect immunofluoresence were associated with a better LVEF and a smaller left ventricular end-diastolic dimension.[32] Gagliardi *et al*[88] followed 20 children with biopsy-proven myocarditis who were treated with cyclosporine and steroids and found that 13 of 20 had persistent myocarditis at 6 months. At 1 year, 10 patients had persistent myocarditis by endomyocardial biopsy, although ventricular size and function had improved on echocardiography. Echocardiography was unable to detect those patients with biopsy-persistent versus biopsy-resolved myocarditis. Despite histologic evidence of myocarditis, no patient died or required transplantation.

IDC

Spontaneous improvement in LVEF (over 10% points) occurs in 20–45% of patients with IDC. Improvement usually occurs within the first 6 months of presentation, but may occur up to 4 years later. Outcome is adversely affected by progressive LV enlargement, RV enlargement, and markedly reduced LVEF. Both LVEF and RV enlargement are independent predictors of survival. Mortality rates of 25–30% at 1 year are noted. Overall, the annual mortality from disease progression is 4–10% but is greater in high-risk subgroups. Twelve per cent of patients with IDC die suddenly, which accounts for 28% of all deaths.[64,65] In a retrospective study of 104 patients with dilated cardiomyopathy, Fuster *et al*[89] noted 77% of patients died. Two thirds of the deaths occurred within the first 2 years. Interestingly, the survival curve for the remaining patients was comparable to

an age- and sex-matched control group. The 1 and 5 year mortality rates were 31% and 64%, respectively. Factors significantly associated with poorer survival were older age (97% mortality rate in patients ≥55 years), cardiothoracic ratio (86% mortality rate if the ratio was >0·55 *v* 40% if <0·55), cardiac index (CI) (mortality rate 89% if CI <3·0 l/min *v* 35% if CI > 3·0 l/min) and LV end-diastolic pressure (mortality rate 87% if ≥20 mmHg). Referral bias and secular trends, new treatment modalities, and the prevalence of disease in the referral population should also be noted, as these may influence overall survival.[90]

By comparison, when one assesses the natural history of asymptomatic IDC, patients have an excellent prognosis, with a 2 year survival of 100%, a 5 year survival of 78 ± 8%, and a 7 year survival of 53 ± 10%. However, there is no improvement in survival in these patients when compared to asymptomatic patients who have previously had symptoms of heart failure. The most common reason for cardiac evaluation in this group of patients is palpitations or an abnormal chest *x* ray or ECG. When compared to patients with a prior history of congestive heart failure symptoms, these patients had a lower prevalence of cardiomegaly in chest *x* rays (31% *v* 57% of patients) and a smaller LV and better EF (33% *v* 29% EF) on echocardiography.[91]

Patients with syncope, a third heart sound, RV dysfunction, hyponatremia, elevated plasma norepinephrine, atrial natriuretic peptide or renin, a maximal systemic oxygen uptake (V_{O_2}) of <10–12 ml/kg/min, CI of <2·5 l/min/m^2, systemic hypotension, pulmonary hypertension, increased central venous pressure, or loss of cardiac myofilaments on high resolution microscopy show increased progression of disease and worse survival.[64,65] Patients with an elevated C-reactive protein (CRP) level (>0·5 mg/dl) and an EF <40% have a poorer 5 year survival. Of those with a CRP level >1·0 mg/dl, 62% died within five years.[92] Persistently elevated levels of troponin T (>0·02 ng/dl) are associated with more cardiac events (hospitalization, arrhythmia) and poorer survival rate.[93] Elevated levels of brain natriuretic peptide are associated with a poor prognosis and may be a useful tool to aid in the diagnosis of heart failure.[94,95]

Myocardial contractile reserve, as evaluated by change in LVEF with exercise, is an independent predictor of survival in patients with mildly symptomatic (NYHA class I or II) dilated cardiomyopathy. A change in LVEF of >4% was associated with a 75% survival versus 25% in those whose EF changed <4% with exercise.[96] Patients with greater improvements in EF with dobutamine (0·09 ± 0·06 *v* 0·05 ± 0·05) had a better survival at 1 year (97% *v* 74%; $P = 0·02$), 2 years (97% *v* 64%; $P = 0·002$) and 3 years (97% *v* 56%; $P < 0·001$). These patients had a shorter duration of heart failure, better functional capacity, better LV and RV EF and smaller LV size. Survivors had a greater improvement in LV and RV EF.[97] Dobutamine-induced improvements in LVEF and LV sphericity are predictive of subsequent recovery in LV function.[98]

Coronary flow reserve is diminished in patients with dilated cardiomyopathy. Treasure *et al*[99] performed coronary angiography and Doppler flow studies of the left anterior descending (LAD) artery to estimate coronary artery flow velocities in seven normal controls and eight patients with dilated cardiomyopathy. The effect of acetylcholine and adenosine on epicardial vasoconstriction in patients with dilated cardiomyopathy was not significantly different from normal controls. However, infusion of intracoronary acetylcholine resulted in a dose-dependent increase in coronary blood flow in normal controls only, suggesting that endothelium-dependent coronary vasodilation is abnormal in dilated cardiomyopathy. There was a similar change in coronary blood flow with adenosine infusion in both groups. Impairment in both coronary microvascular response and epicardial vasodilator response to endothelial-dependant vasodilation with acetylcholine may occur early (<6 months) in the course of the disease.[100]

In infants and children the outcome of IDC is more variable. A retrospective review of 24 patients under 20 years old with IDC revealed that, in 92%, the initial manifestation was heart failure. Thirteen of the patients (54%) had onset of symptoms within 3 months of a viral syndrome although endomyocardial biopsy did not reveal active myocarditis in six. Sixty-three per cent had ECG evidence of LVH and 68% had ST-T wave abnormalities. The mean EF was 26% (5–51%). Fifteen patients died (63%). The cumulative survival was 63% at 1 year, 50% at 2 years, and 34% at 5 years of follow up. Death was most frequently due to progressive heart failure. Of the nine patients who survived, the symptoms resolved in 3–24 months. Severe mitral regurgitation was a predictor of poor outcome. Survivors more frequently had viral symptoms within the preceding 3 months.[101] Five year survival rates of 64–84% have been reported.[64,65] Sudden death is rare.[64,65] A recent review of hospital records in children from the West of Scotland identified 53 patients with IDC or myocarditis who were <12 years old. Of the 39 IDC cases, 38 were diagnosed in life. There were 15 males (M:F ratio = 1:1·6) and 64% were <1 year of age. Coxsackie viral antibodies were positive in 21%. Mitral regurgitation was present in 74% and 77% had cardiomegaly in *x* rays. Twelve patients died, all within a year; 50% within the first week of presentation. Survival was higher if fractional shortening (FS) was >15% (11/28 survived *v* 1/10 survivors), as was mean survival (12·2 years *v* 9·6 years, respectively). Of the 12 who survived, all became asymptomatic and LV size returned to normal in 10 patients. Myocarditis was diagnosed at autopsy in nine of 14 patients who presented within 10 days of illness onset; one additional patient died 4 days after diagnosis. Actuarial survival was 29% at 1 and 9 years. All survivors became asymptomatic.[102]

Comparison of IDC and myocarditis

Grogan *et al*[103] compared 27 patients with active ($n = 17$) or borderline ($n = 10$) myocarditis with 58 IDC patients. A viral illness was reported within the previous 3 months in 40% of patients with myocarditis versus 19% of the IDC patients. The EF was lower ($25 \pm 11\%$) in the group with IDC compared to the myocarditis group ($38 \pm 19\%$). Sixty-three per cent of the patients with IDC were NYHA functional class III–IV compared with only 30% of the patients with myocarditis. There was no difference in survival even when results were analyzed for the presence of active myocarditis, borderline myocarditis, or IDC (54% 5 year survival with IDC *v* 56% with myocarditis).

Summary

While multiple causal factors have been implicated in both myocarditis and IDC, the precise etiology and pathophysiology remain unknown. Spontaneous improvement in left ventricular function may be noted with both myocarditis and IDC. Survival is similar (approximately 55% at 5 years) in both.

Treatment

Treatment of myocarditis: clinical and experimental

General supportive measures for patients with myocarditis include a low sodium diet; discontinuation of ethanol, illicit drug use, and smoking; and salt restriction, especially in the presence of heart failure. Recommendations for the limitation of physical activity are based on the murine model of Coxsackie B3 myocarditis, in which forced exercise during the acute phase of illness was associated with increased inflammatory and necrotic lesions (although there was no effect on death rate).[103] The Task Force[104] on myopericardial diseases recommends a convalescent period of approximately 6 months after onset of clinical manifestations before a return to competitive sports.

Antiviral therapy

The use of the antiviral ribaviron[105] in a murine (DBA/2) model of encephalomyocarditis (ECM) myocarditis improved survival and decreased myocardial viral titers when used in higher doses (200 or 400 mg/kg/day). Therapy resulted in fewer myocardial lesions, more pronounced inhibition of viral replication, a reduced inflammatory response, and less myocardial damage. However, treatment was started immediately after viral inoculation. There are no human studies of antiviral therapy to date and the ability to detect and begin therapy immediately upon onset is limited in the clinical setting.

Angiotensin converting enzyme inhibition

Although there are multiple studies on the use of ACE inhibitors in heart failure (including patients with IDC), their utility in myocarditis has been studied only in the murine model. Studies of Coxsackie B3 myocarditis in CD1 mice reported that early treatment with captopril (starting on day 1 of infection) resulted in less inflammatory infiltrate, myocardial necrosis, and calcification. Heart weight, heart to body weight ratio, and liver congestion diminished. Even when therapy was begun later (10 days after inoculation), a beneficial effect – a reduction in left ventricular mass and liver congestion – was noted.[106]

A comparison of the ACE inhibitors captopril 7·5 g/kg/day and enalapril 1 mg/kg/day with the angiotensin II receptor blocker losartan 60 mg/kg/day in a murine model of ECM myocarditis revealed that only captopril and losartan, started 1 week after viral inoculation, resulted in decreased heart weight, body weight, heart weight to body ratio, and hypertrophy. Left ventricular cavity dimension decreased with the use of captopril and losartan 12 mg/kg/day or 60 mg/kg/day. These results are consistent with an improvement in heart failure and left ventricular hypertrophy. There was less necrosis with enalapril and captopril. However, the inflammatory score was reduced only by captopril.[77]

β Blockers

Similarly, β blockers have been studied in myocarditis only in murine models. Metoprolol was compared with saline in a murine model of acute Coxsackie B3 myocarditis, starting on the day of viral inoculation and continuing for 10 days. The result was an *increased* 30 day mortality (60% *v* 0%) in metoprolol-treated mice associated with *increased* viral replication and myocyte necrosis.[107] The β blocker carteolol has been studied in a murine model (BALB/C and DBA/2 strains) of acute, subacute, and chronic ECM myocarditis. Metoprolol was compared with carteolol in the chronically infected group. There was no difference in survival between mice whose treatment was started on the day of viral inoculation, compared to therapy begun 14 days later. In chronically infected mice, carteolol resulted in a reduction in heart weight and heart weight to body ratio (not seen with metoprolol), and improved histopathologic scores (diminished wall thickness, cavity dimension, fiber diameter, cell necrosis, fibrosis, cellular infiltration, and calcification), suggesting that carteolol may prevent the development of lesions similar to those found in dilated cardiomyopathy.[108] The results suggest that early initiation of β blockers may be harmful, whereas in the chronic stages of illness β blockers improve manifestations of heart failure. In addition, non-cardioselective β blockers may be preferable.

Calcium-channel blockers

In a murine model of ECM induced myocarditis, verapamil pretreatment was associated with a reduction in microvascular necrosis, fibrosis, and calcification. Similar changes were noted if treatment was begun 4 days after viral inoculation. The development of microvascular constriction and microaneurysm formation was prevented when compared to controls. This suggests a possible role for calcium signaling and microvascular spasm in the pathogenesis of this form of viral myocarditis. Verapamil did not reduce mortality although the severity of illness and time to death were delayed.[109] There have been no human myocarditis trials with calcium-channel blockers to date.

Non-steroidal anti-inflammatory agents

The use of ibuprofen during the acute phase of murine Coxsackie B3 myocarditis resulted in significant exacerbation of myocardial inflammation, necrosis, and viral replication, when compared to control mice.[110,111]

Vesnarinone

Vesnarinone suppressed TNF α, resulting in a reduction in myocardial necrosis, when given at a dose of 50 mg/kg, in a murine model of ECM myocarditis. At lower doses (10 mg/kg) the mortality rate was reduced in comparison to control mice, although both groups began to experience mortality on day 5 after viral inoculation.[112]

Immunosuppressants

The data supporting an immunologic basis of myocarditis have resulted in multiple treatment trials of immunosuppressants. The largest of these trials, the Myocarditis Treatment Trial,[32] screened 2333 patients with heart failure of less than 2 years' duration: 214 patients (10%) had endomyocardial biopsy evidence of myocarditis by the Dallas Criteria; 111 had a qualifying LVEF of <45%. Patients were initially divided into three treatment groups: prednisone/azathioprine, prednisone/cyclosporine, and no immunosuppressant treatment. The prednisone/azathioprine group was subsequently eliminated because of limited numbers of patients. Patients were treated for 24 weeks, during which time conventional heart failure therapy was continued. At both 28 and 52 weeks, no difference in pulmonary capillary wedge pressure or change in LVEF was observed (Figure 47.3). In addition, there was no significant change in LVEF in treated patients as compared with untreated (Figure 47.3). At 1 and 5 years, there was no difference in survival between groups or need for cardiac transplantation (Figure 47.4). On multivariate analysis, better baseline LVEF, less intensive conventional therapy, and shorter illness duration were independent predictors of improvement in LVEF during follow up. Immunologic variables (cardiac IgG, circulating IgG, natural killer and macrophage activity, helper T cell level) were not associated with measures of cardiac function. A higher peripheral $CD2^+$ T lymphocyte count was associated with a higher risk of death. At 5 years the combined end point of death or transplantation was 56%.

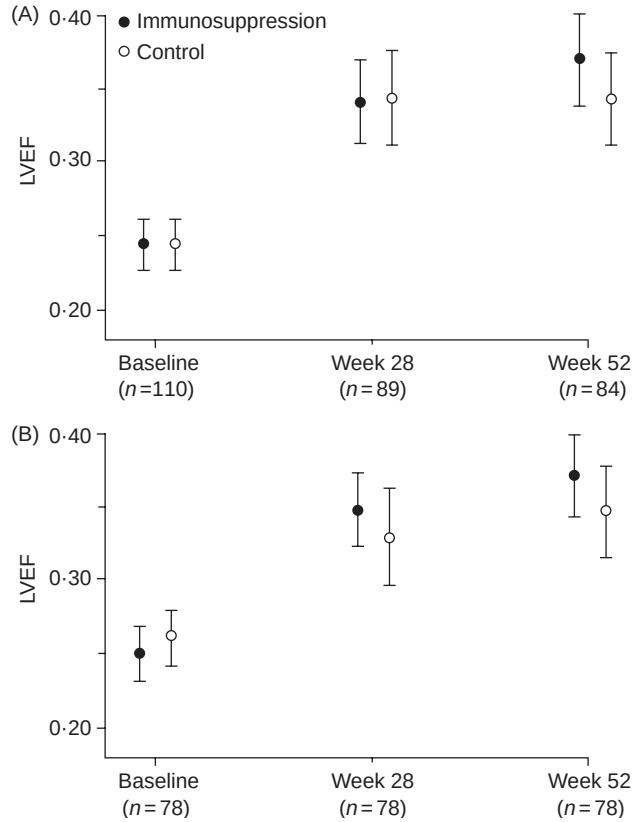
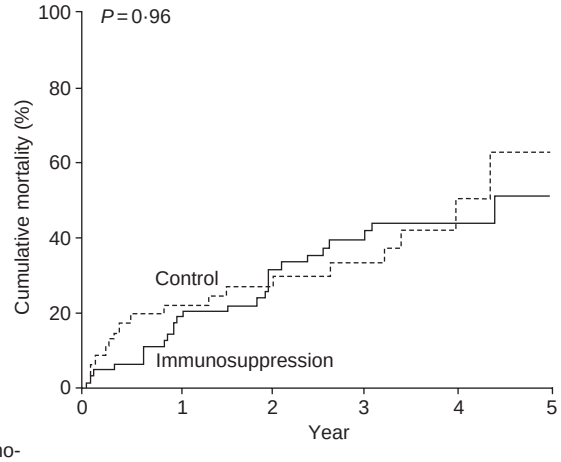


Figure 47.3 Mean (±SE) left ventricular ejection fraction (LVEF) in the immunosuppression and control groups at baseline, week 28, and week 52. (A) shows the mean values for all available studies at each time, with the numbers of patients indicated at the bottom of the panel. There was no difference between the two groups in the mean LVEF at baseline, week 28, or week 52 ($P = 0{\cdot}97$, $P = 0{\cdot}95$, and $P = 0{\cdot}45$, respectively). (B) shows the mean values for the 78 patients for whom data were available at all three times. Again, there was no significant difference between the groups ($P = 0{\cdot}51$, $P = 0{\cdot}60$, and $P = 0{\cdot}50$, respectively). (Adapted with permission from Mason *et al.*[32])

Gagliardi *et al*[88] followed 20 children with biopsy-proven myocarditis who were treated with cyclosporine and prednisone. At 1 year, 10 of 20 patients still had histologic evidence of myocarditis. No patient died or required transplantation. However, there was no control group.

Certain subgroups might nonetheless benefit from immunosuppressant therapy, including those with giant



Immuno-suppression	64	49	37	23	12	0
Control	47	32	23	16	6	0

Figure 47.4 Actuarial mortality (defined as deaths and cardiac transplantations) in the immunosuppression and control groups. The numbers of patients at risk are shown at the bottom. There was no significant difference in mortality between the two groups. (Adapted with permission from Mason *et al.*[32])

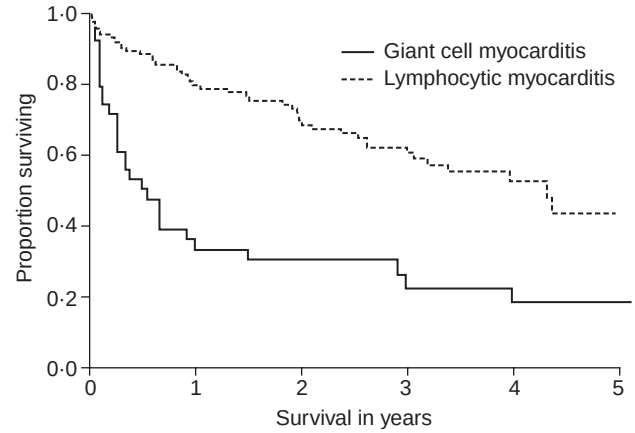


Figure 47.5 Kaplan–Meier survival curves for patients with giant cell myocarditis, showing the duration of survival among 38 patients in whom giant cell myocarditis was diagnosed by endomyocardial biopsy or by examination of a section of ventricular apex. Survival was significantly longer among patients with lymphocytic myocarditis ($P < 0{\cdot}001$ by the log rank test for each comparison). (Adapted with permission from Cooper *et al.*[113])

cell myocarditis, hypersensitivity myocarditis, or cardiac sarcoidosis. With a multicenter database, Cooper[113] reviewed 63 patients with giant cell myocarditis. There was no difference in the number of men versus women, or the age of men versus women. The mean age at onset was 42·6 ± 12·7 years. Eighty-eight per cent were white and 19% had an associated autoimmune disorder. Five patients (8%) had either Crohn's disease or ulcerative colitis, which preceded the onset of myocarditis. Seventy-five per cent presented with heart failure. Approximately half had sustained refractory ventricular tachycardia during the course of the illness. The rate of death or cardiac transplantation was 89% by 3 years. Median survival was 5·5 months from symptom onset to death or transplantation. The median survival in patients treated with corticosteroids was 3·8 months versus 3·0 months in untreated patients. However, patients treated with corticosteroids and azathioprine had an average survival of 11·5 months. Cyclosporine in combination with corticosteroids, corticosteroids/azathioprine, or corticosteroids/azathioprine/OKT3 survived an average of 12·6 months. Survival was unaffected by sex, age, or time to presentation. Cardiac transplantation was performed in 34 patients. Nine (26%) died during an average 3·7 years of follow up. Five of these deaths occurred within 30 days of transplantation. Nine patients had recurrent giant cell myocarditis in the transplanted heart, after an average of 3 years post transplantation. Comparison with 111 patients in the Myocarditis Treatment Trial revealed cumulative mortality was greater in patients with giant cell myocarditis (Figure 47.5). The ongoing Giant Cell Myocarditis Treatment Trial will assess the efficacy of standard medical therapy versus standard care, in addition to therapy with muromonab-CD3 (OKT3), cyclosporine and corticosteroids.

Other potential indications for a trial of immunosuppressant therapy include failure of myocarditis to resolve, progressive LV dysfunction despite conventional therapy, continued active myocarditis on biopsy or fulminant myocarditis that does not improve within 24–72 hours of full hemodynamic support, including mechanical assistance. Myocarditis associated with a known immune-mediated disease, such as systemic lupus erythematosus, may also benefit from immunosuppressive therapy.

These studies call into question the value of routine endomyocardial biopsy and immunosuppressant therapy in adults and children. Immunologic testing may be a more sensitive method of diagnosis and may reduce the sampling error noted with routine histology but awaits development and validation. Consideration of endomyocardial biopsy should be given whenever these specific immunosuppressant-responsive conditions are present or suspected. However, the low incidence of light microscopic evidence of histologic inflammatory disease, the fact that there is no specific therapy for most cases of myocarditis, and the fact that there are potential complications related to the procedure suggest that *routine* endomyocardial biopsy is not warranted.[114]

Smaller studies have used differing immunosuppressant regimens. Kühl *et al*[115] treated 31 patients with biopsies classified as immunohistologically positive (more than two cells per high power field and expression of adhesion molecules), negative Dallas Criteria, and LV dysfunction. Patients were treated with corticosteroids plus conventional therapy

for 3 months followed by gradual tapering of methylprednisolone doses over 24 weeks (following biopsy and LVEF response). Therapy was associated with an improvement in EF in 64% and improved NYHA functional class in 77%. Four patients (12%) had no change in EF despite improvement in inflammatory infiltrates. Three patients (9%) had no change in EF or inflammatory infiltrates. However, study conclusions are limited by the absence of a control group. These findings also reinforce the suggestion that light microscopy may not be the gold standard for the diagnosis of myocarditis or evaluation of therapy. Hopefully, new advances in immunohistochemistry will increase diagnostic and prognostic sensitivity and specificity.

Drucker *et al*[116] retrospectively reviewed 46 children with congestive cardiomyopathy and Dallas Criteria of borderline or definite myocarditis: 21 patients were treated with IV IgG (2 g/kg over 24 hours) and were compared to 25 historic controls. Of the treated patients, four received a second dose of IgG and two were also treated with prednisone. Of the control patients, three received prednisone and two of these three patients also received cyclosporin. One died, one underwent heart transplantation, and one had persistent LV dysfunction. Overall survival was not improved although there was a trend toward improvement in 1 year survival in the treated group. In the IgG group, the mean LV end-diastolic dimension was not significantly different from normal after 3 months. Fractional shortening improved in both groups but returned to normal only in the IgG group. Improvement in ventricular function persisted after adjustment for age, biopsy status, and use of ACE inhibitors and inotropes.

In a comparative study of interferon-α, thymomodulin, and conventional therapy in patients with biopsy-proven myocarditis or IDC, an improvement in the treatment groups was reported for EF (at rest and during exercise), maximum exercise time, functional class, and ECG abnormalities. Three of 12 conventionally treated patients died (one suddenly and two from heart failure), compared with one of 13 treated with interferon-α (sudden death in an IDC patient) and one of 13 treated with thymomodulin (of embolic cerebrovascular accident).[117] The use of intravenous immune globulin in 10 patients (NYHA III–IV) with symptoms of <6 months duration resulted in an improvement in LVEF (Figure 47.6) and functional improvement (NYHA I–II at 1 year of follow up) in all nine patients who survived, regardless of biopsy results.[118]

Ahdoot *et al* reported on five children aged 15 months to 16·5 years, four with histologic evidence of acute myocarditis, who were treated with OKT3 (0·1 mg/kg/IV push for 10–14 days), IV IgG (2 mg/kg over 24–48 hours) and corticosteroids. Three patients also received cyclosporine (for 6 months), three received azathioprine (while maintained on cyclosporine) and one received methotrexate (for 2 months). All presented with severe heart failure, requiring

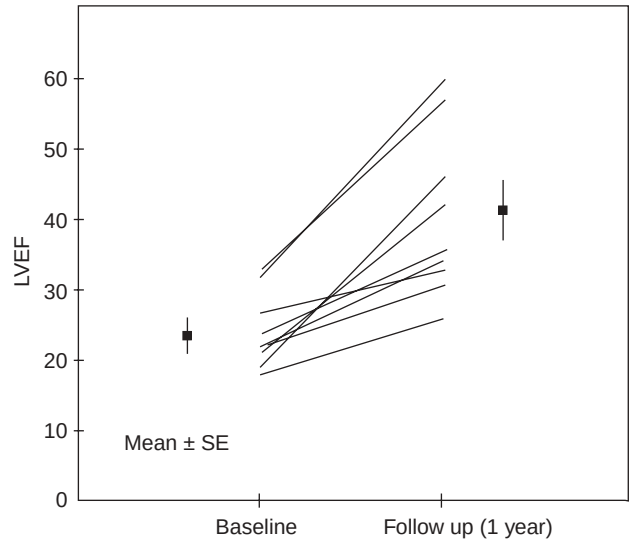


Figure 47.6 Change in LVEF ($P = 0.003$) in patients treated with IV immune globulin. All patients demonstrated functional improvement and at 1 year follow up were NYHA class I or II. No patient has been re-hospitalized for congestive failure. (Adapted with permission from McNamara *et al.*[118])

inotropic and ventilatory support. Four had life-threatening arrhythmias. Four required temporary mechanical circulatory support. One patient died from a thromboembolic event. EF normalized in the four surviving patients. After a mean follow up of 28·8 months (3–56 months), there were no heart failure recurrences or progression to dilated cardiomyopathy.[119]

Perhaps alternative immunosuppressant regimens and different diagnostic criteria may be more successful in demonstrating the usefulness of immunosuppressants. Other immunosuppressants have been studied in the murine model. The use of cyclophosphamide (CYA) in a murine model of Coxsackie B3 myocarditis revealed that therapy begun at the time of viral inoculation resulted in less severe cardiac lesions compared to controls but no improvement in mortality. When therapy was begun later (8 days after viral inoculation), survival was worse in the CYA group despite improvement in cardiac lesions. When therapy was begun even later (day 21), there was no difference in survival or in cardiac infiltrates compared with controls.[120] In a murine model of EMC viral myocarditis, the use of tumor necrosis factor (TNF) resulted in greater myocardial viral content and more extensive myocardial necrosis and cellular infiltration. Anti-TNF monoclonal antibody did not alter mortality or prevent myocardial lesions unless given *before* viral infection.[121] There are no human studies with these agents. Preliminary data on the development of an enterovirus vaccine using chimeric Coxsackie virus B3 in a murine model of myocarditis suggest an attenuation of viral replication and diminished inflammatory infiltrates.[122]

Cardiac transplantation

An analysis of outcome of 14055 cardiac transplant recipients did not confirm the initial concern that there is a worse outcome if transplantation is performed during the acute stage of myocarditis. One year actuarial survival in all groups transplanted (IDC, myocarditis, peripartum cardiomyopathy *v* other diagnoses) was 80%.[123] Nonetheless, myocarditis may recur in the transplanted heart.[124]

Treatment of IDC: clinical and experimental

The same general supportive measures used in myocarditis are applicable in the management of IDC, except that moderate exercise is encouraged once heart failure symptoms have stabilized. Mild to moderate dynamic exercise is preferable to isometric exercise.[125]

Vasodilators, ACE inhibitors, and angiotensin receptor antagonists

The beneficial effects of vasodilators (hydralazine and isosorbide dinitrate) and ACE inhibitors on symptomatic improvement and reduction in mortality have been shown in multiple large clinical trials.[126–130] Trials have included 15–18% of enrolled patients with a diagnosis of IDC.[126–130] These trials have documented a reduction in cardiac size, improvement in functional class, and a reduction in total and cardiovascular mortality. In addition, there is a reduction in the number of hospitalizations.[126–130]

The use of enalapril in asymptomatic patients (EF $<$ 35%) resulted in a *non-significant* decrease in mortality. However, there was a reduction in the incidence of heart failure and related hospital admissions. The time to development of heart failure was shown to be prolonged from 8·3 months to 22·3 months.[128,129] The survival benefit of enalapril was found to be superior to the combination of hydralazine plus isosorbide dinitrate in the Second Vasodilator-Heart Failure Trial (V-HeFT-2).[130]

A short trial (8 weeks) comparing the angiotensin receptor II antagonist (ARB) losartan with enalapril in 166 patients with NYHA class III–IV and an EF of $<$35% suggested comparable efficacy based on results of 6 minute walk test, dyspnea fatigue index, neurohumoral activation (norepinephrine and atrial natriuretic factor levels), laboratory evaluation, and adverse events.[131] In a comparison of losartan (titrated to 50 mg/day) with captopril (50 mg 3×/day) in 722 NYHA class II–IV patients over the age of 65, a 32% relative risk reduction of death and/or hospital admission was observed with the use of losartan (Evaluation of Losartan in the Elderly Study [ELITE]).[132] There was no difference in the number of hospital admissions for heart failure or improvement in functional class. This suggests that losartan may be used as an alternative to, if not preferred to, ACE inhibitors. However, there was no significant difference in mortality, sudden death or resuscitated deaths in the follow up study (ELITE II). While the study failed to show the superiority of losartan, the drug is a safe and effective alternative in patients who cannot tolerate ACE inhibitors.[133]

The Valsartan Heart Trial Investigators[134] reported no significant difference in survival in 5010 patients with class II–IV heart failure (31% IDC) treated with valsartan plus ACE inhibitors versus placebo and ACE inhibitors. However there was a 13% lower incidence of the combined end points of mortality and cardiac arrest necessitating resuscitation, hospitalization for heart failure or need for intravenous inotropes and vasodilators. There was significant improvement in heart failure symptoms and quality of life. Of note, on post hoc analysis, valsartan had an adverse effect on mortality in patients on a combination of ACE inhibitor and β blocker ($P < 0{\cdot}009$). Whether this is a true interaction requires further investigation. Thus, ARBs should be considered an alternative in patients intolerant of ACE inhibitors.[114]

Digitalis

Although the use of digitalis has long been a standard in the treatment of heart failure, only recently have large trials been conducted to assess its safety and efficacy adequately. Withdrawal trials of digitalis in patients with a depressed LVEF treated with diuretics and/or ACE inhibitors, in sinus rhythm, with mild to moderate heart failure, have shown a worsening of exercise performance and NYHA class, lower quality of life score, a need for additional drug therapy, more overall hospitalizations and hospitalizations for heart failure, and an increase in emergency room visits for heart failure compared with patients continued on digitalis. Patients who continued the use of digitalis had an increased time to treatment failure, higher LVEF, and lower heart rate and body weight. Its effect on mortality is neutral, with a balanced reduction in heart failure deaths and an increase in sudden arrhythmic deaths.[135–137] However, digoxin reduced hospitalization for heart failure.[137] Perhaps, unexpectedly, these results were similar in a group of patients with an EF of 45%.[137] The symptomatic benefit of therapy was greatest in patients with an EF of 25%, NYHA class III–IV, and in those with cardiomegaly. Idiopathic dilated cardiomyopathy was the etiology of heart failure in approximately 15–40% of patients enrolled in these trials.[135–137]

Immunosuppressants

The use of immunosuppressants is not as well studied in IDC as in myocarditis. Patients with IDC felt to be immune reactive, based on cellular infiltrate, Ig or complement deposition, elevated sedimentation rate, or a positive gallium scan, were randomized to treatment with prednisone

and compared to untreated controls by Parillo *et al*[138] At 3 months, there was an improvement in EF, but this was not sustained at 9 months.[138] In another study, the use of interferon-α or thymomodulin in IDC appeared to improve EF (at rest and during exercise), maximum exercise time, functional class, and ECG abnormalities when compared with conventional therapy alone.[117]

Ten patients with recent onset of heart failure and biopsy consistent with borderline myocarditis in one patient, non-specific inflammation in one patient, and six with no cellular infiltrate received IV IgG. There was an improvement in both LVEF (Figure 47.6), and functional classification (NYHA I–II at 1 year of follow up) in all nine patients who survived.[118] Conversely, the IMAC investigators randomized 62 patients with recent onset IDC to IV IgG (2g/kg) or placebo. Sixteen per cent had biopsy evidence of cellular inflammation. The improvement noted in EF was identical in both groups. There was no significant difference in event-free survival or functional capacity between the two groups.[139]

Using immunohistological criteria as the basis to qualify for immunosuppressive therapy, Wojnicz *et al* randomized 84 heart failure patients with increased HLA expression on endomyocardial biopsy specimens to therapy with prednisone (1 mg/kg/day, which was tapered to 0·2 mg/kg/day for 90 days) and azathioprine (1 mg/kg for 100 days) versus placebo. Fifty-eight patients completed the study. There was no difference in cardiac death, transplantation or hospital re-admission rate, although the immunosuppressant group had a significant improvement in EF, left ventricular diastolic dimension, and NYHA functional class.[140]

Since the development of autoantibodies may play a role in the initiation and progression of IDC, immunoadsorption for their removal may be of benefit. Felix *et al* randomized 18 patients with severe heart failure to immunoadsorption (IA) followed by IgG (0·5 g/kg) substitution versus conventional therapy. Myocarditis was excluded in all patients. There was a significant decline in β receptor antibody levels in the IA group, when compared to baseline levels ($P < 0{\cdot}01$) and when compared to conventionally treated patients ($P < 0{\cdot}01$). In addition, there were significant improvements in hemodynamics. Cardiac index and stroke volume index increased, while pulmonary and systemic vascular resistance decreased. These changes persisted for 3 months. The hemodynamic improvements were associated with significant improvements in EF ($P < 0{\cdot}01$) and functional class ($P < 0{\cdot}05$). However, this was a small study and follow up was only 3 months.[141]

Since a specific diagnosis is infrequently made in cases of dilated cardiomyopathy (approximately 17% of cases),[59] routine endomyocardial biopsy is not recommended in all heart failure patients.[114] The benefits of endomyocardial biopsy should outweigh the overall risks associated with the procedure, reported at 4·4–8%, although death from myocardial perforation is uncommon (0·02–0·4%).[59,142] As the diagnostic yield and likelihood of therapy being altered by the histopathologic results is low, biopsy should be considered in patients with rapid clinical deterioration, new arrhythmias, history, or symptoms suggestive of secondary causes of dilated cardiomyopathy, or who fail to improve after 1 week of conventional therapy.[114,142]

Growth hormone

Preliminary data suggested growth hormone (GH) might be of therapeutic benefit in patients with IDC. In a recent pilot study, there was an improvement in quality of life, increased maximal exercise capacity, and increased LV mass and wall thickness, with resultant decreased wall stress, decreased chamber size; improved hemodynamics and systolic performance, and decreased myocardial oxygen consumption.[143] However, Isgaard[144] conducted a randomized double blind study of recombinant GH in 22 patients with heart failure of various etiologies. After 3 months of treatment, there was no improvement in systolic or diastolic function or exercise capacity. Plasma markers of neuroendocrine activation (renin activity, aldosterone, angiotensin II, adrenaline, noradrenaline) remained unchanged.

Calcium-channel blockers

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial[145] enrolled 1153 patients with NYHA class III–IV heart failure and an EF of <30%. Treatment with the calcium-channel blocker amlodipine was compared to placebo. On subgroup analysis, patients with dilated cardiomyopathy had a 31% reduction in fatal and non-fatal events and a 46% lower risk of death, although there was no significant reduction in overall mortality or fatal and non-fatal events. The follow up study (PRAISE II) showed no survival benefit with the use of amlodipine (presented at American College of Cardiology Scientific Sessions 15 March, 2000 in Anaheim, CA). Its use in heart failure should be limited to patients with hypertension and angina despite standard heart failure therapy.[114]

Cardiomyopathic Syrian hamsters are known to develop progressive focal myocardial necrosis, similar to lesions found in human cardiac diseases. In these hamsters, the process begins at 1 month of age, ultimately leading to heart failure. Using silicone rubber perfusion studies, Factor and colleagues[146] were able to document microvascular vasoconstriction, diffuse vessel narrowing, and lumenal irregularity associated with adjacent areas of myocytolytic necrosis. They were able to prevent the development of cellular necrosis by pretreatment of 30 day old hamsters (the period when they normally develop these lesions) with verapamil. When treatment was begun at a later time (90 or 150 days), there was no alteration in scar or necrosis. However, verapamil had a positive effect on microvascular spasm, regardless of when treatment was begun, suggesting

abnormal cellular calcium metabolism may be involved in the pathogenesis. Comparable human studies have not been done. These studies lend further support to the potential role of calcium and microvascular spasm.

β Blockers

Initial trials of the use of β blockers in IDC, while uncontrolled, suggested improved cardiac function and survival when they were added to digitalis and diuretics in patients with moderate to severe heart failure.[147] In addition, the withdrawal of such therapy appeared to result in the development of worsening heart failure.[147]

The long-term effects of metoprolol were studied in an early double-blind, randomized study of limited size.[148] Patients also were frequently receiving treatment with digoxin, diuretics, and vasodilators. Patients had symptomatic heart failure with a baseline EF of 49%. In the metoprolol-treated group, a significant improvement in functional class, exercise capacity, mean EF, and LV end-diastolic dimension was observed.[148] The subsequent larger Metoprolol in Dilated Cardiomyopathy (MDC) Trial[149] in symptomatic patients with an EF of $<40\%$ showed a reduction in the composite end point of death or need for transplantation. However, all of the derived benefit was secondary to a reduction in cardiac transplantation, with no independent effect on all-cause mortality. Additional benefit was observed in several other measures; ejection fraction, pulmonary capillary wedge pressure, quality of life, exercise duration, and NYHA functional class improved significantly. The number of hospital re-admissions for all patients and re-admissions per patient were reduced with metoprolol. In a substudy of the Randomized Evaluation of Strategies of Left Ventricular Dysfunction (RESOLVD), of 450 patients with an EF of $\leq 0{\cdot}40$, there was about a 50% risk reduction in mortality ($P = 0{\cdot}052$) and a significant improvement in EF with metoprolol CR compared to placebo over 20 weeks. There was no impact on cardiovascular or total hospitalizations.[150]

The Cardiac Insufficiency Bisoprolol Study (CIBIS)[151] tested bisoprolol in heart failure and found no difference in sudden death or death from documented venous thrombosis. On subgroup analysis, there was a reduction in mortality in IDC patients and those with NYHA class IV. There was also an improvement in functional status and fewer hospitalizations in patients treated with bisoprolol. The follow up study (CIBIS-II) enrolled 2647 patients with class III or IV heart failure and an EF of $<35\%$. The study was terminated early because of a significant mortality benefit in patients treated with bisoprolol (11·8% *v* 17·3%; $P < 0{\cdot}0001$). All-cause mortality was lower and there were fewer sudden deaths in the treated group (3·6% *v* 6·3%; $P = 0{\cdot}0011$). In addition, fewer patients were hospitalized in the treatment group ($P = 0{\cdot}0006$). The beneficial effects of therapy were independent of the etiology or severity of heart failure.[152]

The α/β blocker carvedilol has been tested in patients with an EF of $\leq 35\%$ (NYHA classes II–IV), on digitalis, an ACE inhibitor, and diuretics, and was associated with a 65% reduction of all-cause mortality (not a prospective end point), a 27% reduction in hospitalization, and a 38% reduction in the combined end points of death and hospitalization (primary end point, progression of heart failure). The reduction in mortality was independent of age, sex, cause of heart failure, EF, exercise tolerance, systolic blood pressure, and heart rate.[153] Subsequent studies have confirmed the beneficial effects of carvedilol on survival and improvement in symptomatology in patients with moderate to severe heart failure on a background of ACE inhibitors, diuretics, and digitalis. Additionally, mean EF increased by 5%. There was however, no significant improvement in exercise performance.[154]

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) enrolled 3991 patients with class III–IV heart failure and an EF of $\leq 40\%$. Patients were randomized to long-acting metoprolol or placebo after a 2 week single-blind run-in period; 90% of patients were on diuretics and ACE inhibitors. Approximately 63% were on digitalis. There was a significant reduction in all-cause hospitalization and total mortality (19% risk reduction). There was a 32% risk reduction in death or need for heart transplantation. The number of hospitalizations (451 *v* 317) and hospitalization days (5303 days *v* 3401 days) due to heart failure were significantly reduced when compared to the placebo group. There was a significant improvement in functional class and patient sense of well being, when these criteria were assessed by patients and their physicians.[155] Given the mounting evidence supporting their use, it is recommended that patients with symptomatic LV dysfunction receive treatment with β blockers. Initiation of therapy should begin in stable patients with no or minimal evidence of volume overload and without recent need of IV inotropic agents. Most recent guidelines also recommend their use in patients with asymptomatic LV dysfunction.[114]

Aldactone

The Randomized Aldactone Evaluation Study (RALES) Investigators trial randomized 1663 patients with severe heart failure (class III–IV at time of randomization; EF $<35\%$; 46% non-ischemic etiology). All patients were on a loop diuretic, $>90\%$ on an ACE inhibitor, and $>70\%$ on digitalis. Patients randomized to aldactone had a 30% reduction in risk of death. The mortality reduction was a result of lower risk of death from heart failure and sudden death. In addition, there was a 30% reduction in the risk of hospitalization. Of those on placebo, 33% noted improvement in heart failure symptoms and 48% had worsening heart failure symptoms, as compared to 41% and 38% of patients, respectively on aldactone ($P < 0{\cdot}001$).[156]

Inotropes

Multiple trials of different inotropes, both oral and IV (intermittent or continuous), with various dose ranges, have failed to result in an improvement in survival in patients with heart failure, although several agents may provide transient symptomatic improvement.[157–160] Thus, routine use of these agents cannot be recommended.[114]

Amiodarone

Over 40% of cardiac deaths occur suddenly, presumably from arrhythmias. Both the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA)[118] and the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT)[162] assessed the efficacy of amiodarone therapy in heart failure patients with asymptomatic ventricular arrhythmias.

GESICA[161] enrolled patients with NYHA class III–IV symptoms, an LVEF <35%, who were treated with routine heart failure therapy. The presence or absence of nonsustained ventricular tachycardia on Holter was noted. Patients were prospectively randomized to amiodarone 600 mg/day for 14 days, followed by 300 mg/day for 2 years. A total of 516 (260 in the amiodarone group) patients were enrolled. Within the amiodarone group, there was a 23% risk reduction (RR) in progressive heart failure. There was a 27% RR of sudden death, although there was no difference in non-cardiac deaths. There was also a 31% RR in death or heart failure admissions. On subgroup analysis, the effect of amiodarone was similar regardless of sex, functional class (NYHA class II–IV), and the presence or absence of nonsustained ventricular tachycardia. In addition, a larger proportion of amiodarone-treated patients were in the better functional classes.

CHF-STAT[162] enrolled 674 patients (336 amiodarone treated) with heart failure, >10 PVC/hour (unaccompanied by symptoms), with an EF <40% (PVC = premature ventricular complex). Patients were treated with amiodarone 800 mg/day for 2 weeks, then 400 mg/day for 50 weeks, followed by 300 mg/day until study completion. In contrast to the GESICA trial, there was no significant reduction in heart failure deaths, sudden deaths, or non-cardiac deaths. Survival was unaffected by the suppression of PVCs or elimination of venous thrombosis. Amiodarone-treated patients had a significant improvement in LVEF at 6 months although this did not affect survival. When data were analyzed based on the etiology of heart failure, there was a trend toward improved mortality in non-ischemic patients ($P = 0{\cdot}07$). The difference between these two studies may be related to the different proportion of patients with coronary artery disease in the two trials and the fact that CHF-STAT but not GESICA was double-blind placebo-controlled. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) will examine the role of standard care versus standard care with amiodarone or defibrillator.

Overview of treatment measures

While general supportive measures, with a period of no exercise, are recommended in the treatment of myocarditis, no specific therapies have been approved. ACE inhibitors, β blockers, and calcium-channel blockers have only been studied in animal models. The routine use of immunosuppressants is not supported by the Myocarditis Treatment Trial, although some subgroups may benefit, and other regimens may prove beneficial (Table 47.1).

Supportive measures are also suggested in IDC and exercise is encouraged. Multiple trials support the use of vasodilators, ACE inhibitors, β blockers and digoxin, when appropriate, in IDC (Table 47.2). Angiotensin receptor blockers (ARBs) or nitrates alone, or in combination with hydralazine, may be used as alternatives in patients who cannot be given ACE inhibitors.[114] There are insufficient data to support the use of immunosuppressants for the treatment of IDC. Further studies on the use of selected calcium-channel blockers are underway (PRAISE-II). The routine use of prophylactic antiarrhythmics is also unsupported. Transplantation is a valid treatment option for patients with

Table 47.1 Grading of recommendations and levels of evidence for the treatment of myocarditis

Treatment	Level of evidence	Grade
Supportive measures	5	C
Immunosuppressants	1d,[32] 2,[88] 3,[116] 4[115,118,119]	B
Cardiac transplantation	2, 5	A

Table 47.2 Grading of recommendations and levels of evidence for treatment of dilated cardiomyopathy

Treatment	Level of evidence	Grade
Supportive measures	5	C
β Blockers	1a	A
ACE inhibitors	1a	A
Vasodilators	1a	A
Angiotensin receptor blockers	1a	B
Digitalis	1a	A
Aldactone	1a	A
Amiodarone	1a	B
Transplantation	2, 5	A

end stage IDC and/or refractory myocarditis, although myocarditis may recur. Mechanical circulatory support may be used as a bridge to transplant in patients with low cardiac output states, those dependant on intravenous inotropic support, or with intractable ventricular arrhythmias, or patients who are NHYA class IV with refractory symptoms.[163]

References

1. Richardson P, McKenna W, Bristow M *et al.* Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;**93**: 841–2.
2. Taylor DO, Mason JW. Myocarditis. In: Parmley W, Chatterjee K, Cheitlin MD *et al.,* eds. *Cardiology.* Philadelphia: Lippincott-Raven, 1995.
3. Daly K, Richardson PJ, Olsen EGJ *et al.* Acute myocarditis: role of histological and virological examination in the diagnosis and assessment of immunosuppressive treatment. *Br Heart J* 1984;**51**:30–5.
4. Parillo JE, Aretz HT, Palacios I, Fallon, Block PC. The results of transvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure: endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis. *Circulation* 1984;**69**:93–101.
5. Theoharides TC. Sudden Death of a Healthy College Student Related to Ephedrine Toxicity From Ma Huang-Containing Drink. *J Clin Psychopharmacol* 1997;**17**:437–9.
6. Bowles NE, Richardson PJ, Olsen EGJ, Archard LC. Detection of Coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. *Lancet* 1986;**i**:1120–3.
7. Jin O, Sole MJ, Butany JW *et al.* Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. *Circulation* 1990;**82**:8–16.
8. Grasso M, Arbustini E, Salini E *et al.* Search of Coxsackie B3 RNA in idiopathic dilated cardiomyopathy using gene amplification by polymerase chain reaction. *Am J Cardiol* 1992;**69**: 658–64.
9. Weiss LM, Liu X-F, Chang KL, Billingham ME. Detection of enteroviral RNA in idiopathic dilated cardiomyopathy and other human cardiac tissues. *J Clin Invest* 1992;**90**:156–9.
10. Martin AB, Webber S, Fricker FJ *et al.* Acute myocarditis rapid diagnosis by PCR in children. *Circulation* 1994;**90**:330–9.
11. Schowengerdt KO, Jiyuan N, Denfield SW *et al.* Diagnosis, surveillance, and epidemiologic evaluation of viral infections in pediatric cardiac transplant recipients with the use of the polymerase chain reaction. *J Heart Lung Transplant* 1996;**15**: 111–23.
12. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation* 1995; **92**:2519–25.
13. Dec GW, Palacios IF, Fallon JT *et al.* Active myocarditis in the spectrum of acute dilated cardiomyopathies. Clinical features, histologic correlates, and clinical outcome. *N Engl J Med* 1985;**312**:885–90.
14. Herskowitz A, Beisel KW, Wolfgram LJ, Rose NR. Coxsackie virus B3 murine myocarditis: wide pathologic spectrum in genetically defined inbred strains. *Human Pathol* 1985;**16**: 671–3.
15. Fenoglio JJ, Ursell PC, Kellog CF, Drusin RE, Weiss MB. Diagnosis and classification of myocarditis by endomyocardial biopsy. *N Engl J Med* 1983;**310**:12–18.
16. Godman GC, Bunting H, Melnick JL. The histopathology of Coxsackie virus infection in mice. 1. Morphologic observations with four different viral types. *Am J Pathol* 1952;**28**: 223–45.
17. Woodruff JF. Viral myocarditis. *Am J Pathol* 1980;**101**: 427–79.
18. Olsen EGJ. Endomyocardial biopsy. *Br Heart J* 1978;**40**:95–8.
19. Wolfgram LJ, Beisel KW, Herskowitz A, Rose NR. Variation in the susceptibility of congenic inbred mice to Coxsackie B3 induced myocarditis among different strains of mice. *J Immunol* 1986;**136**:1846–52.
20. Herskowitz A, Wolfgram LJ, Rose NR, Beisel KW. Coxsackie B3 myocarditis: a pathologic spectrum of myocarditis in genetically defined inbred strains. *J Am Coll Cardiol* 1987;**9**: 1131–9.
21. Bhardwaj V, Kumar V, Geysen HM, Sercarz EE. Degenerate recognition of a dissimilar antigenic peptide by MBP-reactive T cells: implications for thymic education and autoimmunity. *J Immunol* 1993;**151**:5000–10.
22. Cunningham MW, Antone SM, Gulizia JM *et al.* Cytotoxic and viral neutralizing antibodies cross react with streptococcal M protein enteroviruses and human cardiac myosin. *Proc Natl Acad Sci USA* 1992;**89**:1320–4.
23. Alvarez FL, Neu N, Rose NR, Craig SW, Beisel KW. Heart-specific autoantibodies induced by Coxsackie virus B3: identification of heart autoantigens. *Clin Immunol Immunopathol* 1987;**43**:129–39.
24. Neu N, Beisel KW, Traystman MD, Rose NR, Craig SW. Autoantibodies specific for the cardiac myosin isoform are found in mice susceptible to Coxsackie B3-induced myocarditis. *J Immunol* 1987;**138**:2488–92.
25. Dahl AM, Beverley PCL, Stauss HJ. A synthetic peptide derived from the tumor-associated protein mdm2 can stimulate autoreactive, high avidity cytotoxic T lymphocytes that recognize naturally processed protein. *J Immunol* 1996;**157**: 239–46.
26. Limas CJ, Goldenberg IF, Limas C. Autoantibodies against beta-adrenoreceptors in human dilated cardiomyopathy. *Circ Res* 1989;**64**:97–103.
27. Schultheiss HP, Schulze K, Huhl U, Ulrich G, Klingenberg M. The ADP/ATP carrier as a mitochondrial autoantigen – facts and perspectives. *Ann NY Acad Sci* 1986;**488**:44–64.
28. Wolff PG, Kühl U, Schultheiss HP. Laminin distribution and autoantibodies to laminin in dilated cardiomyopathy and myocarditis. *Am Heart J* 1989;**117**:1303–9.
29. Ansari AA, Herskowitz A, Danner DJ. Identification of mitochondrial proteins that serve as targets for autoimmunity. *Circulation* 1988;**78**(Suppl.):457 (Abstract).
30. Latif N, Baker CS, Dunn MJ *et al.* Frequency and specificity of antiheart antibodies in patients with dilated cardiomyopathy

detected using SDS-PAGE and Western blotting. *J Am Coll Cardiol* 1993;**22**:1378–84.
31. Maisch B, Bauer E, Cirsi M, Kochsiek K. Cytolytic cross-reactive antibodies directed against the cardiac membrane and viral proteins in Coxsackie B3 and B4 myocarditis. *Circulation* 1993;**87**(Suppl.V):IV-49–IV-65.
32. Mason JW, O'Connell JB, Herskowitz A *et al.* A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;**333**:269–75.
33. Muir P, Tizley AJ, English TAH *et al.* Chronic relapsing pericarditis and dilated cardiomyopathy: serological evidence of persistent enterovirus infection. *Lancet* 1989;**1**:804–7.
34. Cambridge G, MacArthur CG, Waterson AP, Goodwin JF, Oakley CM. Antibodies to Coxsackie B viruses in congestive cardiomyopathy. *Br Heart J* 1979;**41**:692–6.
35. Kawai C. Idiopathic cardiomyopathy: a study on the infection-immune theory as a cause of the disease. *Japan Circ J* 1971; **35**:765–70.
36. Schwaiger A, Umlauft F, Weyrer K *et al.* Detection of enteroviral ribonucleic acid in myocardial biopsies from patients with idiopathic dilated cardiomyopathy by polymerase chain reaction. *Am Heart J* 1993;126:406–10.
37. Schultheiss HP, Bolte HD. Immunological analysis of auto-antibodies against the adenine nucleotide translocator in dilated cardiomyopathy. *J Mol Cell Cardiol* 1985;**17**:603–17.
38. Caforio ALP, Grazzini M, Mann JM *et al.* Identification of a- and b-cardiac myosin heavy chain isoforms as major autoantigens in dilated cardiomyopathy. *Circulation* 1992; **85**:1734–42.
39. Herskowitz A, Neumann DA, Ansari AA. Concepts of autoimmunity applied to idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1993;**22**:1385–8.
40. Carlquist JF, Hibbs JB, Edelman LS, Watt RA, Anderson JL. Coxsackie B3 myocarditis in mice: viral clearance and post-infectious mortality are not associated with increased nitric oxide production. *Circulation* 1996;**94**(Suppl.):I-468 (Abstract).
41. Nishi H, Kimura A, Koga Y, Toshima H, Sasazuki T. DNA typing of class II genes in Japanese patients with dilated cardiomyopathy. *J Mol Cell Cardiol* 1995;**27**:2385–92.
42. McKenna CJ, Codd MB, McCann HA, Sugrue DD. Idiopathic dilated cardiomyopathy: familial prevalence and HLA distribution. *Heart* 1997;**77**:549–52.
43. Olson TM, Thibodeau SN, Lundquist PA, Schaid DJ, Michels VV. Exclusion of a primary gene defect at the HLA locus in familial idiopathic dilated cardiomyopathy. *J Med Genet* 1995;**32**:876–80.
44. Olson TM, Michels VV, Thibodeau SN, Tai YS, Keating MT. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. *Science* 1998;**280**:750–2.
45. Towbin JA, Hejtmancik JF, Brink P *et al.* X-linked dilated cardiomyopathy. Molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. *Circulation* 1993;**87**:1854–65.
46. Li D, Tapscoft T, Gonzalez O *et al.* Desmin mutation responsible for idiopathic dilated cardiomyopathy. *Circulation* 1999;**100**:461–4.
47. Fatkin D, MacRae C, Sasaki T *et al.* Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–24.
48. Charron Ph, Tesson F, Poirier O. Identification of a genetic risk factor for idiopathic dilated cardiomyopathy. Involvement of a polymorphism in the endothelin receptor type a gene. *Eur Heart J* 1999;**20**:1587–91.
49. Tsubata S, Bowles KR, Vatta M *et al.* Mutations in the human delta-sacroglycan gene in familial and sporadic dilated cardiomyopathy. *J Clin Invest* 2000;**106**:655–62.
50. Arimura T, Nakamura T, Hiroi S *et al.* Characterization of the human nebulette gene: a polymorphism in an actin-binding motif is associated with nonfamilial idiopathic dilated cardiomyopathy. *Human Genet* 2000;**107**:440–51.
51. Neu N, Pummerer C, Rieker T, Berger P. T cells in cardiac myosin-induced myocarditis. *Clin Immunol Immunopathol* 1993;**68**:107–10.
52. Smith SC, Allen PM. Expression of myosin-class II major histocompatibility complexes in the normal myocardium occurs before induction of autoimmune myocarditis. *Proc Natl Acad Sci USA* 1992;**89:**9131–5.
53. Badorff C, Lee GH, Lamphear BJ *et al.* Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy. *Nature Med* 1999;**5**:320–6.
54. Gravanis M, Sternby N. Incidence of myocarditis: a 10-year autopsy study from Malmö, Sweden. *Arch Pathol Lab Med* 1991;**115**:390–2.
55. Hufnagel G, Pankuweit S, Richter A *et al.* The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID). *Herz* 2000;**25**:279–85.
56. Herskowitz A, Campbell S, Deckers J *et al.* Demographic features and prevalence of idiopathic myocarditis in patients undergoing endomyocardial biopsy. *Am J Cardiol* 1993;**71**: 982–6.
57. Brown CA, O'Connell JB. Myocarditis and idiopathic dilated cardiomyopathy. *Am J Med* 1995;**99**:309–14.
58. Codd MB, Sugrue DD, Gersh BJ, Melton LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. *Circulation* 1989;**80**:564–72.
59. Felker GM, Hu W, Hare JM. The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients. *Medicine* 1999;**78**:270–83.
60. McDonagh TA. Asymptomatic left ventricular dysfunction in the community. *Curr Cardiol Rep* 2000;**2**:470–4.
61. Mosterd A, Hoes AW, de Bruyne MC *et al.* Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;**20**:447–55.
62. Grunig E, Tasman JA, Kucherer *et al.* Frequency and phenotypes of familial dilated cardiomyopathy. *J Am Coll Cardiol* 1998;**31**:186–94.
63. Baig MK, Goldman JH, Caforio APL. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. *J Am Coll Cardiol* 1998;**31**:195–201.
64. Dec GW, Fuster V. Medical progress: idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;**331**:1564–75.
65. Coughlin SS, Gottdiener JS, Baughman KL *et al.* Black-white differences in mortality in idiopathic dilated cardiomyopathy: the Washington DC Dilated Cardiomyopathy Study. *J Natl Med Assoc* 1994;**86**:583–91.

66.De Maria R, Gavazzi A, Recalcati F *et al.* Comparison of clinical findings in idiopathic dilated cardiomyopathy in women versus men. *Am J Cardiol* 1993;**72**:580–5.
67.Pearson GD, Veille J, Rahimtoola S *et al.* Peripartum cardiomyopathy. National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop Recommendations and Review. *JAMA* 2000;**2823**:1183–8.
68.Lampert MB, Lang RM. Peripartum cardiomyopathy. *Am Heart J* 1995;**130**:860–70.
69.Grogan M, Redfield MM, Bailey KR *et al.* Long-term outcome of patients with biopsy-proved myocarditis: comparison with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1995; **26**:80–4.
70.Lampert MB, Weinert L, Hibbard J *et al.* Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. *Am J Obstet Gynecol* 1997;**176**: 189–95.
71.Midei MG, DeMent SH, Feldman AM, Hutchins GM, Baughman KL. Peripartum myocarditis and cardiomyopathy. *Circulation* 1990;**81**:922–8.
72.Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME. Incidence of myocarditis in peripartum cardiomyopathy. *Am J Cardiol* 1994;**74**:474–7.
73.Felker GM, Jaeger CJ, Klodas E *et al.* Myocarditis and long-term survival in peripartum cardiomyopathy. *Am Heart J* 2000;**140**:785–91.
74.Pearl W. Familial occurrence of peripartum cardiomyopathy. *Am Heart J* 1995;**129**:421–2.
75.Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. *Am J Obstet Gynecol* 1997;**176**: 182–8.
76.Elkayam U, Tummala PP, Rao K *et al.* Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* 2001;**344**:1567–71.
77.Araki M, Kanda T, Imai S *et al.* Comparative effects of losartan, captopril, and enalapril on murine acute myocarditis due to encephalomyocarditis virus. *J Cardiol Pharmacol* 1995;**26**: 61–5.
78.Bozkat B, Villanueva F, Holubkov *et al.* Intravenous immune globulin in the therapy of peripartum cardiomyopathy. *J Am Coll Cardiol* 1999;**34**:177–80.
79.Dec GW, Waldman H, Southern J *et al.* Viral myocarditis mimicking acute myocardial infarction. *J Am Coll Cardiol* 1992;**20**: 85–9.
80.Costanzo-Nordin MR, O'Connell JB, Subramanian R, Robinson JA, Scanlon PJ. Myocarditis confirmed by biopsy presenting as acute myocardial infarction. *Br Heart J* 1985; **53**:25–9.
81.Hufnagel G, Pankuweit S, Richter A *et al.* The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID). *Herz* 2000;**25**:279–85.
82.Aretz HT. Myocarditis: the Dallas Criteria. *Human Pathol* 1987;**18**:619–24.
83.Lieberman EB, Herskowitz A, Rose NR, Baughman KL. A clinicopathologic description of myocarditis. *Clin Immunol Immunopathol* 1993;**68**:191–6.
84.McCarthy RE, Boehmer JP, Hruban RH *et al.* Long term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000;**342**:690–5.
85.Kuhn H, Breithardt G, Knieriern HJ *et al.* Prognosis and possible presymptomatic manifestations of congestive cardiomyopathy (COCM). *Postgrad Med J* 1978;**54**:451–9.
86.Morgera T, Di Lenarda A, Dreas L *et al.* Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *Am Heart J* 1992;**124**:455–66.
87.Mendes LA, Dec GW, Picard MH *et al.* Right ventricular dysfunction: an independent predictor of adverse outcome in patients with myocarditis. *Am Heart J* 1994;**128**:301–7.
88.Gagliardi MG, Bevilacqua M, Squitieri C *et al.* Dilated cardiomyopathy caused by acute myocarditis in pediatric patients: evolution of myocardial damage in a group of potential heart transplant candidates. *J Heart Lung Transplant* 1993;**12**:S224–S229.
89.Fuster V, Gersh BJ, Giuliani ER *et al.* The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;**47**: 525–31.
90.Redfield MM, Gersh BJ, Bailey KR, Ballard DJ, Rodeheffer RJ. Natural history of idiopathic dilated cardiomyopathy: effect of referral bias and secular trend. *J Am Coll Cardiol* 1993;**22**: 1921–6.
91.Redfield MM, Gersh BJ, Bailey KR, Rodeheffer RJ. Natural history of incidentally discovered, asymptomatic idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;**74**:737–9.
92.Kaneko K, Kanda T, Yamauchi Y *et al.* C-reactive protein in dilated cardiomyopathy. *Cardiology* 1998;**91**:215–19.
93.Sato Y, Yamada T, Taniguchi R *et al.* Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic cardiomyopathy are predictive of adverse outcomes. *Circulation* 2001;**103**:369–74.
94.Tsutamota T, Wada A, Maeda K *et al.* Plasma brain natriuretic peptide level as a biochemical marker of morbidity ad mortality in patients with asymptomatic or minimally symptomatic ventricular dysfunction: Comparison with plasma angiotensin II and endothelin-1. *Eur Heart J* 1999;**20**:1799–807.
95.Dao Q, Krishnaswamy P, Kasanegra R *et al.* Usefulness of a rapid, bedside test for brain natriuretic peptide in the evaluation of patients presenting to the emergency room with possible congestive heart failure. *J Am Coll Cardiol* 2000;**35**: 171A (Abstract 1049–152).
96.Nagaoka H, Isobe N, Kubota S *et al.* Myocardial contractile reserve as prognostic determinant in patients with idiopathic dilated cardiomyopathy without overt heart failure. *Chest* 1997;**111**:344–50.
97.Ramahi TM, Longo MD, Cadariu AR *et al.* Dobutamine–induced augmentation of left ventricular ejection fraction predicts survival of heart failure patients with severe non-ischaemic cardiomyopathy. *Eur Heart J* 2001;**22**:849–56.
98.Naqvi TZ, Goel RK, Forrester JS, Siegal RJ. Myocardial contractile reserve on dobutamine echocardiography predicts late spontaneous improvement in cardiac function in patients with recent onset idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1999;**34**;1537–44.
99.Treasure CB, Vita JA, Cox DA *et al.* Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. *Circulation* 1990;**81**:772–9.
100.Mathier MA, Rose GA, Fifeer MA *et al.* Coronary endothelial dysfunction in patients with acute-onset idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1998;**32**:216–24.

101. Taliercio CP, Seward JB, Driscoll DJ *et al.* Idiopathic dilated cardiomyopathy in the young: clinical profile and natural history. *J Am Coll Cardiol* 1985;**6**:1126–31.
102. Venugopalan P, Houston AB, Agarwal AK. The outcome of idiopathic dilated cardiomyopathy and myocaraditis in children from the West of Scotland. *Int J Cardiol* 2001;**78**:135–41.
103. Ilbäck N-G, Fohlman J, Friman G. Exercise in Coxsackie B3 myocarditis: effects on heart lymphocyte subpopulations and the inflammatory reaction. *Am Heart J* 1989;**117**:1298–302.
104. Maron BJ, Isner JM, McKenna WJ. Task Force 3: hypertrophic cardiomyopathy, myocarditis and other myopericardial diseases and mitral valve prolapse. *J Am Coll Cardiol* 1994;**24**:845–99.
105. Matsumori A, Wang H, Abelmann WH, Crumpacker CS. Treatment of viral myocarditis with ribavirin in an animal preparation. *Circulation* 1985;**71**:834–9.
106. Rezkalla S, Kloner RA, Khatib G, Khatib R. Beneficial effects of captopril in acute Coxsackie virus B3 murine myocarditis. *Circulation* 1990;**81**:1039–46.
107. Rezkalla S, Kloner RA, Khatib G, Smith FE, Khatib R. Effect of metoprolol in Coxsackie virus B3 murine myocarditis. *J Am Coll Cardiol* 1988;**12**:412–4.
108. Tominaga M, Matsumori A, Okada I, Yamada T, Kawai C. β-Blocker treatment of dilated cardiomyopathy. Beneficial effects of carvedilol in mice. *Circulation* 1991;**83**:2021–8.
109. Dong R, Liu P, Wee L, Butany J, Sole MJ. Verapamil ameliorates the clinical and pathological course of murine myocarditis. *J Clin Invest* 1992;**90**:2022–30.
110. Costanzo-Nordin MR, Reap EA, O'Connell JB, Robinson JA, Scanlon PJ. A nonsteroid anti-inflammatory drug exacerbates Coxsackie B3 murine myocarditis. *J Am Coll Cardiol* 1985;**6**: 1078–82.
111. Rezkalla S, Khatib G, Khatib R. Coxsackie B_3 murine myocarditis: deleterious effects of nonsteroidal anti-inflammatory agents. *J Lab Clin Med* 1986;**107**:393–5.
112. Matsui S, Matsumori A, Matoba Y, Uchida A, Sasayama S. Treatment of virus-induced myocardial injury with a novel immunomodulating agent, vesnarinone. *J Clin Invest* 1994; **94**:1212–17.
113. Cooper LT, Berry GJ, Shabetai R, for the Multicenter Giant Cell Myocarditis Study Group Investigators. Idiopathic giant-cell myocarditis – natural history and treatment. *N Engl J Med* 1997;**336**:1860–6.
114. Hunt SA, Baker DW, Chin MH *et al.* ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Am Coll Cardiol* 2001;**38**: 2101–13.
115. Kühl U, Schultheiss HP. Treatment of chronic myocarditis with corticosteroids. *Eur Heart J* 1995;**16**:168–72.
116. Drucker NA, Colan SD, Lewis AB *et al.* δ-Globulin treatment of acute myocarditis in the pediatric population. *Circulation* 1994;**89**:252–7.
117. Miri M, Vasiljevi J, Boji M *et al.* Long-term follow up of patients with dilated heart muscle disease treated with human leucocytic interferon alpha or thymic hormones. *Heart* 1996;**75**:596–601.
118. McNamara DM, Rosenblum WD, Janosko KM *et al.* Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. *Circulation* 1997;**95**:2476–8.
119. Ahdot J, Galindo A, Alejos JC *et al.* Use of OKT3 for Acute myocarditis in infants and children. *J Heart Lung Transplant* 2000;**19**:1118–21.
120. Kishimoto C, Thorp KA, Abelmann WH. Immunosuppression with high doses of cyclophosphamide reduces the severity of myocarditis but increases the mortality in murine Coxsackie virus B_3 myocarditis. *Circulation* 1990;**82**:982–9.
121. Yamada T, Matsumori A, Sasayama S. Therapeutic effect of anti-tumor necrosis factor-alpha antibody on the murine model of viral myocarditis induced by encephalomyocarditis virus. *Circulation* 1994;**89**:846–51.
122. Chapman NM, Tracy S. Can recombinant DNA technology provide useful vaccines against viruses which induce heart disease? *Eur Heart J* 1995;**16**:144–6.
123. O'Connell JB, Breen TJ, Hosenpud JD. Heart transplantation in dilated heart muscle disease and myocarditis. *Eur Heart J* 1995;**16**(Suppl. O):137–9.
124. Loria K, Jessurun J, Shumway SJ, Kubo SH. Early recurrence of chronic active myocarditis after heart transplantation. *Human Pathol* 1994;**25**:323–6.
125. Williams JF, Bristow MR, Fowler MB *et al.* Guidelines for the evaluation and management of heart failure. *Circulation* 1995;**92**:2764–84.
126. Cohn JN, Archibald DG, Ziesche S *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–52.
127. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–35.
128. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
129. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685–91.
130. Loeb HS, Johnson G, Henrick A *et al.* Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT Cooperative Studies Group. *Circulation* 1993; **87** (Suppl. 6):VI78–87.
131. Dickstein K, Chang P, Willenheimer R *et al.* Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. *J Am Coll Cardiol* 1995;**26**:438–45.
132. Pitt B, Segal R, Martinez FA *et al.* Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;**349**:747–52.
133. Pitt B, Poole-Wilson PA, Segal R *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – The Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;**355**:1582–7.
134. Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomised trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–75.

135.Uretsky BF, Young JB, Shahidi FE *et al.* Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of PROVED trial. *J Am Coll Cardiol* 1993;**22**:955–62.
136.Packer M, Gheorghiade M, Young J *et al.* Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1993;**329**:1–7.
137.Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–33.
138.Parillo JE, Cunnion RE, Epstein SE *et al.* A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N Engl J Med* 1989;**321**:1061–8.
139.McNamara DM, Holubkov R, Starling RC *et al.* Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation* 2001;**103**:2254–9.
140.Wojnicz R, Nowalany-Kozielska E, Wojciechowska *et al.* Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy. Two-year follow-up results. *Circulation* 2001;**104**:39–45.
141.Felix SB, Stuudt A, Dörffel WV, *et al.* Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy. Three-month results from a randomized study. *J Am Coll Cardiol* 2000;**35**:1590–8.
142.Wu LA, Lapeyre AC, Cooper LT. Current role of endomyocardial biopsy in the management of dilated cardiomyopathy and myocarditis. *Mayo Clin Proc* 2001;**76**:1030–8.
143.Fazio S, Sabatini D, Capaldo B *et al.* A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. *N Engl J Med* 1996;**334**:809–14.
144.Isgaard J, Bergh CH, Caidahl K *et al.* A placebo-controlled study of growth hormone in patients with congestive heart failure. *Eur Heart J* 1998;**19**:1704–11.
145.Packer M, O'Connor CM, Ghali JK *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure (PRAISE). *N Engl J Med* 1996;**335**:1107–14.
146.Factor SM, Minase T, Cho S, Dominitz R, Sonnenblick EH. Microvascular spasm in the cardiomyopathic Syrian hamster: a preventable cause of focal myocardial necrosis. *Circulation* 1982;**66**:342–54.
147.Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Preliminary communications: prolongation of survival in congestive cardiomyopathy by beta receptor blockade. *Lancet* 1979;**1**:1374–6.
148.Engelmeier RS, O'Connell JB, Walsh R *et al.* Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: double-blind, randomized, placebo-controlled trial. *Circulation* 1985;**72**:536–46.
149.Waagstein F, Bristow MR, Swedberg K. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;**342**:1441–6.
150.Tsuyuki RT, Yusuf S, Rouleau JL *et al.* for the RESOLVD Study Investigators. Combination of neurohormonal blockade with ACE inhibitors, angiotensin antagonists and beta-blockers in patients with congestive heart failure: design of the Random Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study. *Can J Cardiol* 1997;**13**:1166–74.
151.CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;**90**:1765–73.
152.CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999;**353**:9–13.
153.Packer M, Bristow MR, Cohn JN *et al.* The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;**334**:1349–55.
154.Packer M, Colucci WS, Sackner-Bernstein JD *et al.* Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. *Circulation* 1996;**94**:2793–9.
155.Hjalmarson A, Goldstein S, Fagerberg B *et al.* Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* 2000;**283**:1295–302.
156.Pitt B, Zannad F, Remme WJ *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–17.
157.Simonton CA, Chatterjee K, Cody RJ *et al.* Milrinone in congestive failure: acute and chronic hemodynamic and clinical evaluation. *J Am Coll Cardiol* 1985;**6**:453–9.
158.DiBianco R, Shabetai R, Kostuk W *et al.* for the Milrinone Multicenter Trial Group. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989; **320**:677–83.
159.Uretsky BF, Jessup M, Konstam MA *et al.* for the Enoximone Multicenter Trial Group. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. *Circulation* 1990;**82**:774–80.
160.Feldman AM, Bristow MR, Parmley WW *et al.* for the Vesnarinone Study Group. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993;**329**:149–55.
161.Doval HC, Nul DR, Grancelli HO *et al.* for Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;**344**: 493–8.
162.Singh SN, Fletcher RD, Fisher SG *et al.* for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; **333**:77–82.
163.Stevenson LW, Kormos RL, Bourge RC *et al.* Mechanical cardiac support 2000. Current applications and future trial designs. *J Am Coll Cardiol* 2001;**37**:340–70.

48 Hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is defined by the presence of left and or right ventricular hypertrophy in the absence of a cardiac or systemic cause. It predisposes to fatal cardiac arrhythmia, and is an important cause of sudden death in individuals aged less than 35 years. The following chapter reviews current data on etiology, diagnosis, and treatment of the disease, and briefly discusses areas of uncertainty.

Genetics

In the majority of cases, HCM is an autosomal dominant inherited disease caused by mutations in genes encoding cardiac sarcomeric proteins: β-myosin heavy chain on chromosome 14q11 (35%), cardiac troponin-T on chromosome 1q3 (15%), cardiac troponin-I on chromosome 19, α-tropomyosin on chromosome 15q2 (<5%), and myosin binding protein-C on chromosome 11p11·2 (15%).[1–5] Less than 1% of patients have mutations affecting the genes encoding the essential and regulatory myosin light chains (on chromosomes 3 and 12 respectively),[6] and cardiac actin on chromosome 15.[7] A further unconfirmed mutation in the gene encoding another sarcomeric protein, Titin on chromosome 2, has also been reported.[8]

A causal association between sarcomeric protein gene abnormalities and HCM is supported by a number of observations: cosegregation of mutation and disease in adult patients, the presence of mutations in patients with familial HCM but not in unrelated unaffected individuals, and an association between *de novo* mutations and sporadic disease.[9] The manner in which specific mutations result in disease is still poorly understood, but it might be expected that point mutations occurring within critical domains of sarcomeric protein molecules would result in predictable cardiac phenotypes. Preliminary studies have suggested that patients with troponin-T gene mutations tend to have mild ventricular hypertrophy and a high prevalence of sudden death, whereas most B-myosin heavy chain mutations that are associated with sudden death have at least moderate hypertrophy. Despite this, mutations affecting identical residues can result in very different clinical outcomes,[10] suggesting that other genetic and environmental factors influence disease expression. One such disease "modifier" may be angiotensin converting enzyme (ACE) gene polymorphism, with several papers suggesting that the DD genotype is associated with more severe hypertrophy than either ID or II genotypes.[11]

Recently, investigation of the functional consequences of sarcomeric protein mutations has been facilitated by the study of mutant β-myosin within human skeletal muscle. The demonstration of selective type 1 fiber atrophy, reduced shortening velocity, and impaired isometric force contraction[12,13] suggest that the characteristic myocardial pathology of HCM is a compensatory response to impaired contractile function. A mouse model, developed by introducing a ^{403}Arginine to glutamine α-myosin mutation, has supported this hypothesis by demonstrating cardiac dysfunction before the development of disarray and myocyte hypertrophy.[14] This study also demonstrated that male mutant mice had more extensive disease than their female counterparts, indicating that gender may also modulate phenotype expression.

Pathology

Although any pattern of ventricular hypertrophy can be seen in HCM, it is usually asymmetrically distributed, affecting the interventricular septum more than the free or posterior walls of the left ventricle.[15] Isolated right ventricular hypertrophy is unreported, but right-sided involvement in association with left ventricular hypertrophy occurs in up to a third of patients. Microscopically, HCM is characterized by disturbance of myocyte-to-myocyte orientation, with cells forming whorls around foci of connective tissue ("disarray"). Individual cells vary in size and length, and there is disruption of the normal intracellular myofibrillar architecture. Myocyte disarray is described in congenital heart disease, hypertension, and aortic stenosis, but it is more extensive in HCM, typically affecting more than 20% of ventricular tissue blocks post mortem and more than 5% of total myocardium. Other characteristic features include myocardial fibrosis and abnormal small intramural arteries.[16] The significance of the latter remains uncertain, but the presence of extensive small vessel disease in areas of fibrosis has suggested that they may cause myocardial ischemia. However, more recent data have shown that small vessel disease may be just as widespread in patients without extensive fibrosis.[17]

Pathophysiology

Hemodynamics

Systolic function is normal or "hyperdynamic" in most patients; 25% have a subaortic pressure gradient temporally associated with contact between the anterior mitral valve leaflet and the interventricular septum in systole.[18] It is thought that the mitral valve leaflet is drawn anteriorly by Venturi forces generated as blood is rapidly ejected through a narrowed left ventricular outflow tract. More recently the importance of abnormal anterior displacement of the papillary muscles during systole and other abnormalities of the mitral valve apparatus such as leaflet elongation have been recognized as contributory factors.[19,20] Although the magnitude of the outflow tract gradient is related to the time of onset and the duration of mitral valve–septal contact, its clinical significance is still debated. Several papers have shown that up to 80% of stroke volume may be ejected before a gradient develops, leading some authorities to suggest that "true" obstruction to flow does not occur.[21] In other patients, however, the presence of rapid deceleration in aortic flow at the time of septal–mitral contact, prolongation of left ventricular ejection time, and continued ventricular shortening after the onset of the outflow gradient in the absence of forward flow, suggest that the gradient is of hemodynamic significance.[22] An analysis of published hemodynamic and echocardiographic data[18] has shown that the percentage of stroke volume ejected before mitral–septal contact is inversely related to the magnitude of the gradient. Using this model, the gradient only becomes hemodynamically "significant" when it exceeds 50 mmHg.

Diastolic function

Up to 80% of patients have a range of diastolic abnormalities that include slow and prolonged isovolumic relaxation, reduced rate of rapid filling, and increased left ventricular stiffness.[23,24] The underlying cause of diastolic abnormalities are difficult to determine in individual patients, although myocardial fibrosis, left ventricular hypertrophy, myocyte disarray, myocardial ischemia, regional asynchrony, abnormal intracellular calcium fluxes, and disordered ventricular geometry may each play a role. While diastolic abnormalities are undoubtedly the cause of symptoms in many patients, they are also observed in asymptomatic individuals. A minority of patients have features resembling restrictive cardiomyopathy with severe diastolic dysfunction, markedly elevated filling pressures, mild or no hypertrophy and bi-atrial dilatation.

Myocardial ischemia

Evidence for myocardial ischemia in HCM includes reduced coronary flow reserve and lactate production during pacing or pharmacologic stress.[25,26] The etiology of myocardial ischemia in HCM is likely to be multifactorial. Abnormal intramural vessels with small lumina, increased metabolic demands of hypertrophied myocardium, elevated left ventricular filling pressures and abnormalities in diastolic filling and relaxation may all contribute.[27] Ischemia may lead to myocardial fibrosis and scarring and, as a consequence, contribute to systolic and diastolic left ventricular dysfunction. Ischemia may also be one of the factors that contribute to the multiplicity of events leading to ventricular arrhythmia and sudden death. In routine clinical practice, however, the evaluation of chest pain remains problematic because standard non-invasive screening tests, such as exercise testing and ^{201}thallium perfusion scintigraphy, are difficult to interpret in the presence of ventricular hypertrophy.[27–29]

Vascular responses to exercise

The physiologic response to exercise in normal individuals consists of an increase in systolic blood pressure associated with a three- to fourfold increase in cardiac output. In one third of patients with HCM the blood pressure fails to rise appropriately or may even fall during exercise, despite an appropriate increase in cardiac output. This abnormal reflex is thought to relate to the inappropriate activation of ventricular baroreceptors, which in turn leads to a withdrawal of efferent sympathetic tone resulting in a fall in systemic vascular resistance. The mechanisms responsible for baroreceptor activation are unknown but may relate to increased wall stress and myocardial ischemia.[30–32]

Clinical aspects

Epidemiology

Six studies have examined the prevalence of HCM[32–37] and, whilst comparison between them is difficult because of the different methodologies and selection criteria used (Table 48.1), most have suggested a figure of at least 0·2%. The exception[35] was based on an analysis of patient records

Table 48.1 Prevalence of hypertrophic cardiomyopathy

Author	*n*	Screening method	Prevalence (%)
Savage 1983[33]	3000	M-mode echo	0·30
Hada 1987[32]	12 841	ECG	0·17
Maron 1994[36]	714	2D-echo	0·50
Codd 1989[35]	3250	Echo/angio	0·02
Maron 1995[34]	4111	2D-echo	0·20

from institutions in Olmsted County, Minnesota. Although, the degree of surveillance of the resident population was admirably high, the fact that we now know that many patients with HCM have normal physical examinations and are asymptomatic makes it likely that some cases escaped detection during the initial clinical screening process. Furthermore, the reliance in the early part of the study on M-mode echocardiography means that many patients with hypertrophy in those regions of the myocardium not within the "sight" of the M-mode beam may have been overlooked, and would not have been allocated to one of the diagnostic codes used to select patients.

Natural history

It remains accepted wisdom that ventricular hypertrophy in patients with HCM usually develops during periods of rapid somatic growth, sometimes during the first year of life, but more typically during adolescence.[38–42] Until quite recently it was thought that the risk of developing hypertrophy after the age of 20 was very small. However, recent data from patients with mutations in myosin binding protein-C gene suggest that disease expression may occur throughout adult life. Patients may develop symptoms at any age, or remain asymptomatic all their lives. While most patients with HCM experience an age-dependent decline in exercise capacity and left ventricular function, only 5–10% of patients go on to develop rapid symptomatic deterioration in association with myocardial wall thinning, reduced systolic performance and increase in left ventricular end-systolic dimensions. Sudden death occurs throughout life, but the precise incidence varies in different series. Data from referral institutions suggest an overall annual mortality of 2%, with a maximum of 2–4% during childhood and adolescence,[38,39] whereas studies from several outpatient-based populations[40–42] suggest a lower figure of approximately 1% per annum. Data in infants with HCM are limited, but sudden death in the first decade is thought to be uncommon.[43]

Symptoms

In referral centers, exertional and atypical chest pains occur in approximately 30% of adult patients.[38,39] Dyspnea is also common in adults, and is probably caused by elevated pulmonary venous pressure secondary to abnormal diastolic function. Paroxysmal nocturnal dyspnea may occur in patients with apparently mild hemodynamic abnormalities. Its mechanism is uncertain, but myocardial ischemia or arrhythmia may be responsible. Approximately 15–25% of patients experience syncope and 20% presyncope. In some this is caused by paroxysmal arrhythmia, left ventricular outflow tract obstruction, conduction system disease or abnormal vascular responses during exercise, but in the majority no underlying cause is identified.

Examination

In most patients with HCM, physical examination is unremarkable. Patients may have a rapid upstroke to the arterial pulse, a forceful left ventricular impulse, and a palpable left atrial beat.[38] In approximately one third of patients, there is a prominent "a" wave in the jugular venous pressure, caused by reduced right ventricular compliance. The first and second heart sounds are usually normal, but a fourth heart sound, reflecting atrial systolic flow into a "stiff" left ventricle may be present. Up to one third of patients have a systolic murmur caused by left ventricular outflow tract turbulence. Physiologic and pharmacologic maneuvers that decrease afterload or venous return (standing, Valsalva, amyl nitrate) increase the intensity of the murmur, whereas interventions that increase afterload and venous return (squatting and phenylephrine) reduce it. The majority of patients with left ventricular outflow murmurs also have mitral regurgitation. Rarely, right ventricular outflow obstruction causes a systolic murmur best heard in the pulmonary area.

Electrocardiogram

While the literature suggests that the ECG is abnormal at least 80% of patients,[44] there are no specific changes diagnostic of HCM. Abnormal QRS morphology, repolarization abnormalities, and right and left atrial enlargement are common.[38,39,44] ST segment depression is frequent during exercise and daily life,[27,28] but is difficult to interpret in the presence of baseline ECG abnormalities. Abnormal Q waves occur in 25–50% of patients,[44–46] most commonly in the inferolateral leads. Suggested causes include abnormal septal activation and myocardial ischemia. Giant negative T waves in the midprecordial leads may be more common in Japanese patients with apical hypertrophy,[47] but they are also seen in Western patients with more extensive hypertrophy. Some patients have a short PR interval with a slurred QRS upstroke, but only a minority (approximately 5% of all patients with HCM)[48] have accessory atrioventricular pathways.

The incidence of arrhythmias detected during 48 hour ambulatory ECG monitoring is age dependent (Figure 48.1). Runs of non-sustained ventricular tachycardia (NSVT) occur in 25% of adults,[49,50] but most episodes are relatively slow, asymptomatic, and occur during periods of increased vagal tone (such as during sleep). Sustained ventricular tachycardia is uncommon and is sometimes associated with apical aneurysms.[51] Paroxysmal supraventricular arrhythmias occur in 30–50% of patients,[52] with sustained atrial fibrillation present in 5% of patients at diagnosis. A further 10% of patients develop atrial fibrillation over the subsequent 5 years.[52]

Echocardiography

When echocardiographic diagnostic criteria for HCM were established using M-mode imaging, asymmetrical

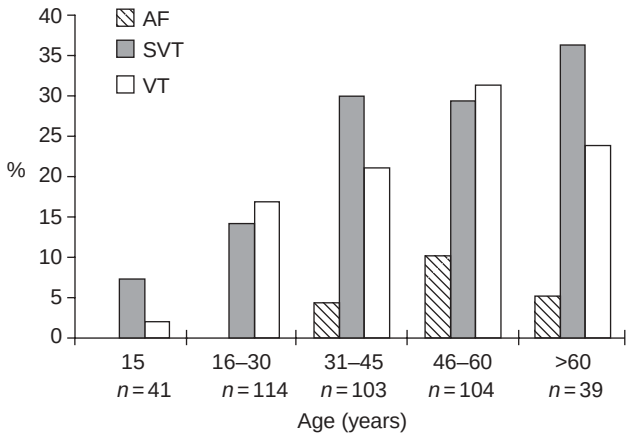

Figure 48.1 The frequency of supraventricular tachycardia (SVT), atrial fibrillation (AF), and non-sustained ventricular tachycardia (VT) at different ages in a consecutively referred population at St George's Hospital, London (unpublished data)

hypertrophy of the interventricular septum (ASH) was considered to be the *sine qua non* of the disease. However, subsequent two-dimensional echocardiographic studies have shown that any pattern of hypertrophy is compatible with the diagnosis.[53] The proportion of patients with concentric versus asymmetric hypertrophy depends on the definition employed. Thus, when a septal to posterior wall thickness ratio of 1·3:1 is used to define asymmetry, only 1–2% of patients have concentric left ventricular hypertrophy.[53] However, this proportion rises to approximately 30% when a ratio of 1·5:1 is used.[54] Criteria for abnormal wall thickness vary, but values exceeding two standard deviations from the mean corrected for age, sex, and height are generally accepted as diagnostic in the absence of any other cardiac or systemic cause. Doppler echocardiography is used to quantify the gradient across the left ventricular outflow tract using the modified Bernoulli equation:

$$\text{peak gradient} = 4V_{max}^2$$

where V_{max} is the maximum velocity across the left ventricular outflow tract. When it is not possible to obtain accurate Doppler measurements, the gradient can be estimated using M-mode recordings of the mitral valve and the formula:

$$\text{peak gradient} = 25(X/Y) + 25$$

where X is the duration of mitral–septal contact, and Y the period from the onset of systolic anterior motion of the mitral valve to the onset of mitral–septal contact.[18]

Cardiopulmonary responses to exercise

In most patients with HCM, peak oxygen consumption is below the predicted value corrected for age, sex, and height. This deficit is thought to relate to impaired oxygen delivery to contracting muscles and possibly abnormal peripheral oxygen utilization. Other indices of cardiopulmonary function that are often abnormal include a reduction in the anaerobic threshold and a reduced or flat oxygen pulse (VO_2/heart rate) due to a failure to maintain an increase in stroke volume during exercise.[55] Exercise testing in HCM provides an objective assessment of exercise capacity and may also be useful in differentiating HCM from other more rare causes of ventricular hypertrophy such as mitochondrial disorders.

Cardiac catheterization

In the modern era, cardiac catheterization is performed only in patients with refractory symptoms (particularly those with severe mitral regurgitation), and in order to exclude epicardial coronary artery disease in older patients with chest pain. In addition to an outflow gradient, a variety of hemodynamic abnormalities are described including elevated left ventricular end-diastolic and pulmonary capillary wedge pressures, and a "spike and dome" appearance in the aortic waveform. Right atrial and right ventricular pressures are usually normal unless there is a substantial right ventricular outflow gradient or severe "restrictive" physiology. Resting cardiac output is typically normal or increased, except in patients with "end stage" ventricular dilatation.

In patients with hypertrophy confined to the distal left ventricle, ventriculography may show a characteristic "spade-shaped" appearance caused by the encroachment of hypertrophied papillary muscles. Coronary arteriography is usually normal, but systolic obliteration of epicardial vessels is described. Muscle bridges are also described but their relevance to an individual patient's symptoms is often difficult to assess.

Radionuclide studies

Several studies have used stress radionuclide imaging to study myocardial perfusion in patients with HCM. Fixed ^{201}thallium perfusion defects have been associated with increased left ventricular cavity dimensions, impaired systolic function, and reduced exercise capacity, and are thought to represent myocardial scars.[29] Reversible regional ^{201}thallium defects are present in over 25% of patients, but correlate poorly with symptomatic status.[27,29] It has been suggested that reversible defects are associated with a poor prognosis, but one large prospective study has failed to demonstrate any relation with medium-term outcome.[56]

Using positron emission tomography (PET) a reduction in coronary vasodilator reserve has been observed both in hypertrophied and non-hypertrophied regions of myocardium during dipyridamole-induced coronary microvascular vasodilatation.[26] The reduction in vasodilator reserve may be more

pronounced in patients with a history of chest pain and ST-segment depression.[26] PET has also demonstrated subendocardial hypoperfusion after dipyridamole infusion across the septum of patients with asymmetrical septal hypertrophy. PET has been used to investigate the relationship between myocardial blood flow and metabolism using fluorine-18 labeled deoxyglucose (FDG).[57,58] Areas of blood flow/FDG mismatch thought to indicate the presence of ischemic myocardium have been described both at rest and during exercise. Other studies, however, have demonstrated selective abnormalities of glucose metabolism, independent of coronary flow[59] and, more recently, studies have suggested that heterogeneous FDG uptake may relate to regional systolic function and age.

Radionuclide angiography has been used to investigate global and regional left ventricular function in HCM, and has shown prolonged isovolumic relaxation, delayed peak filling, reduced relative volume during the rapid filling period, and increased atrial contribution to filling and regional heterogeneity in the timing, rate, and degree of left ventricular relaxation and diastolic filling.[60,61] A reduced peak filling rate has been shown to be associated with an increased disease-related mortality,[61] but its predictive value is not high and adds little to conventional risk stratification.

Differential diagnosis

In adults, unexplained left ventricular hypertrophy exceeding two standard deviations from the normal (typically, >1·5 cm) is usually sufficient to make a diagnosis of HCM. In children and adolescents the diagnosis can be more difficult as young "gene carriers" may not manifest the complete phenotype. A number of rare genetically determined disorders can present with a cardiac phenotype similar to HCM, but most are distinguished by the presence of other clinical features. Rare exceptions include patients with Friedreich's ataxia that present with cardiac disease before the onset of obvious neurological deficit,[62] Noonan syndrome patients with only very mild somatic abnormalities,[63] and patients with primary mitochondrial disease that do not have clinical evidence for neuromuscular disease (unpublished data). Recently mutations in the gene encoding the γ2 subunit of AMP-activated protein kinase (7q36) have been described in two families with left ventricular hypertrophy with Wolff–Parkinson–White syndrome. When activated, this gene functions to protect the cell from critical depletion of ATP by activating glycolysis and fatty acid uptake during hypoxic stress or extreme metabolic demand.[64] In routine clinical practice the two most commonly encountered areas of difficulty are the differentiation of HCM from "secondary" left ventricular hypertrophy as seen in hypertension and the "athlete's heart", and the more recently identified problem of incomplete penetrance in adults.

Hypertension

Left ventricular hypertrophy occurs in up to 50% of hypertensive patients. The hypertrophic response is determined by a number of factors including the degree of hypertension, sex, and race.[65] In general, patients with HCM tend to have more severe hypertrophy than hypertensives, and the presence of a maximal wall thickness of more than 2 cm in a Caucasian patient should always raise the suspicion of HCM (Table 48.2).[66,67] Concentric hypertrophy is more frequent in patients with hypertension, and asymmetric septal hypertrophy more so in HCM, but the specificity of each pattern is not high. In contrast, isolated distal ventricular hypertrophy does seem to be highly predictive of HCM. Systolic anterior motion of the mitral valve occurs in both diseases, but the combination of complete SAM with a substantial left ventricular outflow gradient and asymmetric septal hypertrophy is more indicative of HCM. A number of other echo-derived parameters such as left ventricular cross-sectional area and direction-dependent contraction have been suggested as discriminants, but these require further study.[68]

Table 48.2 Relation of the pattern of left ventricular hypertrophy to underlying etiology

	ASH[a] (%)	Distal (%)	Symmetrical (%)	Wall thickness ≥2.0 cm (%)
Sensitivity	56 (83)[b]	10	81	40 (40)
Specificity	81 (56)	100	66	93 (93)
Predictive value of positive test	83 (70)	100	58	81 (83)

[a] Defined by an interventricular septum to posterior wall thickness ratio of ≥1·5:1.
[b] Values in parentheses from Keller *et al.*
Sensitivity, specificity and predictive value of asymmetric hypertrophy (ASH and distal) in diagnosing hypertrophic cardiomyopathy and symmetrical hypertrophy in diagnosing secondary hypertrophy. The same parameters are shown for a maximal wall thickness or septal thickness of ≥2·0 cm in diagnosing HCM in patients with symmetric hypertrophy. (Taken from Shapiro *et al*[54] and Keller *et al.*[56])

Athlete's heart

While HCM is the commonest cause of unexpected sudden death in young athletes,[69,70] cardiovascular adaptation to regular training can make differentiation of the "athlete's heart" from HCM problematic. The ability to distinguish

these two entities is of crucial importance, as continued competitive activity in a young person with HCM may threaten that individual's life, whereas an incorrect diagnosis of HCM in a normal athlete may unnecessarily deprive them of their livelihood. The presence of symptoms, a family history of HCM and/or premature sudden death should always raise the level of suspicion for HCM. In general, athletic training is associated with only a modest increase in myocardial mass, with <2% of elite athletes having a wall thickness >13 mm.[71] A diagnosis of HCM in an elite athlete is very likely when an individual has a left ventricular wall thickness >16 mm in men or ≥13 mm in women. Other echocardiographic features favoring a diagnosis of HCM include small left ventricular cavity dimensions (athletes tending to have increased left ventricular end-diastolic dimensions), left atrial enlargement, and the presence of a left ventricular outflow gradient.[72] Doppler evidence of diastolic impairment is also highly suggestive of HCM. The "athletic" ECG often displays voltage criteria for left ventricular hypertrophy, sinus bradycardia, and sinus arrhythmia, but Q waves, ST segment depression, and/or deep T wave inversion is highly suggestive of HCM. Incremental exercise testing may also be useful in distinguishing patients with HCM, a maximal oxygen consumption >50 ml/kg/min or 20% above the predicted maximal value being highly suggestive of athletic adaptation.[55] The type of training may also be relevant to diagnosis as hypertrophy is greatest in specific sports such as rowing and cycling. Isometric activities do not appear to cause a substantial hypertrophic response. Very occasionally a period of detraining over 3–6 months is required to distinguish HCM from the athlete's heart.

Incomplete penetrance in adults

It is increasingly recognized that some adults with sarcomeric protein mutations do not fulfill conventional echocardiographic criteria for HCM. New clinical diagnostic criteria for HCM based on the assumption that the probability of disease in a first-degree relative of a patient with HCM is 50%, have recently been proposed (Box 48.1).[75] It is important to realize that they are intended to apply only to *unexplained* ECG and echocardiographic abnormalities in first-degree adult relatives of individuals with proven HCM, and not to isolated cases of minor echocardiographic and ECG abnormalities.

HCM in the elderly

"Inappropriate" or idiopathic left ventricular hypertrophy has long been recognized in patients over the age of 65 years.[74–77] The pattern of disease in this age group is said to differ from that observed in younger patients with HCM in that symptoms occur late in life, the prognosis for most patients is relatively good, and many have mild hypertension. The echocardiographic features of HCM in the elderly are often the same as in the young, but some morphological differences are described: in comparison to their younger counterparts, patients with "elderly HCM" tend to have relatively mild hypertrophy localized to the anterior interventricular septum; the left ventricular cavity is commonly ovoid or ellipsoid rather than crescentic. Elderly patients with left ventricular outflow tract obstruction tend to have more severe narrowing of the left ventricular outflow tract, anterior displacement of the mitral valve apparatus,

Box 48.1 Proposed diagnostic criteria for hypertrophic cardiomyopathy in first-degree relatives of patients with definite diagnosis of hypertrophic cardiomyopathy

MAJOR	MINOR
● *Echocardiography*	
Left ventricular wall thickness ≥13 mm in the anterior septum or posterior wall or ≥15 mm in the posterior septum or free wall	Left ventricular wall thickness of 12 mm in the anterior septum or posterior wall, or of 14 mm in the posterior septum or free wall
Severe SAM (septal leaflet contact)	Moderate SAM (no leaflet-septal contact)
	Redundant MV leaflets
● *Electrocardiography*	
LVH + repolarization changes (Romhilt & Estes)	Complete BBB or (minor) interventricular conduction defects (in LV leads)
T wave inversion in leads I and aVL (≥3 mm) (with QRS-T wave axis difference ≥300), V3–V6 (≥3 mm) or II and III and aVF (≥5 mm)	Minor repolarization changes in LV leads
Abnormal Q waves (>40 ms or >25% R wave) in at least two leads from II, III, aVF (in the absence of left anterior hemiblock), V1–V4; or I, aVL, V5–V6	Deep S in V2 (>25 mm)
	Unexplained syncope, chest pain, dyspnea

It is proposed that diagnosis of hypertrophic cardiomyopathy in first-degree relatives of patients with the disease would be fulfilled in the presence of one major criterion, or two minor echocardiographic criteria, or one minor echocardiographic plus two minor ECG criteria. (From McKenna WJ *et al.*[73].)

restricted anterior excursion of the anterior mitral valve leaflet in systole, and a larger area of contact between the mitral valve leaflet and the septum. Mitral valve calcification is often seen in elderly patients, but it is not associated with a greater degree of left ventricular outflow tract obstruction. The frequency of moderate to severe symptoms is similar in young and elderly patients, but the limited published evidence indicates that the elderly respond well to pharmacologic and surgical therapy and have a relatively good prognosis.[76] In spite of recent evidence demonstrating *de novo* hypertrophy in middle-aged patients with myosin binding protein-C mutations, it remains uncertain whether the majority of patients with this so-called elderly phenotype have a separate disease entity reflecting a polygenic response to hypertrophic stimuli. Hypertension is more frequent in the elderly population, but the failure to demonstrate any difference in left ventricular morphology in hypertensive and non-hypertensive HCM patients (with the possible exception of posterior wall thickness) has led some to suggest that it is not an important factor.[77] Other "hypertrophic" stimuli that may be present in older patients include increased angulation and decreased compliance of the aorta.

Risk stratification in HCM

Markers of sudden death risk in HCM

Although sudden death in HCM is a relatively uncommon event, the fact that it frequently occurs in young asymptomatic individuals gives it a particular significance to families affected by HCM and to the wider community. Clinical risk stratification in patients with HCM is based on the premise that, if sudden death can be prevented, the natural history of the disease for most patients is relatively benign. The absence of risk factors also facilitates reassurance of low risk individuals.

A number of studies have shown that individual sarcomeric protein gene mutations have different prognostic implications (Figure 48.2). For example, most families with troponin-T mutations described to date have a poor prognosis, whereas β-myosin heavy chain mutations may have a benign or malignant course. Early investigations of HCM-related α-tropomyosin disease have suggested a favorable prognosis.[79] In spite of these data, genetic testing at present has a limited role in risk stratification because the number of families studied is small, and even within families there is marked heterogeneity of disease expression.

Clinically a young age at diagnosis is associated with an increased risk of sudden death (Figure 48.3). Other recognized risk markers in this age group include a family history of multiple premature sudden deaths, and recurrent unexplained syncopal episodes.[39] More recently abnormal blood pressure responses during exercise have been shown to be

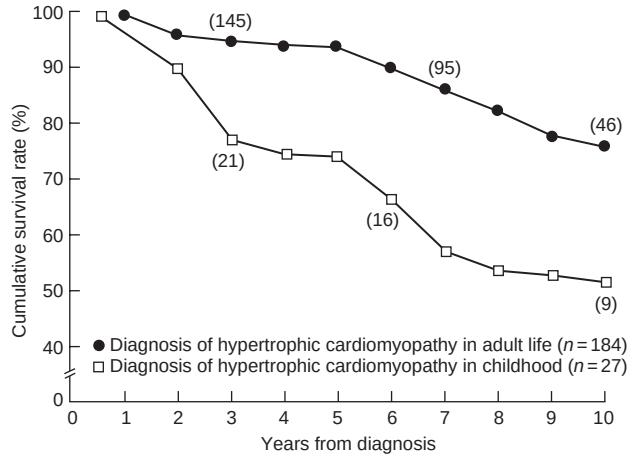

Figure 48.2 Cumulative survival from the year of diagnosis in 211 medically treated patients with hypertrophic cardiomyopathy[92]

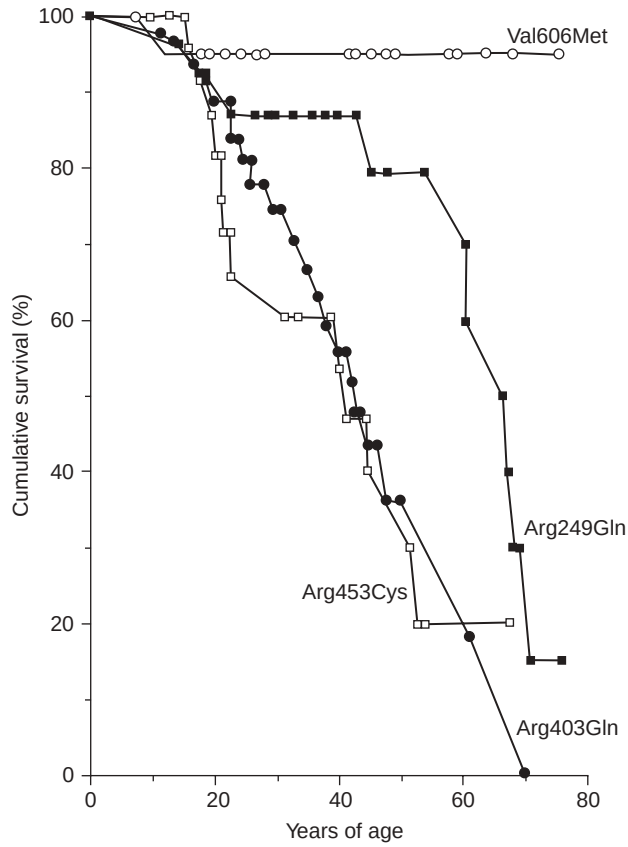

Figure 48.3 Kaplan–Meier survival curves for individuals with HCM and different gene mutations. Two β-myosin points are reported to be associated with near normal survival: Val606→Met (○) and Leu908→Val. The mutations Arg403→Gln (●), Arg453Cys (□), and Arg249Gln (■) are associated with a poorer prognosis[10]

associated with a higher mortality in patients less than 40 years of age.[30] Abnormal blood pressure responses are seen more frequently in patients with a family history of sudden death and small left ventricular cavity dimensions.[31,80]

Two recent studies have shown a correlation between severe left ventricular hypertrophy (defined as a maximal wall thickness ≥30 mm) and prognosis.[81,82] However, taken in isolation, left ventricular hypertrophy has a relatively low positive predictive accuracy; furthermore, the majority of patients who die suddenly have wall thickness values <30 mm. Severe left ventricular hypertrophy may be more prognostically important in the young, but further studies are required.

Two studies[49,50] have shown that NSVT in adults with HCM is associated with an increased risk of sudden death. Its clinical value is however, limited by a modest positive predictive accuracy of 22%, and a low incidence in children. Recently it has been suggested that NSVT is significant only when episodes are repetitive, prolonged and/or associated with symptoms. There are however no data to support this.

A number of other non-invasive and invasive electrophysiologic parameters have been evaluated in an attempt to further refine clinical risk stratification. QT and QTc intervals are often prolonged in patients with HCM, but no study has shown a convincing association with the risk of sudden death.[83–85] QT dispersion may be a more sensitive marker of the propensity to ventricular arrhythmia but further studies in large well-characterized populations are necessary. Abnormal signal averaged ECGs (SAECGs) are relatively common in patients with HCM and NSVT, the best predictor of NSVT being a reduced voltage (<150 μV) in the initial portion of the high gain QRS complex (sensitivity 95%, specificity 74%, positive predictive accuracy 64%).[86] Unfortunately, abnormal SAECGs are not associated with other clinical risk factors and do not identify patients who go on to develop sustained ventricular arrhythmia or sudden death. Similarly, while, global and specific vagal components of heart rate variability (HRV) are reduced in patients with HCM and NSVT, abnormal HRV is not predictive of sudden catastrophic cardiac events.[87]

The role of programmed electrical stimulation in patients with HCM remains controversial. The largest series from a single center[48,88] reports that programmed ventricular stimulation using up to three premature stimuli in the right and/or left ventricle produces sustained ventricular arrhythmia (that is, lasting for more than 30 seconds or associated with hypotension) in 43% of patients selected on the basis of a history of previous cardiac arrest, syncope, palpitations, or non-sustained ventricular tachycardia on Holter. Inducible sustained ventricular arrhythmia was associated with a history of cardiac arrest *or* syncope and, in a subsequent study, was associated with a reduced survival. The sensitivity, specificity, and predictive accuracy for predicting subsequent cardiac events were 82%, 68%, and 17% respectively. However, almost three quarters of the patients with sustained ventricular arrhythmias required three premature stimuli for induction. The experience in other cardiac diseases has shown that, whilst "aggressive" protocols using three or more stimuli are highly sensitive, their specificity is low. In addition 76% of patients had polymorphic ventricular tachycardia or fibrillation rather than sustained monomorphic ventricular tachycardia, which is generally thought to be a more sensitive and specific marker of sudden death risk. The interpretation of these published data in HCM and their translation into clinical practice is further complicated by the selection criteria used to select patients as "low-risk" patients were under-represented in the analysis. The general view at present is that programmed stimulation is of limited use in the assessment of risk in HCM.

Recently, the putative arrhythmogenic substrate in HCM has been investigated by analyzing changes in individual paced ECG transitions ("fractionation") recorded at three sites in the right ventricle.[89] Compared with controls, patients with a history of ventricular fibrillation have prolongation of the paced ECG at relatively long extrastimulus coupling intervals. Patients with a family history of premature sudden death or NSVT exhibit responses that span the range from "high risk" (ventricular fibrillation) to "low risk" (no adverse prognostic features).

Identification of high-risk patients

The identification of individuals at high risk of sudden death has been hampered by the inherent difficulties of studying a disease with a low prevalence and event rate. This is further compounded by the low positive predictive accuracy of most suggested risk markers for sudden death. Recent data have suggested that risk may be assessed using a small number of easily determined risk markers, specifically, non-sustained ventricular tachycardia, left ventricular wall thickness (≥30 mm), abnormal blood pressure response in those under 80 years of age, family history of multiple sudden deaths, and recurrent unexplained syncope. *Patients with none of the above risk factors have <1% estimated annual risk of sudden death compared with patients with two or more risk factors who have a 4–6% annual risk of sudden death.*[90] **Grade B** Risk stratification remains problematic in those patients with a single risk factor, some of whom are clearly at increased risk of sudden death. Further work to identify which of these individuals would benefit from prophylactic therapy is required.

Management of the "high-risk" patient

There is now general agreement that low-risk adult patients – that is, those without symptoms or risk factors – can be readily identified, and in most populations represent the majority of individuals with the disease. For patients who are considered to be at high risk of sudden death,

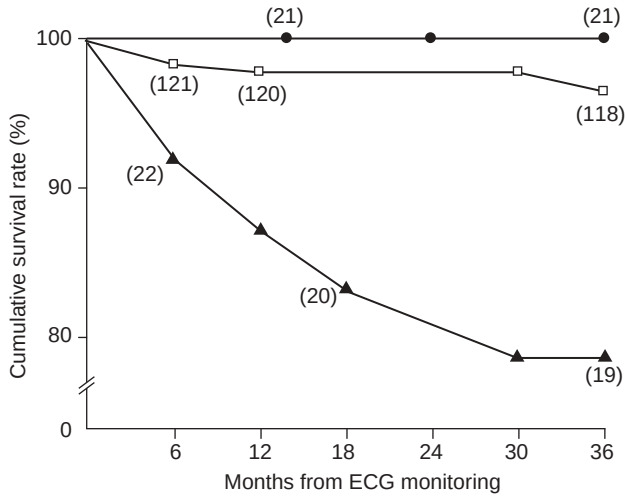

Figure 48.4 Cumulative survival curves for patients with non-sustained ventricular tachycardia treated with either conventional antiarrhythmic drugs (▲) or amiodarone (●), and for patients without non-sustained ventricular tachycardia (□).[91]

implantable cardioverter defibrillators (ICDs) are increasingly seen as the preferred therapy. The ICD has been accepted as a superior treatment to antiarrhythmic medication for the prevention of life-threatening ventricular arrhythmias and sudden death in high-risk patients with other cardiovascular diseases. Although randomized data comparing amiodarone to ICD in high-risk patients with hypertrophic cardiomyopathy are not currently available, ICDs have been shown to be effective in terminating life-threatening tachyarrhythmias. In addition the pacing capabilities of the most recent defibrillators offer protection from cardiac arrest from bradyarrhythmias. Studies have shown that low-dose amiodarone can reduce the incidence of sudden death in adults with NSVT (Figure 48.4),[91] and in children considered to be at risk,[92] although the finding of appropriate discharges in patients with ICDs already taking amiodarone suggests that the ICD may be superior in preventing sudden death. **Grade B** Approximately 30% of patients with HCM and a history of cardiac arrest have a further event within 6 years of their first episode. There is general agreement that, in patients with a history of ventricular fibrillation, arrest ICD is the preferred therapy.[93–97] In patients with multiple risk factors ICDs are increasingly seen as the preferred therapy. In patients with a single risk factor, management needs to be individualized; amiodarone or ICD may be appropriate in selected individuals.

Symptomatic therapy

Obstructive hypertrophic cardiomyopathy

Most physicians still use β blockade as the first-line drug therapy in patients with left ventricular outflow obstruction. **Grade B** While some studies have suggested that up to 70% of patients improve with β blockers, high doses are frequently required and side effects may be limiting. The beneficial effects of β blockers on symptoms (principally dyspnea and chest pain) and exercise tolerance appear to result largely from a decrease in the heart rate with a consequent prolongation of diastole and increased passive ventricular filling and myocardial blood flow. By reducing the inotropic response, β blockers may also lessen myocardial oxygen demand and decrease the outflow tract gradient during exercise, when sympathetic tone is increased.

Verapamil has favorable effects on symptoms secondary to improved ventricular filling and probable reduction in myocardial ischemia. In patients with a substantial outflow tract gradient or markedly elevated pulmonary pressure (or both), verapamil should be used with caution, however, as the drug's vasodilatory effect may lead to serious hemodynamic complications. There is no evidence that the administration of β blockers and verapamil together is more advantageous than the use of either drug alone, and there is no evidence that either protects patients from sudden death.

Disopyramide reduces left ventricular outflow tract gradients and relieves symptoms by virtue of its negative inotropic properties and has been extensively used in some centers for symptomatic therapy in patients with significant outflow obstruction.[99,100] Reduction in SAM (systolic anterior motion), left ventricular ejection time and improved exercise capacity and functional status are all described but, in common with other therapies, the initial hemodynamic and clinical benefits may decrease with time. Because disopyramide may shorten the atrioventricular nodal conduction time and thus increase the ventricular rate during paroxysmal atrial fibrillation, supplementary therapy with β blockers or verapamil in low doses is advisable. The anticholinergic effects of disopyramide (dry mouth, urinary retention, glaucoma) may limit the drug's use, particularly in elderly patients.

When drug therapy fails or is only partially effective, surgery remains the "gold standard" treatment.[101–107] The most frequently performed operation is septal myotomy–myectomy in which a wedge of myocardium is excised from the upper interventricular septum via a transaortic approach. Operative mortality in experienced centers is now 1–2%, but may be higher in less experienced units. Most studies indicate that operative mortality is higher when myectomy is combined with other cardiac operations. The incidence of non-fatal complications such as conduction system disease and ventricular septal defect has declined with modification of surgical practice and the use of intraoperative transesophageal echocardiography. Some data suggest that surgery reduces or abolishes resting gradients in 95% of cases, and that 70% of patients show useful symptomatic and functional improvement. However, at least 10% continue to experience significant symptoms. Mitral valve replacement has been proposed as an alternative to myectomy, its

attraction being that it avoids potential complications of ventricular septal defect and complete heart block. In a series of 58 patients, mitral valve replacement resulted in a substantial reduction in left ventricular outflow gradient, improved symptomatic class, and an actuarial survival at 3 years of 86%.[108] However, early operative mortality was 9%, and only 68% of patients were free from thromboembolism, anticoagulant-related problems, congestive cardiac failure, and reoperation. Thus mitral valve replacement, whilst successfully treating outflow tract obstruction, is usually advocated only in selected patients. These include patients with severe mitral regurgitation from intrinsic abnormalities of the valve apparatus; patients with mid-cavity obstruction from anomalous insertion of papillary muscle into the anterior mitral leaflet; and patients with only mild septal hypertrophy, which suggests that muscular resection would be associated with a high risk of septal perforation or an inadequate hemodynamic result. **Grade B** Mitral valvuloplasty has also been combined with myotomy–myectomy in some patients with particularly elongated mitral leaflets.

Dual chamber pacing has been proposed as a less invasive alternative to surgery. Several studies have described significant gradient reduction in patients treated with atrioventricular synchronous pacemakers programmed with a short atrioventricular delay to ensure constant capture of the right ventricle.[109–113] It was initially thought that pacing reduced the outflow gradient by causing paradoxical movement of the interventricular septum, but it is now realized that many aspects of ventricular activation are altered by right ventricular pacing, and it is likely that reduced or delayed septal thickening, reduced contractility, and altered papillary muscle movement contribute to gradient reduction. In general, outflow gradients can be reduced by approximately 50%, but the translation of this benefit into useful clinical improvement is very variable and unpredictable. Some workers suggest that suboptimal responses to pacing may be caused by short native PR intervals that make it impossible to achieve maximum pre-excitation simultaneously and maintain normal atrial filling of the left ventricle. This can be overcome in some patients by pharmacologically increasing the PR interval with β blockers and/or calcium antagonists, but some groups controversially advocate radiofrequency ablation of the atrioventricular node in order to achieve "optimal" AV pacing. Other unresolved issues include the significance of the appreciable placebo effect of pacing demonstrated in at least two randomized studies, the effect of long-term pacing on left ventricular wall thickness, and the role of pacing in the young. Despite the drawbacks, pacing may be an option in a minority of drug refractory patients in whom surgery poses an unacceptable operative risk.

Several centers are now examining a novel approach to gradient reduction that uses injection of alcohol into the first septal perforator branch of the left anterior descending artery to produce a "chemical myectomy".[114–116] Published data suggest that procedure-related mortality is less than 1% in experienced centers, but deaths from conduction system damage and inadvertent injection of alcohol into other myocardial segments are recognized. This later problem can be minimized by the use of intracoronary myocardial contrast echocardiography. Preliminary data indicate that significant gradient reduction and improvement in symptoms can be achieved. However, as with dual chamber pacing, the actual mechanism of gradient reduction and symptomatic improvement is likely to be more complex than the creation of a "localized" scar in the interventricular septum. The most frequent complication reported to date is complete heart block, although the incidence varies between the small numbers of centers currently performing the procedure. There has been some concern regarding the short- and long-term consequences of deliberately producing a myocardial infarct such as a possible predisposition to ventricular dysarrhythmias and progressive left ventricular wall thinning. *Long-term follow up data is not yet available in patients who have undergone pacing or alcohol septal ablation.*

Non-obstructive HCM

The treatment options in symptomatic patients without an outflow tract gradient are limited. β Blockers and calcium-channel antagonists can be used alone or in combination, and, in patients with symptoms suggestive of pulmonary venous congestion, diuretics may also be helpful. In a small number of patients with severe refractory chest pain, a variety of techniques, such as transcutaneous nerve stimulation and cardiac denervation, have been used with variable success.

For the minority of patients with HCM, who arrive at an end stage characterized by wall thinning, cavity enlargement, and systolic impairment treatment, should include standard therapeutic agents for heart failure associated with systolic dysfunction, including diuretics, ACE inhibitors, and digitalis. Ultimately these patients may become candidates for heart transplantation. **Grade C**

Management of supraventricular arrhythmia

Paroxysmal episodes of supraventricular tachycardias, such as atrial fibrillation or flutter, can lead to rapid clinical deterioration by reducing diastolic filling and cardiac output, usually as a consequence of the high ventricular rate. Conversely chronic supraventricular arrhythmias are often well tolerated if the heart rate is adequately controlled.[47] Established atrial fibrillation/flutter should be cardioverted, but when restoration of sinus rhythm is not possible, β blockers and verapamil are usually efficacious in controlling the heart rate. **Grade B** Occasionally radiofrequency ablation of the atrioventricular node and implantation of a pacemaker may be necessary in selected patients to achieve adequate rate control. In patients with recurrent

supraventricular arrhythmias, treatment is indicated only if they are sustained (>30 seconds) or associated with symptoms. Specific medical therapy with low dose amiodarone (1000–1400 mg/week), or β blockers with class III action (for example, sotalol) is effective in maintaining sinus rhythm, and in controlling the ventricular rate during breakthrough episodes. The role of other drugs such as class 1 agents is uncertain. Atrial fibrillation/flutter in HCM is associated with a significant risk of thromboembolism, and anticoagulation should be considered in all patients when atrial fibrillation/flutter is sustained or recurs frequently.

Conclusion

HCM is a disorder of diverse etiology, pathology, and clinical presentation. While recent advances in molecular genetics and clinical characterization have led to greater understanding of the disease and its management, several clinical issues remain unresolved. Nevertheless, the pace of current research suggests that many of these controversies will be resolved over the next decade.

Summary 1

- The majority of cases of hypertrophic cardiomyopathy (HCM) are caused by mutations in genes encoding cardiac sarcomeric proteins.
- Although symptoms of chest pain, dyspnea, palpitation, and syncope are common, many patients are asymptomatic and may present for the first time with sudden death.
- Recurrent syncope, a family history of premature sudden death, non-sustained ventricular tachycardia during ambulatory ECG, left ventricular wall thickness ≥30 mm, and abnormal exercise blood pressure responses are associated with an increased risk of sudden death.

Summary 2

- Symptomatic patients with left ventricular outflow gradients should be initially treated with β blockers or disopyramide. If drug therapy is ineffective, patients should be considered for surgery. **Grade B**
- Pacing and alcohol septal myectomy are a viable option for patients with symptomatic left ventricular outflow gradient who are unsuitable or not keen on surgery. **Grade B**
- All patients should undergo non-invasive risk stratification using ambulatory electrocardiography and exercise testing. **Grade B**
- Low-risk adults can generally be reassured that their prognosis is good. High-risk patients require further assessment and should be considered for amiodarone or ICD therapy. **Grade B**

References

1. Kimura A, Harada H, Park J-E *et al.* Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. *Nature Genet* 1997;**16**:379–82.
2. Jarcho JA, McKenna WJ, Pare JA *et al.* Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N Engl J Med* 1989;**321**:1372–8.
3. Thierfelder L, MacRae C, Watkins H *et al.* A familial hypertrophic cardiomyopathy locus maps to chromosome 15q2. *Proc Nat Acad Sci USA* 1993;**90**:6270–4.
4. Watkins H, MacRae C, Thierfelder L *et al.* A disease locus for familial hypertrophic cardiomyopathy maps to chromosome 1q3. *Nature Genet* 1993;**3**:333–7.
5. Bonne G, Carrier L, Bercovici J *et al.* Cardiac myosin binding protein C gene splice acceptor site mutation is associated with familial hypertrophic cardiomyopathy. *Nature Genet* 1995; **11**:438–40.
6. Poetter K, Jiang H, Hassanzadeh S *et al.* Mutations in either the essential or regulatory light chains of myosin are associated with a rare myopathy in human heart and skeletal muscle. *Nature Genet* 1996;**13**:63–9.
7. Oslon TM, Doan TP, Kishimoto NY, Whitby FG, Ackerman MJ, Fananapazir L. Inherited and *de novo* mutations in the cardiac actin gene cause hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2000;**32**:1687–94.
8. Satoh M, Takahashi M, Sakamoto T, Hiroe M, Marumo F, Kimura A. Structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. *Biochem Biophys Res Commun* 1999;**262**:411–17.
9. Watkins H, Thierfelder L, Hwang D, McKenna WJ, Seidman JG, Seidman CE. Sporadic hypertrophic cardiomyopathy due to *de novo* myosin mutations. *J Clin Invest* 1992;**90**:1666–71.
10. Watkins H, Rozenzweig A, Hwang DS *et al.* Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med* 1992; **326**:1108–14.
11. Lechin M, Quinones MA, Omran A *et al.* Angiotensin converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. *Circulation* 1995;**92**:1808–12.
12. Rayment I, Holden HM, Sellers JR *et al.* Structural interpretation of the mutations in the beta-cardiac myosin that have been implicated in familial hypertrophic cardiomyopathy. *Proc Nat Acad Sci USA* 1995;**92**:3864–8.
13. Lankford EB, Epstein ND, Fananapazir L, Sweeney HL. Abnormal contractile properties of muscle fibres expressing beta-myosin heavy chain gene mutations in patients with hypertrophic cardiomyopathy. *J Clin Invest* 1995;**95**:1409–14.
14. Geisterfer-Lowrance AA, Christe M, Conner DA, Ingwall JS, Schoen FJ, Seidman CE, Seidman JG. A mouse model of familial hypertrophic cardiomyopathy. *Science* 1996;**272**: 731–4.
15. Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: pathology and pathogenesis. *Histopathology* 1995;**26**: 493–500.
16. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;**8**:545–57.

17.Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* 2000;**84**: 476–82.
18.Wigle ED, Sasson Z, Henderson MA *et al.* Hypertrophic cardiomyopathy: the importance of the site and extent of hypertrophy: a review. *Prog Cardiovasc Dis* 1985;**28**:1–83.
19.Levine RA, Vlahakes GJ, Lefebvre XP *et al.* Papillary muscle displacement causes systolic anterior motion of the mitral valve. Experimental validation and insights into the mechanism of subaortic obstruction. *Circulation* 1995;**91**:1189–95.
20.Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. *Circulation* 1992;**85**:1651–60.
21.Sugrue DD, McKenna WJ, Dickie S *et al.* Relation between left ventricular gradient and relative stroke volume ejected in early and late systole in hypertrophic cardiomyopathy. Assessment with radionuclide cineangiography. *Br Heart J* 1984;**52**:602–9.
22.Maron BJ, Epstein SE. Clinical significance and therapeutic implications of the left ventricular outflow tract pressure gradient in hypertrophic cardiomyopathy. *Am J Cardiol* 1986; **58**:1093–6.
23.Hanrath P, Mathey DG, Siegert R, Biefield W. Left ventricular and filling patterns in different forms of left ventricular relaxation and filling patterns in different forms of left ventricular hypertrophy. An echocardiographic study. *Am J Cardiol* 1980; **45**:15–23.
24.Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;**10**: 733–42.
25.Cannon RO, Rosing DR, Maron BJ *et al.* Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. *Circulation* 1985;**71**:234–43.
26.Camici P, Chiriatti G, Lorenzoni R *et al.* Coronary vasodilatation is impaired in both hypertrophied and non hypertrophied myocardium of patients with hypertrophic cardiomyopathy: A study with Nitrogen-13 ammonia and positron emission tomography. *J Am Coll Cardiol* 1991;**17**:879–86.
27.Cannon RO, Dilsizian V, O'Gara P *et al.* Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation* 1991;**83**:1660.
28.Elliott PM, Kaski JC, Prasad K *et al.* Chest pain during daily life in patients with hypertrophic cardiomyopathy: an ambulatory electrocardiographic study. *Eur Heart J* 1996;**17**: 1056–64.
29.O'Gara PT, Bonow RO, Maron BJ *et al.* Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* 1987;**76**:1214–23.
30.Sadoul N, Prasad K, Slade AKB, Elliott PM, McKenna WJ. Abnormal blood pressure response during exercise is an independent marker of sudden death in young patients with hypertrophic cardiomyopathy. *Circulation* 1997;**96**:2987–91.
31.Frenneaux MP, Counihan PJ, Caforio A, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation* 1990; **82**:1995–2002.
32.Hada Y, Sakamoto T, Amano K *et al.* Prevalence of hypertrophy cardiomyopathy in a population of adult Japanese workers as detected by echocardiographic screening. *Am J Cardiol* 1987;**59**:183–4.
33.Savage DD, Castelli WP, Abbott RD *et al.* Hypertrophic cardiomyopathy and its markers in the general population: the great masquerader revisited: the Framingham Study. *J Cardiovasc Ultrason* 1983;**2**:41–7.
34.Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 1995;**92**:785–9.
35.Codd MB, Sugrue DD, Gersh BJ, Melton LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy: a population based study in Olmsted County, Minnesota, 1975–1984. *Circulation* 1989;**80**:564–72.
36.Maron BJ, Peterson EE, Maron MS, Peterson JE. Prevalence of hypertrophic cardiomyopathy in an outpatient population referred for echocardiographic study. *Am J Cardiol* 1994;**73**: 577–80.
37.Maron BJ, Mathenge R, Casey SA, Poliac LC, Longe TF. Clinical profile of hypertrophic cardiomyopathy identified *de novo* in rural communities. *J Am Coll Cardiol* 1999 May; **33**(6):1590–5.
38.Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis: clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968;**37**:759–88.
39.McKenna WJ, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy. Role of age and clinical, electrocardiographic and haemodynamic features. *Am J Cardiol* 1981;**47**:532–8.
40.Spirito P, Chiarella F, Carratino L, Zoni-Berisso M, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. *N Engl J Med* 1989;**320**:749–55.
41.Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. *J Am Coll Cardiol* 1995;**26**:1529–36.
42.Cannan CR, Reeder GS, Bailey KR, Melton LJ III, Gersh BJ. Natural history of hypertrophic cardiomyopathy. A population based study, 1976 through 1990. *Circulation* 1995;**92**: 2488–95.
43.Maron BJ, Tajik AJ, Ruttenberg HD *et al.* Hypertrophic cardiomyopathy in infants: clinical features and natural history. *Circulation* 1982;**65**:7–17.
44.Savage DD, Seides SF, Clark CE *et al.* Electrocardiographic findings in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. *Circulation* 1978;**58**:402–9.
45.Lemery R, Kleinebenne A, Nihoyannopoulos P, Alfonso F, McKenna WJ. Q-waves in hypertrophic cardiomyopathy in relation to the distribution and severity of right and left ventricular hypertrophy. *J Am Coll Cardiol* 1990;**16**:368–74.
46.Cosio FG, Moro C, Alonso M, Saenz de la Calzada C, Llovet A. The Q-waves of hypertrophic cardiomyopathy. *N Engl J Med* 1980;**302**:96–9.

47.Yamaguchi H, Ishimura T, Nishiyama S *et al.* Hypertrophic nonobstructive cardiomyopathy with giant negative T-waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979;**44**: 401–12.
48.Fananapazir L, Tracey CM, Leon MB *et al.* Electrophysiological abnormalities in patients with hypertrophic cardiomyopathy: a consecutive analysis in 155 patients. *Circulation* 1989;**80**:1259.
49.McKenna WJ, England D, Doi Y, Deanfield JE, Oakley CM, Goodwin JF. Arrhythmia in hypertrophic cardiomyopathy. 1. Influence on prognosis. *Br Heart J* 1981;**46**:168–72.
50.Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. *Am J Cardiol* 1981;**48**:252–7.
51.Alfonso F, Frenneaux MP, McKenna WJ. Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm. *Br Heart J* 1989;**61**:178–81.
52.Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki J, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279–85.
53.Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of the distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide angle, two-dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981;**48**:418–28.
54.Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1983;**2**:437–44.
55.Sharma S, Elliott PM, Whyte G *et al.* Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol* 2000;**36**:864–70.
56.Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993;**22**:796–804.
57.Nienaber CA, Gambhir SS, Moddy FV *et al.* Regional myocardial blood flow and glucose utilization in symptomatic patients with hypertrophic cardiomyopathy. *Circulation* 1993;**87**:1580–90.
58.Grover-McKay M, Schwaiger M, Krivokapich J, Perloff JK, Phelps ME, Schelbert HR. Regional myocardial blood flow and metabolism at rest in mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1989;**13**: 317–24.
59.Gould KL. Myocardial metabolism by positron emission tomography in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1989;**13**:325–6.
60.Betocchi S, Bonow RO, Bacharach SL, Rosing DR, Maron BJ, Green MV. Isovolumic relaxation period in hypertrophic cardiomyopathy: assessment by radionuclide angiography. *J Am Coll Cardiol* 1986;**7**:74–81.
61.Chikamori T, Dickie S, Poloniecki JD, Myers MJ, Lavender JP, McKenna WJ. Prognostic significance of radionuclide-assessed diastolic dysfunction in hypertrophic cardiomyopathy. *Am J Cardiol* 1990;**65**:478–82.
62.Child JS, Perloff JK, Bach PM, Wolfe AD, Perlman S, Kark RA. Cardiac involvement in Friedreich's ataxia. A clinical study of 75 patients. *J Am Coll Cardiol* 1986;**7**:1370.
63.Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna WJ. Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. *J Am Coll Cardiol* 1993;**22**:1189–92.
64.Blaire E, Redwood C, Ashrafian H, Oliveira M, Broxholme J, Kerr B, Salmon A, Ostram-Smith I, Watkins H. Mutations in the gamma (2) subunit of AMP-activated protein kinase cause familial HCM: evidence for the central role of energy compromise in disease pathogenesis. *Hum Mol Genet* 2001;**10**:1215–20.
65.Devereux RB. Cardiac involvement in essential hypertension. Prevalence, pathophysiology and prognostic implications. *Med Clin N Am* 1987;**71**:813–26.
66.Shapiro LM, Kleinebenne A, McKenna WJ. The distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: comparison to athletes and hypertensives. *Eur Heart J* 1985;**6**:967–74.
67.Keller H, Wanger K, Goepfrich M, Stegaru B, Buss J, Heene DL. Morphological quantification and differentiation of left ventricular hypertrophy in hypertrophic cardiomyopathy and hypertensive heart disease. *Eur Heart J* 1990;**11**:65–74.
68.Hattori M, Aoki T, Sekioka K. Differences in direction-dependent shortening of the left ventricular wall in hypertrophic cardiomyopathy and in systemic hypertension. *Am J Cardiol* 1992;**70**:1326–32.
69.Maron BJ, Roberts WC, McAllister HA, Rosing DR, Epstein SE. Sudden death in young athletes. *Circulation* 1980;**62**: 218–29.
70.Burke AP, Farb A, Virmani R, Goodin J, Smialek JE. Sports-related and non-sports related sudden cardiac death in young adults. *Am Heart J* 1991;**121**:568–75.
71.Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;**324**:295.
72.Maron BJ, Pellicia A, Spirito P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. *Circulation* 1995;**91**:1569.
73.McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart* 1997;**77**:130–2.
74.Lewis JF, Maron BJ. Clinical and morphology expression of hypertrophic cardiomyopathy in patients 65 years of age. *Am J Cardiol* 1994;**73**:1105–11.
75.Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *N Engl J Med* 1985:**312**: 277–83.
76.Faye WP, Taliercio CP, Ilstrup DM, Tajik AJ, Gersh BJ. Natural history of hypertrophic cardiomyopathy in the elderly. *J Am Coll Cardiol* 1990;**16**:821–6.
77.Karam R, Lever HM, Healy BP. Hypertensive hypertrophic cardiomyopathy or hypertrophic cardiomyopathy with hypertension? A study of 78 patients. *J Am Coll Cardiol* 1989;**13**: 580–4.

78. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. *Circulation* 2001;**104**:1380–4.
79. Coviello DA, Maron BJ, Spirito P *et al.* Clinical features of hypertrophic cardiomyopathy caused by mutation of a "hotspot" in the alpha-tropomyosin gene. *J Am Coll Cardiol* 1997;**29**:635–40.
80. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of LVH and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:407–8.
81. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;**342**:1778–85.
82. Counihan PJ, Frenneaux MP, Webb DJ, McKenna WJ. Abnormal vascular responses to supine exercise in hypertrophic cardiomyopathy. *Circulation* 1991;**84**:686–96.
83. Dritsas A, Sabarouni E, Gilligan D, Nihoyannopoulos P, Oakley CM. QT-Interval abnormalities in hypertrophic cardiomyopathy. *Clin Cardiol* 1992;**15**:739–42.
84. Fei L, Slade AK, Grace AA, Malik M, Camm AJ, McKenna WJ. Ambulatory assessment of the QT interval in patients with hypertrophic cardiomyopathy: risk stratification and effect of low dose amiodarone. *Pacing Clin Electrophys* 1994;**17**: 2222–7.
85. Buja G, Miorelli M, Turrini P, Melacini P, Nava A. Comparison of QT dispersion in hypertrophic cardiomyopathy between patients with and without ventricular arrhythmias and sudden death. *Am J Cardiol* 1993;**72**:973–6.
86. Kulakowski P, Counihan PJ, Camm AJ, McKenna WJ. The value of time and frequency domain, and spectral temporal mapping analysis of the signal-averaged electrocardiogram in identification of patients with hypertrophic cardiomyopathy at increased risk of sudden death. *Eur Heart J* 1993;**14**: 941–50.
87. Counihan PJ, Fei L, Bashir Y, Farrell TG, Haywood GA, McKenna WJ. Assessment of heart rate variability in hypertrophic cardiomyopathy. Association with clinical and prognostic features. *Circulation* 1993;**88**:1682–90.
88. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy: prognostic evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic and electrophysiological findings. *Circulation* 1992;**86**:730–40.
89. Saumarez RC, Slade AKB, Grace AA, Sadoul N, Camm AJ, McKenna WJ. The significance of paced electrocardiogram fractionation in hypertrophic cardiomyopathy. A prospective study. *Circulation* 1995;**91**:2762–8.
90. Elliott PM, Poloniecki J, Dickie S *et al.* Sudden death in hypertrophic cardiomyopathy: identification of high-risk patients. *J Am Coll Cardiol* 2000;**36**:2212–18.
91. McKenna WJ, Oakley CM, Krikler DM *et al.* Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. *Br Heart J* 1985;**53**:412–16.
92. McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch Dis Childhood* 1984;**59**:971–5.
93. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;**33**:1596–601.
94. Maron BJ, Shen WK, Link MS *et al.* Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000;**342**:365–73.
95. Primo J, Geelen P, Brugada J *et al.* Hypertrophic cardiomyopathy: role of the implantable cardioverter defibrillator. *J Am Coll Cardiol* 1998;**31**:1081–5.
96. Silka MJ, Kron J, Dunnigan A, Dick M. Sudden cardiac death and the use of implantable cardioverter-defibrillator in paediatric patients. *Circulation* 1993;**87**:800–7.
97. Kron J, Oliver RP, Norsted S, Silka MJ. The automatic implantable cardioverter defibrillator in young patients. *J Am Coll Cardiol* 1990;**16**:896–902.
98. Elliott PM, Sharma S, Poloniecki J, Prasad K, Murd'Ah, McKenna WJ. Amiodarone and sudden death in hypertrophic cardiomyopathy. (Abstract) *Circulation* 1997;**96**:I–464.
99. Pollick C. Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. *N Engl J Med* 1982; **307**:997–9.
100. Pollick C. Disopyramide in hypertrophic cardiomyopathy. Hemodynamic assessment after intravenous administration. *Am J Cardiol* 1988;**62**:1248–51.
101. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis: techniques, and the results of pre and postoperative assessments in 83 patients. *Circulation* 1975;**52**:88–102.
102. Maron BJ, Merrill WH, Freier PA, Kent KM, Epstein SE, Morrow AG. Long-term clinical course and symptomatic status of patients after operation for hypertrophic subaortic stenosis. *Circulation* 1978;**57**:1205–13.
103. Williams WG, Wigle ED, Rakowski H, Smallhorn J, LeBlanc J, Trusler GA. Results of surgery for hypertrophic obstructive cardiomyopathy. *Circulation* 1987;**76**(Suppl. V): V104–8.
104. Heric B, Lytle BW, Miller DP, Rosenkranz ER, Lever HM, Cosgrove DM. Surgical management of hypertrophic obstructive cardiomyopathy. Early and late results. *J Thorac Cardiovas Surg* 1995;**110**:195–208.
105. Robbins RC, Stinson Eb. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg* 1996;**111**:586–94.
106. Schulte HD, Bircks WH, Loesse B, Godehardt EAJ, Schwartzkopff B. Prognosis of patients with hypertrophic obstructive cardiomyopathy after transaortic myectomy. Late results up to 25 years. *J Thorac Cardiovasc Surg* 1993;**106**: 709–17.
107. McCully RB, Nishimura RA, Tajik J, Schaff HV, Danielson GK. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. *Circulation* 1996; **94**:467–71.
108. McIntosh CL, Greenberg GJ, Maron BJ, Leon MB, Cannon RO, Clark RE. Clinical and hemodynamic results after mitral valve replacement in patients with hypertrophic cardiomyopathy. *Ann Thorac Surg* 1989;**47**:236–46.

109.Slade AKB, Sadoul N, Shapiro L *et al.* DDD pacing in hypertrophic cardiomyopathy: a multicenter clinical experience. *Heart* 1996;**75**:44–9.
110.Jeanrenaud X, Goy JJ, Kappenberger L. Effects of dual-chamber pacing in hypertrophic obstructive cardiomyopathy. *Lancet* 1992;**339**:1318–23.
111.Fananapazir L, Epstein ND, Curiel RV, Panza JA, Tripodi D, McAreavey D. Long-term results of dual chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy. Evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. *Circulation* 1994;**90**:2731–42.
112.Nishimura RA, Trusty JM, Hayes DL *et al.* Dual chamber pacing for hypertrophic cardiomyopathy: a randomised double-blind crossover trial. *J Am Coll Cardiol* 1997;**29**: 435–41.
113.Kappenberger L, Linde C, Daubert C *et al.* (PIC study Group). Pacing in hypertrophic obstructive cardiomyopathy. A randomised crossover study. *Eur Heart J* 1997;**18**:1249–56.
114.Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet* 1995;**346**:211–14.
115.Gleichman U, Seggewiss H, Faber L, Fassbender D, Schmidt HK, Strick S. [Catheter treatment of hypertrophic cardiomyopathy]. [German]. *Deut Medizin Woch* 1996;**121**:679–85.
116.Knight C, Kurbaan AS, Seggewiss H *et al.* Non-surgical reduction for hypertrophic obstructive cardiomyopathy: outcome in the first series of patients. *Circulation* 1997;**95**: 2075–81.

49 Other cardiomyopathies

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Introduction

From the vast array of clinical entities that comprise the cardiomyopathies, two conditions were selected for this chapter: Chagas' heart disease and endomyocardiofibrosis.

In neither disease have large randomized controlled trials been conducted to support recommendations for therapeutic options. Knowledge of natural history and pathophysiology is based almost entirely on observational studies, mostly of the case series kind. Most are flawed by heterogeneous criteria for patient selection and investigation. Thus, particularly in Chagas' heart disease, a large volume of incomplete and biased information has been obtained, so that meta-analysis of available data has been limited to the etiologic treatment in a subgroup of patients.

Despite the paucity of evidence-based knowledge, the diseases epitomize quite different unique pathophysiological conditions. In essence, Chagas' heart disease is a myocarditis of parasitic origin, although the role of the etiologic agent in the chronic phase of the disease is still somewhat controversial. Endomyocardiofibrosis has no defined etiology or pathogenesis and reasonably good animal models exist only for the study of Chagas' disease.

There are many reasons for the lack of solid evidence-based data in both diseases. However, while the apparently low prevalence of endomyocardiofibrosis is an obvious obstacle, the high prevalence of Chagas' heart disease in many countries has not helped to produce large randomized trials on therapeutic management.

Chagas' heart disease

Epidemiology

Chagas' disease is caused by *Trypanosoma cruzi* infection. Its transmission is mainly vectoral, through the feces of infected bloodsucking insects of the family *Reduviidae* (subfamily *Triatominae*). Many case series reports have also documented that the infection can occur by transplacental and oral transmission, blood transfusion, laboratory contamination, and organ transplantation. Although virtually every organic system may be involved and megaesophagus and megacolon can produce florid clinical conditions, it is the cardiac involvement – the object of this chapter – that constitutes the most serious form of the disease.

The current prevalence of Chagas' heart disease is unknown because no recent large scale screening has been carried out even in endemic countries. Besides, the epidemiological information available from the different countries is strikingly varied. This reflects the diversity of public health programs, including the control of vectoral and transfusional transmission. Thus, a survey carried out from 1988 to 1990 in 850 municipalities of Brazil revealed that serological screening for Chagas' disease was performed in only two thirds of all blood donors.[1] Also, a review of serological surveys for Chagas' infection among blood donors conducted over the 1980s in several countries in the American continent disclosed a highly variable rate of prevalence, from 0% to 63%.[2]

Neither is case reporting reliable, even in high endemicity areas. Rough estimates by the World Health Organization, based upon limited serological surveys, suggest that 15–18 million people are infected in extensive areas of the South American subcontinent.[3] Moreover, some 65 million are at risk.

Cross-sectional epidemiological studies have been carried out in scattered areas of Brazil and Venezuela to assess the prevalence of clinical manifestations and mortality due to Chagas' heart disease. However, probably because of marked variations in the genetic background, parasite strain, climate, socioeconomic and related hygienic alimentary conditions, and healthcare measures, the prevalence of both morbidity and mortality is extremely variable even within each country.[1]

Nevertheless, Chagas' heart disease is by far the most common form of cardiomyopathy in Latin American countries. Further, because of modern migratory trends, it is likely to become ubiquitous. This tendency is shown in the United States, where based on a prevalence of 4·5% of *T. cruzi* infection detected serologically in 205 Latin American immigrants and on rough estimates of the number of such legal and illegal immigrants, 400 000–500 000 infected people are believed to be living there now.[4] Also, rural–urban migration from endemic areas in Brazil is believed to have brought half a million infected people to cities such as São Paulo and Rio de Janeiro in the past three decades.

Chagas' heart disease has a very high social impact. It has been estimated that over 750 000 years of productive life are lost annually due to premature deaths in Latin American countries, at a cost of about US$1200 million/year.[5] These

figures substantiate the need for the elimination of transmission – a goal achieved in some regions[7] and proved to be a highly cost effective public health policy.

Natural history and prognostic factors

There is sound experimental, pathological, and clinical evidence that Chagas' heart disease presents two phases, acute (immediately following infection) and chronic. The long period – 10–30 years – between the acute condition and the clinically manifest chronic Chagas' heart disease is known as the indeterminate form of the disease and constitutes one of its most intriguing features. Its classical definition – now the subject of controversy[6] – requires that the patients be asymptomatic, have no physical signs of Chagas' disease, and normal ECG and radiological exploration of the chest, esophagus and colon.

Megaesophagus and megacolon are also frequently diagnosed in chagasic patients in Brazil, Argentina, and Chile, but not in Mexico, Colombia or Venezuela. The hypothesis that different *T. cruzi* strains or environmental factors may cause this difference in morbidity[8] has not been evaluated by appropriately designed studies.

The natural history of Chagas' heart disease is relatively well known from observational studies conducted mainly in endemic areas in Brazil, Argentina, and Venezuela since the early 1940s. There is also a wealth of case series reports dealing with acute Chagas' disease acquired through non-vector transmission. Most of these investigations consist of cross-sectional observations of infected people in rural areas. Very few studies have been conducted using case–control populations of chagasic and non-chagasic people.

There have also been some observational investigations focusing on the description and follow up of hospital based cohorts of chagasic patients.

Both the rural and the hospital based studies have limitations. There is usually no adequate identification of cardiac involvement provided in the rural based studies. Furthermore, because of the protracted course of heart involvement, from the acute phase to end stage heart failure, no prospective studies encompassing the whole span of the disease are available. Conversely, in hospital based studies the heart disease is often well characterized, but results could not be extended to the whole chagasic population.

Prognosis in the acute phase

Case series using serological tests in endemic areas have shown that in no more than 10% of the acute cases were clinical manifestations sufficient to make a correct diagnosis.[9] This is a major deterrent for understanding the transition from the acute to the chronic stages of Chagas' disease. However, the scarce clinical data are in general agreement with findings from experimental models of Chagas' disease.

For the minority of patients in whom the clinical diagnosis was possible, cardiac involvement occurred in around 90% of 313 successive cases; in 70–80%, cardiac enlargement was seen on *x* rays, contrasting with only 50% of cases showing ECG abnormalities. The severity of myocarditis was inversely proportional to age; signs of heart failure were twice as intense in children aged up to 2 years than in those aged between 3 and 5 years.[9] Mortality in the acute phase, as seen in the 313 cases, was 8·3%. This was higher than the 3–5% reported in similar studies in other endemic areas in Brazil, Argentina, and Uruguay. The ECG was normal in 63·3% of the non-fatal cases and in only 14·3% of those who died in the acute phase. Seventy-five per cent of all deaths were seen in children aged under 3 years. Heart failure was the constant finding in all fatal cases, with or without concomitant encephalitis.[9]

Survival is characterized by disappearance of symptoms and signs of heart failure within 1–3 months and normalization of the ECG in over 90% of the cases after 1 year of the infection. However, there is no evidence of spontaneous cure of the infection, as demonstrated by serial xenodiagnosis and serological tests in studies of several hundreds of chagasic patients.

Of 172 patients who were followed in Bambuí (central Brazil) for up to 40 years after the acute infection, the development of cardiac involvement (based on clinical signs, ECG, and chest *x* ray changes) occurred in 33·8%, 39·3%, and 58·1% for follow up periods of 10–20 years, 21–30 years, and 31–40 years respectively.[9] In another review from the same area, for 268 patients whose acute phase of the disease had been diagnosed an average of 27 years before, the general mortality for the period was 13·8%.[9]

Prognosis in the indeterminate phase

Factors that affect the varying rates of disease progression are currently unknown. A 1–3% per year rate of appearance of heart involvement has been observed in several studies. Of 400 young adults followed for 10 years, 91 (23%) showed clinical, ECG or chest *x* ray markers of cardiac disease. Of note, eight deaths were recorded in that period, of which only one could be ascribed to reagudization (that is, a full-blown infective illness with parasitemia) of Chagas' heart disease.[10]

Another longitudinal study in Bambui, central Brazil, contrasted the evolution of 885 young chagasic patients in the indeterminate phase for 10 years with that of 911 chagasic patients with initially abnormal ECGs in the same period. Survival after 10 years was 97·4% and 61·3% respectively for the indeterminate group and the group with cardiac involvement.[11]

A third longitudinal study in a rural Venezuelan community, with 47% prevalence of positive serology for Chagas' disease, followed 364 patients for a mean period of 4 years.

It revealed the appearance of heart disease at a rate of 1·1% per year in seropositive individuals. Mortality was 3% in the 4 years of follow up and Chagas' heart disease was the cause of death in 69% of all fatal cases.[12]

In 1973 a longitudinal study was initiated in a rural community in northeast Brazil. In the initial cross-sectional study, of 644 individuals aged >10 years, 53·7% were seropositive. The population initially described in 1973–1974 was re-examined in 1977, 1980, and 1983. The overall rate of development of abnormal ECG was 2·57% in seropositive (248) as compared to 1·25% per year in seronegative (332) individuals, a relative risk of 2 for the same geographical area. The age adjusted mortality rate was higher in seropositive (8·9/1000/year of 488 patients) than in seronegative individuals (7·8/1000/year of 509 individuals). Mortality in this study was strongly associated with ventricular conduction defects and arrhythmias.[13]

These results were obtained in chagasic populations with more than 50% of the patients younger than 20 years. It is relevant that fewer indeterminate cases are found in the older age groups because of the evolutive nature of the disease (that is, more aging patients presenting clinical signs of cardiac or digestive involvement).

Key points

- As long as the patients remain in the indeterminate phase, their prognosis is good. **Grade B2**
- After 10 years almost 80% of patients remain in the indeterminate phase of the disease and probably 50% of the entire population will have no signs of heart disease throughout their lives. **Grade B2**
- There are no clues as to why some chagasic patients remain in the indeterminate phase, while others sooner or later go through the chronic phase of heart involvement.

Prognosis of chronic Chagas' heart disease

The evidence provided by the studies mentioned above shows that the mere appearance of ECG changes entails a bad prognosis. Also, a retrospective analysis of seropositive individuals followed over 18 years revealed that right bundle branch block was three times more common in fatal cases than in survivors.[14]

Another important negative prognostic factor once heart disease is manifest is male gender. This is borne out by several studies carried out with long-term follow up of different cohorts of chagasic patients.[15]

Only two case–control follow up studies have been reported in Brazilian endemic areas. In central Brazil[16] two cross-sectional clinical assessments (1974 and 1984) included 12-lead ECG and radiological evaluation of heart size. Seropositive patients and controls were matched by age and gender. In the first cross-sectional study 264 pairs of subjects were evaluated, of which 110 were re-examined after the 10 year follow up period with the same clinical, ECG, and chest *x* ray assessment. The incidence of heart disease in previously healthy but serologically positive individuals was 38·3% in the 10 year period. In those patients with previous heart involvement, a rate of 34·5% of deterioration was observed in the same period. In the chagasic population the overall 10 year mortality was 23%, compared to 10·3% in the controls. Moreover, cardiac mortality, including sudden death and death in heart failure, was 17% among chagasic patients and only 2·3% in the control population. Again, the overall mortality was much higher in chagasic males and largely predominated in the group aged 30–59 years.[13] The same group of investigators, applying similar methods in northeastern Brazil, showed that mortality rates were 1·6% and 0% for 125 matched pairs of respectively chagasic and non-chagasic patients followed for 4·5 years.[17] Progression of disease as assessed by ECG changes occurred in 10·4% of patients, as compared to 4·8% of controls. The hypothesis that the different morbidity and mortality rates in the two regions were due to differences in the pathogenicity characteristics of *T. cruzi* strains was not substantiated by direct evidence.

There is persuasive evidence to support the concept that the mortality associated with Chagas' disease strongly correlates with severity of the myocardial dysfunction. For example, survival 2 years after the first episode of heart failure was only 33·4% in 160 cases.[18] Of note, 10% of deaths were sudden. In addition, 98% of the deceased people were autopsied, revealing <20% prevalence of amastigote forms of *T. cruzi* in the cardiac tissue, but with a clear predominance of this finding in male patients.[18]

In a study of 107 chagasic patients followed for 10 years, a significant reduction in life expectancy, as compared to that of 22 non-chagasic patients, was detected only in those with ECG or clinical changes. A mortality rate of 82% over the 10 year follow up period was seen in the group of 34 patients with signs of heart failure at the beginning of the study. In contrast, a 65% 10 year survival was associated with ECG abnormalities but in the absence of signs of heart failure.[19]

Another study of 104 male chagasic patients admitted to hospital with heart failure revealed a mortality rate of 52% after 5 years. The strongest predictors of survival were reduced LV ejection fraction and maximal oxygen uptake during exercise.[20]

In a series of 42 patients with Chagas' heart disease in the United States 11 deaths occurred during a mean follow up of nearly 5 years, always in association with global or regional LV dysfunction. Established or developing heart failure was a strong predictor of mortality but aborted sudden death or the presence of sustained ventricular tachycardia were not predictors for mortality in this series.[21] These results conflict with the evidence from 44 chagasic patients

followed for a mean period of 2 years that ventricular tachycardia detected during exercise testing is a marker of increased risk of sudden death.[22] This discrepancy probably reflects the limitations of small numbers and relatively short follow up in both studies.

Key points

- There is substantial evidence that the most important prognostic factor in established Chagas' heart disease is the degree of myocardial dysfunction. However, ECG changes also herald increased risk. **Grade B2**
- Once overt cardiac failure ensues the prognosis is poor and approaches 50% in 4 years. **Grade B2**
- It is possible – but not proven by good evidence – that ventricular dysrhythmia and sudden death play a more prominent role in mortality due to Chagas' disease than in heart failure due to other etiologies. **Grade B4**

Clinical features of Chagas' heart disease

Cardiac abnormalities are present in all stages of Chagas' disease, but their clinical expression is highly variable. The paucity of clinical indicators of the typical myocarditis of acute Chagas' disease has already been pointed out. There is also solid evidence – from necropsy studies as well as from *in vivo* investigations – that virtually all patients, even in the indeterminate phase of the disease, have some subtle degree of cardiac structural or functional involvement.[23–29]

Patients with Chagas' heart disease are classified following the criteria shown in Table 49.1. The anatomical and functional disturbances detected during life are consistent with the autopsy findings reported on several series of chagasic patients who died in the various stages of the disease.[23,24,30]

It is not uncommon for patients with ECG and marked LV regional abnormalities to be asymptomatic hard workers and capable of performing as such under laboratory conditions.[26] When symptoms occur, they are usually in the form of fatigue and exertional dyspnea, palpitations, dizziness and syncope or chest pain. These are the expression of a reduction of the cardiac reserve (including minor early signs of diastolic dysfunction), the presence of ventricular dysrhythmias, and atrioventricular block. The chest pain is usually atypical for myocardial ischemia but in sporadic cases may mimic an acute coronary syndrome.

Systemic and pulmonary embolism, arising from mural thrombi in the cardiac chambers, is a conspicuous complication of Chagas' heart disease, but post-mortem findings show they are often overlooked. In 1345 necropsies on patients with Chagas' heart disease, 595 cases (44%) had cardiac thrombi and/or visceral thromboembolism. The presence of cardiac thrombi was related to severity of ventricular enlargement. Embolism most frequently involved lungs (36%), kidneys (36%), spleen (14%), and brain (10%).[31]

Congestive heart failure is more commonly expressed by prominent signs of systemic congestion, with less intense pulmonary congestion.[32] This peculiar feature of Chagas' heart disease is linked to early severe damage of the RV, a chamber frequently neglected in investigations of cardiac function.[33,34]

Sudden unexpected death occurs with undefined but not negligible frequency even in patients previously asymptomatic. It is usually precipitated by physical exercise and associated with ventricular tachycardia and fibrillation or, more rarely, with complete AV block. Limited evidence from autopsy studies in these patients indicates variable degrees of inflammatory and neuronal cardiac alterations.[24]

Patients with chronic Chagas' heart disease invariably have one or more positive serological tests. There is also recent and limited experience with polymerase chain reaction-based methods for detecting *T. cruzi* DNA sequences in the blood of chagasic patients. This method is likely to replace the cumbersome and unreliable method of direct demonstration of parasite infection by xenodiagnosis.[35]

ECG abnormalities are present in most patients with chronic Chagas' heart disease, mainly in the form of conduction disturbances and ventricular arrhythmias. In more advanced stages pathological Q waves are found, compatible with extensive areas of myocardial fibrosis. The combination of right bundle branch block and left anterior hemiblock is very typical in chronic Chagas' heart disease. Nevertheless, no ECG changes can be considered specific to the disease.

Many case series reports have documented the typical feature of striking segmental-wall motion abnormalities in several hundreds of chronic chagasic patients. The most characteristic lesion is the apical aneurysm, but it is the posterior basal dysynergy that best correlates with the occurrence of malignant ventricular arrhythmia. A few small retrospective studies have evaluated the correlation between ventricular arrhythmia and symptoms in Chagas' heart disease. It is apparent that complex ventricular dysrhythmia may occur in asymptomatic patients, but it is usually a conspicuous manifestation associated with poor LV function. The aneurysms are also sources of emboli.

In spite of chest pain being a common complaint in many chagasic patients, coronary angiography is usually normal. However, functional abnormalities in the myocardial blood flow regulation have been described and all types of myocardial perfusion defects have been detected in several small groups of selected patients, possibly implying microvascular coronary disturbances.[28]

Cardiac autonomic dysfunction, mainly parasympathetic, has been shown in various groups of several hundreds of chagasic patients (including those with isolated digestive disease) whose response to various autonomic tests was

Table 49.1 A clinical classification of Chagas' heart disease

	Clinical phase				
	Acute	Indeterminate		Overt heart disease	Heart failure
		IA	IB		
Symptoms	Fairly common	Absent	Absent	Minimal	Present
Physical	Usually Abnormal	Normal	Normal	May be abnormal	Abnormal
ECG changes	Common	Absent	Absent	RBBB, LAHB, AVB, PVCs	+ Q waves VT
Heart size (*x* rays)	Usually abnormal	Normal	Normal	Normal	Enlarged
RV function	Usually abnormal	Normal	May be depressed	Usually abnormal	Abnormal
LV diastolic function	?	?	Mild impairment	Abnormal	Abnormal
LV systolic function	Abnormal	Normal	Mild segmental dysynergy	Segmental dysynergy	Global depression
Perfusion defects	?	Mild abnormalities	Mild abnormalities	Common	Common
Autonomic function	?	May be abnormal	May be abnormal	May be abnormal	Usually abnormal
RV biopsy	Abnormal	May be abnormal	Usually abnormal	Abnormal	Abnormal
Exercise stress test	?	Normal	May be abnormal – Arrhythmia – Chronotropic deficit	May be abnormal – Arrhythmia – Chronotropic deficit	Abnormal Reduced exercise capacity
Arrhythmia/Sudden death	?	Absent	Very uncommon	May be detected	Common

Abbreviations: AVB, atrioventricular block; ECG, electrocardiogram; LAHB, left anterior hemiblock; LV, left ventricle; PVCs, premature ventricular complexes; RBBB, right bundle branch block; RV, right ventricle; VT, ventricular tachycardia; ?, unknown

compared to that of control subjects.[28,34,36,37] However, in Chagas' disease patients, the autonomic abnormalities do not correlate with any symptoms or cause postural hypotension. Recent scintigraphic studies demonstrated early sympathetic denervation, topographically related to the segmental-wall motion and perfusional abnormalities often detected in patients with more advanced stages of disease.[38]

Pathophysiology and pathogenetic mechanisms

The clinical manifestations arising during the acute phase are closely related to parasite presence in target organs such as the gastrointestinal tract, central nervous system and heart, coexisting with high grade parasitemia. Lymphadenopathy, liver and spleen enlargement are markers of widespread immunologic reaction.

As the parasitemia abates and the systemic inflammatory reaction subsides, it is believed that a silent, relentless, focal myocarditis ensues during the indeterminate phase. In predisposed hosts, encompassing approximately 30–50% of the infected population, this chronic myocarditis may evolve to cumulative destruction of cardiac fibers and marked reparative fibrosis. During this phase ventricular arrhythmias and sudden death may rarely occur as manifestations of the underlying focal inflammatory process, and possibly, of the early autonomic denervation. The incessant myocarditis

is eventually responsible for myocardial mass loss attaining critical degrees, thereby leading to regional and global ventricular remodeling, chamber dilation and setting the anatomic substrate for malignant dysrhythmia.

This hypothesis is based on experimental models for Chagas' heart disease. Additional evidence has been provided by studies correlating clinical and pathological findings in autopsied humans dying in all phases of the disease. Most studies included case series of dozens of patients for the acute and indeterminate phases and ranging from hundreds to thousands of cases for the chronic phase.

The most intriguing challenge for understanding the pathophysiology of Chagas' heart disease lies in the complex host-parasite relationship.[39,40] It is not clear why in many patients (who remain in the indeterminate phase) the myocardial aggression is controlled at low levels, whereas in others the development of full blown chronic Chagas' cardiomyopathy is triggered. In brief, *auto-immune mediated myocardial injury* is probably sustained and exacerbated by continuous antigen presentation related to *low grade persistent T. cruzi tissue parasitism*.

Evidence gathered from pathophysiological studies in animal models and in humans is consistent with the hypothesis that four main pathogenetic mechanisms participate in the genesis of chronic Chagas' heart disease:

- neurogenic mechanisms
- parasite-dependent inflammatory aggression
- microvascular disturbances
- immune mediated cardiac damage.

Neurogenic mechanisms – As discussed above, abnormal autonomic cardiac regulation, preceding the development of myocardial damage, has been conclusively shown in many functional investigations.[28,34,36,37,38,41–46] Accordingly, intense neuronal depopulation has been clearly demonstrated in several pathologic studies.[30,47]

Antibodies against autonomic receptors may be detected in experimental and human chronic Chagas' disease. Functional abnormalities in the cardiac electrogenesis can be caused by auto-antibodies against beta1-adrenergic and muscarinic M2-receptors.[42–46] It is still speculative whether receptor stimulation or inhibition thus triggered could mediate myocardial damage.

However, various kinds of evidence militate against neurogenic derangements being a main pathogenetic mechanism. Even in endemic areas cardiac denervation shows marked individual variability in intensity and frequency.[37,48] Also, no correlation has been shown between cardiac parasympathetic denervation and the extent of myocardial dysfunction or the presence of dysrhythmia. Moreover, the typical chagasic cardiomyopathy is found in geographical regions where the disease is apparently caused by parasite strains devoid of neurotropism. Interestingly, in such regions, the typical chagasic digestive syndromes – considered to be causally related to parasympathetic denervation of the esophagus and colon – are rarely described.[37] Furthermore, no follow up studies correlating autonomic regulation, myocardial function, and cardiac rhythm assessment have been reported.

In conclusion, the role of dysautonomia remains to be determined. Furthermore, the attractive hypothesis implicating autonomic impairment in triggering sudden death has never been appropriately tested.

Parasite-dependent inflammatory aggression – A direct cause-effect relationship between parasitism and inflammatory findings in the chronic phase of Chagas' heart disease was initially discarded.[47] Very low-grade parasitemia was detected by xenodiagnosis. Also, the scanty tissular nests of amastigotic *T. cruzi* bear no topographic relation with the diffuse focal inflammation, as seen by classical histopathological staining techniques.

However, more sensitive molecular biology methods have shown that parasitemia may be persistent in the chronic phase of Chagas' disease.[49,50] In myocardial biopsy specimens from chronic chagasic patients techniques using amplification of DNA sequences of *T. cruzi*[51] and immunofluorescent monoclonal antibodies[52,53] showed parasite antigens in the inflammatory infiltrates.

Microvascular disturbances – Several independent studies in animal models[54,55] and in humans with Chagas' disease,[56–59] focusing on histopathological changes, platelet activation and endothelial function disturbances support the hypothesis of microvascular abnormalities. These derangements may cause ischemic-like symptoms and transient ECG changes often detected in chagasic patients. They might also constitute the mechanism responsible for the myocardial perfusion abnormalities described in chagasic patients with angiographically normal coronary arteries.[4,28]

On the basis of the evidence from these investigations, it has been postulated that microvascular derangements could be a relevant mechanism for the amplification and perpetuation of myocardial damage triggered by the inflammatory process;[55] however, there is no information on their prognostic implications.

Immune mediated cardiac damage – Studies in humans and in animal experiments provide evidence for the role played by immunological mechanisms in chronic Chagas' heart disease. It is widely accepted that mononuclear inflammatory infiltrates seen in chronic chagasic myocarditis are the expression of cell mediated aggression. Ultrastructural microscopic studies in animal models show that immune effector cells cause lysis of non-parasitized myocardial

cells.[60] Depletion of the TDC^{4+} lymphocyte subpopulation prevents myocardial injury in the murine model of Chagas' heart disease.[61] Conversely, myocardial damage is induced in non-chagasic animals, by passive transfer of TDC^{4+} lymphocytes from infected mice.[61,62] Furthermore, the identification of antigenic epitopes related to cross-reactivity between *T. cruzi* and myocardial protein has been reported.[63,64]

These findings support the notion of an organ-specific autoimmune aggression against self-antigens modified since the acute phase. Also plausible is an incessant aggression maintained by persistent presentation of cross-reacting parasite antigens to the macrophage system, as a consequence of lifelong tissue parasitism.

Key points

- The evidence gathered from pathophysiological studies in animal models and in humans is consistent with the hypothesis of immune mediated injury being a key pathogenetic mechanism in chronic Chagas' heart disease.
- The immune responses are probably related to the persisting low-grade *T. cruzi* tissue parasitism but the mechanisms triggering exacerbated responses in some cases and deterring significant immune damage in others are still unknown.
- The presence of the parasite (or its remnants) in direct topographic relation to the inflammatory foci has potential therapeutic implication.
- Microvascular disturbances probably constitute important amplification mechanisms for the inflammatory myocardial injury.
- Cardiac dysautonomia is a well characterized feature that may precede other manifestations of myocardial damage but its pathogenetic role is still debated.

Management of Chagas' heart disease

Etiologic treatment

Although recent developments in basic biochemistry of the parasite allowed the identification of potential targets for chemotherapy, such as protein prenylation, sterol, proteases and phospholipid metabolism,[65] few antitrypanosomal agents are currently available for clinical use. Nifurtimox and benznidazole have been shown to be comparable in efficacy and high incidence of side effects including dermatitis, polyneuritis, leukopenia, gastrointestinal intolerance. This often warrants discontinuation of treatment, and nifurtimox was abandoned in most centers.

Acute phase – There is consensus that in the acute phase etiologic treatment is mandatory to control symptoms and life threatening myocarditis and encephalitis. Guidelines have been developed to recommend etiologic treatment also for laboratory or surgical accidents and in organ transplant recipient and donors.[66,67] After adequate treatment a negative xenodiagnosis is found in over 90% of cases and serological tests are negative in 80%. A more recent study suggested that molecular methods can be more effective to show parasite persistence; the etiologic treatment in the acute phase led to PCR negative results in 73% of the cases, while xenodiagnosis was negative in 86% after 3 years.[68]

Despite these current recommendations, in the absence of long-term follow up trials, there is no evidence for the prevention of chronic organ damage even for patients treated in the acute phase. The impact on prognosis has not been established, again due to lack of appropriately designed follow up studies.

Chronic phase – From experimental studies there is scarce evidence for benefit of trypanocide treatment against the development of chronic tissue damage.[69] Also, evidence for potential benefits of etiologic chemotherapy in chronic human Chagas' disease is extremely limited, due mainly to misleading criteria being employed in small trials.

Besides several case-series studies, a prospective, non-randomized, controlled trial involving 131 patients treated with benznidazole (5 mg/kg/day for 30 days) and 70 untreated patients with a mean follow up period of 8 years has been reported.[70] Progression of disease was assessed by ECG changes. Treated patients presented fewer ECG changes than the control group (4·2% *v* 30%) and less deterioration in the clinical condition (2·1% *v* 17%). These results suggest that etiologic treatment may impact favorably in the chronic phase.

However the parasitological criterion of persistent negativity of the xenodiagnosis is unreliable as this test is commonly negative in the chronic phase of Chagas' disease – 60–80% – despite the presence of overt and progressive cardiac involvement. Moreover, large fluctuations of parasitemia occur over time. There may also be bias in the trials caused by selection of patients with persistent parasitemia in the pre-treatment period. Furthermore, results of experimental studies have shown that in the chronic phase the parasitemia is low or not detectable at all, while there is a predominant tissular parasitism by amastigotic forms of *T. cruzi*.

Conversely, because persistently positive serological tests may merely reflect mechanisms of immunological memory or be associated with crossreactivity to altered host antigens, results of any of the serological criteria used to assess etiological treatment are clearly inadequate. In fact, the observed rate of negativation of serological tests following treatment in the chronic phase is consistently low (4–8%) in trials suffering the same methodological limitations discussed above.

Thus, until an adequate laboratory method is available for assessment of cure, the only acceptable criteria for etiologic

treatment must be based on the prevention of the appearance of the clinical manifestation or the arrest of damage already detected. For this, a long follow up period of large cohorts of patients would be required.

Using better diagnostic tests and research designs, more recent clinical trials have reported high rates of parasitologic cure in children with early chronic *T. cruzi* infection and claimed trypanocidal therapy for the indeterminate phase.[71]

A recent systematic review of studies testing the efficacy of trypanocide therapy in the chronic asymptomatic *T. cruzi* infection has been carried out.[72] Only five studies met the inclusion criteria requiring that published trials randomly allocated participants with chronic *T. cruzi* infection without symptomatic Chagas' heart disease to one or more of the trypanocidal drugs (benznidazole, nifurtimox, allopurinol) given for at least 30 days at any dose, and to control treatment with or without placebo.[71–76] Studies had to report on at least one of the following outcomes: all-cause mortality, sudden death, incidence of heart failure, side effects of treatment, ECG changes (collectively named here as "clinical outcomes") or reduction in parasite load, reduction in antibody titres to *T. cruzi* or negative seroconversion (collectively named as "parasite-related outcomes"). General characteristics of the five studies included are shown in Table 49.2. Data synthesis for pooled outcomes including all information available are shown in Figure 49.1.

The most important finding in this review was that trypanocide therapy improved parasite-related outcomes. The strongest effect was found for benznidazole that significantly reduced the proportion of positive xenodiagnosis in both children and adults and increased the rate of negative seroconversion in children, when serology was tested using the ELISA with Antigen-total stimulation (AT ELISA) technique. Allopurinol and itraconazole failed to demonstrate a significant effect on these outcomes and had severe side effects. Although these results are in favor of the use of trypanocide therapy in children and asymptomatic adults for reducing antibodies or the parasite load respectively, whether this effect will result in clinical benefit remains to be proven. None of these trials was designed primarily to assess clinical outcomes and failed to report key methodological issues. In addition, because of the variability in their designs and the small size of each trial, the meta-analysis performed for the pooled outcomes could never include all randomized participants. Thus, all observations on the effects of these agents for chronic asymptomatic *T. cruzi* infection should be interpreted in the light of the small number of participants in studies not intended to evaluate clinical outcomes. Hence, at present, no experimental evidence is available to support any recommendation on the clinical use of trypanocide therapy for improving clinical outcomes in chronic asymptomatic *T. cruzi* infection. Large randomized controlled studies encompassing

Table 49.2 General characteristics of included studies

Author country (year)	Participants (% IP)	Interventions (*n* randomized) dose	Outcomes[a] (Primary and secondary)
Andrade Brazil (1996)	School children (90%)	Benznidazole (64) 7·5 mg/kg/day – 8 weeks *v* placebo (65)	Seroconversion Antibodies changes
Apt Chile (1998)	Adults (70%)	Allopurinol (187) 8·5 mg/kg/day – 8 weeks *v* itraconazol (217) 6 mg/kg/day – 16 weeks *v* placebo[b] (165)	Seroconversion *n* positive xenodiagnosis ECG changes Side effects
Coura Brazil (1997)	Adults (NA)	Benznidazole (26) 5 mg/kg/day – 4 weeks *v* nifurtimox (27) 5 mg/kg/day – 4 weeks *v* placebo (24)	*n* positive xenodiagnosis
Gianella Bolivia (1997)	Adults (NA)	Allopurinol (20) 300 mg tid – 8 weeks *v* placebo (20)	*n* positive xenodiagnosis
Sosa-Estani Argentina (1998)	School children (95%)	Benznidazole (55) 5 mg/kg/day – 8 weeks *v* placebo (51)	Seroconversion Antibodies changes

[a]As stated by the authors in the report.
[b]Participants initially in placebo arm were re-allocated to one of the active arms after two months of treatment.
Abbreviations: NA, information not available; IP, indeterminate phase. Reproduced with permission[72]

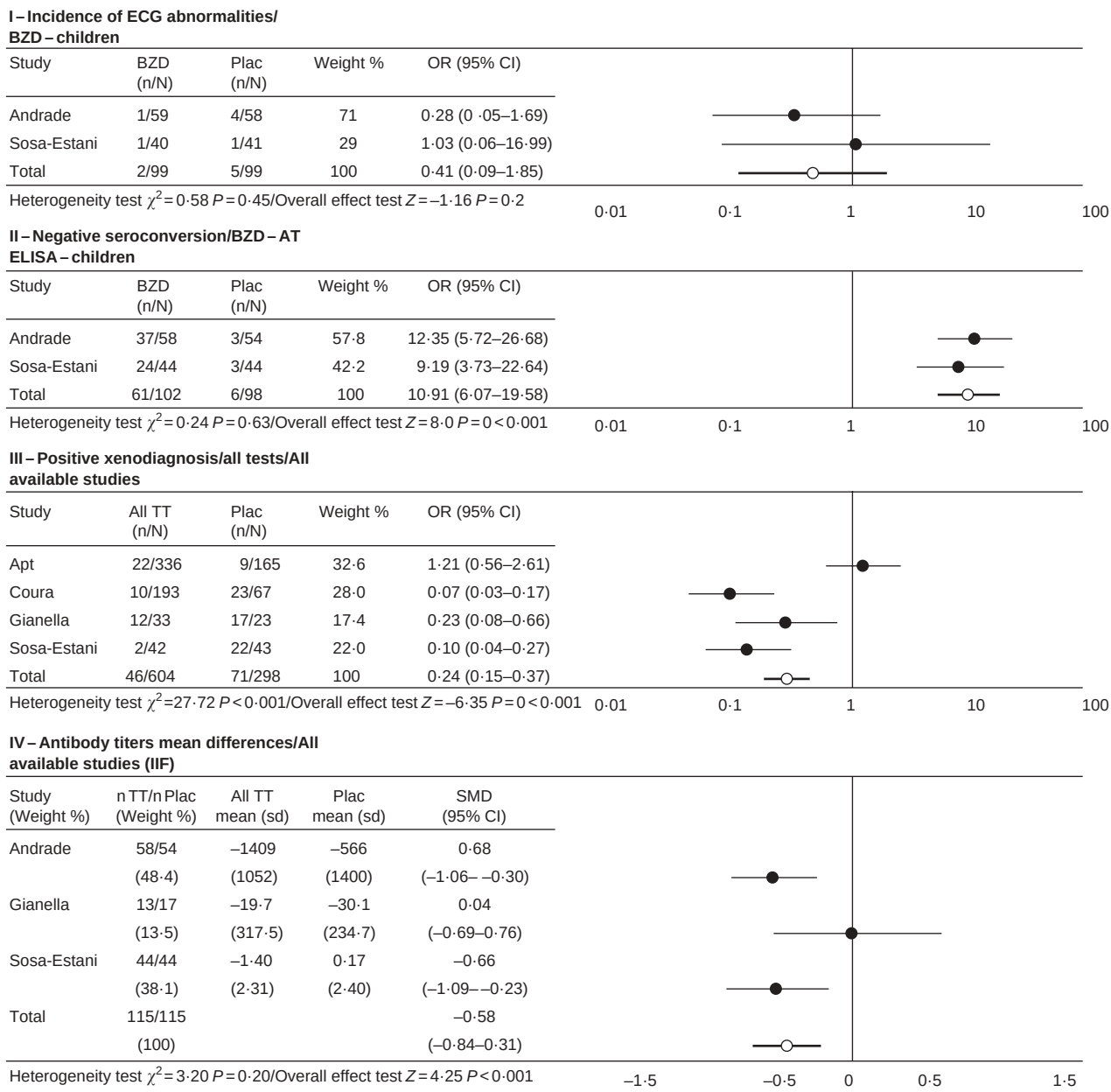

Figure 49.1 Overview of the effect, estimates for data on four outcomes pooled. Estimates are expressed as odds ratios, using the method proposed by Yusuf and Peto (Peto OR), or standardized mean differences (SMD) and its 95% confidence intervals using the fixed models statistical approach (95% CI Fixed). Antibodies mean changes are given in the units originally reported by authors. A negative sign means reduction of levels after being treated. Reproduced from Villar *et al*[72] with permission.

patients in different stages of disease have to be performed to overcome the current dilemma.

Prevention of reagudization

Trypanosomicide therapy has been shown in several cases to prevent the parasitological reactivation of Chagas' disease following corticosteroid therapy.[77] It is debatable whether primary chemoprophylaxis would be justifiable in all patients undergoing treatment with immunosuppressant drugs for associated diseases.[78]

Treatment of congestive heart failure

Hemodynamic derangements in chronic chagasic patients with heart failure are comparable to those reported in

dilated cardiomyopathies of other etiologies. Similarly, the classic therapeutic interventions – sodium restriction, diuretics, digitalis, and vasodilation with nitrates and hydralazine – have been successful in relieving congestive symptoms. Small studies have documented short-term hemodynamic beneficial effects of these agents and, to a lesser extent, improvement in exercise tolerance in chronic chagasic patients. However, no studies reported improvement in survival or even in long-term outcome.

Small prospective studies on ACE inhibitors have shown promising results in heart failure complicating Chagas' disease. A multicenter, prospective, non-controlled trial assessed the impact of adding an ACE inhibitor to conventional therapy in 115 patients with heart failure (of whom 20 were chagasics). At the end of 12 weeks, irrespective of etiology, the NYHA functional class was significantly improved in most patients (85·2%).[79] A single-blind, crossover trial of ACE inhibitor and placebo for 6 weeks each, with a washout period of 2 weeks, was reported on 18 NYHA class IV chagasic patients.[80] Treatment with the ACE inhibitor was associated with significant reduction in neuro-humoral activation and ventricular arrhythmias. These results indicate a potentially beneficial role for this class of drugs in reducing active mechanisms related to sudden death. However, no long-term controlled study has assessed the impact on survival of chagasic patients treated with ACE inhibitors.

Other neuro-humoral blocking drugs such as beta adrenergics and spironolactone have not been objectively tested in any clinical trial including a large enough number of chagasic patients to permit efficacy assessment comparative to other etiologies of congestive heart failure.

Surgical treatment

Heart transplantation – Heart transplantation has been performed in small numbers of patients with refractory heart failure due to Chagas' disease. However, transplantation is limited by socioeconomic factors in the areas where the disease is endemic and by problems related to the obligatory immunosuppression.

Acute myocarditis with marked transitory LV systolic depression has previously been reported in small case series as a frequent complication in patients receiving the usual dose cyclosporin therapy.[81] Although the reactivation of acute infection was usually responsive to antiparasite therapy, the possibility of definitive damage to the allograft could not be ruled out and early concern was raised that this could constitute a severe limitation or even contraindication for heart transplantation in Chagas' disease. Nevertheless, recent data have shown more encouraging results to circumvent this limitation, through the use of reduced immunosuppression regimen. The long-term impact of heart transplantation in chagasic patients has recently been described in a subgroup of a large cohort of 792 patients submitted to orthotopic heart transplantation in 16 centers in Brazil, The mean overall follow up period was 2·87±3·05 years, and 117 patients with chronic Chagas' heart disease constituted the subgroup. The entire cohort population also included 407 patients with idiopathic dilated cardiomyopathy and 196 with ischemic heart disease.[82] Among chagasic patients the reported criteria and contraindications for transplantation were similar to those used for non-chagasic patients, except for the detection of megacolon or megaesophagus, also considered a contraindication for transplantation. The survival rate of Chagas' disease patients at 1 and 12 years was respectively 76%, and 46%. These survival rates were statistically better in comparison with the rest of the cohort group in which the respective survival rates were 72% and 27%. It is worthy of note that reactivation of *T. cruzi* infection with myocarditis and meningoencephalitis was rarely reported, and was the cause of death, in only 0·3% of the entire chagasic cohort. Even allowing for the poor control of other relevant characteristics of chagasic and non-chagasic patients in this retrospective analysis of a cohort study, the results suggest that heart transplantation is a valid therapeutic option in end stage Chagas' heart disease with expected survival rate at least comparable to other patients submitted to this procedure.

Dynamic cardiomyoplasty – Reported experience with this procedure in chagasic patients is limited. While initial results in very few patients showed encouraging symptom and LV function improvement,[83] a survey of surgical centers in South America (112 patients of whom 96 had heart failure due to dilated cardiomyopathy and 13 due to Chagas' heart disease) was less optimistic.[84] Comparative analysis showed survival rates of 86·1% and 49·8% for patients with dilated cardiomyopathy and 40% and 9·5% for chagasic patients at 1 and 5 years follow up respectively. These results were corroborated by another recent observational study, again including a quite reduced number of chagasic patients.[85] There are no clues from these data to elucidate why the prognosis for chagasic patients was worse.

Clearly large controlled randomized trials are needed to define any value of dynamic cardiomyoplasty as a temporary approach, before refractory heart failure due to Chagas' heart disease can be treated by more radical interventions such as cardiac transplantation.[86]

Partial left ventriculectomy and synchronization therapy – The so-called Batista operation has been performed in small numbers of chagasic patients in many scattered surgical centers in Brazil, without any systematic approach specific for this disease. Because no systematic outcome information is available, and also due to the lack of consistent results with the procedure in other etiologies, currently, partial left

ventriculotomy can not be recommended for the treatment of chagasic heart failure. Also, recent small case-series studies reported acute symptomatic and hemodynamic improvement after dual-chamber or multisite pacemaker implantation, but on an entirely empirical basis.

Prevention of thromboembolic events

There is very limited clinical information on the risk of embolism in patients with mural thrombus or apical aneurysm. In 65 selected patients with apical aneurysm, a follow up study ranging from 19 to 176 months documented 17 episodes of thromboembolism in 14 patients (24·5%)[87] – seven to the brain, nine to the lung and one to the iliac artery. These patients also had congestive heart failure and 11 died in the observation period. In eight of those patients, the cause of death was related to heart failure and in three it was a consequence of cerebral embolism.

Another small study in an endemic region of South America addressed the contribution of Chagas' heart disease in 69 patients having embolic strokes.[88] Of 13 patients with non-ischemic dilated cardiomyopathy, Chagas' heart disease was detected in nine (13·0%). It was the third most frequently identified cause of embolism after atrial fibrillation (29%) and rheumatic valvular heart disease (20·3%).

However, the real risk of thromboembolism in patients with Chagas' heart disease is unknown, as no specific studies have addressed this problem.

Furthermore, despite the preliminary evidence that thromboembolic events are relevant factors in the natural history of Chagas' disease, no clinical studies have been conducted to date on adequate treatment and prevention. Current recommendations for anticoagulant therapy are based on information derived from other dilated cardiomyopathies. Thus, chagasic patients presenting global LV dysfunction, atrial fibrillation, previous embolic episodes, and dyskinetic areas with detected mural thrombus are candidates for treatment with intravenous and/or oral anticoagulants. Social and economic factors limit the implementation of this treatment, however, even in chagasic patients with otherwise apparently clear indications for prevention of thromboembolism.

Management of rhythm disturbances

A wide spectrum of rhythm disturbances is one of the main hallmarks of Chagas' heart disease. Sinus node dysfunction and other atrial dysrhythmias are common findings and usually present at the early appearance of symptoms. Management of rhythm disturbances does not differ from that recommended for other cardiomyopathies, although there is no sound evidence to support any specific treatment.

Complex ventricular dysrhythmia is the most important disturbance because of its implication for sudden death. It is believed that this is more common in chagasic patients than in other dilated cardiomyopathies, but no adequate comparative study has been reported to support this hypothesis. As may be expected, there is reasonable evidence that the more complex and frequent the ventricular dysrhythmia, the worse the ventricular function. However, there is convincing evidence that complex ventricular dysrhythmia may also occur in chagasic patients with preserved global LV function. This is more remarkable when dyskinesia in the posterior basal LV region seems to provide the electrophysiologic substrate for refractory ventricular tachycardia. Although no prospective controlled trial has been conducted, the scarce experience reported suggests that this subgroup may benefit from surgical excision of fibrotic tissue following careful electrophysiologic mapping of LV dyskinetic regions. Equally limited is the reported experience with implantable cardioverter defibrillators in chagasic patients surviving episodes of sudden death.[4,89]

Except for several small case series reports, very scanty information has been published on the efficacy of pharmacological antiarrhythmic therapy in Chagas' heart disease. A prospective, double-blind, placebo-controlled, randomized crossover study in a reduced number of patients reported similar effects of disopyramide and amiodarone for controlling ventricular dysrhythmia.[90] Another prospective open, parallel, randomized study in 81 chagasic patients with ventricular dysrhythmia compared the efficacy of flecainide and amiodarone.[91] The final evaluation by Holter monitoring after 60 days showed a significant and comparable reduction in the frequency of ventricular tachycardia achieved with both flecainide (96·5%) and amiodarone (92·6%). However, the follow up was insufficient for conclusions to be drawn on the long-term efficacy or the impact of arrhythmia control on the incidence of sudden death.

Two moderately large randomized trials included chagasics among patients treated with amiodarone. The GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) study concluded after 2 years of follow up that low-dose amiodarone was effective in reducing mortality and hospital admission in patients with severe heart failure, independent of the presence of complex ventricular dysrhythmia.[92] Unfortunately, the subgroup of chagasic patients was very modest (48 of 516 patients) and subgroup analysis was not provided. Neither would it have been likely to be useful.

An ongoing prospective, multicenter, randomized, controlled study designed to evaluate the impact of amiodarone on survival of treatment of asymptomatic ventricular arrhythmia also included chagasic patients.[93] In its pilot phase, this trial enrolled 127 patients (24 with Chagas' heart disease) with LVEF $<35\%$, presenting frequent ventricular premature complexes and/or repetitive forms of asymptomatic ventricular arrhythmia. The preliminary results after 12 months of follow up showed a significant

reduction in the incidence of sudden death in the amiodarone group (7·0% *v* 20·4%). However, owing to a high dropout rate (16%), follow up data were obtained in only 106 patients. Nevertheless, it is to be hoped that the final results, recruiting a larger number of chagasic patients, will provide some helpful evidence on treating ventricular dysrhythmia with amiodarone in Chagas' disease.

Complete atrioventricular block may also contribute to low cardiac output and cause syncope and sudden death in chagasic patients. In this situation pacemakers are used, as in other cardiac conditions. The evidence on the effects of pacemaker implantation comes from limited case series reports with historic control series of patients in whom this treatment was not possible.[89]

The common association of atrioventricular disturbances and ventricular complex dysrhythmia in the same patient also requires pacemaker implantation associated with pharmacological antiarrhythmic therapy. This management is regarded as prophylactic, although it is not based on unquestionable evidence.

Key points

- Etiologic treatment is clearly warranted for treatment of acute phase or chronic infection reactivation associated with immune-suppressive states. **Grade A/B4** Despite recent evidence supporting the participation of persistent tissue parasitism in the chronic phase of disease, and preliminary persuasive evidence that treatment of chronic asymptomatic patients results in benefit from the parasite outcomes point-of-view, there is no evidence that clinical outcomes are influenced. **Grade A/C, 1c and 5**
- Digitalis, diuretics and neurohumoral blocking drugs are empirically used for treating chagasic patients with heart failure. **Grade B2**
- Heart transplantation can be considered a promising treatment for refractory heart failure in Chagas' patients, even though this position is based in only one prospective multicenter cohort including small number of patients. **Grade B2**
- Pharmacological, surgical, and device-based strategies for the treatment of ventricular dysrhythmia in chagasic patients are empirical and not supported by any large randomized, controlled trials. **Grade B4**

Endomyocardial fibrosis (EMF)

EMF is a restrictive cardiomyopathy with still unknown etiology occurring most frequently in tropical and subtropical countries. Major endocardial fibrotic involvement of the inflow portion of one or both ventricles, including the subvalvular region, leads to cavity obliteration, restriction of diastolic filling, and clinical manifestations of congestive heart failure and valvular regurgitation. A remarkably similar cardiac involvement occurring in non-tropical countrieshas been described as endomyocardial disease. This is commonly named Löffler endocarditis or hypereosinophilic syndrome.

Although a still disputed issue, it has been postulated that the two conditions represent different stages of the same disease.[94] Another controversial hypothesis is that eosinophil-derived factors have a toxic role in the pathogenesis of endomyocardial damage. A recent report combines circumstancial evidence for the association of vector-borne etiology and helminth hypereosinophilia as an etiologic hypothesis for endemic EMF in tropical rain forest zones.[95]

Epidemiology and natural history

The low prevalence of EMF inhibits the study of the epidemiology and natural history. Even the larger published series have included only around 100 patients.

Symptoms and signs

Biventricular involvement has been documented in approximately half of the patients with EMF, while isolated right or left ventricular disease is variably described in 10–40% of cases in different published series. Depending upon predominant involvement of either chamber, symptoms and signs related to pulmonary congestion (left-sided) and systemic congestion (right-sided disease), and to mitral or tricuspid reflux, will tend to be more conspicuous.

Constrictive pericarditis is an important differential diagnosis in EMF, especially when the right ventricle is markedly involved.[96] Demonstration of ventricular obliteration by imaging techniques is essential for the diagnosis, but endomyocardial biopsy can be decisive in selected patients.

The magnitude of symptoms, the grade of ventricular obliteration (especially of the right ventricle), and the occurrence of valvar regurgitation are important prognostic determinants of mortality in this disease. These clinical markers are useful in selecting patients for surgery since a good long-term prognosis has been reported for patients who have mild ventricular dysfunction and no valvular regurgitation.[97]

Surgical management

Extensive surgical excision of the fibrotic tissue, preserving or replacing the atrioventricular valves, can ameliorate symptoms and improve hemodynamics and has been suggested to improve the long-term prognosis.[98] An operative mortality ranging from 4·6% to 25·0% has been reported in small case series studies. Ten year 70% and 17 year 55% survival rates have been respectively reported in European and Latin American series.[99,100]

It must be emphasized that no reports based on randomized controlled trials of treatment strategies are available.

Key points

- The etiology and pathogenesis of EMF are still to be determined.
- The epidemiology, natural history, and pathophysiology are very incompletely understood, with available data based solely on retrospective evidence from small observational investigations. **Grade B4**
- Promising preliminary results obtained with surgical approaches await validation in large randomized, controlled studies before any general recommendation for improving quality of life and survival rates can be made. **Grade B4**

References

1. Wanderley DMV, Corrêa FMA. Epidemiology of Chagas' heart disease. *São Paulo Med J* 1995; **113**: 742–9.
2. Schmunis GA. *Trypanosoma cruzi*, the etiologic agent of Chagas' disease: status in the blood supply in endemic and nonendemic countries. *Transfusion* 1991;**31**:547–57.
3. WHO. *Control of Chagas' disease*. WHO Technical Report Series 811. Geneva: World Health Organization, 1991.
4. Hagar JM, Rahimtoola SH. Chagas' heart disease. *Curr Prob Cardiol* 1995;**10**:825–928.
5. Schofield CJ, Dias JCP. A cost benefit analysis of Chagas' disease control. *Mem Inst Oswaldo Cruz* 1991;**86**:285–95.
6. Acquatella H, Catalioti F, Gomez-Mancebo JR, Davalos V, Villalobos L. Long-term control of Chagas' disease in Venezuela: effects on serologic findings, electrocardiographic abnormalities, and clinical outcome. *Circulation* 1987;**76**: 556–62.
7. Prata A. Clinical and epidemiological aspects of Chagas disease. *Lancet Infect Dis* 2001;**1**:92–100.
8. Miles MA, Póvoa MM, Prata A, Cedillos RA, De Souza AA, Macedo V. Do radically dissimilar trypanosoma cruzi strains (Zymodemes) cause Venezuelan and Brazilian forms of Chagas' Disease? *Lancet* 1981;**20**:1338–40.
9. Dias JCP. Cardiopatia chagásica: história natural. In: Cançado JR, Chuster M. eds. *Cardiopatia chagásica*. Belo Horizonte Fundação: Carlos Chagas de Pesquisa Médica, 1985.
10. Dias JCP. The indeterminate form of human chronic Chagas' disease. A clinical epidemiological review. *Rev Soc Bras Med Trop* 1989;**22**:147–56.
11. Forichon E. *Contribution aux estimations de morbidité et de mortalité dans la maladie de Chagas*. Toulouse: Universite Paul-Sabatier, 1974.
12. Puigbó JJ, Rhode JRN, Barrios HG, Yépez CG. A 4-year follow up study of a rural community with endemic Chagas' disease. *Bull World Health Organ* 1968;**39**:341–8.
13. Mota EA, Guimarães AC, Santana OO *et al.* A nine year prospective study of Chagas' disease in a defined rural population in northeast Brazil. *Am J Trop Med* 1990;**42**:429–40.
14. Dias JCP, Kloetzel K. The prognostic value of the electrocardiographic features of chronic Chagas' disease. *Rev Inst Med Trop São Paulo* 1968;**10**:158–62.
15. Lima e Costa MFF, Barreto SM, Guerra HL, Firmo JOA, Uchoa E, Vidigal PG. Ageing with *Trypanosoma cruzi* infection in a community where the transmission has been interrupted: the Bambuí Health and Ageing Study (BHAS). *Int J Epidemiol* 2001;**30**:887–93.
16. Coura JR, Abreu LL, Pereira JB, Willcox HP. Morbidade da doença de chagas. IV. Estudo longitudinal de dez anos em Pains e Iguatama, Minas Gerais. *Mem Inst Oswaldo Cruz* 1985; **80**:73–80.
17. Pereira JB, Cunha RV, Willcox HP, Coura JR. Development of chronic human Chagas' cardiopathy in the hinterland of Paraìba, Brazil, in a 4·5 year period. *Rev Soc Bras Med Trop* 1990;**23**:141–7.
18. Pugliese C, Lessa I, Santos Filho A. Estudo da sobrevida na miocardite crônica de chagas descompensada. *Rev Inst Med Trop São Paulo* 1976;**18**:191–201.
19. Espinosa R, Carrasco HA, Belandria F *et al.* Life expectancy analysis in patients with Chagas' disease: prognosis after one decade (1973–1983). *Int J Cardiol* 1985;**8**:45–56.
20. Mady C, Cardoso RHA, Barreto ACP *et al.* Survival and predictors of survival in congestive heart failure due to Chagas' cardiomyopathy. *Circulation* 1994;**90**:3098–102.
21. Hagar JM, Rahimtoola SH. Chagas' heart disease in the United States. *N Engl J Med* 1991;**325**:763–8.
22. de Paola AA, Gomes JA, Terzian AB *et al.* Ventricular tachycardia on exercise testing is significantly associated with sudden cardiac death in patients with chronic chagasic cardiomyopathy and ventricular arrhythmias. *Br Heart J* 1995;**74**:293–5.
23. Laranja FS, Dias E, Nobrega G, Miranda A. Chagas' disease: a clinical, epidemiologic, and pathologic study. *Circulation* 1956;**14**:1035–59.
24. Lopes ER, Chapadeiro E, Almeida HO, Rocha A, Rocha A. Contribuição ao estudo da anatomia patológica dos corações de Chagásicos falecidos subitamente. *Rev Soc Bras Med Trop* 1975;**9**:269–82.
25. Marin-Neto JA, Simoes MV, Sarabanda AVL. Chagas' heart disease. *Arq Bras Cardiol* 1999;**72**:264–80.
26. Gallo Jr L, Maciel BC, Marin-Neto JA *et al.* Control of heart rate during exercise in health and disease. *Brazilian J Med Biol Res* 1995;**28**:1179–84.
27. Barreto ACP, Arteaga-Fernandez E. RV endomyocardial biopsy in chronic Chagas' disease. *Am Heart J* 1986;**111**:307–12.
28. Marin-Neto JA, Marzullo P, Marcassa C. Myocardial perfusion defects in chronic Chagas' disease. Assessment with thallium-201 scintigraphy. *Am J Cardiol* 1992;**69**:780–4.
29. Barreto ACP, Ianni BM. The undetermined form of Chagas' heart disease: concept and forensic implications. *São Paulo Med J* 1995;**113**:797–801.
30. Oliveira JSM. A natural human model of intrinsic heart nervous system denervation: Chagas' cardiopathy. *Am Heart J* 1985;**110**:1092–8.
31. Oliveira JSM, Araújo RRC, Mucillo G. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. *Am J Cardiol* 1983;**52**:147–51.
32. Prata A, Andrade Z, Guimarães AC. Chagas' heart disease. In: Shaper AG, Hutt MSR, Fejfar Z, eds. *Cardiovascular disease in the tropics*. London: British Medical Association, 1974.
33. Marin-Neto JA, Marzullo P, Sousa ACS *et al.* Radionuclide angiographic evidence for early predominant right ventricular

involvement in patients with Chagas' disease. *Can J Cardiol* 1988;**4**:231–6.
34. Marin-Neto JA, Bromberg-Marin G, Pazin-Filho A, Simões MV, Maciel BC. Cardiac autonomic impairment and early myocardial damage involving the right ventricle are independent phenomena in Chagas' disease. *Int J Cardiol* 1998;**65**:261–9.
35. Britto C, Cardoso A, Silveira C, Macedo V, Fernandes O. Polymerase chain reaction (PCR) as a laboratory tool for the evaluation of the parasitological cure in Chagas' disease after specific treatment. *Medicina (B Aires)* 1999;**59**:176–8.
36. Marin-Neto JA, Gallo L Jr, Manço JC, Rassi A, Amorin DS. Mechanisms of tachycardia on standing: studies in normal individuals and in chronic Chagas' heart patients. *Cardiovasc Res* 1980;**14**:541–50.
37. Amorim DS, Marin-Neto JA. Functional alterations of the autonomic nervous system in Chagas' heart disease. *São Paulo Med J* 1995;**113**:772–83.
38. Simões MV, Pintya AO, Marin GB *et al.* Relation of regional sympathetic denervation and myocardial perfusion disturbances to wall motion impairment in Chagas' cardiomyopathy. *Am J Cardiol* 2000;**86**:975–81.
39. Rassi Jr A, Rassi A, Little WC. Chagas' heart disease. *Clin Cardiol* 2000;**23**:883–9.
40. Higuchi ML. Chronic chagasic cardiopathy: the product of a turbulent host-parasite relationship. *Rev Inst Med Trop Sao Paulo* 1997;**39**:53–60.
41. Ribeiro ALP, Moraes RS, Ribeiro JP *et al.* Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas' disease. *Am Heart J* 2001;**141**:260–5.
42. Sterin-Borda L, Gorelik G, Postan M, Gonzalez CS, Borda E. Alterations in cardiac beta-adrenergic receptors in chagasic mice and their association with circulating beta-adrenoceptor-related antibodies. *Cardiovasc Res* 1999;**41**:116–25.
43. Wallukat G, Nissen E, Morwinski R, Muller J. Autoantibodies against the beta- and muscarinic receptors in cardiomyopathy. *Herz* 2000;**25**:261–6.
44. Chiale PA, Ferrari I, Mahler E *et al.* Differential profile and biochemical effects of antiautonomic membrane receptor antibodies in ventricular arrhythmias and sinus node dysfunction. *Circulation* 2001;**103**:1765–71.
45. Mahler E, Sepulveda P, Jeannequin O *et al.* A monoclonal antibody against the immunodominant epitope of the ribosomal P2beta protein of *Trypanosoma cruzi* interacts with the human beta 1-adrenergic receptor. *Eur J Immunol* 2001;**31**:2210–16.
46. Costa PCS, Fortes FSA, Machado AB *et al.* Sera from chronic chagasic patients depress cardiac electrogenesis and conduction. *Braz J Med Biol Res* 2000;**33**:439–46.
47. Köberle F. Chagas' heart disease and Chagas' syndromes: the pathology of American trypanosomiasis. *Adv Parasitol* 1968; **6**:63–116.
48. Amorim DS, Manço JC, Gallo L Jr, Marin-Neto JA. Chagas' heart disease as an experimental model for studies of cardiac autonomic function in man. *Mayo Clin Proc* 1982;**57**:48–60.
49. Avila HA, Sigman DS, Cohen LM, Millikan RC, Simpson L. Polymerase chain reaction amplification of *Trypanosoma cruzi* kinetoplast minicircle DNA isolated from whole blood lysates: diagnosis of chronic Chagas' disease. *Mol Biochem Parasitol* 1991;**48**:211–21.
50. Monteon-Padilha V, Hernandez-Becerril N, Ballinas-Verdugo MA, Aranda-Faustro A, Reyes PA. Persistence of *Trypanosoma cruzi* in chronic chagasic cardiopathy patients. *Arch Med Res* 2001; **32**:39–43.
51. Jones EM, Colley DG, Tostes S *et al.* A *Trypanosoma cruzi* DNA sequence amplified from inflammatory lesions in human chagasic cardiomyopathy. *Trans Assoc Am Phys* 1992; **105**:182–9.
52. Bellotti G, Bocchi EA, Moraes AV *et al. In vivo* detection of *Trypanosoma cruzi* antigens in hearts of patients with chronic Chagas' disease. *Am Heart J* 1996;**131**:301–7.
53. Anez N, Carrasco H, Parada H *et al.* Myocardial parasite persistence in chronic chagasic patients. *Am J Trop Med Hyg* 1999;**60**:726–32.
54. Morris SA, Tanowitz HB, Wittner M, Bilezikian JP. Pathophysiological insights into the cardiomyopathy of Chagas' disease. *Circulation* 1990;**83**:1900–9.
55. Rossi MA. Microvascular changes as a cause of chronic cardiomyopathy in Chagas' disease. *Am Heart J* 1990;**120**:233–6.
56. Reis DD, Jones EM, Tostes S. Expression of major histocompatibility complex antigens and adhesion molecules in hearts of patients with chronic Chagas' disease. *Am J Trop Med Hyg* 1993;**49**:192–200.
57. Torres FW, Acquatella H, Condado J, Dinsmore R, Palacios I. Coronary vascular reactivity is abnormal in patients with Chagas' heart disease. *Am Heart J* 1995;**129**:995–1001.
58. Simões MV, Ayres-Neto EM, Attab-Santos JL, Maciel BC, Marin-Neto JA. Chagas' heart patients without cardiac enlargement have impaired epicardial coronary vasodilation but no vasotonic angina. *J Am Coll Cardiol* 1996;**27**:394–5A.
59. Higuchi ML. Human chronic chagasic cardiopathy: participation of parasite antigens, subsets of lymphocytes, cytokines and microvascular abnormalities. *Mem Inst Oswaldo Cruz* 1999;**94**:263–7.
60. Andrade ZA, Andrade SG, Correa R, Sadigursky M, Ferrans VJ. Myocardial changes in acute *Trypanosoma cruzi* infection. *Am J Pathol* 1994;**144**:1403–11.
61. Santos RR, Rossi MA, Laus JL *et al.* Anti-CD4 abrogates rejection and re-establishes long-term tolerance to syngeneic newborn hearts grafted in mice chronically infected with *Trypanosoma cruzi*. *J Exp Med* 1992;**175**:29–39.
62. Ribeiro-dos-Santos R, Mengel JO, Postol E *et al.* A heart-specific CD4+ T-cell line obtained from chronic chagasic mouse induces carditis in heart-immunized mice and rejection of normal heart transplants in the absence of *Trypanosoma cruzi*. *Parasite Immunol* 2001;**23**:93–101.
63. Cunha-Neto E, Duranti M, Gruber A *et al.* Autoimmunity in Chagas' disease cardiopathy: biological relevance of a cardiac myosin-specific epitope crossreactive to an immunodominant *Trypanosoma cruzi* antigen. *Proc Natl Acad Sci* USA 1995;**92**: 3541–5.
64. Giordanengo L, Maldonado C, Rivarola HW *et al.* Induction of antibodies reactive to cardiac myosin and development of cardiac alteration in cruzipain-immunized mice and their offspring. *Eur J Immunol* 2000;**30**:3181–9.
65. Docampo R. Recent developments in the chemotherapy of Chagas' disease. *Curr Pharm Des* 2001;**7**:1157–64.
66. Cançado JR. Etiological treatment of chronic Chagas' disease. *Rev Inst Med Trop Sao Paulo* 2001;**43**:173–81.

67. Sosa-Estani S, Segura EL. Treatment of *Trypanosoma cruzi* infection in the undetermined phase. Experience and current guidelines of treatment in Argentina. *Mem Inst Oswaldo Cruz* 1999;**94**:363–5.
68. Solari A, Ortiz S, Soto A *et al.* Treatment of *Trypanosoma cruzi*-infected children with nifurtimox: a 3 year follow up by PCR. *J Antimicrob Chemother* 2001;**48**:515–19.
69. Andrade SG, Stocker-Guerret S, Pimentel AS, Grimaud JA. Reversibility of cardiac fibrosis in mice chronically infected with *Trypanosoma cruzi*, under specific chemotherapy. *Mem Inst Oswaldo Cruz* 1991;**86**:187–200.
70. Viotti R, Vigliano C, Armenti H, Segura E. Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow up. *Am Heart J* 1994;**127**:151–62.
71. Andrade AL, Zicker F, deOliveira RM *et al.* Randomized trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet* 1996;**348**:1407–13.
72. Villar JC, Marin-Neto JA, Ebrahim S, Yusuf S. Trypanocidal drugs for chronic asymptomatic *Trypanosoma cruzi* infection (Cochrane Review). In: The Cochrane Library 2002; (Issue 2). Oxford: Update Software CD003463.
73. Coura JR, de Abreu LL, Faraco Willcox HP, Petana W. Estudo comparativo controlado com emprego de Benznidazole, Nifurtimox e placebo, na forma crônica da doença de Chagas, em uma área de campo com transmissão interrompida. Avaliação preliminar. *Rev Soc Bras Med Trop* 1997;**30**: 139–44.
74. Gianella A, Holzman A, Lihoshi N, Barja Z, and Peredo Z. Eficacia del Alopurinol en la enfermedad de Chagas crónica. Resultados del estudio realizado en Santa Cruz, Bolivia. *Bol Cientif CENETROP* 1997;**16**:25–30.
75. Sosa-Estani S, Segura EL, Velazquez E, Ruiz AM, Porcel BM, Yampotis C. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. *Am J Trop Med Hyg* 1998;**59**:526–9.
76. Apt W, Aguilera X, Arribada A *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998;**59**:133–8.
77. Rassi A, Amato Neto V *et al.* [Protective effect of benznidazole against parasite reactivation in patients chronically infected with *Trypanosoma cruzi* and treated with corticoids for associated diseases]. *Rev Soc Bras Med Trop* 1999;**32**:475–82.
78. Nishioka Sde A. [Benznidazole in the primary chemoprophylaxis of the reactivation of Chagas' disease in chronic chagasic patients using corticosteroids at immunosuppressive doses: is there sufficient evidence for recommending its use?]. *Rev Soc Bras Med Trop* 2000;**33**:83–5.
79. Batlouni M, Barretto AC, Armaganijan D *et al.* Treatment of mild and moderate cardiac failure with captopril. A multicenter trial. *Arq Bras Cardiol* 1992;**58**:417–21.
80. Roberti RR, Martinez EE, Andrade JL *et al.* Chagas' cardiomyopathy and captopril. *Eur Heart J* 1992;**13**:966–70.
81. Bocchi EA, Bellotti G, Mocelin AO *et al.* Heart transplantation for chronic Chagas' heart disease. *Ann Thorac Surg* 1996;**61**:1727–33.
82. Bochi EA, Fiorelli A. On behalf of the First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. The Paradox of Survival Results after Heart Transplantation for Cardiomyopathy caused by *T. cruzi*. *Ann Thor Surg* 2001;**71**:1833–8.
83. Jatene AD, Moreira LF, Stolf NA *et al.* Left ventricular function changes after cardiomyoplasty in patients with dilated cardiomyopathy. *J Thorac Cardiovasc Surg* 1991;**102**:132–8.
84. Moreira LF, Stolf NA, Braile DM, Jatene AD. Dynamic cardiomyoplasty in South America. *Ann Thorac Surg* 1996;**61**: 408–12.
85. Braile DM, Godoy MF, Thevenard GH *et al.* Dynamic cardiomyoplasty: long-term clinical results in patients with dilated cardiomyopathy. *Ann Thorac Surg* 2000;**69**:1445–7.
86. Bocchi EA. Cardiomyoplasty for treatment of heart failure. *Eur J Heart Fail* 2001;**3**:403–6.
87. Albanesi-Filho FM, Gomes JB. O tromboembolismo em pacientes com lesão apical da cardiopatia chagásica crônica. *Rev Port Cardiol* 1991;**10**:35–42.
88. Rey RC, Lepera SM, Kohler G, Monteverde DA, Sica RE. Cerebral embolism of cardiac origin. *Medicina (Buenos Aires)* 1992;**52**:206–16.
89. Rassi Jr A, Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol* 2001;**76**:75–96.
90. Carrasco HA, Vicuna AV, Molina C *et al.* Effect of low oral doses of disopyramide and amiodarone on ventricular and atrial arrhythmias of chagasic patients with advanced myocardial damage. *Int J Cardiol* 1985;**9**:425–38.
91. Rosembaum M, Posse R, Sgammini H *et al.* Comparative multicenter clinical study of flecainide and amiodarone in the treatment of ventricular arrhythmias associated to chronic Chagas cardiopathy. *Arch Inst Cardiol Mex* 1987;**57**: 325–30.
92. Doval HC, Nul DR, Grancelli HD *et al.* Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;**344**:493–8.
93. Garguichevich JJ, Ramos JL, Gambarte A *et al.* Effect of amiodarone therapy on mortality in patients with left ventricular dysfunction and asymptomatic complex ventricular arrhythmias: Argentine pilot study of sudden death and amiodarone (EPAMSA). *Am Heart J* 1995;**130**:494–500.
94. Olsen EGJ, Spry CJF. Relationship between eosinophilia and endomyocardial disease. *Prog Cardiovasc Dis* 1985;**27**: 241–54.
95. Ogunowo PO, Akpan NA, Odigwe CO, Ekanem IA, Esin RA. Helminth associated hypereosoniphilia and tropical endomyocardiofibrosis (EMF) in Nigeria. *Acta Trop* 1998;**69**:127–40.
96. Somers K, Brenton DP, Sood NK. Clinical features of endomyocardial fibrosis of the right ventricle. *Br Heart J* 1968;**30**: 309–21.
97. Barreto ACP, Luz PL, Mady C, Bellotti G, Pilleggi F. Determinants of survival in patients with endomyocardial fibrosis. *Circulation* 1988;**78**:526–30.
98. Oliveira SA, Barreto ACP, Mady C, Bellotti G, Pilleggi F. Surgical treatment of endomyocardial fibrosis: a new surgical approach. *J Am Coll Cardiol* 1990;**5416**:1246–51.
99. Schneider U, Jenni R, Turina J, Turina M, Hess OM. Long-term follow up of patients with endomyocardial fibrosis: effects of surgery. *Heart* 1998;**79**:362–7.
100. Moraes F, Lapa C, Hazin S, Tenorio E, Gomes C, Moraes CR. Surgery for endomyocardiofibrosis revisited. *Eur J Cardiothorac Surg* 1999;**15**:309–12.

Part IIIf

Specific cardiovascular disorders: Pericardial disease

Bernard J Gersh, *Editor*

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

50 Pericardial disease: an evidence-based approach to diagnosis and treatment

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Pericardial disease is a potentially curable cause of heart disease that accounts for about 7% of all patients who are hospitalized for cardiac failure in Africa.[1] Although there are no good epidemiologic data on the incidence or prevalence of pericarditis in different populations,[2] hospital-based series indicate that the spectrum of pericardial disease is determined by the epidemiologic setting of the patient. In Western countries, most cases of primary pericarditis are of unknown cause, whereas tuberculosis accounts for the majority of patients in the developing world.[3,4] Thus, evidence-based guidelines should be adapted according to the prevalence of certain diseases in particular geographic areas and patient populations.

A discussion of the large number of diseases that may affect the pericardium[5] (Box 50.1) cannot be covered in this short chapter. Consequently, this overview will focus on the diagnosis and treatment of idiopathic and tuberculous pericarditides. It will, in particular, aim to examine the extent to which existing treatments are supported by evidence from well-designed prospective studies. The findings reported here are based on a comprehensive search of electronic databases and bibliographies of articles on pericarditis.

Box 50.1 Causes of acute pericarditis[5]

- Malignant tumor
- Idiopathic pericarditis
- Uremia
- Bacterial infection
- Anticoagulant therapy
- Dissecting aortic aneurysm
- Diagnostic procedures
- Connective tissue disease
- Postpericardiotomy syndrome
- Trauma
- Tuberculosis
- Other
  - radiation
  - drugs inducing lupus-like syndrome
  - myxedema
  - postmyocardial infarction syndrome
  - fungal infections
  - AIDS-related pericarditis

Primary acute pericardial disease

Acute pericarditis may be caused by a variety of disorders (Box 50.1). Among the secondary forms of pericarditis, the underlying disorder is usually evident before pericardial involvement. The most challenging dilemma for the physician is the patient with acute pericardial disease without apparent cause at the initial evaluation (primary acute pericardial disease). In Western series a specific etiology has been found in only 14–22% of these patients when they are subjected to a prospective diagnostic protocol (Table 50.1).[3,6]

Diagnosis

Acute pericarditis is the occurrence of two or more of the following: characteristic chest pain, pericardial friction rub (pathognomonic of acute pericarditis), and an electrocardiogram (ECG) showing characteristic ST segment elevation or typical serial changes.[7] The chest radiograph, echocardiogram, and radionuclide scans are of little diagnostic value in uncomplicated acute pericarditis.

The first step in the etiologic diagnosis of acute pericarditis consists of a search for an underlying disease that may require specific therapy. In most cases of suspected viral pericarditis, special studies for etiologic agents are not necessary because of the low diagnostic yield of viral studies and lack of specific therapy for viral disease.[7] However, a treatable condition such as *Mycoplasma*-associated pericarditis must be considered and treated with antibiotics if the serologic test is consistent with the diagnosis.[8] The Permanyer-Miralda *et al* protocol[3] for the evaluation of acute pericardial disease is discussed under "Pericardial effusion" below.

Treatment

Although there are no controlled trials, it is generally accepted that bed rest and oral non-steroidal anti-inflammatory drugs

Table 50.1 Etiology of primary acute pericarditis in the West

	Permanyer-Miralda *et al* 1985[3] (*n* = 231)	Zayas *et al* 1995[5] (*n* = 100)
Acute idiopathic pericarditis	199 (86%)	78 (78%)
Neoplastic pericarditis	13 (6%)	7 (7%)
Tuberculous pericarditis	9 (4%)	4 (4%)
Other infections	6 (3%)	3 (3%)
Collagen vascular disease	2 (0.5%)	3 (3%)
Other	2 (0.5%)	5 (5%)

(NSAIDs) are effective in most patients with acute pericarditis.[7] The use of corticosteroids for acute idiopathic pericarditis when the disease does not subside rapidly is also untested in randomized trials, but it may be unnecessary and even dangerous in acute non-relapsing pericarditis in view of the availability of other agents, such as the parenteral NSAID ketorolac tromethamine.[9] Ketorolac is an extremely potent analgesic agent that appears to cause rapid resolution of symptomatic acute pericarditis. However, the limitation of this study of 20 patients with acute pericarditis was that there was no control group for comparison.[9]

Idiopathic relapsing pericarditis is the most troublesome complication of acute pericarditis, affecting about 20% of cases. There are no established therapeutic guidelines for patients who do not respond to NSAIDs.[7] Corticosteroids provide symptomatic relief in most of these patients, but symptoms recur in many when the prednisone dosage is reduced and severe complications are associated with prolonged steroid use.[10] Claims of effectiveness have been made in small uncontrolled studies for pericardiectomy, azathioprine, high-dose oral and intravenous corticosteroids, and colchicine (Table 50.2).[10] The results of these studies are inconsistent and the effectiveness of these potentially harmful therapeutic modalities remains to be established in well-designed randomized studies. Nevertheless, colchicine, used on the basis of its efficacy in the recurrent polyserositis seen in familial Mediterranean fever,[16] has aroused much interest following the dramatic effects which were initially reported with its use in recurrent pericarditis.[15] The accumulating experience with colchicine indicates that, whilst its long-term use is well tolerated, it is associated with a variable remission rate of 33–100% (Table 50.2), and there is a tendency for a small proportion of patients to relapse after cessation of therapy.[16] In a multicenter cohort study involving 51 patients with recurrent pericarditis who did not respond to conventional treatments, colchicine induced remission in 86%, and 60% remained recurrence-free after discontinuation of the drug.[20] These data support the use of colchicine to prevent recurrent attacks of pericarditis as an adjunct to conventional treatment, although the effectiveness of the agent remains to be evaluated in randomized controlled trials. **Grade B**

Table 50.2 Therapeutic strategies previously evaluated in recurrent pericarditis (after failure of non-steroidal anti-inflammatory drugs)

Study	Patients (*n*)	Therapeutic strategy evaluated	Remission rate
Fowler[10]	9	Pericardiectomy	2/9 (22%)
Hatcher[11]	24	Pericardiectomy	20/24 (83%)
Asplen[12]	2	Azathioprine	2/2 (100%)
Melchior[13]	2	IV Methylprednisolone as pulse therapy	2/2 (100%)
Marcolongo[14]	12	High-dose prednisone with aspirin	11/12 (92%) Major side effects in 3
Guindo[15] and de la Serna[16]	9	Colchicine	9/9 (100%)
Spodick[17]	8	Colchicine	3/9 (33%)
Adler[18]	8	Colchicine	4/8 (50%)
Millaire[19]	19	Colchicine	14/19 (74%)
Guindo [20]	51	Colchicine	44/51 (86%)

Pericardial effusion

The spectrum of causes of pericardial effusion is similar to acute pericarditis (Box 50.1). However, prospective studies indicate that large pericardial effusions are more likely to be a result of serious underlying illnesses such as tuberculosis and cancer, where rapid diagnosis may lead to earlier therapy and improved survival.[3] The clinical features vary depending on the rate of accumulation of the fluid, the amount of fluid that accumulates, and the stage at which the patient is first seen.

Diagnosis

The radiographic signs of pericardial effusion include an enlarged cardiac silhouette, a pericardial fat stripe, a predominant left-sided pleural effusion, and an increase in transverse cardiac diameter compared with previous chest radiographs. However, these signs cannot reliably confirm or exclude the presence of pericardial effusion, thus making radiography poorly diagnostic of pericardial effusion.[21] Similarly, ECG is useful only in that it may suggest a cardiac abnormality. The QRS complexes are usually small, with generalized T wave inversion. Electrical alternans, which suggests the presence of massive pericardial effusion, is uncommon. Even more uncommon is total electrical alternans (P-QRS-T alternation), which is pathognomonic of tamponade.[22]

Echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) can accurately detect and quantify pericardial effusion. Echocardiography, which is relatively inexpensive, sensitive (capable of detecting as little as 17 ml pericardial fluid), harmless, and widely available, is the diagnostic method of choice for pericardial effusion.[5] Furthermore, it may also provide prognostic information. A large effusion with a circumferential echo-free space of >1 cm in width at any point is reported to be a powerful predictor of tamponade[23] and intrapericardial echo images are associated with an increased likelihood of subsequent constriction.[24]

Permanyer-Miralda *et al*[3] have evolved a systematic approach for the evaluation of acute primary pericardial disease in developed countries with a low prevalence of tuberculosis (Table 50.3). It is based on a prospective study of 231 consecutive patients who were evaluated to determine the safest and most sensitive approach to the etiologic diagnosis of acute pericardial disease. The findings were confirmed in a subsequent prospective study of a similar diagnostic protocol involving 100 patients with primary pericardial disease.[5] First, these prospective studies indicate that a specific etiology is found in only 14–22% of patients with acute primary pericardial disease (Table 50.1). Secondly, while therapeutic pericardiocentesis is absolutely indicated for cardiac tamponade, it is not warranted as a routine investigation because of low diagnostic yield. The indications for diagnostic pericardiocentesis are the clinical suspicion of purulent or tuberculous pericarditis and those with an illness lasting longer than 1 week. Thirdly, the diagnostic yield of pericardiocentesis and pericardial biopsy is similar. Whereas biopsy is more invasive and may entail the need for general anesthesia, it is a safe procedure and direct histologic examination of the pericardium may allow immediate diagnosis in the case of tuberculosis. Furthermore, pericardial biopsy may allow a more direct visualization of the pericardium. However, even when detailed investigations are performed, including pericardioscopy and surgery, the etiology of pericardial effusion remains obscure in a significant number of patients.[25]

Table 50.3 Protocol for evaluation of primary acute pericardial disease[3]

Stage	Evaluation
Stage I	
General studies and echocardiogram	Electrocardiogram Chest radiograph Tuberculin skin test Serologic tests
Stage II	
Pericardiocentesis	Therapeutic pericardiocentesis: absolutely indicated for cardiac tamponade Diagnostic pericardiocentesis: clinical suspicion of purulent or tuberculous pericarditis Illness lasting for more than 1 week
Stage III	
Surgical biopsy of the pericardium	"Therapeutic" biopsy: as part of surgical drainage in patients with severe tamponade relapsing after pericardiocentesis Diagnostic biopsy: in patients with more than 3 weeks illness and without an etiologic diagnosis having been reached by previous procedures
Stage IV	
Empirical antituberculous treatment	Fever and pericardial effusion of unknown origin persisting for more than 5–6 weeks

Cardiac tamponade

A pericardial effusion may result in the life-threatening complication of cardiac tamponade, a condition caused by

compression of the heart and impaired diastolic filling of the ventricles. It is an indication for pericardiocentesis.

Cardiac tamponade is a clinical diagnosis, which is confirmed by echocardiography. The clinical examination shows elevated systemic venous pressure, tachycardia, dyspnea, and pulsus paradoxus.[26] Pulsus paradoxus may be absent in some instances such as left ventricular dysfunction, atrial septal defect, regional tamponade, and positive pressure breathing. Systemic blood pressure may be normal, decreased, or even elevated. The diagnosis is usually confirmed by the echocardiographic demonstration of a large circumferential pericardial effusion and some of the features listed in Table 50.4. However, as a diagnostic test for tamponade, echocardiography may lack both sensitivity and specificity in certain clinical situations. For example, echocardiographic features of right heart collapse may be absent in the presence of loculated effusions causing regional left ventricular compression or in patients with pulmonary hypertension. This is particularly important after cardiac surgery when the absence of a circumferential effusion and right atrial collapse and right ventricular diastolic collapse may not exclude the presence of life-threatening tamponade.[27,28] Furthermore, a dilated non-collapsing inferior vena cava and an abnormal respiratory pattern of diastolic flow are not specific signs of tamponade (Table 50.4).

Constrictive pericarditis

The etiology of constrictive pericarditis has changed over the past four decades.[29] Tuberculous constrictive pericarditis, which was a common cause of constriction worldwide before the 1960s, has since declined in incidence and is now rare in Western countries. In these countries the diminished importance of tuberculous pericarditis has been associated with a large contribution made by idiopathic cases. Postradiotherapy constriction, which was first recognized as an important disease in the 1960s, continues to feature prominently among the causes of constrictive pericarditis, while postsurgical constriction has emerged as an important cause.

Constrictive pericarditis is characterized anatomically by an abnormally thickened and non-compliant pericardium that limits ventricular filling in mid to late diastole. Consequently, nearly all ventricular filling occurs very rapidly in early diastole. This results in elevated cardiac filling pressures and the characteristic hemodynamic waveforms during which the diastolic pressures of the cardiac chambers equalize. The clinical manifestations of constrictive pericarditis, which are secondary to systemic venous congestion, mimic a variety of cardiopulmonary disorders, making the diagnosis of this condition difficult in some cases.

Diagnosis

The chest radiograph and ECG are usually abnormal, drawing attention to the heart, but the abnormalities are largely non-specific. Chest radiography may reveal a small, normal, or enlarged cardiac silhouette, pleural effusions in 60%, and pericardial calcification in 5–50% of cases.[29–31] Calcification is not specific for constrictive pericarditis, as a calcified pericardium does not necessarily imply constriction. Nonspecific but generalized T wave changes are seen in most cases, while low voltage complexes occur in about 30%.

The ideal imaging technique for the accurate preoperative diagnosis of pericardial constriction would simultaneously provide both anatomic data describing the thickness of the pericardium and physiologic/hemodynamic data describing

Table 50.4 Echocardiographic features of cardiac tamponade[26]

Echocardiographic/Doppler criteria	Comments
1. Right heart collapse: right atrial compression, right ventricular diastolic collapse	Changes in blood volume may affect the sensitivity and specificity of right heart collapse as a sign of tamponade. False positives and false negatives may occur
2. Abnormal respiratory changes in ventricular dimensions	Inconstant finding
3. Abnormal respiratory changes in tricuspid and mitral flow velocities	May also be seen in obstructive airways disease, pulmonary embolism, and right ventricular infarction
4. Dilated inferior vena cava with lack of inspiratory collapse	Often seen with congestive heart failure and constrictive pericarditis
5. Left ventricular diastolic collapse	Frequent sign of regional cardiac tamponade and useful marker of tamponade in postoperative patients in a retrospective investigation[27]
6. Swinging heart	Not sensitive, specificity unknown

the characteristic differential diastolic filling to the left ventricle and the right ventricle with respiration. In these regards, echocardiographic findings of abnormal ventricular septal motion (septal bounce or shudder), dilated inferior vena cava, and hepatic veins in patients with right heart failure are suggestive of constrictive pericarditis. Respiratory variation in mitral inflow velocities and hepatic veins is quite characteristic for constrictive pericarditis, although the lack of respiratory variation does not exclude constrictive pericarditis. Specificity of these Doppler findings of constrictive pericarditis is enhanced by demonstrating no significant respiratory variation in the superior vena cava velocity. In patients with increased respiratory effort such as chronic obstructive pulmonary disease, which simulates the interventricular dependence resulting in similar two-dimensional and Doppler echocardiographic findings, superior vena caval velocities are markedly increased with inspiration.[32] New tissue Doppler recording of mitral annulus velocity adds more confidence in distinguishing constrictive pericarditis from restrictive process because of myocardial disease (Table 50.5).[33]

CT and MRI can demonstrate the extent and distribution of pericardial thickening. While this does not make the diagnosis of constriction, it is often very useful to know that the pericardium is abnormal in a patient in whom this diagnosis is suspected. In addition, CT or MRI features of myocardial atrophy or fibrosis predict a poor outcome following pericardiectomy.[34] A promising new imaging technique is cine-CT, which simultaneously provides both anatomic and physiologic data that may allow accurate preoperative diagnosis of pericardial constriction.[35] Unless the diagnosis is very obvious, cardiac catheterization is usually performed. The characteristic finding is equal end-diastolic pressures in the two ventricles, persisting with respiration and fluid challenge. However, the diagnosis of constrictive pericarditis remains a challenge because it is often mimicked by restrictive cardiomyopathy. A number of studies, using different techniques, have attempted to distinguish the two conditions, including studies of left ventricular filling rate, mitral and tricuspid diastolic flow patterns, pulmonary venous flow velocity, hepatic flow velocity patterns, hemodynamic

Table 50.5 The differentiation of constrictive pericarditis from restrictive cardiomyopathy

Type of evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical examination	Regurgitant murmurs uncommon	Regurgitant murmurs may be present
Chest radiography	Pericardial calcification may be present	Pericardial calcification absent
Echocardiography	Normal wall thickness	Increased wall thickness, thickened cardiac valves and granular sparkling texture (amyloid). Enlarged atria
	Pericardium may be thickened[a]	Pericardium usually normal
	Prominent early diastolic filling with abrupt displacement of interventricular septum due to increased ventricular interaction	
Doppler studies	Early mitral flow is reduced with onset of inspiration and reciprocal effect on tricuspid flow	No respiratory variation in diastolic flow with short deceleration time
	Expiratory increase of hepatic vein diastolic flow reversal	Inspiratory increase of hepatic vein diastolic flow reversal
		Mitral and tricuspid regurgitation may be present
	Mitral annulus velocity ≥7 cm/s	Mitral annulus velocity <7 cm/s
Cardiac catheterization	RVEDP and LVEDP usually equal	LVEDP often >5 mmHg greater than RVEDP, but may be identical
	RV systolic pressure <50 mmHg	RV systolic pressure ≥50 mmHg
	RVEDP >one third of RV systolic pressure	
Endomyocardial biopsy	May be normal or show non-specific myocyte hypertrophy or myocardial fibrosis	May reveal specific cause of restrictive cardiomyopathy
CT/MRI	Pericardium may be thickened ≥3 mm[a]	Pericardium usually normal

Abbreviations: CT, computed tomography; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; MRI, magnetic resonance imaging; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure

[a] Normal thickness of the pericardium does not rule out pericardial constriction.

investigations, endomyocardial biopsy, and CT and MRI studies.[36] Table 50.5 summarizes the important differences between the two conditions. No technique is totally reliable and in some patients, the only way of making the diagnosis is to perform a pericardiectomy.[37]

Treatment

The treatment for chronic constrictive pericarditis is complete resection of the pericardium. The average hospital mortality following pericardiectomy in several series ranges from about 5% to 16%.[29,38–40] Poor outcome is related mainly to preoperative disability, the degree of constriction, and myocardial involvement. The majority of early deaths are associated with low cardiac output, which has been attributed to myocardial atrophy. Thus, early pericardiectomy is recommended in patients with non-tuberculous constrictive pericarditis before severe constriction and myocardial atrophy occur.

Among patients who survive the operation, symptomatic improvement can be expected in about 90% and complete relief of symptoms in about 50%. The 5 year survival rate ranges from 74% to 87%. Long-term survival and symptomatic relief do not appear to be influenced by age, choice of median sternotomy or left thoracotomy, or transient low output syndrome postoperatively. However, long-term survival is unfavorably influenced by the presence of severe preoperative functional disability (NYHA class III or IV, diuretic use), renal insufficiency in the preoperative state, the presence of extensive non-resectable calcifications, incomplete pericardial resection, and the presence of radiation pericarditis, which is commonly complicated by myocardial fibrosis and restrictive myocardial disease.

Tuberculous pericarditis

The prevalence of tuberculous pericarditis follows the same pattern as that of tuberculosis in general. It is the most common cause of pericarditis in developing countries where tuberculosis remains a major public health problem, but accounts for only about 5% of cases in the West.[3,4] In Africa the incidence of tuberculous pericarditis is rising as a direct result of the human immunodeficiency virus epidemic[41] and this trend is likely to occur in other parts of the world where the spread of AIDS is leading to the resurgence of tuberculosis. Tuberculosis caused by drug resistant *Mycobacterium tuberculosis* has emerged in the past few years as a serious threat to global public health, but its impact on pericardial tuberculosis has not been studied.

Tuberculous pericarditis appears to be more common in blacks than whites and males than females,[42,43] although the sex difference was reversed in the large prospective studies of Strang *et al*[30,44] The disease can occur at any age.

Tuberculous pericardial effusion

Tuberculous pericarditis is usually detected clinically either in the effusive stage or after the development of constriction. Tuberculous pericarditis has a variable clinical presentation and it should be considered in the evaluation of all instances of pericarditis without a rapidly self-limited course.[43] While tuberculous pericarditis may cause effusions that do not produce cardiac compression, more commonly there is at least some degree of cardiac compression, which may be severe, causing tamponade.

Tuberculous pericardial effusion usually develops insidiously, presenting with non-specific systemic symptoms such as fever, night sweats, fatigue, and loss of weight.[4,42,45] Chest pain, cough, and breathlessness are common.[45–47] Severe pericardial pain of acute onset characteristic of idiopathic pericarditis is unusual in tuberculous pericarditis.[42,45,48] Right upper abdominal aching due to liver congestion is also common in these patients.[4,42,45] In South African patients with tuberculous pericardial effusion, evidence of chronic cardiac compression that mimics heart failure is by far the most common presentation (Table 50.6).[4,47,49] While there is marked overlap between the physical signs of pericardial effusion and constrictive pericarditis, the presence of increased cardiac dullness extending to the right of the sternum favors a clinical diagnosis of pericardial effusion.

Diagnosis

A definite diagnosis of tuberculous pericarditis is based on the demonstration of tubercle bacilli in pericardial fluid or on histologic section of the pericardium and a probable diagnosis is made when there is proof of tuberculosis elsewhere in a patient with unexplained pericarditis. A definite or probable diagnosis is made in up to 73% of patients treated for tuberculous pericarditis.[44,50] The chest radiograph shows features of active pulmonary tuberculosis in only 30% and pleural effusion is present in 40–60% of cases.[43] The ECG is usually abnormal, drawing attention to the heart.[44,51] The ST segment elevations characteristic of acute pericarditis are usually absent. ECG findings are not specific for a tuberculous etiology.[50]

Pericardiocentesis is recommended in all patients in whom tuberculosis is suspected. The pericardial fluid is bloodstained in 80% of cases[4] and, since malignant disease and the late effects of penetrating trauma cause bloody pericardial effusion, confirmation of tuberculosis as the cause is important. The difficulty in finding tubercle bacilli in the direct smear examination of pericardial fluid is well known. Culture of tubercle bacilli from pericardial effusions can be improved considerably by inoculation of the fluid into double strength liquid Kirchner culture medium at the bedside. A prospective study of the value of the double strength liquid Kirchner culture medium in patients considered to have

Table 50.6 Physical signs documented by a single observer in 88 patients with pericardial effusion and 67 patients with constrictive pericarditis in South Africa[4]

Signs	Pericardial effusion ($n = 88$)	Constrictive pericarditis ($n = 67$)
Hepatomegaly	84 (95%)	67 (100%)
Increased cardiac dullness	83 (94%)	17 (25%)
Raised jugular venous pulse	74 (84%)	67 (100%)
Soft heart sounds	69 (78%)	51 (76%)
Sinus tachycardia	68 (77%) (Transient AF in 3)	47 (70%) (Persistent AF in 2)
Ascites	64 (73%)	60 (89%)
Apex palpable	53 (60%)	39 (58%)
Significant pulsus paradoxus	32 (36%)	32 (48%)
Edema	22 (25%)	63 (94%)
Pericardial friction rub	16 (18%)	–
Pericardial knock	–	14 (21%)
Third heart sound	–	30 (45%)
Sudden inspiratory splitting of the second heart sound	–	24 (36%)

Abbreviation: AF, atrial fibrillation

tuberculosis reported a 75% yield compared to a 53% yield with conventional culture.[52] For *Mycobacterium tuberculosis*, the radiometric method (BACTEC) permits an average recovery and drug sensitivity testing time of 18 days, compared to 38·5 days for conventional methods, but the low yield of 54% is the major disadvantage of the former method.[52] Sputum with acid-fast bacilli will be found in only about 10% of patients.[4] Gastric washings from such patients may be studied and urine culture and lymph node biopsy may also demonstrate tubercle bacilli.

In developing countries tuberculin skin testing is of little value owing to the high prevalence of primary tuberculosis, mass BCG immunizations and the likelihood of cross-sensitization from mycobacteria present in the environment.[53] Furthermore, the limited utility of the tuberculin skin test has also been documented in a prospective study performed in a non-endemic area.[43]

There is considerable urgency to establish the correct diagnosis of tuberculosis since early initiation of therapy is associated with a favorable outcome.[45] Since tubercle bacilli are often not found on stained smears of pericardial fluid[46,54] and their growth on culture requires 3–6 weeks, there is a need for other means of making an early diagnosis. Unfortunately, a rapid, simple, inexpensive, sensitive, and specific diagnostic test for pericardial tuberculosis is not available.[53] Pericardial biopsy is an important option, but a normal result does not exclude the diagnosis.

Recently, the usefulness of measuring adenosine deaminase activity for the rapid diagnosis of pericardial tuberculosis has been reported in different study populations with consistent results showing a pericardial fluid activity of $\geq$40 U/l to have a sensitivity and specificity of more than 90%.[55–57] An analysis of the largest prospective study of the usefullness of the adenosine deaminase test for the diagnosis of pericardial tuberculosis,[58] which included a wide spectrum of patients with pericardial effusion, yielded a likelihood ratio of 3·8 and 0·05 for positive and negative tests respectively (Table 50.7). Fagan's nomogram (Figure 50.1) for interpreting diagnostic test results can be used to determine the usefulness of a positive (adenosine deaminase $\geq$40) or negative (adenosine deaminase $<$40) test result.[59,60] Although the likelihood ratio for a positive test is 3·8, a high pretest probability of 80% is associated with a post-test probability of 95% if the adenosine deaminase result is positive. The likelihood ratio of a negative adenosine deaminase test is 0·05, which should confer conclusive changes on pretest to post-test probabilities.

In addition to the adenosine deaminase test, the measurement of interferon γ levels in pericardial fluid may offer another means of early diagnosis. A study involving 12 patients, with definite tuberculous pericardial effusion, and 19 controls indicated that elevated interferon γ measured by radioimmunoassay in pericardial aspirate is a sensitive (92%) and highly specific (100%) marker of a tuberculous etiology in patients with a pericardial effusion.[61] This promising report needs confirmation in larger studies.

The polymerase chain reaction is useful in detecting *Mycobacterium tuberculosis* DNA in pericardial fluid,[62–64]

Table 50.7 Test properties of the adenosine deaminase (ADA) assay derived from Latouf *et al*[58]

ADA level	Definite diagnosis of pericardial tuberculosis				Likelihood ratio
	Present		Absent		
	n	Proportion	*n*	Proportion	
ADA ≥40 U/l	77	77/80 = 0·963	26	26/103 = 0·253	3·80
ADA <40 U/l	3	3/80 = 0·038	77	77/103 = 0·748	0·05
Total	80		103		

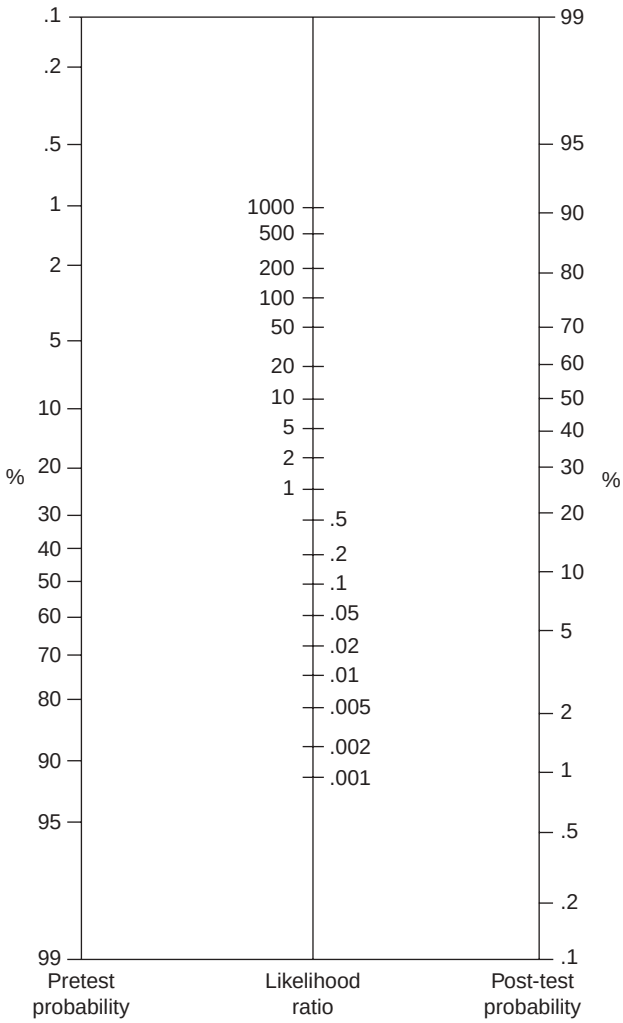

Figure 50.1 Nomogram for interpreting diagnostic test results. (Adapted from Fagan[59,60])

but the technique is less sensitive than established methods and is prone to contamination and false positive results and thus not yet suitable for routine clinical use.[53,64] At present, serum antibody tests against specific tuberculoprotein epitopes have not offered a significant diagnostic advance over other methods.[53]

Treatment

In areas and communities with a high prevalence of tuberculosis, a pericardial effusion is often considered to be tuberculous, unless an alternative cause is obvious, and treatment often has to be commenced before a bacteriologic diagnosis is established.[52] A definite diagnosis is not made in about a third of patients treated for tuberculous pericarditis and an adequate response to antituberculous chemotherapy serves as confirmation. When systematic investigation fails to yield a diagnosis in patients living in non-endemic areas, good prospective data indicate that there is no justification for starting antituberculous treatment empirically.[7] **Grade A**

Antituberculous chemotherapy dramatically increases survival in tuberculous pericarditis. In the preantibiotic era, mortality was 80–90% and currently it ranges from 8% to 17%.[47,65,66] A regimen consisting of rifampicin, isoniazid, and pyrazinamide in the initial phase of at least 2 months, followed by isoniazid and rifampicin for a total of 6 months of therapy has been shown to be highly effective in treating patients with extrapulmonary tuberculosis.[67,68] Treatment for 9 months or longer gives no better results and has the added disadvantages of increased costs and poor compliance.[68] Short-course chemotherapy is also highly effective in curing tuberculosis in HIV-infected patients,[69] although it has not been evaluated specifically in tuberculous pericarditis.

In 1988 Strang *et al*[44] reported a prospective double-blind evaluation of patients with tuberculous pericardial effusion treated with antituberculous drugs who were randomly allocated to prednisolone or placebo during the first 11 weeks of therapy (Figure 50.2): 240 patients entered the study and 198 were evaluated at 24 months; 42 patients (18%) were excluded from analysis mainly owing to loss to follow up and non-compliance with medication. In this trial, five of 97 patients given prednisolone compared with 11 of 101 given placebo died of pericarditis; seven and 17 needed repeat pericardiocentesis; three and seven open surgical drainage, and 91 and 88 had a favorable functional status at 24 months, respectively. Table 50.8 shows the outcomes for patients in the prednisolone and control groups together with the associated odds ratios (95% CI) and *P* values for the 198 patients who were analyzed in the trial. Patients treated with prednisolone were significantly less likely to

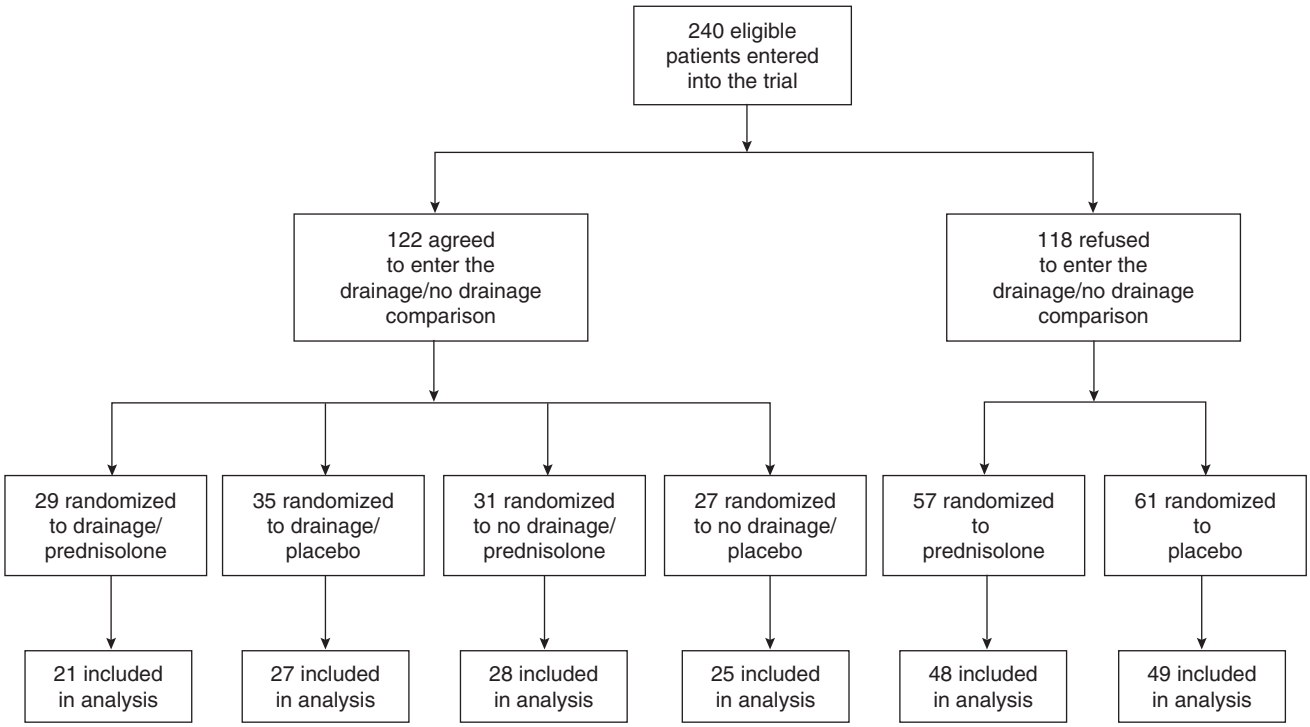

Figure 50.2 Tuberculous pericardial effusion trial profile.[44] A total of 198 patients were included in the analysis.

Table 50.8 Pericardial effusion: prednisolone versus placebo[44]

Outcome	Group prednisolone ($n = 97$)	Group placebo ($n = 101$)	Peto's odds ratio (95% CI)	*P* value
1. Favorable status at 24 months[a]	91/97	88/101	2·15 (0·84–5·53)	0·11
2. Repeat pericardiocentesis	7/97	17/101	0·41 (0·17–0·95)	0·04
3. Subsequent open drainage	3/97	7/101	0·45 (0·13–1·60)	0·22
4. Pericardiectomy	7/97	10/101	0·71 (0·26–1·92)	0·50
5. Total with one or more adverse events[b]	21/97	35/101	0·53 (0·29–0·98)	0·04
6. Death from pericarditis	5/97	11/101	0·46 (0·17–1·29)	0·14

[a] Patients were classified as having a favorable status if the following criteria were fulfilled or if only one was still abnormal: pulse rate ≤100, jugular venous pulse ≤5 cm, arterial pulsus paradoxus ≤10 mmHg, ascites and edema absent/just detectable, physical activity unrestricted, cardiothoracic ratio ≤55%, and electrocardiogram voltage ≥6 mm in V6 or ≥4 mm along the frontal axis.
[b] Includes outcomes numbered 2, 3, 4, and 6.

require repeat pericardiocentesis and had fewer combined adverse events than the placebo group. Although there is a suggestion that prednisolone may have a beneficial effect with regard to death from pericarditis, the 95% confidence intervals are consistent with a null effect.

It appears from these data that the adjuvant use of prednisolone in tuberculous pericarditis is associated with a reduced risk of reaccumulation of pericardial fluid and less morbidity during the treatment period, which may be clinically significant. It should, however, be noted that the exclusion of a high proportion of randomized patients from the analysis may be a source of substantial bias in the findings reported in this study. In support of the possibility of bias, a re-analysis of this trial that includes all the participants in the groups to which they were randomized showed that the tendency for prednisolone to reduce the incidence of cardiac tamponade requiring pericardiocentesis was not statistically significant (RR = 0·43, 95% CI 0·19–1·01).[70] Similarly, the effect of prednisolone on all-cause mortality showed a promising but non-significant effect (RR = 0·53,

95% CI 0·23–1·18). Therefore, on the basis of the currently available data, prednisolone cannot be recommended for routine use in patients with tuberculous pericardial effusion. We concur with the recommendation that corticosteroids should be reserved for critically ill patients with recurrent large effusions who do not respond to pericardial drainage and antituberculous drugs alone.[31]

Grade A In the study by Strang *et al*,[44] which compared prednisolone and placebo, those who were willing were also randomized to open complete drainage by substernal pericardiotomy and biopsy under general anesthesia followed by suction drainage on admission or percutaneous pericardiocentesis as required to control symptoms and signs (Figure 50.2); 101 patients participated in this comparison. Complete open drainage abolished the need for pericardiocentesis (odds ratio 0·12, 95% CI 0·04–0·39) but did not influence the need for pericardiectomy for subsequent constriction (odds ratio 0·45, 95% CI 0·10–2·06) or the risk of death from pericarditis (odds ratio 1·51, 95% CI 0·33–6·96).

The impact of antituberculous treatment on the development of constrictive pericarditis in patients with chronic pericardial effusion of unknown cause has been investigated in a randomized trial in India:[71] Twenty-five adults were randomized in a prospective 2:1 fashion to receive either three-drug antituberculous treatment (group A) or placebo (group B) for 6 months; 21 patients (14 in group A and seven in group B) completed the study protocol, and were included in the analysis. The primary end points were the development of pericardial thickening diagnosed by CT scan and constrictive pericarditis diagnosed by cardiac catheterization. There was no significant difference between the groups in the development of the combined end point of pericardial thickening and constrictive pericarditis (group A: $n = 3$, 21·4% *v* group B: $n = 2$, 29·6%; $P =$ NS); and pericardial fluid had disappeared in 10 patients (six in group A and four in group B). Thus, antituberculous treatment did not prevent the development of constrictive pericarditis and did not alter the clinical course in patients with large chronic pericardial effusions of undetermined etiology in an endemic area. However, the results of this trial should be considered with caution because of the small sample size involved. Nevertheless, the study makes a very important observation that requires further evaluation. In endemic areas antituberculous chemotherapy, which is not without hazard, is often administered to patients with large pericardial effusions in the absence of proof of tuberculosis.[4]

Recently, Hakim *et al*[72] reported the first double-blind randomized placebo controlled trial of adjunctive steroids in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. This Zimbabwean study randomized 58 HIV positive patients aged 18–55 years with suspected tuberculous pericarditis to receive prednisolone ($n = 29$) or placebo ($n = 29$) for 6 weeks, in addition to standard short-course antituberculous chemotherapy. The primary end points were resolution of pericardial fluid and death over an 18-month period of observation. There was no difference in the rate of radiologic and echocardiographic resolution in pericardial effusion. By contrast, there were fewer deaths in the intervention group (5/29) compared with the placebo group (10/29), but the numbers were small and the result could have occurred by chance (RR = 0·50, 95% CI 0·19–1·28). Thus the trials of steroids for the treatment of tuberculous pericarditis suggest that prednisolone has a potentially large beneficial effect on survival in immunocompetent and HIV seropositive patients, but the individual trials were too small to be sure that this is a true effect.[70] We believe that well-designed and adequately powered trials of steroids in tuberculous pericarditis are warranted.

Tuberculous pericardial constriction

Constrictive pericarditis is one of the most serious sequelae of tuberculous pericarditis and it occurs in 30–60% of patients despite prompt antituberculous treatment and the use of corticosteroids.[42,43] Tuberculosis is the most frequent cause of constrictive pericarditis in developing countries.[3,4] The presentation is highly variable, ranging from asymptomatic to severe constriction. The diagnosis is often missed on cursory clinical examination (Table 50.6). The diastolic lift (pericardial knock) with a high-pitched early diastolic sound and sudden inspiratory splitting of the second heart sound are subtle but specific physical signs, and found in 21–45% of patients with constrictive pericarditis. These signs are often missed by the inexperienced observer unless specifically sought. Furthermore, if the investigation is not clinically guided, echocardiography has the potential to miss the signs that are suggestive of this diagnosis.

Diagnosis

Most patients with constrictive pericarditis in South Africa have the subacute variety, in which a thick fibrinous exudate fills the pericardial sac, compressing the heart and causing a circulatory disturbance. As a result, calcification of the pericardium will be absent in the majority.[30] The chest radiograph findings are non-specific. In a study reported by Strang *et al*, 70% of 143 patients had a cardiothoracic ratio greater than 55% and only 6% had a ratio greater than 75%.[30] It is uncommon to find concomitant pulmonary tuberculosis. Nonspecific but generalized T wave changes are seen in most cases, while low voltage complexes occur in about 30% of cases. Atrial fibrillation occurs in less than 5% of cases, is persistent, and usually occurs with a calcified pericardium. As with tuberculous pericardial effusion, the ECG is useful only in drawing attention to the presence of a cardiac abnormality.

Echocardiography is particularly valuable in confirming the diagnosis of subacute constrictive pericarditis. Typically,

a thick fibrinous exudate is seen in the pericardial sac and is associated with diminished movements of the surface of the heart, normal sized chambers, absence of valvular heart disease, and absence of myocardial hypertrophy.[30] In time, the pericardial exudate condenses into a thick skin surrounding the heart, which usually, but not always, can be distinguished from myocardium.

Treatment

The treatment of tuberculous pericardial constriction involves the use of antituberculous drugs and pericardiectomy for persistent constriction in the face of drug therapy. In a double-blind, randomized, controlled trial in South Africa, 143 patients with tuberculous pericarditis and clinical signs of a constrictive physiology were allocated to receive prednisolone or placebo in addition to antituberculous drugs during the first 11 weeks of treatment (Figure 50.3)[30]: 114 patients were available for evaluation at 24 months; 20% of patients were excluded from analysis mainly due to loss to follow up and non-compliance with medication. Although clinical improvement occurred more rapidly in the prednisolone group and there was a lower mortality from pericarditis at 24 months (4% *v* 11%) and a lower requirement for pericardiectomy (21% *v* 30%), these findings were not statistically significant (Table 50.9). The remarkable finding of this study is that constriction resolved on antituberculous chemotherapy within 6 months in most patients, and only 29 (25%) of the 114 patients with constrictive pericarditis required pericardiectomy for persistent or worsening constriction.

No controlled studies have compared early pericardiectomy with late pericardiectomy in this condition. We recommend pericardiectomy if the patient's condition is static

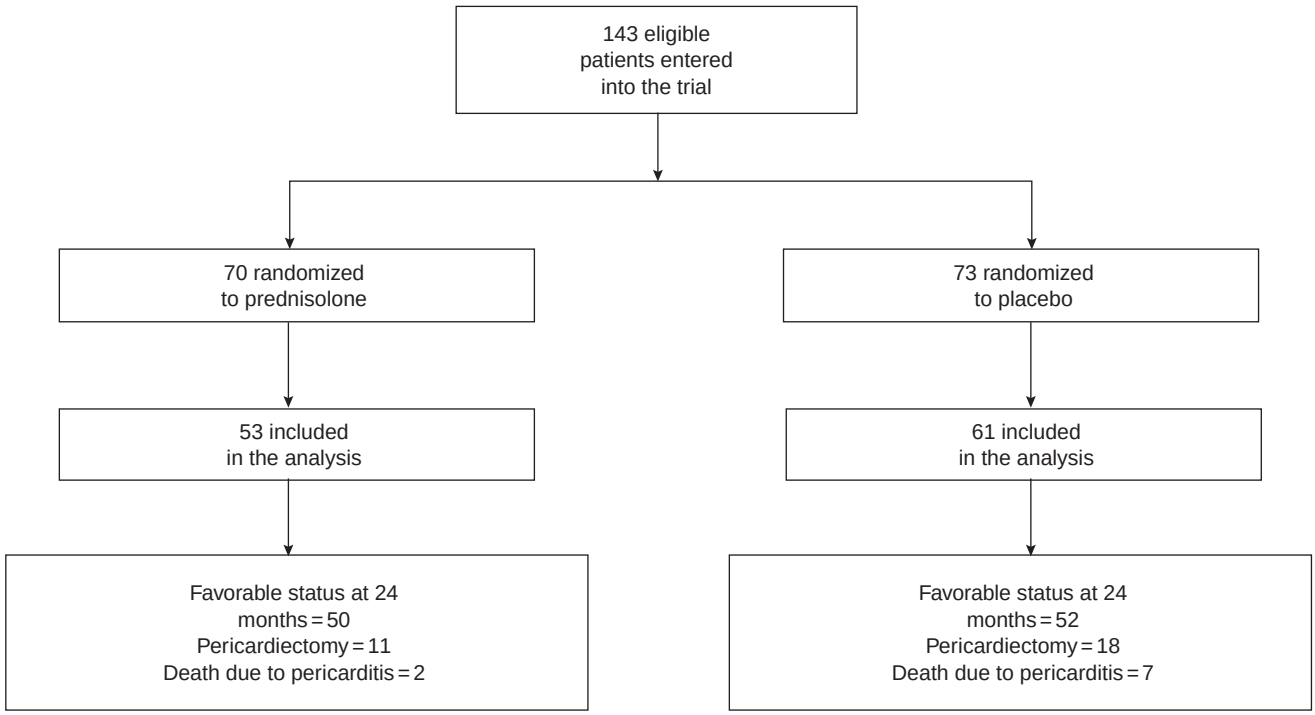

Figure 50.3 Tuberculous constrictive pericarditis trial profile[30]

Table 50.9 Constrictive pericarditis: prednisolone versus placebo[30]

Outcome	Group prednisolone ($n = 53$)	Group placebo ($n = 61$)	Peto's odds ratio (95% CI)	*P* value
1. Favorable status at 24 months[a]	50/53	52/61	2·60 (0·79–8·59)	0·116
2. Pericardiectomy	11/53	18/61	0·63 (0·27–1·47)	0·29
3. Death from pericarditis	2/53	7/61	0·35 (0·09–1·36)	0·13

[a] See note [a] in Table 50.8.

hemodynamically or deteriorating after 4–6 weeks of antituberculous therapy. However, if the disease is associated with pericardial calcification, which is a marker of chronic disease, surgery should be undertaken earlier under the antituberculous drug cover. The reported risks of death with pericardiectomy in patients with tuberculous constrictive pericarditis are variable, ranging from 3% to 16%.[40,73] **Grade C**

Effusive constrictive tuberculous pericarditis

This mixed form is a common presentation in Southern Africa. There is increased pericardial pressure owing to effusion in the presence of visceral constriction and the venous pressure remains elevated after pericardial aspiration. In addition to physical signs of pericardial effusion, a diastolic knock may be detected on palpation and an early third heart sound on auscultation.

In patients with the effusive constrictive syndrome echocardiography may show a pericardial effusion between thickened pericardial membranes, with fibrinous pericardial bands apparently causing loculation of the effusion.

The treatment of effusive constrictive pericarditis is a problem because pericardiocentesis does not relieve the impaired filling of the heart and surgical removal of the fibrinous exudate coating the visceral pericardium is not possible. Antituberculous drugs should be given in the standard fashion and serial echocardiography performed to detect the development of a pericardial skin, which is amenable to surgical stripping. The place of corticosteroids in such patients is unknown.

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References

1. Maharaj B. Causes of congestive heart failure in black patients at King Edward VIII Hospital, Durban. *Cardiovasc J S Afr* 1991;**2**:31–2.
2. Maisch B. Pericardial diseases, with a focus on etiology, pathogenesis, pathophysiology, new diagnostic imaging methods and treatment. *Curr Opin Cardiol* 1994;**9**:379–88.
3. Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol* 1985;**56**:623–9.
4. Strang JIG. Tuberculous pericarditis. *Clin Cardiol* 1984;**7**: 667–70.
5. Fowler NO. Pericardial disease. *Heart Dis Stroke* 1992;**1**: 85–94.
6. Zayas R, Anguita M, Torres F *et al.* Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. *Am J Cardiol* 1995;**75**:378–82.
7. Permanyer-Miralda G, Sagrista-Sauleda J, Shebatai R *et al.* Acute pericardial disease: an approach to etiologic diagnosis and treatment. In: Soler-Soler J *et al.*, eds. *Pericardial disease: new insights and old dilemmas*. Dordrecht: Kluwer Academic Publishers, 1990.
8. Farraj RS, McCully RB, Oh JK, Smith TF. *Mycoplasma*-associated pericarditis. *Mayo Clin Proc* 1997;**72**:33–6.
9. Arunsalam S, Siegel RJ. Rapid resolution of symptomatic acute pericarditis with ketorolac tromethamine: a parenteral nonsteroidal antiinflammatory agent. *Am Heart J* 1993;**125**: 1455–8.
10. Fowler NO, Harbin AD. Recurrent pericarditis: follow-up of 31 patients. *J Am Coll Cardiol* 1986;**7**:300–5.
11. Hatcher CR, Logue RB, Logan WD *et al.* Pericardiectomy for recurrent pericarditis. *J Thorac Cardiovasc Surg* 1971;**62**: 371–8.
12. Asplen CH, Levine HD. Azathioprine therapy of steroid responsive pericarditis. *Am Heart J* 1970;**80**:109–11.
13. Melchior TM, Ringsdal V, Hildebrandt P, Torp-Pedersen C. Recurrent acute idiopathic pericarditis treated with intravenous methylprednisolone given as pulse therapy. *Am Heart J* 1992;**123**:1086–8.
14. Marcolongo R, Russo R, Lavender F, Noventa F, Agostini C. Immunosuppressive therapy prevents recurrent pericarditis. *J Am Coll Cardiol* 1995;**26**:1276–9.
15. Guindo J, Rodriguez de la Serna A, Ramio J *et al.* Recurrent pericarditis. Relief with colchicine. *Circulation* 1990;**82**: 1117–20.
16. Rodriguez de la Serna A, Guindo Soldevila J, Marti Claramunt V, Bayes de Luna A. Colchicine for recurrent pericarditis. *Lancet* 1987;**ii**:1517.
17. Spodick DH. Colchicine therapy for recurrent pericarditis. *Circulation* 1991;**83**:1830.
18. Adler Y, Zandman-Goddard G, Ravid M *et al.* Usefulness of colchicine in preventing recurrences of pericarditis. *Am J Cardiol* 1994;**73**:916–17.
19. Millaire A, deGroote P, Decoulx E *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994;**15**:120–4.
20. Guindo J, Adler Y, Spodick H *et al.* Colchicine for recurrent pericarditis: 51 patients followed up for 10 years. *Circulation* 1997;**96**(Suppl. I):I-29 (Abstract).
21. Eisenberg MJ, Dunn MM, Kanth N, Gamsu G, Schiller NB. Diagnostic value of chest radiography for pericardial effusion. *J Am Coll Cardiol* 1993;**22**:588–92.
22. Spodick DH. Electrical alternation of the heart. Its relation to the kinetics and physiology of the heart during cardiac tamponade. *Am J Cardiol* 1962;**10**:155–65.
23. Eisenberg MJ, Oken K, Guerrero S, Saniei MA, Schiller NB. Prognostic value of echocardiography in hospitalized patients with pericardial effusion. *Am J Cardiol* 1992;**70**:934–9.
24. Sinha PR, Singh BP, Jaipuria N *et al.* Intrapericardial echogenic images and development of constrictive pericarditis in patients with pericardial effusion. *Am Heart J* 1996; **132**: 1268–72.
25. Nugue O, Millaire A, Porte H *et al.* Pericardioscopy in the etiologic diagnosis of pericardial effusion in 141 consecutive patients. *Circulation* 1996;**94**:1635–41.
26. Fowler NO. Cardiac tamponade: a clinical or an echocardiographic diagnosis? *Circulation* 1993;**87**:1738–41.

27.Chuttani K, Pandian NG, Mohanty PK *et al.* Left ventricular diastolic collapse: an echocardiographic sign of regional cardiac tamponade. *Circulation* 1991;**83**:1999–2006.
28.Chuttani K, Tischler MD, Pandian MG, Lee RT, Mohanty PK. Diagnosis of cardiac tamponade after cardiac surgery: relative value of clinical, echocardiographic and hemodynamic signs. *Am Heart J* 1994;**127**:913–18.
29.Ling LH, Oh JK, Schaff HV *et al.* Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. *Circulation* 1999;**100**: 1380–6.
30.Strang JIG, Kakaza HHS, Gibson DG *et al.* Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987;**ii**:1418–22.
31.Lorell BH. Pericardial diseases. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 1997.
32.Boonyaratavej S, Oh JK, Tajik AJ, Appleton CP, Seward JB. Comparison of mitral inflow and superior vena cava Doppler velocities in chronic obstructive pulmonary disease and constrictive pericarditis. *J Am Coll Cardiol* 1998;**32**:2043–8.
33.Ha J-W, Oh JK, Ling LH, Nishimura RA, Seward JB. Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. *Circulation* 2001;**104**:976–8.
34.Reinmuller R, Gurgan M, Erdmann E *et al.* CT and MR evaluation of pericardial constriction: a new diagnostic and therapeutic concept. *J Thorac Imaging* 1993;**8**:108–21.
35.Oren RM, Grover-McKay M, Stanford W, Weiss RM. Accurate preoperative diagnosis of pericardial constriction using cine computed tomography. *J Am Coll Cardiol* 1993; **22**:832–8.
36.Fowler NO. Constrictive pericarditis: its history and current status. *Clin Cardiol* 1995;**18**: 341–50.
37.Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med* 1997;**336**:267–76.
38.Tirilomis T, Unverdorben S, von der Emde J. Pericardiectomy for chronic constrictive pericarditis: risks and outcome. *Eur J Cardiothor Surg* 1994;**8**:487–92.
39.McCaughan BC, Schaff HV, Piehler JM *et al.* Early and late results of pericardiectomy for constrictive pericarditis. *J Thorac Cardiovasc Surg* 1985;**89**:340–50.
40.Bashi VV, John S, Ravikumar E *et al.* Early and late results of pericardiectomy in 118 cases of constrictive pericarditis. *Thorax* 1988;**43**:637–41.
41.Cegielski JP, Ramaiya K, Lallinger GJ, Mtulia IA, Mbaga IM. Pericardial disease and human immunodeficiency virus in Dar es Salaam, Tanzania. *Lancet* 1990;**335**:209–12.
42.Schrire V. Experience with pericarditis of Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases over a six-year period. *S Afr Med J* 1959;**33**:810–17.
43.Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Tuberculous pericarditis: ten-year experience with a prospective protocol for diagnosis and treatment. *J Am Coll Cardiol* 1988;**11**:724–8.
44.Strang JIG, Kakaza HHS, Gibson DG *et al.* Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988;**ii**:759–64.
45.Hageman JH, d'Esopo ND, Glenn WWL. Tuberculosis of the pericardium: a long-term analysis of forty-four proved cases. *N Engl J Med* 1964;**270**:327–32.
46.Fowler NO, Manitsas GT. Infectious pericarditis. *Prog Cardiovasc Dis* 1973;**16**:323–36.
47.Desai HN. Tuberculous pericarditis: a review of 100 cases. *S Afr Med J* 1979;**55**:877–80.
48.Quale JM, Lipschik GY, Heurich AE. Management of tuberculous pericarditis. *Ann Thorac Surg* 1987;**43**:653–5.
49.Heimann HL, Binder S. Tuberculous pericarditis. *Br Heart J* 1940;**2**:165–76.
50.Fowler NO. Tuberculous pericarditis. *JAMA* 1991;**266**: 99–103.
51.Schrire V. Pericarditis (with particular reference to tuberculous pericarditis). *Aust Ann Med* 1967;**16**:41–51.
52.Strang G, Latouf S, Commerford P *et al.* Bedside culture to confirm tuberculous pericarditis. *Lancet* 1991;**338**:1600–1.
53.Ng TTC, Strang JIG, Wilkins EGL. Serodiagnosis of pericardial tuberculosis. *Quart J Med* 1995;**88**:317–20.
54.Schepers GWH. Tuberculous pericarditis. *Am J Cardiol* 1962; **9**:248–76.
55.Koh KK, Kim EJ, Cho CH *et al.* Adenosine deaminase and carcinoembryonic antigen in pericardial effusion diagnosis, especially in suspected tuberculous pericarditis. *Circulation* 1994; **89**:2728–35.
56.Martinez-Vasquez JM, Ribera E, Ocana I *et al.* Adenosine deaminase activity in tuberculous pericarditis. *Thorax* 1986; **41**:888–9.
57.Komsouglu B, Goldeli O, Kulan K, Komsouglu SS. The diagnostic and prognostic value of adenosine deaminase in tuberculous pericarditis. *Eur Heart J* 1995;**16**:1126–30.
58.Latouf SE, Levetan BN, Commerford PJ. Tuberculous pericardial effusion: analysis of commonly used diagnostic methods. *S Afr Med J* 1996;**86**(Suppl.):15 (Abstract).
59.Fagan TJ. Nomogram for Bayes' theorem (C). *N Engl J Med* 1975;**293**:257.
60.Jaeschke R, Guyatt GH, Sackett DL III. How to use an article about a diagnostic test: B. What are the results and will they help me in caring for my patients? *JAMA* 1994;**271**:703–7.
61.Latouf SE, Ress SR, Lukey PT, Commerford PJ. Interferon-gamma in pericardial aspirates: a new, sensitive and specific test for the diagnosis of tuberculous pericarditis. *Circulation* 1991;**84**(Suppl.):II-149.
62.Brisson-Noel A, Gicquel B, Lecossier D *et al.* Rapid diagnosis of tuberculosis by amplification of mycobacterial DNA in clinical samples. *Lancet* 1989;**ii**:1069–71.
63.Godfrey-Faussett P, Wilkins EGL, Khoo S, Stoker N. Tuberculous pericarditis confirmed by DNA amplification. *Lancet* 1991;**337**:176–7.
64.Cegielski JP, Blythe BH, Morris AJ *et al.* Comparison of PCR, culture, and histopathology for diagnosis of tuberculous pericarditis. *J Clin Microbiol* 1997;**35**:3254–7.
65.Harvey AM, Whitehill MR. Tuberculous pericarditis. *Medicine* 1937;**16**:45–94.
66.Bhan GL. Tuberculous pericarditis. *J Infect* 1980;**2**:360–4.
67.Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly directly-observed, cost-effective regimen. *Ann Intern Med* 1990;**112**:407–15.

68. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity and acceptability. The report of final results. *Ann Intern Med* 1990;**112**:397–406.
69. Perriens JH, St Louis M, Mukadi YB *et al.* Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment for either 6 months or 12 months. *N Engl J Med* 1995;**332**:779–84.
70. Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis (Cochrane Review). In: Cochrane Collaboration. *Cochrane Library*, Issue 2. Oxford: Update Software, 2001.
71. Dwivendi SK, Rastogi P, Saran RK, Rarain VS, Puri VK, Hasan M. Antituberculous treatment does not prevent constriction in chronic pericardial effusion of undetermined aetiology. *Indian Heart J* 1997;**49**:411–14.
72. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; **84**:183–8.
73. Pitt Fennell WM. Surgical treatment of constrictive tuberculous pericarditis. *S Afr Med J* 1982;**62**:353–5.

Part IIIg

Specific cardiovascular disorders: Valvular heart disease

Bernard J Gersh, *Editor*

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

51 Rheumatic heart disease: prevention and acute treatment

Edmund AW Brice, Patrick J Commerford

Rheumatic fever is the most important cause of acquired heart disease in children and young adults worldwide. Initiated by an oropharyngeal infection with group A β hemolytic streptococci (GAS) and following a latent period of approximately 3 weeks, the illness is characterized by an inflammatory process primarily involving the heart, joints, and central nervous system. Pathologically, the inflammatory process causes damage to collagen fibrils and connective tissue ground substance (fibrinoid degeneration) and thus rheumatic fever is classified as a connective tissue or collagen vascular disease. It is the destructive effect on the heart valves that leads to the important effects of the disease, with serious hemodynamic disturbances causing cardiac failure or embolic phenomena resulting in significant morbidity and mortality at a young age.

There have been many publications concerning the primary and secondary prevention of rheumatic fever and the treatment of the acute attack. The evidence from randomized controlled clinical trials is strongest in the field of primary prevention or the treatment of pharyngitis caused by GAS. There are few randomized trials concerning secondary prevention. In the treatment of the acute attack, most publications have been observational studies with only a small minority of randomized trials.

Epidemiology

In the developed countries of the world, the incidence of rheumatic fever fell markedly during the 20th century. For example, in the USA the incidence per 100 000 was 100 at the start of this century, 45–65 between 1935 and 1960, and is currently estimated to be approximately 2 per 100 000. This decrease in rheumatic fever incidence preceded the introduction of antibiotics and is a reflection of improved socioeconomic standards, less overcrowded housing, and improved access to medical care. The current prevalence of rheumatic fever in the USA and Japan, 0·6–0·7 per 1000 population, contrasts sharply with that in the developing countries of Africa, Asia, and South America, where rates as high as 15–21 per 1000 have been reported. For example, in a study of 12 050 schoolchildren in Soweto, South Africa, a peak prevalence of rheumatic heart disease of 19·2/1000 children was reported.[1]

As GAS pharyngitis and rheumatic fever are causally related, both diseases share similar epidemiologic features. The age of first infection is commonly between 6 and 15 years. Also, the risk for developing rheumatic fever is highest in situations where GAS is more common, for example where people live in crowded conditions.

Pathogenesis

Clinical, epidemiologic, and immunologic observations tend to support strongly the causative role of untreated GAS pharyngitis in rheumatic fever. Beyond this, however, the pathogenesis of acute rheumatic fever and clinical heart disease remains unclear and several important and unexplained observations render the management of this important disease extremely difficult. These are:

- individual variability of susceptibility to GAS pharyngitis;
- individual variability of development of symptomatic GAS pharyngitis;
- individual variability of development of acute rheumatic fever after an episode of GAS pharyngitis;
- individual variation in the development of carditis and chronic rheumatic heart disease after an attack of acute rheumatic fever;
- the development of chronic rheumatic heart disease in patients who have no definite history of acute rheumatic fever.

Streptococcal skin infection (impetigo) has not been shown to cause rheumatic fever. While effective antibiotic treatment virtually abolishes the risk of rheumatic fever, in situations of untreated epidemic GAS pharyngitis up to 3% of patients develop it.[2] Worryingly, as many as a third of patients who develop rheumatic fever do so after virtually asymptomatic GAS and in more recent outbreaks, 58% denied preceding symptoms.[3] This does not augur well for the primary prevention of rheumatic fever where prompt diagnosis of GAS pharyngitis and treatment are essential.

The virulence of the streptococcal infection is dependent on the organisms' M protein serotype, which determines the antigenic epitopes shared with human heart tissue, especially sarcolemmal membrane proteins and cardiac myosin.[4] It is

these variations in virulence, as a result of M protein variation, that are thought to explain the occasional outbreaks of rheumatic fever in areas of previously low incidence.[5] Other factors influencing the risk for rheumatic fever are the magnitude of the immune response and the persistence of the organism during the convalescent phase of the illness.[2]

Evidence suggests that host factors play a role in the risk for rheumatic fever. In patients who have suffered an attack of rheumatic fever, the incidence of a repeat attack is approximately 50%. A specific B cell alloantigen has been found to be present in 99% of patients with rheumatic fever versus 14% of controls.[6] Certain HLA antigens appear to be associated with increased risk for rheumatic fever. Approximately 60–70% of patients worldwide are positive for HLA-DR3, DR4, DR7, DRW53, or DQW2.[7] Such genetic markers for rheumatic fever risk may be useful to identify those in need of GAS prophylaxis. However, in view of the frequency with which these markers occur, they are unlikely to be of practical benefit in the short term.

Clinical features

While there is no specific clinical, laboratory or other test to confirm conclusively a diagnosis of rheumatic fever, the diagnosis is usually made using the clinical criteria first formulated in 1944 by T Duckett Jones[8] and subsequently modified by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young (American Heart Association).[9] The revised criteria emphasize the importance of diagnosing *initial* attacks of rheumatic fever. The criteria are often incorrectly applied to the diagnosis of recurrent attacks, for which they were not originally intended. The diagnosis is suggested if, in the presence of preceding GAS infection, two major criteria (carditis, chorea, polyarthritis, erythema marginatum, and subcutaneous nodules) or one major and two minor criteria (fever, arthralgia, elevated erythrocyte sedimentation rate, elevated C-reactive protein, or a prolonged PR interval on ECG) are present. Evidence of preceding GAS infection, essential for the diagnosis, may be obtained from throat swab culture (only positive in approximately 11% of patients at the time of diagnosis of acute rheumatic fever)[3] or by demonstrating a rising titer of antistreptococcal antibodies, either antistreptolysin O (ASO) or anti-deoxyribonuclease B (anti-DNase B).

Prevention

The most recent recommendations on the prevention of rheumatic fever have been published by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young (American Heart Association).[10]

Prevention of rheumatic fever may be considered to be either prevention of the initial attack (primary prevention) or prevention of recurrent attacks (secondary prevention). *True primary prevention* of rheumatic fever depends more on socioeconomic than medical factors. Upgrading housing and other aspects of urban renewal will do more toward eradicating the disease than antibiotic prophylaxis.

Primary prevention

Prevention of the initial attack of rheumatic fever depends on the prompt recognition of GAS pharyngitis and its effective treatment. Whilst it has been demonstrated that therapy initiated as long as 9 days after the onset of GAS pharyngitis can prevent an attack of rheumatic fever,[11] early treatment reduces both the morbidity and the period of infectivity.

The first report of the use of penicillin for the treatment of GAS pharyngitis and prevention of most attacks of rheumatic fever was published in 1950.[11] Over the following 40 years, attention focused on accurate diagnosis and treatment of GAS pharyngitis. A single dose of intramuscular benzathine penicillin G became the most common mode of treatment and avoided problems of non-compliance. Subsequently, as a result of the pain and possibility of allergic reaction associated with benzathine penicillin G, oral penicillin became the treatment of choice[12] and remains so today.[13] In situations where compliance with a 10 day course of oral penicillin would be unreliable, a single dose of IM benzathine penicillin G would be preferred (dosage 1·2 million U if >27 kg, otherwise 600 000 U).

Early studies established a 10 day course of oral penicillin as optimal[14,15] and this has been supported in more recent studies.[16,17] Shorter treatment periods are associated with significant decreases in bacteriological cure while longer courses of treatment do not increase cure rate.

Current recommendations[10] for penicillin therapy in children cite a dose of 250 mg ×2–3/day. These recommendations are based on trials (Table 51.1) of 250 mg given ×2–4/day resulting in equivalent cure rates.[18–21] A dose of 750 mg/day penicillin yielded significantly worse results than 250 mg ×3/day when compared in a randomized study.[22] There is no evidence available for optimal doses of penicillin in adults but 500 mg ×2–3/day is currently recommended.[10] **Grade A**

Over the past decade, many trials have been published comparing penicillin VK to a variety of other antimicrobial agents, most commonly cephalosporins and macrolides. This has been prompted by the reported increase in treatment failures with penicillin. It has been suggested that treatment failure rates of up to 38% are possible. This contention, however, has been thoroughly investigated in a study by Markowitz *et al*[23] in which treatment failure rates of penicillin were compared between two time periods,

Table 51.1 Cure rates for various penicillin dosage schedules used in treatment of streptococcal pharyngitis

Reference	Agent/dose	Bacteriologic cure rate (%)
Gerber *et al.* (1985)[21]	Pen V 250 mg 2×/day ×10 days	82·0
	Pen V 250 mg 3×/day ×10 days	71·5
Gerber *et al.* (1989)[22]	Pen V 750 mg 1×/day ×10 days	78·0
	Pen V 250 mg 3×/day ×10 days	92·0
Vann and Harris (1972)[19]	Potassium Pen G 80 000 U 2×/day ×10 days	88·0
Spitzer and Harris (1977)[20]	Pen V 500 mg 2×/day ×10 days	83·0
	Pen V 250 mg 3×/day ×10 days	84·0

Abbreviation: Pen, penicillin

1953–1979 and 1980–1993. Of the almost 2800 patients with GAS serotyping, treatment failures ranged between 10·5% and 17%, with no significant difference between each time period. It was thus concluded that the over-reporting of treatment failures was due to problems with the design of the individual studies.

An increased bateriologic cure rate for streptococcal pharyngitis by cephalosporins was demonstrated in a meta-analysis[24] of 19 randomized comparisons of a variety of cephalosporins with 10 days of oral penicillin therapy. Throat swab cultures were used to determine the presence of GAS and clearance after treatment. The results showed a statistically significant advantage of cephalosporins for which a bacteriologic cure rate of 92% was reported versus 84% for penicillin. The corresponding clinical cure rates were 95% and 89% respectively. It is suggested that the resistance of cephalosporins to penicillinase-producing anaerobes and staphylococci present in the pharyngeal flora may explain these findings. This difference in efficacy would mean that 12–13 patients would require cephalosporin treatment to potentially prevent one penicillin bacteriological treatment failure.

More recently, a multicenter comparison of 10 day therapy with cefibuten oral suspension (9 mg/kg/day in one dose) and penicillin V (25 mg/kg/day in three divided doses)[25] revealed a bacteriological cure rate of 91% versus 80% respectively (corresponding clinical cure rates were 97% *v* 89%). **Grade A** Shorter courses of selected cephalosporins[26] (4 or 5 days) have been shown to be effective, but current recommendations[10] suggest that further study of these regimens is required before their adoption. The cephalosporins offer statistically significant advantages over penicillin in controlled clinical trials. It remains to be demonstrated, however, whether this statistical benefit can be translated into clinical or epidemiological benefit in regions where the disease is endemic. Given the financial constraints on healthcare resources of developing nations and the considerable cost difference, it would seem that this is unlikely in the foreseeable future. Greater benefit is likely to be achieved by concerted efforts to identify, treat, and ensure compliance in large numbers of patients with the established, albeit inferior, penicillin schedules.

In patients allergic to penicillin, erythromycin has been shown to have an equivalent cure rate.[27] The recommended dosage for erythromycin estolate is 20–40 mg/kg/day in 2–4 divided doses, and for erythromycin ethylsuccinate, it is 40 mg/kg/day in 2–4 divided doses, both for 10 days.[28] **Grade A** The efficacy of erythromycin estolate is superior to that of erythromycin ethylsuccinate and is associated with fewer gastrointestinal tract side effects.[29] GAS strains resistant to erythromycin have been reported in some parts of the world.[30]

Thus, penicillin V remains the treatment of choice in non-penicillin allergic patients as it has a long record of efficacy and is probably the most cost effective option.

Appropriate antibiotic therapy in children with streptococcal pharyngitis should result in a clinical response within 24 hours – most children will become culture negative within the first or second day of treatment.[31] After completion of therapy, only patients who have persistent or recurring symptoms, or those at an increased risk for recurrence, require repeat throat swab culture. If symptomatic patients are still harboring GAS in the oropharynx, a second course of antibiotics, preferably with another agent (amoxicillin clavulanate, cephalosporins, clindamycin or penicillin and rifampicin), is recommended.[10] Failure to eradicate GAS occurs more frequently following the administration of oral penicillin than IM benzathine penicillin G.[32] Further treatment of asymptomatic patients, who are frequently chronic GAS carriers, is only indicated for those with previous rheumatic fever or their family members.

Secondary prevention

Following an initial attack of rheumatic fever, there is a high risk of recurrent attacks, which increase the likelihood of cardiac damage, and continuous antibiotic therapy is required. This is especially important as GAS infections need not be symptomatic to trigger a recurrence of rheumatic fever,

nor does optimal GAS treatment preclude a recurrence. It is recommended that patients who have suffered either proven attacks of rheumatic fever or Sydenham's chorea be given long-term prophylaxis following the initial treatment to eradicate the pharyngeal GAS organisms. Recommendations regarding the duration of such prophylaxis are largely empiric and based on observational studies.

The duration of prophylaxis should be individualized and take into account the socioeconomic conditions and risk of exposure to GAS for that patient. Individuals who have suffered carditis, with or without valvular involvement, are at higher risk for recurrent attacks[33,34] and should receive prophylaxis well into adulthood and perhaps for life. If valvular heart disease persists then prophylaxis is indicated for at least 10 years after the last attack of rheumatic fever and at least until 40 years of age. Those patients who have not suffered rheumatic carditis can receive prophylaxis until 21 years of age or 5 years after the last attack.[35]

The choice of prophylactic agent has to be made with due regard for the likelihood of compliance with a regimen over a period of many years. **Grade A** Therefore, despite associated pain *(which can be ameliorated by using lidocaine as a diluent[36])*, intramuscular injection of benzathine penicillin G is the method of choice in most situations. The recommended dose is 1·2 million U every 3–4 weeks. A comparison of 3 weekly ($n = 90$) versus 4 weekly ($n = 63$) benzathine penicillin prophylaxis[37] demonstrated the superiority of the 3 weekly dosage. The only prophylaxis failure in the 3 weekly dosage group was due to partial compliance versus five true failures in the 4 weekly dosage group. A long-term follow up study[38] for a mean period of 6·4 years (range 1–12 years) in 249 consecutively randomized patients to 3 or 4 weekly regimens further supported the former schedule (0·25% *v* 1·29% prophylaxis failures respectively). Assays for penicillin levels in blood have also shown that 4 weekly dosage did not provide adequate drug levels throughout the intervening period between doses.[39] Therefore, only those considered at low risk should receive a 4 weekly dose.

Oral prophylaxis has been shown to be less effective than intramuscular penicillin G prophylaxis, even when compliance is optimal.[32] Penicillin V 250 mg ×2/day for adults and children is the recommended dose. No published data exist on other penicillins, macrolides, or cephalosporins for secondary prophylaxis of rheumatic fever. However erythromycin, at a dose of 250 mg ×2/day is usually recommended for those allergic to penicillin.

Patients who have either had prosthetic valves inserted and/or who are in atrial fibrillation require warfarin anticoagulation. This is a situation that may necessitate the use of an oral prophylaxis regimen. In such patients intramuscular injections of penicillin may carry the risk of hematoma formation, especially in patients rendered asthenic as a consequence of their underlying illness. This important circumstance is, as far as we are aware, not addressed in the literature.

Acute management

The aim of the acute treatment of a proven attack of rheumatic fever is to suppress the inflammatory response and so minimize the effects on the heart and joints, to eradicate the GAS from the pharynx, and provide symptomatic relief.

The longstanding recommendation of bed rest would appear to be appropriate, mainly in order to lessen joint pain. **Grade C** The duration of bed rest should be individually determined but ambulation can usually be started once the fever has subsided and acute phase reactants are returning towards normal. Strenuous exertion should be avoided, especially for those with carditis.

Even though throat swabs taken during the acute attack of rheumatic fever are rarely positive for GAS, it is advisable for patients to receive a 10 day course of penicillin V (or erythromycin if penicillin allergic). Although conventional, this strategy is untested. Thereafter, secondary prophylaxis should commence as described in the previous section.

The choice of anti-inflammatory agent is between salicylates and corticosteroids. **Grade A** Recently, a meta-analysis of trials comparing these two agents has been published.[40] In this review, a total of 130 publications from 1949 were assessed. While 11 studies had been randomized, only five (Table 51.2)[41–45] fulfilled the meta-analysis criteria of:

- adequate case definition by the Jones criteria;
- proper randomization to either salicylates or some form of corticosteroid;
- non-overlap of subjects between studies; and
- follow up for at least 1 year for assessment of the presence of an apical systolic murmur suggesting structural cardiac damage as a result of carditis.

The trials varied in the use of steroid agent used, either cortisone, ACTH, or prednisone.

The largest study of the five selected for the meta-analysis was that of the Rheumatic Fever Working Party where ACTH, cortisone, and aspirin were compared in a trial involving 505 children in the USA and UK.[44] This study found no long-term advantage to be associated with either therapy. While apical systolic murmurs disappeared more rapidly in the steroid-treated groups, the prevalence of a cardiac murmur at 1 year follow up was the same as for the salicylate-treated group. The erythrocyte sedimentation rate was found to normalize and nodules resolved faster in the steroid group.

When the five studies were examined in the meta-analysis, it was found that the advantage of corticosteroids over salicylates, in preventing the development of a pathologic apical

Table 51.2 Randomized trials of acute rheumatic fever treatment

Reference	Number of patients analyzed	Agent/dose	Apical murmur present at 1 year (%)
Combined Rheumatic Fever Study Group (1960)[41]	57	Prednisone 60 mg/day ×21 days then taper *v* ASA 50 mg/lb/day ×9 weeks, then taper	Steroids 57·1% *v* ASA 37%
Combined Rheumatic Fever Study Group (1965)[42]	73	Prednisone 3 mg/lb/day ×7 days then taper *v* ASA 50 mg/lb/day × 6 weeks	Steroids 25·3% *v* ASA 32·1%
Dorfman *et al* (1961)[43]	129	Hydrocortisone 250 mg then taper and/or ASA to 20–30 mg%	Steroids 12·5% *v* ASA 34·4%
Rheumatic Fever Working Party (1955)[44]	497	ACTH 80–120 U and taper *v* cortisone 300 mg and taper *v* ASA 60 mg/lb/day and taper	Steroids 48·6% *v* ASA 44%
Stolzer *et al* (1965)[45]	128	ASA 30–60 mg/lb/day ×6 weeks *v* cortisone 50–300 mg/day *v* ACTH 20–120 *v* mg/day	Steroids 26·3% *v* ASA 34·6%

systolic murmur after 1 year of treatment, was not statistically significant (estimated odds ratio 0·88, 95% CI 0·53–1·46).

All these trials may be criticized on two important points. Firstly, the method used to assess cardiac involvement was clinical with the development or persistence of an apical systolic murmur the usual criterion. It could be argued that observer error and interobserver variability of clinical methodology could invalidate the results and that the question should be re-examined using modern non-invasive techniques. It has, however, been shown that, at least during the acute phase of the illness, transthoracic two-dimensional echocardiography with color flow imaging does not add significantly to the clinical evaluation of the degree of cardiac involvement.[46] The second point relates to the duration of follow up. Lack of clinical evidence of cardiac involvement at 1 or 2 years following the initial attack of acute rheumatic fever is no guarantee that the important sequelae of valvular incompetence or stenosis will not develop in the ensuing decades.

Appropriate dosages of anti-inflammatory agents are aspirin 100 mg/kg/day in four or five divided doses or prednisone 1–2 mg/kg/day. Patients with severe cardiac involvement appear to respond more promptly to corticosteroids.[47]

The duration of therapy must be gauged from the severity of the attack, the presence of carditis, and the rate of response to treatment. Milder attacks with little or no carditis may be treated with salicylates for approximately a month or until inflammation has subsided, as assessed by clinical and laboratory evidence. More severe cases may require 2–3 months of steroid therapy before this can be gradually weaned. Up to 5% of patients may still have rheumatic activity despite treatment at 6 months. Occasionally a "rebound" of inflammatory activity can occur when anti-inflammatory therapy is reduced, and may require salicylate treatment.

Alternative non-steroidal anti-inflammatory agents have not been adequately assessed in trials and would be of benefit only in individuals allergic to or intolerant of aspirin.

A recent prospective randomized controlled trial demonstrated no benefit for intravenous immunoglobulin over placebo when administered during the first episode of rheumatic fever.[48]

In patients whose initial attack of rheumatic fever is inadequately treated, there is a high risk that the rheumatic activity will continue and result in valvular incompetence, most commonly of the mitral valve. The end result of an ongoing rheumatic process with deteriorating valvular function is heart failure. Experience has shown that in such cases prompt surgical management[49] is the sole option and can result in the survival of up to 90% of patients.[50] It has been suggested that the reduction in cardiac workload following valve surgery results in a settling of the rheumatic process – akin to the beneficial effect observed for bed rest.

Conclusion

While questions regarding the pathogenesis of rheumatic fever remain, sufficient evidence is available to offer guidance on the appropriate prevention and acute treatment of this common illness (Table 51.3). It must be remembered that as most sufferers of this disease are in poor socioeconomic environments and in countries where resources are scarce, the regimens used must be cost effective and chosen with a view to maximizing patient compliance.

Table 51.3 Recommendations for prophylaxis and therapy

Agent	Dose	Route	Duration
Primary prevention			
Benzathine penicillin G	600 000 U if ≤27 kg, 1 200 000 U if >27 kg	Intramuscular injection	Once
Penicillin V	Children 250 mg, ×2–3/day Adults 500 mg ×2–3/day	Oral	10 days
Erythromycin estolate	20–40 mg/kg/day ×2–4/day (max 1g/day)	Oral	10 days
Secondary prevention (prevention of recurrent attacks)[a]			
Benzathine penicillin G	1 200 000 U every 3 weeks (low risk, every 4 weeks)	Intramuscular injection	
Penicillin V	250 mg ×2/day	Oral	
Erythromycin	250 mg ×2/day	Oral	

Treatment of the acute attack of rheumatic fever:

- Bed rest
- Salicylates 100 mg/kg/day in 4–5 doses (in severe attacks with cardiac involvement, prednisone 1–2 mg/kg/day)
- Valve repair/replacement surgery for severe valve dysfunction.

[a] Duration of secondary prophylaxis depends on history of carditis and if valvular involvement persists. For details see text.

A recent study of the effect of a 10 year education program on the reduction of rheumatic fever incidence[51] demonstrated what can be achieved by a structured approach to patient identification, community education, and effective diagnosis and treatment. This intervention resulted in a 78% reduction in the incidence of rheumatic fever within 10 years. Much could be achieved through the establishment of similar programs where rheumatic fever is rife.

References

1. McLaren MJ, Hawkins DM, Koornhof HJ *et al.* Epidemiology of rheumatic heart disease in black schoolchildren of Soweto, Johannesburg. *BMJ* 1975;**3**:474–8.
2. Siegel AC, Johnson EE, Stollerman GH. Controlled studies of streptococcal pharyngitis in a pediatric population. 1. Factors related to the attack rate of rheumatic fever. *N Engl J Med* 1961;**265**:559–65.
3. Dajani AS. Current status of nonsuppurative complications of group A streptococci. *Pediatr Infect Dis J* 1991;**10**:S25–7.
4. Dale JB, Beachey EH. Sequence of myosin cross-reactive epitopes of streptococcal M protein. *J Exp Med* 1986;**164**: 1785–90.
5. Schwartz B, Facklam RR, Breiman RF. Changing epidemiology of group A streptococcal infection in the U.S.A. *Lancet* 1990;**336**:1167–71.
6. Khanna AK, Buskirk DR, Williams RC *et al.* Presence of non-HLA B cell antigen in rheumatic fever patients and their families as defined by a monoclonal antibody. *J Clin Invest* 1989;**83**:1710–16.
7. Haffejee I. Rheumatic fever and rheumatic heart disease: the current state of its immunology, diagnostic criteria and prophylaxis. *Quart J Med* 1992;**84**:641–58.
8. Jones TD. Diagnosis of rheumatic fever. *JAMA* 1944;**126**: 481–4.
9. Dajani AS, Ayoub EM, Bierman FZ *et al.* Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992. *JAMA* 1992;**268**:2069–73.
10. Dajani A, Taubert K, Ferrieri P *et al.* Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. *Paediatrics* 1995;**96**:758–64.
11. Denny FW, Wannamaker LW, Brink WR, Rammelkamp CH Jr, Custer EA. Prevention of rheumatic fever: treatment of the preceding streptococci infection. *JAMA* 1950;**143**: 151–3.
12. Gerber MA, Markowitz M. Management of streptococcal pharyngitis reconsidered. *Pediatr Infect Dis* 1984;**4**:518–26.
13. Nelson JD, McCracken GH Jr, Streptococcal infections (editorial). *Pediatr Infect Dis J Newsletter* 1993;**12**:12.
14. Wannamaker LW, Rammelkemp CR Jr, Denny FW *et al.* Prophylaxis of acute rheumatic fever by the treatment of the preceding streptococcal infection with varying amounts of depot penicillin. *Am J Med* 1951;**10**:673–95.
15. Breese BB. Treatment of beta haemolytic streptococcal infections in the home: relative value of available methods. *JAMA* 1953;**152**:10–14.
16. Schwartz RH, Wientzen RL, Pedreira F *et al.* Penicillin V for group A streptococcal pharyngotonsillitis: a randomised trial of seven vs. ten day therapy. *JAMA* 1981;**246**:1790–5.
17. Gerber MA, Randolf MF, Chanatry J *et al.* Five vs. ten days of penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child* 1987;**141**:224–7.
18. Breese BB, Disney FA, Talpey WB. Penicillin in streptococcal infections: total dose and frequency of administration. *Am J Dis Child* 1965;**110**:125–30.
19. Vann RL, Harris BA. Twice a day penicillin therapy for streptococcal upper respiratory infections. *South Med J* 1972;**65**: 203–5.

20.Spitzer TG, Harris BA. Penicillin V therapy for streptococcal pharyngitis: comparison of dosage schedules. *South Med J* 1977;**70**:41–2.
21.Gerber MA, Spadaccini LJ, Wright LL, Deutsch L, Kaplan EL. Twice daily penicillin in the treatment of streptococcal pharyngitis. *Am J Dis Child* 1985;**139**:1145–8.
22.Gerber MA, Randolf MF, DeMeo K, Feder HM, Kaplan EL. Failure of once-daily penicillin therapy for streptococcal pharyngitis. *Am J Dis Child* 1989;**143**:153–5.
23.Markowitz M, Gerber MA, Kaplan EL. Treatment of streptococcal pharyngotonsillitis: reports of penicillin's demise are premature. *J Pediatr* 1993;**123**:679–85.
24.Pichichero ME, Margolis PA. A comparison of cephalosporins and penicillins in the treatment of group A beta-haemolytic streptococcal pharyngitis: a meta analysis supporting the concept of microbial copathogenicity. *Pediatr Infect Dis J* 1991;**10**:275–81.
25.Pichichero ME, McLinn SE, Gooch WM IIIrd *et al.* Cefibuten vs. penicillin V in group A beta-haemolytic streptococcal pharyngitis. Members of the Cefibuten Pharyngitis International Study Group. *Pediatr Infect Dis J* 1995; **14**: S102–7.
26.Aujard Y, Boucot I, Brahimi N, Chiche D, Bingen E. Comparative efficacy and safety of four-day cefuroxime axetil and ten day penicillin treatment of group A beta-haemolytic streptococcal pharyngitis in children. *Pediatr Infect Dis J* 1995;**14**:295–300.
27.Shapera RM, Hable KA, Matsen JM. Erythromycin therapy twice daily for streptococcal pharyngitis: a controlled comparison with erythromycin or penicillin phenoxymethyl four times daily or penicillin G benzathine. *JAMA* 1973;**226**: 531–5.
28.Derrick CW, Dillon HC. Erythromycin therapy for streptococcal pharyngitis. *Am J Dis Child* 1976;**130**:175–8.
29.Ginsberg CM, McCracken GH Jr, Crow SD *et al.* Erythromycin therapy for group A streptococcal pharyngitis. Results of a comparative study of the estolate and ethylsuccinate formulations. *Am J Dis Child* 1984;**138**:536–9.
30.Seppala H, Missinen A, Jarvinen H *et al.* Resistance to erythromycin in group A streptococci. *N Engl J Med* 1992;**326**: 292–7.
31.Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis placebo controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA* 1985;**253**:1271–4.
32.Feinstein AR, Wood HF, Epstein JA *et al.* A controlled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children. *N Engl J Med* 1959;**260**:697–702.
33.Majeed HA, Yousof AM, Khuffash FA *et al.* The natural history of acute rheumatic fever in Kuwait: a prospective six year follow up report. *J Chronic Dis* 1986;**39**:361–9.
34.Kuttner AG, Mayer FE. Carditis during second attacks of rheumatic fever – its incidence in patients without clinical evidence of cardiac involvement in their initial rheumatic episode. *N Engl J Med* 1963;**268**:1259–61.
35.Berrios X, delCampo E, Guzman B, Bisno AL. Discontinuing rheumatic fever prophylaxis in selected adolescents and young adults. *Ann Intern Med* 1993;**118**:401–6.
36.Amir J, Ginat S, Cohen YH *et al.* Lidocaine as a diluent for administration of benzathine penicillin G. *Pediatr Infect Dis J* 1998;**17**:890–3.
37.Lue HC, Wu MH, Hseih KH *et al.* Rheumatic fever recurrences: controlled study of 3-week versus 4-week benzathine penicillin prevention programs. *J Pediatr* 1986;**108**: 299–304.
38.Lue HC, Wu MH, Wang JK *et al.* Long-term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. *J Pediatr* 1994;**125**:812–6.
39.Kaplan EL, Berrios X, Speth J *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; **115**:146–50.
40.Albert DA, Harel L, Karrison T. The treatment of rheumatic carditis: a review and meta-analysis. *Medicine (Baltimore)* 1995;**74**:1–12.
41.Combined Rheumatic Fever Study Group (RFSG). A comparison of the effect of prednisone and acetylsalicylic acid on the incidence of residual rheumatic carditis. *N Engl J Med* 1960;**262**:895–902.
42.Combined Rheumatic Fever Study Group (RFSG). A comparison of short-term intensive prednisone and acetyl salicylic acid therapy in the treatment of acute rheumatic fever. *N Engl J Med* 1965;**272**:63–70.
43.Dorfman A, Gross JI, Lorincz AE. The treatment of acute rheumatic fever. *Pediatrics* 1961;**27**:692–706.
44.Rheumatic Fever Working Party (RFWP) of the MRC, Great Britain, and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. The treatment of acute rheumatic fever in children: a cooperative clinical trial of ACTH, cortisone and aspirin. *Circulation* 1955;**11**: 343–71.
45.Stolzer BL, Houser HB, Clark EJ. Therapeutic agents in rheumatic carditis. *Arch Intern Med* 1955;**95**:677–88.
46.Vasan RS, Shrivastava S, Vijayakumar M *et al.* Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. *Circulation* 1996;**94**:73–82.
47.Czoniczer G, Amezcua F, Pelargonio S, Massel BF. Therapy of severe rheumatic carditis: comparison of adrenocortical steroids and aspirin. *Circulation* 1964;**29**:813–19.
48.Voss LM, Wilson NJ, Neutze JM *et al.* Intravenous immunoglobulin in acute rheumatic fever: a randomized controlled trial. *Circulation* 2001;**103**:401–6.
49.Lewis BS, Geft IL, Milo S, Gotsman MS. Echocardiography and valve replacement in the critically ill patient with acute rheumatic carditis. *Ann Thorac Surg* 1979;**27**:529–35.
50.Barlow JB, Kinsley RH, Pocock WA. Rheumatic fever and rheumatic heart disease. In: Barlow JB, ed. *Perspectives on the mitral valve*. Philadelphia: FA Davis, 1987.
51.Bach JF, Chalons S, Forier E *et al.* 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. *Lancet* 1996;**347**:644–8.

52 Mitral valve disease: indications for surgery

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Introduction

In mitral valve disease symptomatic status, ventricular functional status and the kind of operation that will ultimately be performed all affect the indication for valve surgery. This chapter will integrate these aspects into a strategy for surgical correction. It should be noted that in surgery for valve disease there are few large controlled trials of therapy. Most knowledge of the response of valve disease to surgery accrues from reports of surgical outcome in both selected and unselected patients.

Mitral regurgitation

Surgical objectives

Like all valvular lesions, mitral regurgitation imposes a hemodynamic overload on the heart. Ultimately, this overload can only be corrected by surgically restoring valve competence. For valve surgery in general, the timing of surgery has two opposing tenets. First, as surgery has an operative risk and, if a prosthesis is inserted, imposes the risks inherent in valve prosthesis, surgery should be delayed for as long as possible. Second, surgery which is delayed until the hemodynamic overload has caused irreversible left ventricular dysfunction will result in a suboptimal outcome. In some patients, far advanced left ventricular dysfunction may militate against operating at all.

The timing of valve surgery is made even more complex in mitral regurgitation, as frequently valve repair rather than valve replacement can be effected. Because valve repair does not involve the use of a valvular prosthesis, and because it also helps to preserve left ventricular function, it is applicable at the two ends of the spectrum of mitral regurgitation. Repair might be considered in asymptomatic patients with normal left ventricular function because the disease could be cured then without the need for intense follow up and without the use of a valve prosthesis.[1] At the other end of the spectrum, patients with severe impairment of left ventricular function who might not be candidates for mitral valve replacement with chordal disruption might have a good result from valve repair.[2] However, for most patients mitral valve surgery is performed for the relief of symptoms or to prevent worsening of asymptomatic left ventricular dysfunction.

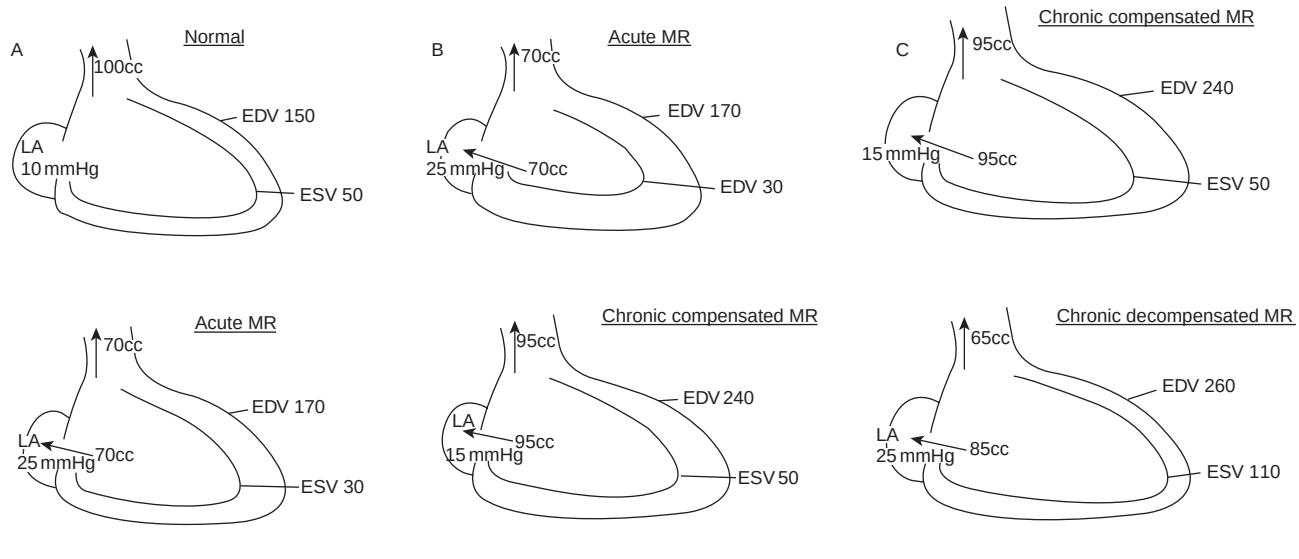
Etiology

The mitral valve apparatus consists of the mitral valve annulus, the valve leaflets, the chordae tendineae and the papillary muscles. Abnormalities of any of these structures may cause mitral regurgitation. The common causes of mitral regurgitation include infective endocarditis, the mitral valve prolapse syndrome with myxomatous degeneration of the valve, spontaneous chordal rupture, rheumatic heart disease, collagen disease such as Marfan's syndrome, and coronary artery disease leading to papillary muscle ischemia or necrosis. These etiologies are especially important with regard to surgical correction. For instance, the spontaneous rupture of a posterior chorda tendinea leads to mitral valve repair in almost 100% of cases. On the other hand, severe rheumatic deformity of the valve which has led to mitral regurgitation may be irreparable, necessitating replacement.

Pathophysiology

Hemodynamic phases of mitral regurgitation

Figure 52.1 depicts the pathophysiologic phases of mitral regurgitation.[3] In the acute phase, such as might occur with spontaneous chordal rupture, there is sudden volume overload on both the left ventricle and the left atrium. The regurgitant volume, together with the venous return from the pulmonary veins, distends both chambers. Distention of the left ventricle increases use of the Frank–Starling mechanism, by which increased sarcomere stretch increases end-diastolic volume modestly and also increases left ventricular stroke work. The new orifice for left ventricular ejection (the regurgitant pathway) facilitates left ventricular emptying and end-systolic volume decreases. Acting in concert, these two effects increase ejection fraction and total stroke volume. However, as shown in Figure 52.1, panel A, if only 50% of the total stroke volume is ejected into the aorta there is a net loss of 30% of the initial forward stroke volume. At the same time, volume overload on the left atrium increases



	Preload SL μ	Afterload ESS Kdyne/cm²	CF	EF	RF	FSV CC's
N	2·07	90	N	·67	·0	100
AMR	2·25	60	N	·82	·50	70

	Preload SL μ	Afterload ESS Kdyne/cm²	CF	EF	RF	FSV CC's
AMR	2·25	60	N	·62	·5	70
CCMR	2·19	90	N	·79	·5	95

	Preload SL μ	Afterload ESS Kdyne/cm²	CF	EF	RF	FSV CC's
CCMR	2·19	90	N	·79	·50	95
CDMR	2·19	120	↓	·58	·57	65

Figure 52.1 (Panel A) Normal hemodynamic state compared to acute mitral regurgitation (AMR). In AMR, total stroke volume and ejection performance increase as preload is increased and afterload is reduced. However, forward stroke volume is reduced and left atrial pressure increased. (Panel B) AMR compared to chronic compensated mitral regurgitation (CCMR). In CCMR, increased end-diastolic volume permitted by eccentric hypertrophy increases both total and forward stroke volume. Enlargement of atrium and ventricle allows increased volume to be accommodated at lower filling pressure. Increase in afterload toward normal in this state of compensation reduces ejection performance slightly. (Panel C) Chronic decompensated mitral regurgitation (CDMR) compared with CCMR: contractile function is reduced and afterload is increased in CDMR. Both reduce ejection performance and forward cardiac output. There is further cardiac dilation in CDMR, leading to worsening mitral regurgitation, further compromising pump function by reducing forward stroke volume and increasing filling pressure. CF, contractile function; EDV, end-diastolic volume; EF, ejection fraction; ESS, end-systolic stress; ESV, end-systolic volume; FSV, forward stroke volume; LA, left atrial pressure; N, normal hemodynamic state; RF, regurgitant fraction; SL, sarcomere length. (Reproduced with permission from Carabello.[3])

left atrial pressure. At this point in time the patient suffers from low output and pulmonary congestion and appears to be in left ventricular failure, although left ventricular muscle function is either normal or even augmented by sympathetic reflexes. Acute severe mitral regurgitation may lead to shock and pulmonary edema, requiring intra-aortic balloon counterpulsation and urgent mitral valve repair or replacement. However, if the patient can be maintained in a relatively stable condition, he or she may then enter the chronic compensated phase (Figure 52.1, panel B) within 3–6 months.

In the chronic compensated phase of mitral regurgitation, eccentric cardiac hypertrophy, in which sarcomeres are laid down in series, allows enlargement of the left ventricle, enhancing its total volume pumping capacity. Total stroke volume is increased, allowing normalization of forward stroke volume. Enlargement of the left atrium accommodates the volume overload at a lower pressure, eliminating pulmonary congestion. In this phase the patient may be remarkably asymptomatic, able to perform normal daily activities, and can even engage in sporting events of modest physical demands.[4]

The patient may remain in the compensated phase for months or years. However, eventually the persistent volume overload leads to a decline in left ventricular function (Figure 52.1, panel C). A loss of myofibrils or an insensitivity to cyclic AMP may be responsible, at least in part, for loss of left ventricular contractility.[5,6] In this phase, left ventricular end-systolic volume increases because the reduced force of contraction results in poor left ventricular emptying, forward stroke volume falls, and left ventricular dilation may worsen the mitral regurgitation. At this time there is re-elevation of the left atrial pressure, resulting again in pulmonary congestion. Notably, the still favorable loading conditions of mitral regurgitation (increased preload and normal afterload) permit a "normal" ejection fraction even though left ventricular dysfunction has developed.

Importance of the mitral valve apparatus

Although the contribution of the mitral valve apparatus to left ventricular function was noted by Rushmer and Lillehei

decades ago,[7,8] its physiologic significance and impact on patient care have only recently received widespread appreciation. It is quite clear that the mitral valve apparatus has a wider role than simply to prevent mitral regurgitation. Rather, the apparatus is an integral part of the left ventricular internal skeleton. In early systole, tugging on the apparatus by the chordae tendineae may shorten the major axis while lengthening the minor axis, in turn augmenting preload there during the pre-ejection phase of systole. In addition, the apparatus helps to maintain the normal and efficient ellipsoid shape of the left ventricle.

Transection of the chordae causes an immediate fall in left ventricular function.[9] Until the importance of chordal preservation during mitral valve surgery was recognized, ejection fraction almost always fell following surgery. This was attributed to increased afterload from surgical closure of the low-impedance pathway which, preoperatively, had facilitated ejection into the left atrium. However, it is now clear that closure of the same low-impedance pathway in which chordal integrity is maintained results in no fall in ejection fraction, or only a modest decline, suggesting that the increased postoperative load theory is not the sole mechanism for ejection fraction falls.[2,11–13] In fact, chordal preservation can actually effect a lowering of systolic wall stress (afterload) instead of an increase as left ventricular radius decreases following surgery [stress = pressure × radius/2 × thickness].[10] Thus, chordal integrity should be maintained whenever possible. A recent randomized study demonstrated that maintenance of just the posterior apparatus lowers mortality and leads to superior postoperative function compared to posterior and anterior chordal transection.[14]

Apart from the benefits on left ventricular function, if mitral valve repair can be performed instead of replacement, operative mortality is lower, postoperative survival is better and the need for anticoagulation is removed while thromboembolism remains low.[14–17] Even if the mitral valve is so badly damaged that a prosthesis must be inserted, chordal preservation, especially of the posterior chords, can usually be performed, resulting in better ventricular function than if all the chords were removed.[10] Unfortunately, despite recognition of the importance of the mitral valve apparatus, repair is only performed in about 30% of all operations for mitral regurgitation, varying from zero in some institutions to 90% in others.

Indications for surgery

Severity of mitral regurgitation Grade B

Under most circumstances only severe mitral regurgitation is corrected surgically. Mild to moderate regurgitation (regurgitant fraction < 40%) under most circumstances neither causes symptoms nor leads to left ventricular dysfunction, even over a protracted period of time. Severity is difficult to ascertain by physical examination alone, especially in acute mitral regurgitation. As noted above, in acute mitral regurgitation there has been no time for cardiac dilation to occur. Thus, palpation of the precordium does not reveal a hyperdynamic left ventricular impulse. Although the murmur of mitral regurgitation is present, severity cannot be gauged from its intensity. In most cases of severe mitral regurgitation an S3 should be present. This finding does not necessarily indicate heart failure, but may simply be the result of a large regurgitant volume filling the left ventricle under a higher than usual left atrial pressure. In chronic mitral regurgitation there should be evidence on physical examination of an enlarged hyperdynamic left ventricle, unless the patient's size or habitus makes physical examination difficult. Failure to find evidence of an enlarged heart suggests that the mitral regurgitation is not either severe enough or chronic enough to cause left ventricular enlargement.

In chronic severe mitral regurgitation the chest radiograph should also show cardiac enlargement, and the electrocardiogram is likely to demonstrate left atrial abnormality and left ventricular hypertrophy.

In most cases, quantification of regurgitant severity is estimated during echocardiography, with Doppler interrogation of the mitral valve. In acute mitral regurgitation, transthoracic echocardiography may underestimate regurgitant severity.[18] In such cases, transesophageal echocardiography is helpful. It should be noted that Doppler flow studies visually demonstrate blood flow velocity across the mitral valve, and not true flow. Because of this, both under- and overestimation of regurgitant severity is possible. Flow mapping, which expresses the regurgitant jet in terms relative to left atrial size, has been used extensively. However, the limitations of this method are well known and the technique is semiquantitative at best.[19,20] Other methods, such as the proximal isovelocity surface area, have been employed experimentally and in clinical investigations.[21–23] In using proximal isovelocity surface area to estimate regurgitation flow, the area of convergence of the regurgitant jet on the ventricular side of the mitral valve is measured at the point of aliasing. By multiplying proximal isovelocity surface area by the known aliasing velocity, actual flow is obtained, which should be a better indication of regurgitant severity. Unfortunately, the convergence pattern is often difficult to pinpoint clinically and is not applicable in many cases. As with mitral valve repair, practice varies from center to center, with some centers routinely accurately quantifying the severity of disease[24] whereas others rely on a visual estimation.

When regurgitation severity is in doubt because of discordance between left ventricular size and the regurgitant signal, that is a small left ventricle and left atrium suggesting mild disease and a Doppler signal suggesting severe disease, the issue should be resolved at cardiac catheterization. During cardiac catheterization, hemodynamics and a left ventriculogram give

additional (although also imperfect) information about the degree of mitral regurgitation. The left ventriculogram, unlike the Doppler study, visualizes the actual flow of contrast medium from the left ventricle into the left atrium. Care must be taken to inject enough contrast agent (at least 60 ml) to opacify both the enlarged left ventricle and the left atrium in mitral regurgitation. Coronary arteriography is also performed at cardiac catheterization if there is any suspicion of an ischemic etiology for mitral regurgitation, or when risk factors for coronary disease coexist.

Acute mitral regurgitation **Grade C**

In almost all cases of severe acute mitral regurgitation the patient is symptomatic. The acute hemodynamic changes noted above cause decreased forward output and sudden left atrial hypertension, resulting in pulmonary congestion, reduced forward flow, and the symptoms of dyspnea, orthopnea, exercise intolerance and fatigue. Vasodilator therapy may be successful in alleviating symptoms by preferentially increasing forward flow while simultaneously decreasing left ventricular size, thereby partially restoring mitral valve competence.[25] If vasodilators fail, or if the patient is so severely decompensated that hypotension contraindicates their use, intra-aortic balloon counterpulsation is necessary. In such cases surgery should follow soon after. This is especially true for the patient with ischemic mitral regurgitation. Such patients may have a volatile course, with initially mild heart failure which progresses unpredictably in severity. These patients require close follow up.[26,27] In milder cases where symptoms can be relieved by medical therapy, patients should be given a trial of medical therapy, during which they may enter the compensated chronic phase. In such cases patients may then become asymptomatic for months or years. However, one study[28] suggests that such patients are at risk of sudden death. If confirmed, this would indicate that relief of symptoms with medical therapy might be masking hemodynamic or electrical instability, and thus be dangerous.

Chronic mitral regurgitation

Symptomatic disease **Grade B** – The onset of symptoms of congestive heart failure, or a more subtle decrease in exercise tolerance, is usually indicative of a change in physiologic status which usually has important clinical significance. The onset of new atrial fibrillation is also probably indicative of a significant change in disease status. Further, atrial fibrillation by itself leads to increased morbidity and decreased cardiac output. In most cases, the onset of symptoms or persistent atrial fibrillation is an indication for mitral valve surgery even when objective indicators of left ventricular function do not show advancement to dysfunction. Early surgery in the mildly symptomatic patient is especially indicated when there is a high probability that mitral valve repair can be effected. In this circumstance there is no need to delay longer, waiting for more severe symptoms or the onset of more apparent left ventricular dysfunction. A valve repair will allow improvement in lifestyle while at the same time avoiding the risks of a prosthesis. Early surgery may be especially important when mitral regurgitation is due to a flail leaflet, because this condition may be associated with a modest increase in the risk of sudden death.[29] If preoperative evaluation indicates that repair is unlikely, close follow up of the patient is indicated. If symptoms continue to worsen, or if left ventricular dysfunction develops, mitral competence should be restored.

In the patient with mild symptoms and normal left ventricular function, transesophageal echocardiography to determine valve anatomy is crucial. This procedure is the best preoperative test to define whether or not repair can be performed or if replacement will be necessary.

Assessment of left ventricular function – A major goal in the management of the patient with mitral regurgitation is to correct the lesion prior to the development of irreversible left ventricular contractile dysfunction. Unfortunately, contractility is difficult to measure clinically. Standard ejection phase indices, such as ejection fraction, which are used to gauge left ventricular function in most cardiac diseases, are confounded by the abnormal loading conditions present in mitral regurgitation, necessitating alterations in the way these indices are used.[30] Because ejection fraction is augmented by increased preload in mitral regurgitation[31] the value for ejection fraction should be supernormal in the face of normal contractility. A "normal" ejection fraction for the patient with mitral regurgitation is probably 0·65–0·75. Indeed, Enriquez-Sarano and colleagues[32] have demonstrated that once the ejection fraction falls to less than 0·60 in patients with mitral regurgitation, long-term mortality is increased, suggesting that left ventricular dysfunction has already developed at that threshold for ejection fraction.

End-systolic dimension, which is less dependent upon preload, has also been developed as an important indicator of left ventricular dysfunction in this disease. As demonstrated in Figure 52.2, when the end-systolic dimension exceeds 45 mm, the postoperative outcome is worsened.[33] This figure, or its angiographic equivalent, has been found to be predictive in other studies.[34,35] Careful evaluation of the patient with mitral regurgitation with history and physical examination, augmented by serial echocardiograms, should avoid the situation in which unrecognized left ventricular dysfunction develops. Yearly follow up is probably adequate as long as the ejection fraction exceeds 0·65 and the end-systolic dimension is less than 40 mm. If the ejection fraction is lower or the end-systolic dimension is higher, more

frequent follow up is indicated. When the ejection fraction approaches 0·60 or when the end-systolic dimension approaches 45 mm, surgery should be contemplated.

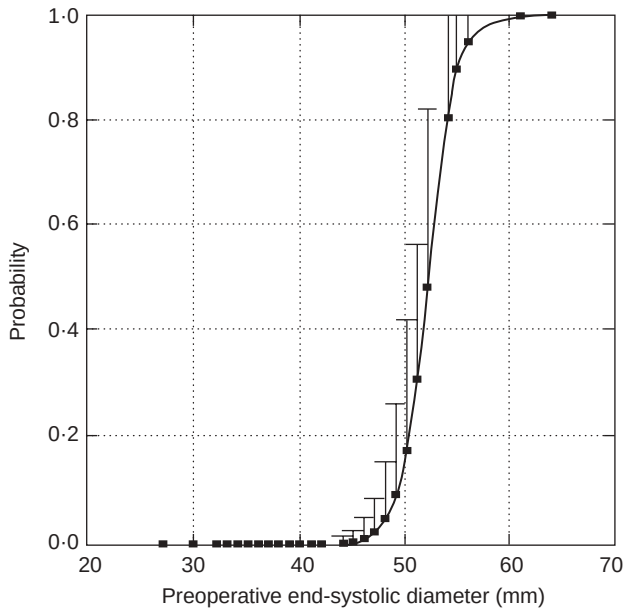


Figure 52.2 Plot of an S-shaped curve-related computed probability of postoperative death or severe heart failure to measured preoperative end-systolic diameter. Individual data coordinates are indicated by solid squares and bars represent upper 95% confidence intervals that were computed from the standard error (some points are overlapping; total $n = 61$). (Reproduced with permission from Wisenbaugh *et al.*[31])

Indications for surgery in the asymptomatic patient with mitral regurgitation

Patients with normal left ventricular function **Grade B** – At first glance the asymptomatic patient with mitral regurgitation who has normal left ventricular function would not seem to require surgery. In this patient, surgery will neither improve lifestyle nor prevent reversible left ventricular dysfunction from developing imminently. However, patients with flail leaflet may become symptomatic within the next year[29] and may be at some increased risk for sudden death. In other cases where it is apparent that the severity of mitral regurgitation will eventually necessitate surgery, it could be argued that if mitral valve repair can be performed, little is to be gained by waiting. This circumstance is much like atrial septal defect, where at low operative mortality (less than 1%) the defect can be repaired without the use of a prosthesis before unwanted sequelae develop (in the case of atrial septal defect, persistent atrial arrhythmias and pulmonary hypertension; in the case of mitral regurgitation, left ventricular dysfunction). If this approach is taken it must be clear that repair rather than replacement can be effected. If the asymptomatic patient with normal left ventricular function is ultimately treated with a prosthesis when a repair had been anticipated, it should be considered a complication of surgery, as the unwanted risks of a prosthesis could have been at least temporarily avoided.

Asymptomatic patients with left ventricular dysfunction **Grade B** – It is the asymptomatic patient with left ventricular dysfunction at whom serial follow up is aimed. If left ventricular dysfunction has developed (ejection fraction $< 0{\cdot}6$, endsystolic dimension > 45 mm), surgery should be performed to prevent further irreversible left ventricular dysfunction even if it entails a prosthetic valve. As left ventricular dysfunction has already been indicated by non-invasive testing in such patients, every effort should be made to spare at least part of the mitral valve apparatus to prevent a further decline in left ventricular function postoperatively.

Asymptomatic elderly patients **Grade C** – Patients over the age of 75 with mitral regurgitation are at increased risk for operative death and a poor outcome. This is especially true if replacement instead of repair is performed, or if concomitant coronary disease – a consequence of aging – is present.[12,36] Thus, elderly asymptomatic patients with mild left ventricular dysfunction should probably be managed medically. Only patients with severe symptoms in whom medical therapy is ineffective should undergo this relatively high-risk procedure. A summary of indications for surgery is given in Table 52.1.

Table 52.1 Indications for mitral surgery in asymptomatic patients with severe non-ischemic mitral regurgitation

Repair likely	Repair unlikely
Patient aged <75 with flail leaflet	–
Patient aged <75 with persistent atrial fibrillation	–
Patient aged <75 with EF <0·60 or ESD >45 mm	Patient aged < 75 with EF < 0·60 or ESD > 45 mm

Abbreviations: EF, ejection fraction; ESD, end-systolic minor axis dimension

Establishment of symptom status – Because of the insidious nature of mitral valve disease, patients may subtly alter their lifestyle to maintain their asymptomatic status. Thus, history alone may fail to identify this gradual decline in exercise tolerance. Therefore, in patients with mitral valve disease, formal exercise testing is useful to objectively quantify changes in exercise tolerance over the time of follow up and to separate truly asymptomatic patients from those who avoid situations that produce symptoms.

Far advanced disease Grade B

Occasionally patients reach the first attention of the physician when in severe congestive heart failure, with far advanced left ventricular dysfunction. Many patients in this category may benefit from surgery because correction of mitral regurgitation will lower left atrial pressure and perhaps increase forward output. However, in such cases postoperative left ventricular function will remain depressed and lifespan is likely to be shortened. It is often difficult to decide whether left ventricular dysfunction is so far advanced that surgery should not be performed. The answer to this question is predicated upon the kind of operation that is contemplated. If repair with sparing of most chordal structures can be performed, patients with an ejection fraction as low as 30% can survive surgery with postoperative ejection performance maintained at this relatively low level.[2] However, for patients with an ejection fraction $<40\%$ in whom only mitral valve replacement can be performed, operative mortality might be prohibitive. Wisenbaugh[33] has further suggested that if the end-systolic dimension exceeds 50 mm in patients with rheumatic mitral regurgitation, postoperative risk is extremely high whether repair can be effected or not.

Ischemic mitral regurgitation Grade C

The prognosis for ischemic mitral regurgitation remains substantially worse than for non-ischemic disease.[37,38] A worsened prognosis probably accrues from the automatic presence of a second potentially fatal and independently progressive cardiac disease, and from the presence of ischemic myocardial dysfunction. Guidelines for surgery are not well developed. Common sense indicates that surgery should be performed when ischemic mitral regurgitation has caused shock or intractable pulmonary congestion.

Medical therapy Grade C

Apart from the use of prophylactic antibiotics against infective endocarditis, there is no proven medical therapy for chronic mitral regurgitation. Although vasodilators are effective in treating the acute disease, no large long-term trials have been performed to examine their effect in chronic disease. The trials that have been performed differ regarding benefit from this therapy.[39,40] Further, because afterload is not typically elevated in chronic mitral regurgitation, the physiologic underpinnings for vasodilators used for afterload reduction are less clear. In fact, vasodilators in this case might lead to cardiac atrophy, potentially putting the patient at a disadvantage when mitral valve replacement is finally performed.

Summary

Patients with acute mitral regurgitation and severe hemodynamic instability require surgical correction. In less severe situations medical therapy may allow the patient to enter the chronic compensated phase, in which surgery can be delayed.

When symptoms develop in chronic mitral regurgitation, they are usually an indication for valve surgery. This is especially true if left ventricular dysfunction is developing, or if it is certain that a mitral valve repair can be performed. In asymptomatic patients with normal ventricular function surgery should only be contemplated when there is a certainty of repair. On the other hand, if left ventricular dysfunction is developing surgery should be performed to prevent further deterioration, whether or not a repair can be effected.

Mitral stenosis

Etiology and pathophysiology

Most mitral stenosis in adults is acquired through rheumatic heart disease. In developed countries it typically appears in women in their fourth or fifth decade. In developing nations, where the rheumatic process appears to be more aggressive, stenosis may develop in adolescence or early adulthood.

As mitral stenosis worsens, a gradient develops between the left atrium and left ventricle during diastole. At the same time the stenotic valve impairs left ventricular filling, limiting cardiac output. The combination of pulmonary congestion caused by left atrial hypertension and diminished forward cardiac output caused by inflow obstruction mimics the hemodynamics of left ventricular failure, even though the left ventricle itself is usually spared from the rheumatic process, especially in developed countries.[41] However, in approximately one third of patients left ventricular ejection performance is reduced despite no impairment in contractility.[42] Reduced ejection fraction is caused by reduced preload from the impairment of left ventricular filling and from increased left ventricular afterload secondary to reflex systemic vasoconstriction in the face of decreased cardiac output. Ejection performance may return to normal shortly after mitral stenosis is relieved.[43]

Although the left ventricle is usually spared from direct involvement in this disease, the right ventricle experiences pressure overload because it supplies the hemodynamic force propelling blood across the stenotic mitral valve. Thus, as left atrial pressure rises, pulmonary pressure and right ventricular pressure also must increase, placing a pressure overload on the right ventricle. For reasons that are unclear, as the disease progresses reversible pulmonary vasoconstriction develops, leading to a worsening of pulmonary hypertension and eventually to right ventricular failure.

Indications for surgery Grade B

In most cases mitral stenosis can be relieved by balloon valvotomy, which offers results comparable to those of open commissurotomy, as shown in a randomized trial.[44] Surgery is reserved for those cases in which valve anatomy is unfavorable for balloon valvotomy, or in which balloon valvotomy has been attempted and failed. Although in some instances open surgical commissurotomy can be successful even though balloon valvotomy was predicted to be unsuccessful, the unfavorable anatomy for balloon valvotomy will also be unfavorable for commissurotomy, necessitating valve replacement. Thus when surgery is anticipated, the risks and complications of a prosthesis should also be anticipated.

The timing of surgery for mitral stenosis can largely be predicated on symptomatic status, as shown in Figure 52.3.[45]

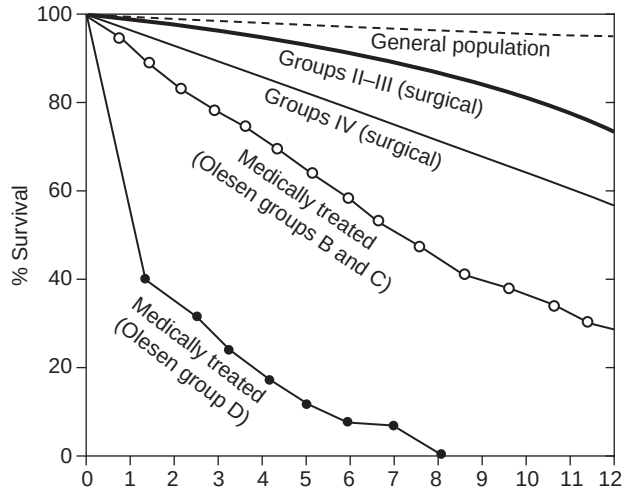


Figure 52.3 Comparison between surgical and medical treatment in patients with mitral stenosis. Groups II, III and IV, equivalent to NYHA classifications II, III and IV, are approximately similar to the groups represented by letters B, C and D, respectively. Class IV patients had better improved survival when treated surgically than did class D patients who were treated medically. Class II and III patients also had better survival when treated surgically than did the patients in groups B and C, although the difference is not as dramatic. (Reproduced with permission from Roy and Gopinath.[45])

Once more than New York Heart Association (NYHA) class II symptoms develop, mortality increases abruptly and surgery should be performed before class III symptoms appear. In addition, some studies indicate that the presence of pulmonary hypertension substantially increases operative risk,[35,46] and so surgery should be contemplated in patients who develop asymptomatic pulmonary hypertension (pulmonary artery systolic pressure >50 mmHg). When surgery precedes severe pulmonary hypertension, operative mortality, even with the insertion of a prosthesis, is 1–3%.

The most difficult situation for timing surgery arises in the young woman who wishes to bear children. In such patients in whom balloon valvotomy has already been ruled out because of unfavorable valve anatomy, the choice of prosthetic valve becomes quite difficult. If a mechanical valve is placed it will require anticoagulation, which is problematic during pregnancy. Administration of warfarin causes a particularly high incidence of fetal malformation, especially when used during the first trimester. It can be substituted by daily injections of heparin, but serious thrombotic complications have occurred in such circumstances, suggesting that this therapy is inadequate in at least some cases.[47] On the other hand, if a bioprosthesis is placed in a young woman it is likely to degenerate within a decade or sooner, forcing the patient to have a reoperation with its attendant increased surgical risk. There is no correct solution to this dilemma, and the prosthesis that is eventually inserted is chosen after lengthy consultation between patient and surgeon.

Summary Grade B

In most cases mitral stenosis can be treated successfully with balloon valvotomy. However, if this procedure is unfeasible, open commissurotomy or valve replacement is indicated for those with NYHA symptoms greater than class II, or for the development of pulmonary hypertension.

References

1. Carabello BA. Timing surgery for mitral regurgitation in asymptomatic patients. *Choices Cardiol* 1991;**5**:137–8.
2. Goldman ME, Mora F, Guarino T, Fuster V, Mindich BP. Mitral valvuloplasty is superior to valve replacement for preservation of left ventricular function. An intraoperative two-dimensional echocardiographic study. *J Am Coll Cardiol* 1987;**10**:568–75.
3. Carabello BA. Mitral regurgitation, Part 1: basic pathophysiologic principles. *Mod Concepts Cardiovasc Dis* 1988;**57**:53–8.
4. Cheitlin MD, Douglas PS, Parmley WW. 26th Bethesda Conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task Force 2: acquired valvular heart disease. *J Am Coll Cardiol* 1994;**24**:874–80.
5. Urabe Y, Mann DL, Kent RL *et al.* Cellular and ventricular contractile dysfunction in experimental canine mitral regurgitation. *Circ Res* 1992;**70**:131–47.

6. Mulieri LA, Leavitt BJ, Martin BJ, Haeberle JR, Alpert NR. Myocardial force–frequency defect in mitral regurgitation heart failure is reversed by forskolin. *Circulation* 1993;**88**:2700–4.
7. Rushmer RF. Initial phase of ventricular systole: asynchronous contraction. *Am J Physiol* 1956;**184**:188–94.
8. Lillehei CW, Levy MJ, Bonnabeau RC. Mitral valve replacement with preservation of papillary muscles and chordae tendineae. *J Thorac Cardiovasc Surg* 1964;**47**:532–43.
9. Hansen DE, Cahill PD, DeCampli WM *et al.* Valvular-ventricular interaction: importance of the mitral apparatus in canine left ventricular systolic performance. *Circulation* 1986; **73**:1310–20.
10. Rozich JD, Carabello BA, Usher BW *et al.* Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation. Mechanisms for differences in postoperative ejection performance. *Circulation* 1992; **86**:1718–26.
11. David TE, Burns RJ, Bacchus CM, Druck MN. Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae. *J Thorac Cardiovasc Surg* 1984;**88**:718–25.
12. Enriquez-Sarano M, Schaff HV, Orszulak TA *et al.* Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995;**91**:1022–8.
13. Duran CG, Pomar JL, Revuelta JM *et al.* Conservative operation for mitral insufficiency: critical analysis supported by postoperative hemodynamic studies in 72 patients. *J Thorac Cardiovasc Surg* 1980;**79**:326–37.
14. Horskotte D, Schulte HD, Bircks W, Strauer BE. The effect of chordal preservation on late outcome after mitral valve replacement: a randomized study. *J Heart Valve Dis* 1993;**2**:150–8.
15. Cohn LH, Couper GS, Aranki SF *et al.* Long-term results of mitral valve reconstruction for regurgitation of the myxomatous mitral valve. *Cardiovasc Surg* 1994;**107**:143–51.
16. Cosgrove DM, Chavez AM, Lytle BW *et al.* Results of mitral valve reconstruction. *Circulation* 1986;**74**(Suppl. I):I-82–I-87.
17. Wells FC. Conservation and surgical repair of the mitral valve. In: Wells FC, Shapiro LM, eds. *Mitral valve disease*, 2nd edn. Oxford: Butterworth–Heinemann, 1996.
18. Castello R, Fagan L Jr, Lenzen P, Pearson AC, Labovitz AJ. Comparison of transthoracic and transesophageal echocardiography for assessment of left-sided valve regurgitation. *Am J Cardiol* 1991;**68**:1677–80.
19. Smith MD, Kwan OL, Spain MG, DeMaria AN. Temporal variability of color Doppler jet areas in patients with aortic and mitral regurgitation. *Am Heart J* 1992;**123**:953–60.
20. Slater J, Gindea AJ, Freedberg RS *et al.* Comparison of cardiac catheterization and Doppler echocardiography in the decision to operate in aortic and mitral valve disease. *J Am Coll Cardiol* 1991;**17**:1026–36.
21. Recusani F, Bargiggia GS, Yoganathan AP *et al.* A new method for quantification of regurgitant flow rate using color Doppler flow imaging of the flow convergence region proximal to a discrete orifice: an in vitro study. *Circulation* 1991;**83**: 594–604.
22. Utsunomiya T, Ogawa T, Doshi R *et al.* Doppler color flow "proximal isovelocity surface area" method for estimating volume flow rate: effects of orifice shape and machine factors. *J Am Coll Cardiol* 1991;**17**:1103–11.
23. Vandervoort PM, Rivera JM, Mele D *et al.* Application of color Doppler flow mapping to calculate effective regurgitant orifice area: an in vitro study and initial clinical observations. *Circulation* 1993;**88**:1150–6.
24. Enriquez-Sarano M, Miller FA Jr, Hayes SN *et al.* Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol* 1995;**25**:703–9.
25. Yoran C, Yellin EL, Becker RM *et al.* Mechanisms of reduction of mitral regurgitation with vasodilator therapy. *Am J Cardiol* 1979;**43**:773–7.
26. Nishimura RA, Schaff HV, Shub C *et al.* Papillary muscle rupture complicating acute myocardial infarction: analysis of 17 patients. *Am J Cardiol* 1983;**51**:373–7.
27. Nishimura RA, Schaff HV, Gersh BJ, Holmes DR Jr, Tajik AJ. Early repair of mechanical complications after acute myocardial infarction. *JAMA* 1986;**256**:47–50.
28. Grigioni F, Enriquez-Sarano M, Ling LH *et al.* Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol* 1999;**34**:2078–85.
29. Ling LH, Enriquez-Sarano M, Seward JB *et al.* Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;**335**:1417–23.
30. Eckberg DL, Gault JH, Bouchard RL, Karliner JS, Ross J Jr. Mechanics of left ventricular contraction in chronic severe mitral regurgitation. *Circulation* 1973;**47**:1252–9.
31. Wisenbaugh T, Spann JF, Carabello BA. Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation. *J Am Coll Cardiol* 1984;**3**:916–23.
32. Enriquez-Sarano M, Tajik AJ, Schaff HV *et al.* Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation* 1994;**90**:830–7.
33. Wisenbaugh T, Skudicky D, Sareli P. Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. *Circulation* 1994;**89**:191–7.
34. Zile MR, Gaasch WH, Carroll JD, Levine HF. Chronic mitral regurgitation: predictive value of preoperative echocardiographic indexes of left ventricular function and wall stress. *J Am Coll Cardiol* 1984;**3**:235–42.
35. Crawford MH, Souchek J, Oprian CA *et al.* Determinants of survival and left ventricular performance after mitral valve replacement. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. *Circulation* 1990;**81**:1173–81.
36. Nair CK, Biddle WP, Kaneshige A *et al.* Ten-year experience with mitral valve replacement in the elderly. *Am Heart J* 1992;**124**:154–9.
37. Connolly MW, Gelbfish JS, Jacobowitz IJ *et al.* Surgical results for mitral regurgitation from coronary artery disease. *J Thorac Cardiovasc Surg* 1986;**91**:379–88.
38. Akins CW, Hilgenberg AD, Buckley MJ *et al.* Mitral valve reconstruction versus replacement for degenerative or ischemic mitral regurgitation. *Ann Thorac Surg* 1994;**58**: 668–75.
39. Schon HR, Schroter G, Barthel P, Schomig A. Quinapril therapy in patients with chronic mitral regurgitation. *J Heart Valve Dis* 1994;**3**:303–12.
40. Wisenbaugh T, Sinovich V, Dullabh A, Sareli P. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral

and isolated aortic regurgitation. *J Heart Valve Dis* 1994;**3**:197–204.
41. Hildner FJ, Javier RP, Cohen LS *et al.* Myocardial dysfunction associated with valvular heart disease. *Am J Cardiol* 1972;**30**: 319–26.
42. Gash AK, Carabello BA, Cepin D, Spann JF. Left ventricular ejection performance and systolic muscle function in patients with mitral stenosis. *Circulation* 1983;**67**:148–54.
43. Liu C-P, Ting C-T, Yang T-M *et al.* Reduced left ventricular compliance in human mitral stenosis. Role of reversible internal constraint. *Circulation* 1992;**85**:1447–56.
44. Reyes VP, Raju BS, Wynne J *et al.* Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med* 1994;**331**:961–7.
45. Roy SB, Gopinath N. Mitral stenosis. *Circulation* 1968; **38**(Suppl. V):V68–76.
46. Ward C, Hancock BW. Extreme pulmonary hypertension caused by mitral valve disease. Natural history and results of surgery. *Br Heart J* 1975;**37**:74–8.
47. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;**71**:196–201.

53 Indications for surgery in aortic valve disease

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Evidence-based management of patients with aortic valve disease is limited by the absence of prospective randomized trials of surgery versus medical therapy. There is one prospective randomized trial evaluating patient outcome with use of a pharmacologic agent in patients with aortic valve regurgitation. However, evidence can also be obtained from retrospective studies. This evidence is extremely useful and important in the management of patients.

Sir Thomas Lewis pointed out 80 years ago the inadequacy of knowledge of prognosis in patients with heart disease. He proposed a system for prospective follow up of patients, which we now call "databases" or "registries". The latter are, of course, the major evidence used in this chapter to delineate the indications for surgery. The American College of Cardiology and American Heart Association published *Guidelines for the management of patients with valvular heart disease*.[1] This document has provided an important framework upon which clinical decisions can be based.

Aortic valve stenosis

Etiology

A wide variety of disorders may produce aortic valve obstruction;[2] however, those that result in severe stenosis in adults are:

- congenital
- acquired
  - calcific (degenerative)
  - autoimmune
- rheumatic.

The most common cause of aortic stenosis in younger adults is a congenital bicuspid valve, which is found in 1–2% of the general population. Rheumatic heart disease is still common in developing countries. In most patients aged ≥40 years, the severely stenotic valve is calcified. In patients aged ≥65 years, 90% of severely stenotic valves are tricuspid. Non-rheumatic calcified valves are thought to be "degenerative" but recent data suggest that it may be the result of an autoimmune reaction to antigens present in the valve;[3] and that the initial process may be an atherosclerotic lesion.[4,5]

Grading the degree of stenosis

The natural history of aortic stenosis is variable depending on the degree of stenosis and the rate at which it progresses. Cardiac catheterization and echocardiographic–Doppler ultrasound studies indicate the systolic pressure gradient increases on an average by 10–15 mmHg per year. The 10–15 mmHg increase is a linearized value whereas the increase is not linear but a stepwise function with periods of steady state interspersed by an increase in gradient. The range of progression is also wide. Recent data suggest that the progression of aortic stenosis may be related to cardiovascular risk factors.[6] The systolic gradient across the stenotic aortic valve is dependent on the following:

- the stroke volume (not the cardiac output because the gradient and valve area are a per beat, and not a per minute, function)
- the systolic ejection period
- systolic pressure in the ascending aorta.

The stenotic valve area is inversely related to the square root of the mean systolic gradient. Thus, measurement of valve area is an important part of the assessment of the severity of aortic valve stenosis. The valve area may decrease by as much as $0{\cdot}12 \pm 0{\cdot}19\ cm^2$ per year.[7]

Valve area is related to the body surface area and increases in larger individuals, probably because of the need for a larger stroke volume and cardiac output. The normal aortic valve area ranges from 3 to 4 cm^2. It is reduced to half its size before a systolic gradient occurs.[8] The orifice area has to be reduced to one third of its size before significant hemodynamic changes are seen;[9] gradients increase precipitously after that. The obvious clinical problem is that in an individual patient with aortic stenosis one usually does not know the valve area prior to the onset of disease. Echocardiography is usually the initial procedure used to confirm the presence and determine the severity of aortic valve stenosis.[10] In an experienced center the severity of aortic stenosis determined by Doppler echocardiography correlates reasonably well with the severity determined by

cardiac catheterization.[11] A comprehensive echocardiographic examination in aortic valve stenosis should include assessment of the aortic valve peak and mean gradient as well as aortic valve area.[12] When the clinical picture does not correlate with the hemodynamic data obtained by Doppler echocardiography, re-evaluation by cardiac catheterization is indicated.

The outcome of patients with severe aortic valve stenosis was described by Ross and Braunwald[13] after review of seven autopsy studies published before 1955, and Horstkotte and Loogen[14] reported on 35 patients (10 of whom were asymptomatic) with aortic valve area of $<0{\cdot}8\,cm^2$ by cardiac catheterization who refused surgery. The findings are shown in Table 53.1.

The mortality of symptomatic patients with "severe" aortic stenosis from eight studies[15] is given in Table 53.2.

Mild aortic stenosis

The classification of the severity of aortic valve stenosis was defined in the guidelines provided by the Committee on Valvular Heart Disease.[1] In this document aortic valve stenosis is defined as mild when the aortic valve area was $>1{\cdot}5\,cm^2$. In two studies, patients with aortic valve area $>1{\cdot}5\,cm^2$ by catheterization had no mortality on follow up. At the end of 10 years, in one study 8% had severe stenosis, and in the other 15% had a cardiac event. At the end of 20 years, aortic stenosis had become severe in only 20% and continued to be mild in 63%.[14,15]

Table 53.1 Survival, according to symptoms, of patients with "severe" aortic stenosis

Symptoms	Average survival	
	Autopsy data[a] (years)	Post cardiac catheterization[b] (months)
Overall	3	23
Angina[c]	5	45
Syncope	3	27
Heart failure	<2	11

[a] Data of Ross and Braunwald.[13]
[b] Data of Horstkotte and Loogen.[14]
[c] Angina in patients with aortic stenosis occurs even in those without associated obstructive CAD.

Moderate aortic stenosis

Moderate aortic valve stenosis is defined as a valve area of $>1{\cdot}0$–$1{\cdot}5\,cm^2$. In one study in which patients were followed after cardiac catheterization, the 1 year and 10 year mortality was 3% and 15%, respectively; and at 10 years 65% of patients had had a cardiac event.[15]

Severe aortic stenosis

Several criteria have been used to define severe aortic stenosis. The guidelines provided by the Committee on Valvular Heart Disease[1] describes severe aortic valve stenosis as an aortic valve area $\leq 1{\cdot}0\,cm^2$ and a mean aortic pressure gradient, in the setting of normal cardiac output, of >50 mmHg. This definition was supported by data from a large multicenter database (492 patients) which suggested that the 1 year mortality of those with aortic valve areas after catheter balloon valvuloplasty for calcific aortic stenosis of $\leq 0{\cdot}7\,cm^2$ versus that of those with valve areas $>0{\cdot}7\,cm^2$ was 37% versus 42%, respectively.[16] Kennedy and coworkers[17] reported on 66 patients with aortic valve areas of $0{\cdot}7$–$1{\cdot}2\,cm^2$ ($0{\cdot}92 \pm 0{\cdot}15\,cm^2$), normal left ventricular volumes and ejection fraction, whose average age was 67 years. In an average follow up of 35 months, 21% died and 32% had valve replacement; at 4 years, the actuarial incidence of death or valve replacement was 41%.[17] Thus, these studies show that patients with aortic valve areas of $0{\cdot}7$–$1{\cdot}0\,cm^2$ have an outcome without valve replacement that is not benign, and is not consonant with moderate

Table 53.2 Mortality of symptomatic patients with "severe" aortic stenosis[15]

Authors	Year of publication	Patients (*n*)	Mortality follow up time (years)					
			1	2	3	5	10	11
Frank *et al*[23]	1973	15			36%	52%	90%	
Rapaport[84]	1975					62%	80%	
Chizner *et al*[85]	1980	23	26%	48%		64%		94%
Schwarz *et al*[30]	1982	19			79%			
O'Keefe *et al*[86]	1987	50	43%	63%	75%			
Turina *et al*[87]	1987	50	40%					
Kelly *et al*[88]	1988	39	38%					
Horstkotte *et al*[14]	1988	35			82%			

stenosis; these patients should be considered as having severe stenosis. Since gradients are frequently measured initially by Doppler ultrasound, a suggested conservative guideline for relating Doppler ultrasound gradient to severity of aortic stenosis (AS) in adults with normal cardiac output and normal average heart rate is shown in Table 53.3.

A suggested grading of the degree of aortic stenosis is given in Table 53.4.

Table 53.3 Doppler ultrasound gradient as an indicator of severe aortic stenosis (AS)

Peak gradient	Mean gradient	AS severe
≥80 mmHg	≥70 mmHg	High likely
60–79 mmHg	50–69 mmHg	Probable
<60 mmHg	<50 mmHg	Uncertain

From Rahimtoola,[15] with permission

Table 53.4 Grading of stenosis by aortic valve area (AVA)

Aortic stenosis	AVA (cm^2)	AVA index (cm^2/m^2)
Mild	>1·5	>0·9
Moderate	1·1–1·5	>0·6–0·9
Severe[a]	≤1·0	≤0·6

[a] Patients with AVAs that are at borderline values between the moderate and severe grades (0·9–1·1 cm^2; 0·55–0·65 cm^2/m^2) should be individually considered.
From Rahimtoola[15] with permission

Natural history

The duration of the asymptomatic period after the development of severe aortic stenosis is uncertain. In a study of asymptomatic patients with varying degrees of severity of aortic stenosis, 21% of 143 patients[18] with a mean age of 72 years required valve replacement within 3 months of evaluation at a referral center. At 2 years the mortality was 10% and the event rate (death/valve replacement) in the remaining patients was 26%. Moreover, it is important to recognize that most patients in this study had only *moderate* aortic stenosis. In another study of 123 asymptomatic adults,[7] also with varying grades of severity of aortic stenosis aged 63±16 years, only the actuarial probability of death or aortic valve surgery is provided. It was 7±5% at 1 year, 38±8% at 3 years and 74±10% at 5 years. The event rate at 2 years for aortic jet velocity by Doppler ultrasound of >4·0 m/s (peak gradient by Doppler ultrasound >64 mmHg) was 79±18%, for a velocity of 3·0–4·0 m/s (peak gradient 36–64 mmHg) was 66±13%, and for a velocity of <3·0 m/s (peak gradient of <36 mmHg) was 16±16%.[7] Aortic jet velocity is influenced by the same parameters as aortic valve gradient (see above). Thus, the duration of the asymptomatic period, particularly in those aged ≥60 years, is probably very short.[19,20]

Paul Dudley White in 1951[21] credited the first recorded occurrence of sudden death to T Bonet in 1679.[22] In the past 70 years the reported incidence of sudden death in eight series has ranged from 1 to 21%. Ross and Braunwald,[13] after reviewing seven autopsy series published before 1955, concluded the incidence was 3–5%. The incidence in asymptomatic adult patients has been 33% (one in three)[23] and 30% (three of ten).[14] This information is difficult to use in clinical decision making because important data are not available – that is, the incidence by actuarial analysis of sudden death in a significant number of asymptomatic patients with severe stenosis. It is reasonable to conclude that the true incidence of sudden death in adults with severe aortic valve stenosis is unknown and that sudden death usually occurs after the onset of symptoms, however minor or minimal the symptoms may be. The incidence of sudden death is believed to be higher in children.

The development of symptoms of angina, syncope, or heart failure, changes the prognosis of the patient with aortic valve stenosis. Average survival after the onset of symptoms is <2–3 years. Nearly 80% of asymptomatic patients with peak aortic valve velocity measured by Doppler echocardiography ≥4 m/s develop symptoms within 3 years, and therefore careful clinical monitoring for the development of symptoms and progressive disease is indicated.

Management

Patients with valvular heart disease need antibiotic prophylaxis against infective endocarditis; those with rheumatic valves need additional antibiotic prophylaxis against recurrences of rheumatic fever.[24] **Grade A**

Surgery is recommended in those with severe valve stenosis and is the only specific and direct therapy for most adults with severe aortic stenosis. Rarely, in young patients, the aortic valve is suitable for balloon or surgical valvotomy. In most adults, surgery for aortic stenosis means valve replacement.[24,25] **Grade B**

The operative mortality of valve replacement is ≤5%.[25–27] In those without associated coronary artery disease, heart failure or other comorbid conditions, it is ≤2% in experienced and skilled centers.[28] Aortic valve replacement in conjunction with coronary artery bypass carries a surgical mortality of about 7%.[27] The operative mortality in those ≥70 years and in octogenarians is much higher, averaging 8% for valve replacement and 13% for those undergoing valve replacement and associated coronary bypass surgery;[25] however, operative mortality in these patients is also dependent on the associated factors listed above.[29]

Patients with associated coronary artery disease (CAD) should have coronary bypass surgery at the same time as valve replacement, because it results in a lower operative mortality (4·0% *v* 9·4%) and better 10 year survival (49% *v* 36%).[28] This was in spite of the fact that those who underwent coronary bypass surgery had more CAD (34% had three vessel disease, 11% had left main artery disease, and 38% had single vessel disease) than those who did not undergo coronary bypass surgery (13% had three vessel disease, 1% had left main disease, and 65% had single vessel disease).[28] Although this approach to CAD is generally approved, there are no randomized trials to support these recommendations. The presence of CAD, its site and severity can be estimated only by selective coronary angiography, which should be performed in all patients 35 years of age or older who are being considered for aortic valve surgery, and in those aged <35 years if they have left ventricular dysfunction, symptoms or signs suggesting CAD, or they have two or more risk factors for premature CAD (excluding gender).[25] The incidence of associated CAD will vary considerably depending on the prevalence of CAD in the population;[15,24] in general, in persons 50 years of age or older it is about 50%.[25]

In severe aortic stenosis, valve replacement results in an improvement of survival (Figure 53.1) even if they have normal left ventricular function preoperatively.[14,30]

Normal preoperative left ventricular function remains normal postoperatively if perioperative myocardial damage has not occurred.[31] Left ventricular hypertrophy regresses toward normal;[31,32] after 2 years, the regression continues at a slower rate up to 10 years after valve replacement.[32]

In patients with excessive preoperative left ventricular hypertrophy,[33] the hypertrophy may regress slowly or not

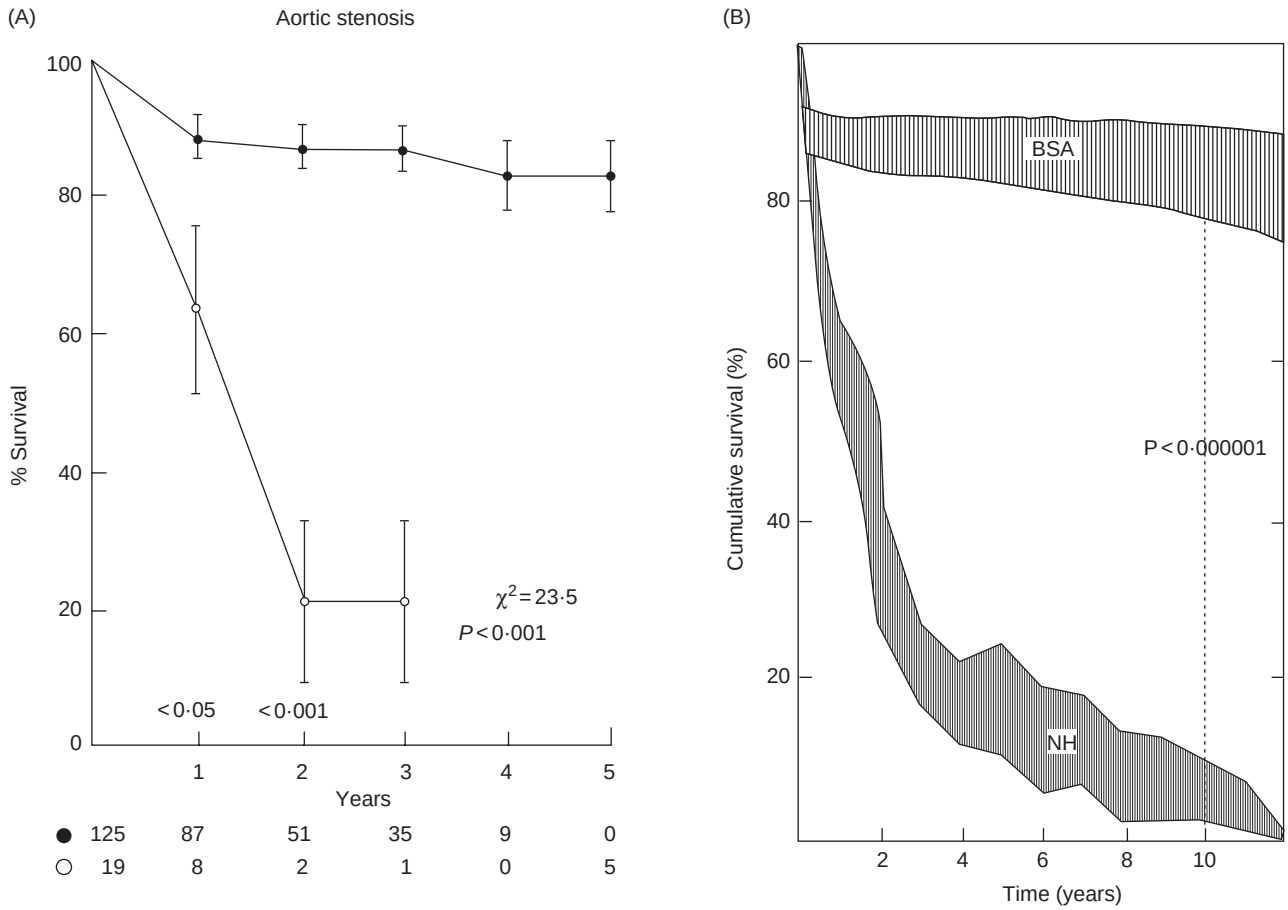


Figure 53.1 There are no prospective randomized trials of aortic valve replacement in severe aortic stenosis (AS), and there are unlikely to be any in the near future. Two studies have compared the results of aortic valve replacement with medical treatment in their own center during the same time period in symptomatic patients with normal left ventricular systolic pump function. (A) Patients who had valve replacement (closed circles) had a much better survival than those treated medically (open circles). (From Schwarz *et al*[30] with permission.) (B) Patients who were treated with valve replacement (BSA) had a better survival than those treated medically (NH). (From Horstkotte and Loogen[14] with permission.) These differences in survival between those treated medically and surgically are so large that there is a great deal of confidence that aortic valve replacement significantly improves the survival of those with severe aortic stenosis. **Grade A**

at all. Preoperatively, these patients have a small left ventricular cavity, severe increase in wall thickness, and "supernormal" ejection fraction; this occurs in 42% of women and 14% of men in those aged ≥60 years.[33] After valve replacement their clinical picture often resembles that of hypertrophic cardiomyopathy without outflow obstruction, which is a difficult clinical condition to treat, both in the early postoperative period and after hospital discharge;[33] therefore, surgery should be performed prior to development of excessive hypertrophy. Surviving patients are functionally improved.[25]

After valve replacement, the 10 year survival is ≥60% and 15 year survival is about 45%.[25,34] One half or more of the late deaths are not related to the prosthesis but to associated cardiac abnormalities and other comorbid conditions.[34] Thus, the late survival will vary in different subgroups of patients. The older patients (≥60 years) have a 12 year actuarial survival of ≥60%.[35] Relative survival refers to survival of patients compared to age- and gender-matched people in the population. The relative 10 year survival after surgery is significantly better in those aged ≥65 than in those aged ≤65 years (94% *v* 81% respectively, Figure 53.2);[36] the 94% relative survival is not significantly different from the 100% relative survival. Thus, surgery should not be denied to those ≥60–65 years old and should be performed early.[25,35–37]

Patients who present with heart failure related to aortic valve stenosis should undergo surgery as soon as possible. Medical treatment in hospital prior to surgery is reasonable but ACE inhibitors should be used with great caution in such patients, and in such a dosage that hypotension and significant fall of blood pressure is avoided. They should not be used if the patient is hypotensive. If heart failure does not respond satisfactorily and rapidly to medical therapy, surgery becomes a matter of considerable urgency.[25] Catheter balloon valvuloplasty has a very limited role in adults with calcific aortic stenosis and carries a risk of >10%. In addition, restenosis and clinical deterioration occur within 6 to 12 months. In adults with aortic stenosis, balloon valvuloplasty is not a substitute for valve replacement but can be a bridge procedure in selected patients.[38] It usually improves patients' hemodynamics and may make them better candidates for valve replacement.

The operative mortality for patients with heart failure has declined: 25 years ago the operative mortality was <20%,[39] but in the current era it is ≤10%.[40] Although this is higher than in patients without heart failure, the risk is justified, because late survival in those who survive the operation is excellent and is far superior to that which can be expected with medical therapy. The 7 year survival of patients who survive operation is 84%.[41] The 5 year survival in those without associated CAD is greater than in those with CAD (69% *v* 39%, $P = 0{\cdot}02$).[40] Left ventricular function improves in most patients provided there has been no perioperative myocardial damage and becomes normal in two thirds of the patients, unless there was irreversible preoperative myocardial damage (Figure 53.3).[39,40] In addition, the operative survivors are functionally much improved.[39,40] Left ventricular hypertrophy and left ventricular dilation, if present preoperatively, regress toward normal.[39] Despite the excellent results of valve replacement in patients with severe aortic stenosis who are in heart failure, these results are not as good as for those who are not in heart failure; therefore, it is important to recognize that surgery should not be delayed until heart failure develops. **Grade B**

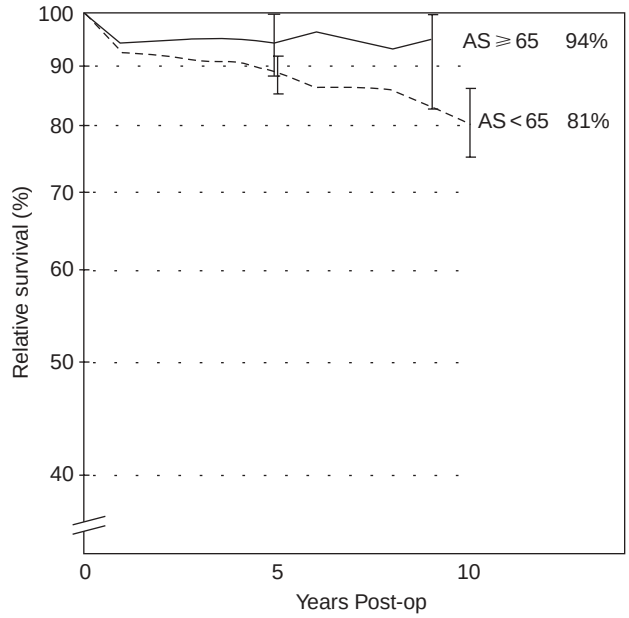


Figure 53.2 Data from the Karolinska Institute in Sweden has provided an interesting perspective on the long-term survival after valve replacement in patients with aortic stenosis (AS) aged ≥65 years. They have examined the relative survival – compared the survival of the patient who has undergone aortic valve replacement with another age and sex matched person in the same population. Actuarial survival ±95% confidence interval is shown. Patients under the age of 65 had a relative survival of 81% which is significantly lower than 100%, and is also lower than that of those aged ≥65 years. On the other hand, patients who underwent valve replacement at age ≥65 had a relative survival of 94% at the end of 10 years and this was not significantly different from 100%. These data indicate that survival following valve replacement for aortic stenosis in patients aged ≥65 is not significantly different from age- and sex-matched individuals in the population without aortic stenosis; and the late relative survival of patients aged ≥65 years is much better than that of patients aged <65. (From Lindblom *et al*[36] with permission.)

Six per cent of older patients with aortic stenosis present in cardiogenic shock.[38] The hospital mortality in such patients is near 50%. The subsequent mortality is also very high if the patients have not had their aortic stenosis relieved.[38] Thus, these patients need to be managed aggressively by emergency surgery with or without catheter balloon valvuloplasty as a "bridge" procedure.[38]

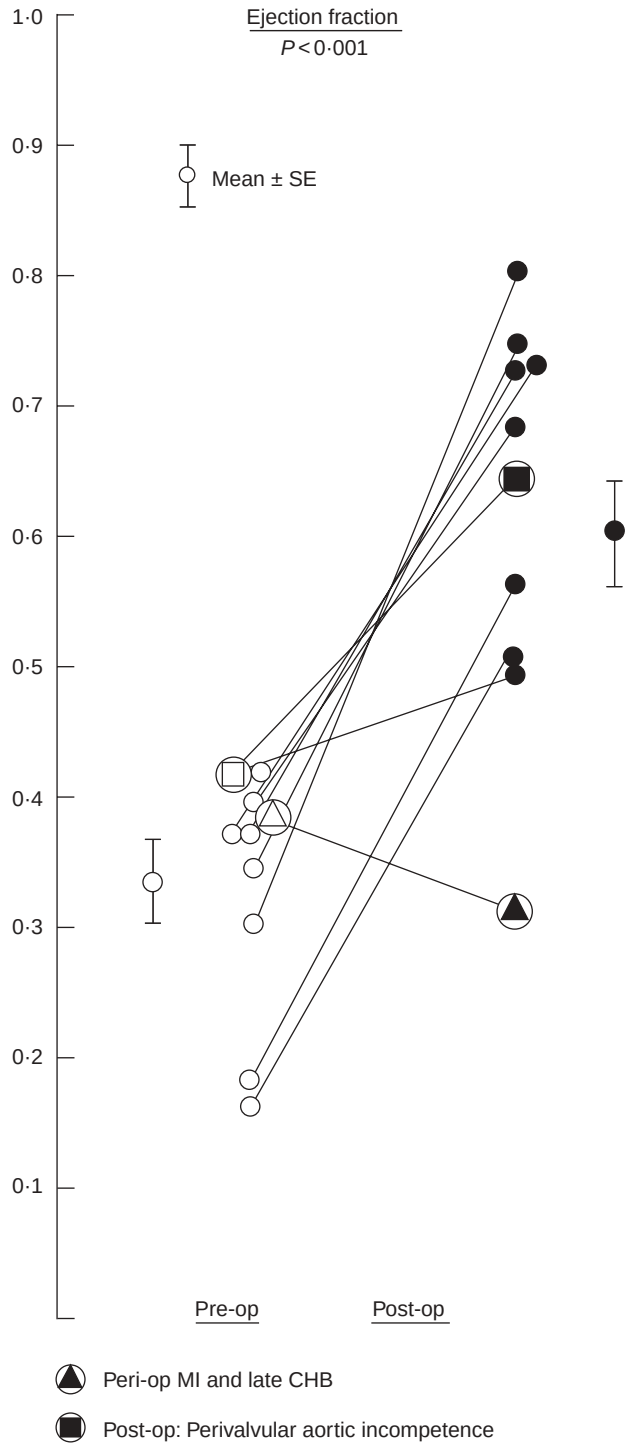


Figure 53.3 Examination of changes in LVEF in each individual patient among those who had left ventricular systolic dysfunction and clinical heart failure. After valve replacement the LVEF improved from 0·34 to 0·63. All but one patient showed an improvement in LVEF; the only patient who showed deterioration in ejection fraction suffered a perioperative myocardial infarction and had a complete heart block; and the only patient who showed only a small increase in ejection fraction had had a myocardial infarct prior to valve replacement. Note that ejection fraction normalized in two thirds of the patients and, in the two patients with the lowest ejection fraction (0·18 and 0·19), ejection fraction normalized in both. These data indicate that there is probably no lower limit of ejection fraction at which time these patients become inoperable. This also indicates that the lower the ejection fraction, the more urgent the need for valve replacement. (From Smith *et al*[39] with permission.)

Boxes 53.1 and 53.2 summarize the results of valve replacement in those with severe aortic stenosis and the factors predictive of a worse postoperative survival, less recovery of left ventricular function, and less improvement of symptoms in those with severe aortic stenosis and preoperative left ventricular systolic dysfunction.[15,25,29–32,34–36,39–41]

Box 53.1 Results of valve replacement in patients with severe aortic valve stenosis

- Improved symptoms and survival in symptomatic patients, especially in those with left ventricular systolic dysfunction, clinical heart failure, and in those aged ≤65 years
- Improvement in left ventricular systolic dysfunction, which normalizes in two thirds of patients
- Regression of left ventricular hypertrophy
- Improvement in functional class, more marked in those with severe symptoms preoperatively

Box 53.2 Factors predictive of a less favorable outcome

- Extent and severity of associated comorbid conditions
- Presence and severity of clinical heart failure preoperatively
- Severe associated coronary artery disease
- Severity of depression of preoperative left ventricular ejection fraction
- Duration of preoperative left ventricular systolic dysfunction
- Extent of preoperative irreversible myocardial damage
- Skill and experience of operating and other associated professional teams
- Extent of perioperative myocardial damage
- Complications of a prosthetic heart valve

Patients with severe left ventricular dysfunction, low aortic valve gradient, and small calculated aortic valve area represent a difficult patient population. There is controversy regarding the best management of these patients, in part related to the difficulty differentiating patients with true severe aortic valve stenosis from patients with moderate aortic valve stenosis and severe left ventricular dysfunction. Differentiating these two patient groups may have an important impact on the management decision and the operative outcome. Thus, patients with low gradient aortic valve stenosis should not be denied aortic valve replacement. A recent series confirms that

the surgical mortality is high and late survival lower than expected. Importantly however, most survivors experienced improvement in functional class and ejection fraction.[42]

A small gradient across the valve may be associated with a small calculated aortic valve area that would be in a range indicating severe aortic stenosis. There are at least two possible causes for this clinical circumstance. First, there is a small or reduced stroke volume and a normal or near normal systolic ejection time; thus, the gradient is small and the calculated aortic valve area correctly indicates severe aortic stenosis. The second consideration is that the stroke volume is reduced, and thus the valve needs to open only to a small extent to allow the left ventricle to eject the small stroke volume. The calculated aortic valve area accurately reflects the extent to which the valve has opened but overestimates the severity of aortic stenosis. Use of a provocative test using an inotropic agent, such as dobutamine,[43,44,45] may allow one to make the correct differentiation between the two. Dobutamine increases systolic flow per second owing to increases in stroke volume or shortening of ejection time or both. In the first circumstance described above, dobutamine will result in an increase in gradient but the calculated valve area remains more or less unchanged. On the other hand, in the second circumstance described above, the gradient may or may not increase with dobutamine but the calculated valve area increases significantly, indicating that the stenosis is not severe. When the dobutamine test is used, it is important to measure cardiac output and simultaneous left ventricular and aortic pressures both before and during dobutamine infusion. Alternatively, the gradient and valve area may be assessed by echocardiography/Doppler during dobutamine infusion; however, one needs to be certain that cardiac output has increased significantly with dobutamine. **Grade B**

Surgery should be advised for the symptomatic patient who has severe aortic stenosis. In young patients, if the valve is pliable and mobile, simple balloon valvuloplasty or surgical commissurotomy may be feasible. Older patients and even young patients with calcified, rigid valves will require valve replacement.

In view of the dismal natural history of symptomatic patients with severe aortic stenosis, the excellent outcome after surgery, and the uncertain natural history of the asymptomatic patient, it is reasonable to recommend aortic valve replacement in select asymptomatic patients in centers with the appropriate skill and experience. The combined risk of surgery and late complications of a valve prosthesis must be weighed against the risk of sudden death. There is no consensus about valve replacement in the truly asymptomatic patient. Clearly, if the patient has left ventricular dysfunction, obstructive CAD or other valve disease that needs surgery, and has severe aortic stenosis, then aortic valve replacement should be performed. Some would recommend valve replacement in all asymptomatic patients with severe aortic stenosis, while others would recommend it in all those with aortic valve area of $\leq 0{\cdot}70\,cm^2$ and in selected patients only with aortic valve area of $0{\cdot}71–1{\cdot}0\,cm^2$.

Exercise testing should be avoided in symptomatic patients with aortic stenosis but has been used by some cardiologists to help determine which patients with asymptomatic aortic stenosis should be referred for aortic valve replacement.[19] In a small series, Amato and colleagues reported no serious exercise-related complications. During follow up, 6% of the asymptomatic patients (4/66) experienced sudden death; all had a positive exercise test and an aortic valve area of $\leq 0{\cdot}6\,cm^2$. The exercise test was considered positive if there was a horizontal or down sloping ST segment depression of ≥ 1 mm in men or ≥ 2 mm in women, or an up sloping ST segment depression of ≥ 3 mm in men, measured 0·08 seconds after the J point. The exercise test was also considered positive if precordial chest pain or near syncope occurred, if the ECG showed a complex ventricular arrhythmia, or if systolic blood pressure failed to rise by ≥ 20 mmHg during exercise compared with baseline. **Grade B** It must be emphasized that this is a controversial issue. Some cardiologists advise against exercise testing in any patient with severe aortic valve stenosis, especially when the extent of coronary artery disease is not known.

Recommendations: aortic valve replacement/repair in severe aortic stenosis[1]

Indication	Class
● Symptomatic patients	I
● Asymptomatic patients with:	
• associated significantly obstructed CAD needing surgery	I
• other valve or aortic disease needing surgery	I
• left ventricular systolic dysfunction	IIa
• aged ≥60–65 years	IIa
• abnormal response to exercise	IIa
• severe left ventricular hypertrophy (≥15 mm)	IIb
• significant arrhythmias	IIb
• left ventricular dysfunction on exercise	IIb
• Prevention of sudden death in asymptomatic patients	III

CAD, coronary artery disease

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefullness/efficacy of a procedure or treatment.

IIa: Weight of evidence or opinion is in favor of usefullness/efficacy.

IIb: Usefullness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful, and in some cases, may be harmful.

Chronic aortic valve regurgitation

Etiology

The causes of chronic aortic regurgitation are:[46]

- aortic root/annular dilation
- congenital bicuspid valve
- previous infective endocarditis
- rheumatic
- in association with other diseases.

In developed countries, aortic root/annular dilation and congenital bicuspid valve are the commonest causes of severe chronic aortic regurgitation.

Natural history

During the first world war, Sir Thomas Lewis and his colleagues[47] at Hampstead and Colchester Military Hospitals reported to the Medical Research Council highlighting the inadequacy of the knowledge of heart disease, especially from the standpoint of prognosis. Sir Thomas Lewis proposed a system,[48] subsequently called "after histories",[48] which was a prospective follow up of patients. All patients in RT Grant's "after histories"[48] had valvular heart disease – most had aortic regurgitation – in which the patient characteristics were defined and described in detail, particularly by the degree of cardiac enlargement and the grade of cardiac failure. This probably was the start of databases or registries in cardiovascular medicine.

Chronic aortic valve regurgitation is a condition of combined volume and pressure overload. With progression of the disease, compensatory hypertrophy and recruitment of preload reserve permit the left ventricle to maintain a normal ejection performance despite the elevated afterload. The majority of patients remain asymptomatic throughout the compensated phase, which may last decades. The natural history of chronic aortic valve regurgitation can be considered by three different eras: the era of syphilis, the era of rheumatic fever/carditis, and the current era of noninvasive quantification of left ventricular function.

Era of syphilis

The data are from the 1930s and 1940s, and thus largely prior to availability of antibiotics.[49] The duration from syphilis infection to death was 20 years. The duration of the asymptomatic period after aortic regurgitation was 5 years in 60% of patients; and the 5 year survival was 95%. Once symptoms had developed, the 10 year survival ranged from 40 to 60%. Heart failure was associated with a 1 year survival of 30–50%, and 10 year survival of 6%. In a study of 161 patients reported in 1935, the 10 year survival after heart failure had developed was 34% but was 66% in those treated with arsenic.[49] Syphilis still occurs, but current therapy of syphilis is cheap and efficacious if diagnosed early. Syphilitic aortic regurgitation is not common, and the outcome in syphilitic aortic regurgitation may be more benign in the current era.

Era of rheumatic fever/carditis

Although the incidence of rheumatic valve disease is low in developed countries, rheumatic heart disease remains the most common form of valve disease in many parts of the world. Moreover, some people now domiciled in the developed world have had their initial attack(s) of acute rheumatic fever whilst living in less developed countries.

The detection of a murmur after the episode of acute rheumatic fever averages 10 years.[49] The average interval from detection of murmur to development of symptoms is 10 years and the percentage of patients remaining symptom-free 10 years after detection of the murmur is 50%.[49]

In 1971, Spagnuolo and coworkers[50] reported the 15 year actuarial follow up of 174 young people who had a median follow up of 10 years. Patients were considered to be in a cumulative high-risk group if they had systolic blood pressure <140 mmHg and/or diastolic blood pressure >40 mmHg, moderate or marked left ventricular enlargement on chest radiography, and two of three ECG abnormalities (S in V2+R in V5 ≥ 51 mm, ST segment depression or T wave inversion in left ventricular leads). The group's findings are summarized in Table 53.5.

Table 53.5 Reported outcome in 174 young people followed for a mean of 10 years after an episode of rheumatic fever

Symptoms/outcome	Outcome (years)	%
Cumulative high-risk group		
• mortality	6	30
• angina	7	60
• heart failure	6	60
• mortality or angina or heart failure	6	87
Cumulative low-risk group		
• Mortality	6	0
	15	5[a]
• Angina	5	2
• Heart failure	6	2
	15	5
• Mortality or angina or heart failure	15	8

[a] The one patient (of the 72 patients) in this subgroup who died had developed two of the three risk factors.

In 1973, Goldschlager and coworkers[51] reported on the duration of the asymptomatic period in 126 patients with varied etiology (Table 53.6).

Table 53.6 Asymptomatic period observed in 126 patients following an episode of rheumatic fever

Age group (years)	Patients symptomatic at 10 years[a] (%)
11–20	0
21–30	24
31–40	35
41–50	71
51–60	77
61–70	89

[a] Symptoms were those of dyspnea, fatigue and, less frequently, chest pain and palpitations. Patients deteriorated from NYHA functional Class I to Classes II, III, or IV.
From Goldschlager *et al.*[50]

Current era

In the current era, patients have been followed after noninvasive tests (echocardiography/Doppler ultrasound, radionuclide LVEF) or after invasive studies (cardiac catheterization or angiography). Reported outcomes are shown in Table 53.7.

As outlined in Table 53.7,[52–58,64] the natural history of patients with chronic aortic valve regurgitation depends on the presence or absence of symptoms and on the status of the left ventricle. In asymptomatic patients with normal left ventricular function, data would suggest the progression to symptoms and or left ventricular systolic dysfunction in approximately 4% per year. Sudden death occurs very rarely, 0·1% per year, and asymptomatic left ventricular dysfunction occurs at a rate of 1–3% per year, depending on the frequency of follow up.

There are limited data on asymptomatic patients with reduced left ventricular systolic function. However, available data would suggest that most of these patients will develop symptoms warranting surgery within two to three years, at an average rate of >25% per year.

Limited data are available on the natural history of symptomatic patients with severe aortic valve regurgitation. These patients have a poor prognosis despite medical therapy, with reported mortality rates of 10 and 20% per year in patients with angina and heart failure, respectively.

Important limitations of some of the studies in the literature must be kept in mind. For example, the "natural history" group in one study was composed of several subsets of patients[53] and 36% of this group were on medications for symptoms. Another concern is the true rate of the development of asymptomatic left ventricular dysfunction.[54] At least 25% of patients who develop left ventricular systolic dysfunction do so before they have symptoms, thus emphasizing the need for quantitative assessment of left ventricular systolic function at follow up in asymptomatic patients with severe aortic regurgitation and normal left ventricular systolic function. More recent studies indicate a poor outcome of symptomatic patients with medical therapy, even among those with preserved systolic function (Table 53.8).[57,65]

Table 53.7 Outcomes of patients with severe aortic regurgitation

Outcome	Incidence
Asymptomatic patients with normal left venticular systolic function[52–59]	
progression to symptoms and/or left ventricular systolic dysfunction	2·4–5·7% per year (average 3·8% per year)
progression to asymptomatic left ventricular dysfunction:	
follow up at 12 month intervals[a54]	0·9% per year
follow up at 6 month intervals[a58]	3·4% per year
Sudden death	0·1% per year
Asymptomatic patients with left ventricular systolic dysfunction[60–61]	
progression to cardiac symptoms	>25% per year
Symptomatic patients[50,62–64]	
mortality rate	average >10% per year
angina	>10% per year
heart failure	>20% per year

[a] See text for details.

Sir William Broadbent[66] stated 100 years ago that "The *age* of the patient at the time when the lesion is acquired is

Table 53.8 Likelihood of symptoms or left ventricular dysfunction or death

● Left ventricular end-diastolic dimension	
≥70 mm	10% per year
<70 mm	2% per year
● Left ventricular end-systolic dimension	
≥50 mm	19% per year
End-systolic dimension >25 mm/m^2	8% per year
40–49 mm	6% per year
<40 mm	0% per year

the most important consideration in prognosis…". In asymptomatic patients with normal left ventricular systolic function, the independent predictors of symptoms, left ventricular systolic dysfunction, and death by multivariate analysis were: older age, decreasing resting LVEF, and left ventricular dimension on M-mode echocardiography.[54] However, in many of these patients, M-mode images were not obtained from two dimensionally directed echocardiograms. Very importantly, most of these dimensions were obtained in the United States, and US women have smaller left ventricular dimensions than men, even when they become symptomatic.[67] Thus, it is unlikely that the above criteria apply to women and almost certainly will not be applicable to populations of smaller body size, for example, Asians, Latin Americans, sub-Saharan Africans, and Orientals. The left ventricular dimension should be corrected to body surface area.[68] Patients also develop symptoms and/or left ventricular systolic dysfunction at a faster rate if their initial left ventricular end-diastolic volume is $\geq 150\,ml/m^2$ when compared to those with volumes $<150\,ml/m^2$.[53] Older age also appears to increase the annual mortality.[68]

Patients with severe ventricular dilation when exercised have shown mean pulmonary artery wedge pressure ≥ 20 mmHg and/or exercise ejection fraction $<0{\cdot}50$, and such patients have demonstrated reduced exercise capacity, with reduced maximum V_{O_2}.[69,70]

Patients who present with ventricular tachycardia, ventricular fibrillation or syncope and have inducible ventricular tachycardia on electrophysiologic studies have an 80% probability of a serious arrhythmic event up to 4 years of follow up, versus 47% in those in whom ventricular tachycardia could not be induced ($P< 0{\cdot}005$).[71]

Acute severe aortic valve regurgitation usually causes sudden severe symptoms of heart failure or cardiogenic shock. The sudden large regurgitant volume load is imposed on a normal size left ventricle causing marked elevation in left ventricular end-diastolic pressure and left atrial pressure. Echocardiography is invaluable in determining the severity and etiology of aortic valve regurgitation.[10] The etiology of acute aortic valve regurgitation may have an important impact on the treatment, which is usually emergency surgery.

Management options

Angina is a result of a relative reduction of myocardial blood flow because of an increased need or associated obstructive CAD or both.[25] It does not respond to nitrates as well as in aortic stenosis. The options are to reduce the amount of aortic regurgitation and/or to revascularize the myocardium by coronary bypass surgery or by percutaneous catheter techniques. Clinical heart failure is treated with the traditional first-line triple therapy, that is, digitalis, diuretics, and ACE inhibitors. Parenteral inotropic and vasodilator therapy may be needed for those in severe heart failure.[72] The only direct method(s) to reduce the amount of regurgitation is by arterial dilators[73] and valve surgery – that is, valve replacement or valve repair.

Arterial dilators

In chronic aortic valve regurgitation, therapy with vasodilating agents is designed to improve forward stroke volume and reduce regurgitant volume. These effects should translate into reductions in left ventricular end-diastolic volume, wall stress, and afterload, resulting in preservation of left ventricular systolic function and reduction in left ventricular mass. These effects have been observed in small numbers of patients receiving hydralazine.[73] In a trial of 80 patients over 2 years[74] in which 36% of patients were symptomatic (NYHA class II) and were being treated with digitalis and diuretics, hydralazine produced very minor improvements of left ventricular size and function.[74] Side effects associated with long-term use of hydralazine seriously impaired compliance and only 46% of the patients completed the trial. Hydralazine is rarely used currently. Occasionally it is used for a short period of time, to tide the patient over an acute reversible complication or in preparation for elective surgery in selected patients with left ventricular dysfunction. Less consistent results have been reported with ACE inhibitors, depending on the degree of reduction in arterial pressure and end-diastolic volume. In an acute study in the catheterization laboratory, 20 patients were randomized to either oral nifedipine or oral captopril.[75] Nifedipine produced a reduction of regurgitant fraction but captopril did not. Nifedipine produced a greater increase of forward stroke volume and cardiac output and a greater fall of systemic vascular resistance. This study showed that, acutely, nifedipine was superior to an ACE inhibitor. A short-term 6 month randomized trial of a small number of patients showed that the results with captopril were similar to placebo – that is, there were no significant changes in M-mode echocardiographic left ventricular dimensions.[76]

A randomized trial of 72 patients for 12 months of long-acting nifedipine showed statistically significant reductions of left ventricular end-diastolic volume index and left ventricular mass, and increase of LVEF.[58] The role of long-acting nifedipine on *patient outcome* has been evaluated in a prospective, randomized trial of 143 asymptomatic patients with chronic, severe aortic valve regurgitation, and normal left ventricular systolic function; 69 patients were randomized to long-acting nifedipine and 74 patients to digoxin. The patients were evaluated at 6 month intervals for medication complication and had a history, physical examination, ECG, chest radiograph, and echocardiographic/Doppler study. Two independent blinded observers read each echocardiographic/Doppler study. Criteria for valve replacement were established prior to the start of the study. If left ventricular dysfunction developed, this had to be

confirmed by a repeat echocardiographic/Doppler study at 1 month and by preoperative left ventricular angiographic study. At 6 years, the need for valve replacement was 34±6% in the digoxin-treated group and 15±3% in the nifedipine-group, $P < 0{\cdot}001$ (Figure 53.4).[58] Thus, for every 100 patients treated with nifedipine, 19 fewer valve replacements were needed at the end of 6 years; note that even after 6 years, the curves are not parallel and do not converge (see Figure 53.4). Compared to the digoxin group, the nifedipine-treated group demonstrated a reduction in left ventricular volume and mass. Ejection fraction increased in the digoxin arm of the trial, and left ventricular volumes and mass increased. After aortic valve replacement, 12 of 16 patients (75%) in the digoxin group and all six patients in the nifedipine group who had an abnormal LVEF before surgery had a normal ejection fraction. Eighty-five per cent of patients in the digoxin arm of the trial, who underwent valve replacement, developed an abnormal ejection fraction and only three patients had valve replacement for symptoms. Moreover, patients in the digoxin arm of the trial had an outcome similar to that reported in the natural history studies.

Long-acting nifedipine is the drug of choice for asymptomatic patients with severe chronic aortic valve regurgitation and normal left ventricular systolic function unless there is a contraindication to its use.[25] The goal of vasodilator therapy is to reduce systolic blood pressure. The dose should be increased until there is a measurable decrease in blood pressure or side effects. Vasodilator therapy is not indicated

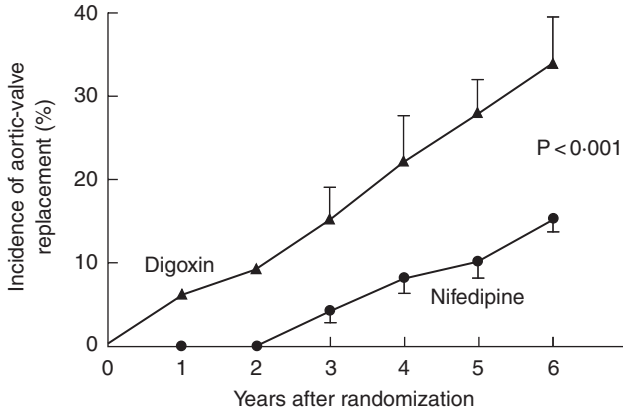


Figure 53.4 The role of long term, long acting nifedipine therapy in asymptomatic patients with severe aortic regurgitation and normal left ventricular systolic pump function was evaluated in 143 asymptomatic patients in a prospective randomized trial. By actuarial analysis, at 6 years, 34 ± 6% of patients in the digoxin group underwent valve replacement versus 15 ± 3% of those in the nifedipine group ($P < 0{\cdot}001$). This randomized trial demonstrates that long term arteriolar dilator therapy with long acting nifedipine reduces and/or delays the need for aortic valve replacement in asymptomatic patients with severe aortic regurgitation and normal left ventricular systolic pump function. (From Scognamiglio *et al*[52] with permission.)

in patients with normal left ventricular dimension and/or normal blood pressure. ACE inhibitors are not of proven benefit in asymptomatic patients with severe chronic aortic valve regurgitation and normal left ventricular systolic function. **Grade A**

Valve surgery (replacement/repair)

Surgery for aortic valve regurgitation should only be considered when the degree of regurgitation is severe. However, the presence of severe aortic valve regurgitation does not mandate surgery. The critical issue is to choose the best time for surgical intervention. Aortic valve repair or replacement should be performed in most symptomatic patients irrespective of the degree of left ventricular dysfunction. Postoperative survival is better after valve replacement in symptomatic patients with normal or mildly impaired left ventricular systolic function (ejection fraction [EF] ≥ 0·45) than in those with greater impairment of left ventricular systolic function (EF < 0·45).[77] In one study, patients with preoperative left ventricular EF of ≥0·60 had a better survival than those with left ventricular EF of <0·60.[78] Extreme left ventricular dilation (end-diastolic dimension >80) associated with aortic valve regurgitation occurs primarily in men and is often associated with left ventricular dysfunction. Extreme left ventricular dilation, however, is not a marker of irreversible left ventricular dysfunction. Operative risk and late postoperative survival are acceptable in these patients.[79] In the setting of severe left ventricular dysfunction (EF <0·25), the risk of aortic valve surgery increases and potential benefits decline, since left ventricular dysfunction may be on the basis of irreversible myocardial damage. However, even in the highest risk patients, the risk of surgery and postoperative medical therapy for heart failure are usually less than the risk of long-term medical management alone. **Grade B**

Aortic valve surgery for asymptomatic patients is more controversial but is indicated in the setting of left ventricular dysfunction with an EF ≤0·50 and in the setting of severe left ventricular dilation (end-diastolic dimension >75 mm or end systolic dimension >55 mm), even if the ejection fraction is normal. The threshold values of end-diastolic and end-systolic dimension recommended for aortic valve replacement in asymptomatic patients may need to be adjusted to body surface area. In one series, it was noted that a left ventricular end-systolic dimension corrected for body surface area (LVS/BSA) of ≥25 mm/m^2 was associated with increased mortality when followed conservatively.[1,68,79]

After valve replacement, patients with normal preoperative left ventricular systolic function have reductions of left ventricular volumes and hypertrophy.[80] In the majority of patients with normal preoperative left ventricular function, there is an increase in EF after valve replacement, presumably because of a reduction of myocardial stress.[31,81] Left

ventricular hypertrophy continues to decline for up to 5–8 years in those with normal preoperative left ventricular systolic function, but at a slower rate after 18–24 months.[31,81] Most patients are symptomatically improved and are in NYHA class I.[25]

After valve replacement in those with abnormal preoperative left ventricular systolic function (EF 0·25–0·49), there is a reduction of heart size and left ventricular end-diastolic pressure, end-diastolic and end-systolic volumes and hypertrophy.[77] Left ventricular EF improves or normalizes only if the EF was abnormal for ≤12 months prior to surgery.[81] Very early after valve replacement, there may be a reduction in EF. The left ventricular end-diastolic volume has not yet decreased but the regurgitant volume has been eliminated; this causes a decline in EF. An early decrease in left ventricular end-diastolic dimension is a good indicator of functional success of aortic valve replacement as the magnitude of reduction in end-diastolic dimension after operation correlates with the magnitude of late increase in EF.[1] Moreover, unless there is a perioperative complication, most patients are symptomatically improved and are in NYHA class I or II.[25]

Box 53.3 Results of valve replacement in patients with severe chronic aortic valve regurgitation

- Improved survival in those with mild to moderate impairment of left ventricular systolic function and in those with severe left ventricular enlargement irrespective of their symptomatic status
- Improvement in left ventricular systolic dysfunction; function normalizes if the dysfunction is of ≤12 months' duration preoperatively
- Regression of left ventricular hypertrophy
- Improvement in functional class, particularly in those with preoperative mild to moderate impairment and in those with preoperative left ventricular dysfunction

Box 53.4 Factors predictive of a less favorable outcome

- Extent and severity of associated comorbid conditions
- Severe obstructive coronary artery disease
- Presence and severity of clinical heart failure preoperatively
- Severity of depression of preoperative LVEF
- Duration of preoperative left ventricular systolic dysfunction
- Extent of preoperative irreversible myocardial damage
- Severity of increase in left ventricular end-diastolic and end-systolic size (left ventricular end-diastolic and end-systolic volumes of ≥210 and ≥110 ml/m^2, respectively, or end-diastolic and end-systolic dimensions of ≥80 mm and ≥60 mm, respectively)
- Skill and experience of operating and associated professional teams, for example, anesthetists
- Extent of perioperative myocardial damage
- Complications of a prosthetic heart valve

In those with severe symptoms and severe reduction of EF or severe left ventricular dilation preoperatively, survival as well as the beneficial effects on left ventricular function and functional class are less marked.[80,82]

Boxes 54.3 and 54.4 summarize the results of valve replacement in those with severe chronic aortic valve regurgitation and the factors predictive of a worse postoperative survival, less recovery of left ventricular function, and less improvement in symptomatic state in those with severe regurgitation and preoperative left ventricular systolic dysfunction.

There are two controversial questions regarding patients with severe aortic valve regurgitation. First, when does the symptomatic patient become inoperable? Second, when should one operate on asymptomatic patients with severe aortic valve regurgitation (assuming that associated comorbid conditions do not make the patient inoperable or at high risk for surgery)?

Severe left ventricular systolic dysfunction is the major factor that makes the patient with severe aortic valve regurgitation inoperable. In the published study of left ventricular dysfunction in which the patient and left ventricular function improved after valve replacement, the patients had an EF of 0·25–0·49.[77,80] Personal experience indicates that with skilled and experienced surgery, patients with an EF of 0·18–0·24 are improved with operation. There are limited data on the results of valve replacement in patients with severe aortic valve regurgitation and severe left ventricular systolic dysfunction with a left ventricular EF of <0·18, these patients are very high risk for conventional valve surgery and many would consider such patients inoperable.

The asymptomatic patient with severe aortic valve regurgitation poses a challenging clinical dilemma. If patients have developed left ventricular systolic dysfunction, then their outcome is poor without surgery, and left ventricular dysfunction, if present for 12 months or longer, does not normalize after surgery;[81] therefore, surgery is advisable. Patients who need surgery for associated conditions, for example, obstructive CAD, thoracic aortic disease, such as an aortic aneurysm, or another valve lesion, should have surgery for the severe aortic regurgitation. Patients who have developed severe left ventricular dilation are on the edge of developing symptoms at a high rate. One could wait for symptoms to develop and follow these patients very carefully at frequent intervals. Asymptomatic patients who do not have severe left ventricular dilation and those who do not have left ventricular dysfunction at rest or exercise should not have surgery for chronic aortic valve regurgitation. The current status of aortic valve repair prevents recommending this as an early prophylactic procedure. It is difficult to determine which aortic valves will be amenable to repair. In addition, the current rate of reoperation is at a level that prevents regular use of this procedure in asymptomatic patients with minimal left ventricular enlargement.[83]

Recommendations: aortic valve replacement/repair in severe chronic aortic regurgitation

Indication	Class
Symptomatic patients with:	
• NYHA class III or IV symptoms and normal LV systolic function (LVEF ≥ 0·5)	I
• NYHA class II symptoms, preserved systolic function (LVEF ≥ 0·5) but with progressive LV dilation or declining EF at rest, or declining exercise capacity on exercise testing	I
• Canadian Heart Association class II or greater angina with or without CAD	I
• NYHA class II symptoms with preserved LV systolic function (LVEF ≥ 0·5) with stable LV size and systolic function on serial studies and stable exercise tolerance	IIa
• LV systolic dysfunction	
—LVEF 0·25–0·49	I
—LVEF 0·18–0·24	IIb
Asymptomatic patients with:	
• LV systolic dysfunction	
—LVEF 0·25–0·49	I
—LVEF 0·18–0·24	IIb
• normal LV function and:	
• associated severe obstructive CAD needing surgery	I
• other valve or thoracic aortic disease needing surgery	I
• severe LV dilation with EDD ≥70 mm *or* ESD ≥55 mm and normal LV systolic function (LVEF ≥0·50)	IIb
• normal systolic function at rest (LVEF ≥0·5) but decline in EF (<0·50) on exercise radionuclide angiography	IIb
• normal systolic function at rest (LVEF ≥0·5) but decline in EF (<0·50) on stress echocardiography	III
• LV dilation is not severe (EDD <70 mm, ESD <50 mm)	III

Abbreviations: NYHA, New York Heart Association; EDD, end-diastolic dimension; ESD, end-systolic dimension; LVEF, left ventricular ejection fraction; EF, ejection fraction; LV, left ventricular

For definition of classes, see p. 773

References

1. Bonow R, Carabello B, de Leon A *et al.* Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation* 1998;**98**:1949–84.
2. Rahimtoola S. *Aortic valve stenosis*. St. Louis: CV Mosby; 1997.
3. Olsson N, Dalsgaaro C, Haegerstrand A, Rosenqvist M, Ryden L, Nilson J. Accumulation of T lymphocytes and expression of interluken-2 receptors in nonrheumatic stenotic aortic valves. *J Am Coll Cardiol* 1994;**23**:1162–70.
4. Otto C, Kuusisto J, Reichenbach D, Gown A, O'Brien K. Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994;**90**:844–53.
5. Otto C. Aortic stenosis – listen to the patient, look at the valve. *N Engl J Med* 2000;**343**:652–4.
6. Pohle K, Maffert R, Ropers D *et al.* Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* 2001;**104**:1927–32.
7. Otto C, Burwask I, Legget M *et al.* Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997; **95**:2262–70.
8. Rahimtoola S. The problem of valve prosthesis–patient mismatch. *Circulation* 1978;**58**:20–4.
9. Tobin J Jr, Rahimtoola S, Blundell P, Swan H. Percentage of left ventricular stroke workloss: a simple hemodynamic concept for estimation of severity in valvular aortic stenosis. *Circulation* 1967;**35**:868–79.
10. Cheitlin M, Alpert J, Armstrong W *et al.* ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation* 1997;**95**:1686–744.
11. Currie P, Seward J, Reeder G *et al.* Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation* 1985;**71**:1162–9.
12. Rahimtoola S. "Prophylactic" valve replacement for mild aortic valve disease at time of surgery for other cardiovascular disease? No. *J Am Coll Cardiol* 1999;**33**:2009–15.
13. Ross JJr, Braunwald E. Aortic stenosis. *Circulation* 1968;**36** (Suppl. IV):61–7.
14. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J* 1988;(Suppl. E):57–64.
15. Rahimtoola S. *Perspective on valvular heart disease: Update II*. New York: Elsevier, 1991.
16. O'Neill W. Predictors of long-term survival after percutaneous aortic valvuloplasty: report of the Mansfield Scientific Balloon Aortic Valvuloplasty registry. *J Am Coll Cardiol* 1991;**17**:193–8.
17. Kennedy K, Nishimura R, Holmes DJ, Bailey K. Natural history of moderate aortic stenosis. *J Am Coll Cardiol* 1991;**17**: 313–19.
18. Pellikka P, Nishimura R, Bailey K, Tajik A. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;**15**:1012–27.
19. Amato M, Moffa P, Werner K, Ramires J. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart* 2001;**86**:361–2.
20. Rosenhek R, Binder T, Porenta G *et al.* Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; **343**:611–17.

21.White P. *Heart Disease, 4th ed.* New York: Macmillan, 1951.
22.Bonet T. *Sepulchretum, sire Anatomia Practica, 4th ed.* Geneva: Leonard Chouet; New York: Macmillan, 1951.
23.Frank S, Johnson A, Ross JJ. Natural history of valvular aortic stenosis. *B Heart J* 1973;**35**:41–6.
24.Rahimtoola S. *Aortic valve stenosis, 10th ed.* New York: McGraw-Hill, 2001.
25.Rahimtoola S. *Aortic valve regurgitation, 9th ed.* New York: McGraw-Hill, 1998.
26.Sethi GK, Miller DC, Souchek J *et al.* Clinical, hemodynamic and angiographic predictors of operative mortality in patients undergoing single valve replacement. *J Thorac Cardiovasc Surg* 1987;**93**:884–7.
27.Edwards F, Peterson E, Coombs L *et al.* Predication of operative mortality after valve replacement surgery. *J Am Coll Cardiol* 2001;**37**:885–92.
28.Mullany C, Elveback E, Frye R *et al.* Coronary artery disease and its management: influence on survival in patients undergoing aortic valve replacement. *J Am Coll Cardiol* 1987;**10**: 66–72.
29.Rahimtoola S. Lessons learned about the determinants of the results of valve surgery. *Circulation* 1988;**78**:1503–7.
30.Schwarz F, Banmann P, Manthey J *et al.* The effect of aortic valve replacement on survival. *Circulation* 1982;**66**:1105–10.
31.Pantely G, Morton M, Rahimtoola S. Effects of successful uncomplicated valve replacement on ventricular hypertrophy, volume, and performance in aortic stenosis and aortic incompetence. *J Thorac Cardiovasc Surg* 1978;**75**:383–91.
32.Monrad E, Hess O, Murakami T, Nonogi H, Corin W, Krayenbuehl H. Time course of regression of left ventricular hypertrophy after aortic valve replacement. *Circulation* 1988; **77**:1345–55.
33.Carroll J, Carroll EP, Feldman T *et al.* Sex-associated differences in left ventricular function in aortic stenosis of the elderly. *Circulation* 1992;**86**:1099–107.
34.Hammermeister K, Sethi G, Henderson W, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. *N Engl J Med* 1993;**328**:1289–96.
35.Murphy E, Lawson R, Starr A, Rahimtoola S. Severe aortic stenosis in patients 60 years of age and older: left ventricular function and ten-year survival after valve replacement. *Circulation* 1981;**64**(Suppl. II):184–8.
36.Lindblom D, Lindblom U, Qvist J LundströmH Long-term relative survival rates after heart valve replacement. *J Am Coll Cardiol* 1990;**15**:566–73.
37.Sprigings D, Forfar J. How should we manage symptomatic aortic stenosis in the patient who is 80 or older? *Br Heart J* 1995;**74**:481–4.
38.Rahimtoola S. Catheter balloon valvuloplasty for severe calcific aortic stenosis: a limited role. *J Am Coll Cardiol* 1994; **23**:1076–8.
39.Smith N, McAnulty J, Rahimtoola S. Severe aortic stenosis with impaired left ventricular function and clinical heart failure: results of valve replacement. *Circulation* 1978;**58**:255–64.
40.Connolly H, Oh J, Orszulak T *et al.* Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation* 1997;**95**:2395–2400.
41.Rahimtoola S, Starr A. *Valvular surgery*. New York: Grune and Stratton, 1982.
42.Connolly H, Oh J, Schaff H *et al.* Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000;**101**:1940–6.
43.deFilippi C, Willett D, Brickner M *et al.* Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol* 1995;**75**:191–4.
44.Monin J, Monchi M, Gest V, Duval-Moulin A, Dubois-Rande J, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. *J Am Coll Cardiol* 2001;**37**:2101–7.
45.Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation* 2002;**106**(Suppl. 7):809–13.
46.Rahimtoola S. *Aortic valve regurgitation*. St. Louis: CV Mosby, 1997.
47.Lewis TS. *Special Report Series of the National Health Insurance Joint Committee, Medical Research Committee, Report No. 8*. London: MRC, 1917.
48.Grant R. After histories for 10 years of a thousand men suffering from heart disease. *Heart* 1933;**16**:275–334.
49.McKay C, Rahimtoola S. *Natural history of aortic regurgitation*. New York: Kluwer, 1980.
50.Spagnuolo M, Kloth H, Taranta A, Doyle E, Pasternack B. Natural history of rheumatic aortic regurgitation. Criteria predictive of death, congestive heart failure, and angina in young patients. *Circulation* 1971;**34**:368–80.
51.Goldschlager N, Pfeifer J, Cohn K, Popper R, Selze R. Natural history of aortic regurgitation: a clinical and hemodynamic study. *Am J Med* 1973;**54**:577–88.
52.Scognamiglio R, Fasoli G, Dalla Volta S Progression of myocardial dysfunction in asymptomatic patients with severe aortic insufficiency. *Clin Cardiol* 1986;**9**:151–6.
53.Siemienczuk D, Greenberg B, Morris C *et al.* Chronic aortic insufficiency: factors associated with progression to aortic valve replacement. *Ann Intern Med* 1989;**110**:587–92.
54.Bonow R, Lakatos E, Maron B, Epstein S. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation* 1991;**84**:1625–35.
55.Scognamiglio R, Fasoli G, Ponchia A, Dalla Volta S Long-term nifedipine unloading therapy in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 1990; **16**:424–9.
56.Tornos M, Olona M, Permanyer-Miralda G *et al.* Clinical outcome of severe asymptomatic chronic aortic regurgitation. A long-term prospective follow-up study. *Am Heart J* 1995; **130**:333–9.
57.Ishii K, Hirota Y, Suwa M, Kita Y, Onaka H, Kawamura K. Natural history and left ventricular response in chronic regurgitation. *Am J Cardiol* 1996;**78**:357–61.
58.Scognamiglio R, Rahimtoola S, Fasoli G, Nistri S, Dalla Volta S. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994;**331**:689–95.

59.Henry W, Bonow R, Rosing D, Epstein S. Observations on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic evaluation of asymptomatic patients. *Circulation* 1980;**61**:484–92.
60.McDonald I, Jelinek V. Serial M-mode echocardiography in severe chronic aortic regurgitation. *Circulation* 1980;**62**: 1291–6.
61.Bonow R. Radionuclide angiography in the management of asymptomatic aortic regurgitation. *Circulation* 1991;**84**: I.296–I.302.
62.Hegglin R, Scheu H, Rothlin M. Aortic insufficiency. *Circulation* 1968;**38**(Suppl. 15):V77–V92.
63.Rapaport E. Natural history of aortic and mitral valve disease. *Am J Cardiol* 1975;**35**:221–7.
64.Rahimoola S. Aortic *Valve regurgitation, 10th ed.* New York: McGraw-Hill, 2001.
65.Aronow W, Ahn C, Kronzon I, Nanna M. Prognosis of patients with heart failure and unoperated severe aortic valvular regurgitation and relation to ejection fraction. *Am J Cardiol* 1994;**74**:286–8.
66.Broadbent W. Aortic incompetence. In: *Heart disease: with special reference to prognosis and treatment.* London: Baillière, Tindall & Cox, 1897.
67.Klodas E, Enriquez-Sarano M, Tajik A, Mullany C, Bailey K, Seward J. Surgery for aortic regurgitation in women: contrasting indications and outcomes compared with men. *Circulation* 1996;**94**:2472–8.
68.Dujardin K, Enriquez-Sarano M, Schaff H, Bailey K, Seward J, Tajik A. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* 1999; **99**:1851–7.
69.Boucher C, Wilson R, Kanarek D *et al.* Exercise testing in asymptomatic or minimally symptomatic aortic regurgitation: relationship of left ventricular ejection fraction to left ventricular filling pressure during exercise. *Circulation* 1983;**67**: 1091–1100.
70.Kawanishi D, McKay C, Chandraratna P *et al.* Cardiovascular response to dynamic exercise in patients with chronic symptomatic mild-moderate and severe aortic regurgitation. *Circulation* 1986;**73**:62–72.
71.Martinez-Rubio A, Schwammenthal Y, Schwammenthal E *et al.* Patients with valvular heart disease presenting with sustained ventricular tachyarrhythmias or syncope: results of programmed ventricular stimulation and long-term follow-up. *Circulation* 1997;**96**:500–8.
72.Rahimtoola S. Management of heart failure in valve regurgitation. *Clin Cardiol* 1992;**15**(Suppl. I):22–7.
73.Rahimtoola S. Vasodilator therapy in chronic, severe aortic regurgitation. *J Am Coll Cardiol* 1990;**16**:430–2.
74.Greenberg B, Massie B, Bristow J *et al.* Long-term vasodilator therapy of chronic aortic insufficiency: a randomized double-blind, placebo-controlled clinical trial. *Circulation* 1988;**78**: 92–103.
75.RöthlisbergerC, Sareli P, Wisenbaugh T. Comparison of single-dose nifedipine and captopril for chronic severe aortic regurgitation. *Am J Cardiol* 1993;**72**:799–804.
76.Wisenbaugh T, Sinovich V, Dullabh A, Sareli P. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral and isolated aortic regurgitation. *J Heart Valve Dis* 1994;**3**:197.
77.Greves J, Rahimtoola S, Clinic M *et al.* Preoperative criteria predictive of late survival following valve replacement for severe aortic regurgitation. *Am Heart J* 1981;**101**:300–8.
78.Cunha C, Giuliani E, Fuster V, Seward J, Brandenburg R, McGoon D. Preoperative M-mode echocardiography as a predictor of surgical results in chronic aortic insufficiency. *J Thorac Cardiovasc Surg* 1980;**79**:256–65.
79.Klodas E, Enriquez-Sarano M, Tajik A, Mullany C, Bailey K, Seward J. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol* 1997;**30**:746–52.
80.Clark D, McAnulty J, Rahimtoola S. Valve replacement in aortic insufficiency with left ventricular dysfunction. *Circulation* 1980;**61**:411–21.
81.Bonow R, Dodd J, Maron B *et al.* Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. *Circulation* 1988;**78**:1108–20.
82.Klodas E, Enriquez-Sarano M, Tajik A, Mullany C, Bailey K, Seward J. Aortic regurgitation complicated by extreme left ventricular dilation: long-term outcome after surgical correction. *J Am Coll Cardiol* 1996;**27**:670–7.
83.Izumoto H, Kawazoe K, Ishibashi K *et al.* Aortic valve repair in dominant aortic regurgitation. *Japan J Thorac Cardiovasc Surg* 2001;**49**:355–9.
84.Rapaport E. Natural history of aortic and mitral valve disease *Am J Cardiol* 1975;**35**(Suppl. 2):221–7.
85.Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. *Am Heart J* 1980;**99**(Suppl. 4):419–24.
86.O'Keefe JH Jr, Vlietstra RE, Bailey KR, Holmes DR Jr. Natural history of candidates for balloon aortic valvuloplasty. *Mayo Clin Proc* 1987;**62**(Suppl. 11):986–91.
87.Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J* 1987;**8**(Suppl. 5): 471–83.
88.Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol* 1988:**61**(Suppl. 1):123–30.

54 Balloon valvuloplasty: aortic valve

Daniel J Diver, Jeffrey A Breall

Aortic stenosis: natural history and prognosis

Grade A There are three major etiologies for valvular aortic stenosis in the adult patient: rheumatic aortic stenosis; congenital bicuspid aortic stenosis with secondary calcification; and senile calcific or degenerative aortic stenosis. In rheumatic aortic stenosis the major pathologic feature is commissural fusion, with associated thickening and fibrosis of the valve leaflets. Symptoms may not occur until the age of 50 or 60 and are often accompanied by evidence of other valvular disease, usually mitral. Patients with congenital bicuspid aortic stenosis develop progressive narrowing and calcification of the aortic valve over time, with symptoms often present by age 40–50. Degenerative calcific (senile) aortic stenosis appears to result from years of normal mechanical stress on the aortic valve, with progressive immobilization of cusps secondary to calcium accumulation in the pockets of the aortic cusps, and eventual fibrosis. Degenerative calcific aortic stenosis is now the most common cause of aortic stenosis in patients presenting for aortic valve replacement.[1]

Most data regarding the natural history of aortic stenosis are derived from clinical experience during the presurgical era. The natural history of aortic stenosis is characterized by a long latent period marked by slowly increasing obstruction and adaptive myocardial hypertrophy. The majority of patients are free of cardiovascular symptoms until relatively late in the course of the disease. However, once patients with aortic stenosis develop symptoms of angina, syncope or heart failure, survival with medical therapy is dismal, with death occurring within 2–5 years in most patients following the development of symptoms (Figure 54.1). Average survival in patients with aortic stenosis and angina or syncope is 2–3 years, and may be as short as 1·5 years in patients with aortic stenosis who develop heart failure.[2] Concomitant atrial fibrillation decreases survival in all symptom groups.

Asymptomatic patients with aortic stenosis have an excellent prognosis and rarely die without premonitory symptoms. A study by Pellikka *et al*[4] showed that mortality was slightly higher in asymptomatic patients treated with "prophylactic" valve replacement than in patients not operated on until symptoms develop. A recent study by Otto and colleagues reported follow up of 123 patients with asymptomatic aortic stenosis. During the 2·5 year, follow up period there were no sudden cardiac deaths. This study suggested that the rate of hemodynamic progression and clinical outcome in adults with asymptomatic aortic stenosis may be predicted by echocardiographic aortic jet velocity. Of those patients who entered the study with a peak aortic jet velocity >4 m/s only 21% were alive and free of valve replacement 2 years later.[5]

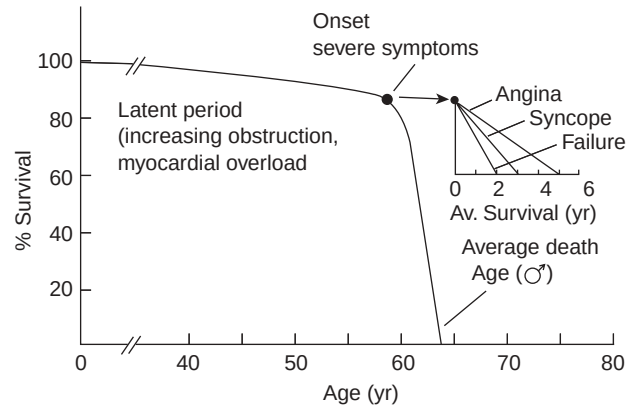


Figure 54.1 Natural history of aortic stenosis without operative treatment. (Reproduced with permission from Ross and Braunwald.[3])

The timing of aortic valve replacement in patients with aortic stenosis is predicated on the development of symptoms or deterioration in left ventricular performance, rather than severity of valve gradient or reduction in valve orifice area. Carabello[6] has proposed a definition of "critical" aortic stenosis as that valve area small enough to cause the symptoms of aortic stenosis that often presage sudden death: a "critical" situation indicating the need for aortic valve replacement. The aortic valve area associated with such symptom development varies significantly from patient to patient.

Aortic stenosis: natural history and prognosis

- Long latent period without symptoms
- Poor prognosis following symptom development with death in 2–5 years
- Prognosis significantly improved by valve replacement surgery.

Surgery for aortic stenosis

Grade B The initial surgical approach to treatment of aortic stenosis involved surgical valvuloplasty. In contrast to the situation with pulmonary and mitral stenosis, the stenotic aortic valve did not respond favorably to surgical valvuloplasty techniques. Closed aortic commissurotomy was associated with a high incidence of acute aortic regurgitation and operative mortality, and was abandoned after the development of open aortic valve surgical techniques. Surgical valvuloplasty under direct vision for aortic stenosis was first described in 1956, but was limited by a high rate of restenosis leading to subsequent aortic valve replacement, as well as a significant incidence of complications, including aortic regurgitation, infective endocarditis and systemic embolization.[7] Although ultrasonic decalcification and careful surgical sculpting procedures carried out under direct vision are initially effective in some patients, restenosis remains a serious problem.[8] However, open surgical valvulotomy remains an important treatment for infants and children with critical aortic stenosis, a situation where initial prosthetic valve replacement is undesirable.

The development and refinement of surgical aortic valve replacement significantly improved morbidity and mortality in patients with symptomatic aortic stenosis. Although there is no prospective randomized controlled study comparing aortic valve replacement with medical therapy in such patients, long-term follow up in high-quality case series has convincingly demonstrated the long-term benefits of aortic valve replacement, including hemodynamic improvement, regression of left ventricular hypertrophy, improvement of left ventricular function and improved survival.[9–11] Operative mortality for aortic valve replacement ranges from 2 to 8%, but may be as low as 1% in patients less than 70 years of age without significant comorbidity.

Aortic valve replacement, however, is associated with increased morbidity and mortality in certain subgroups.[10,12–15] Aortic valve replacement in the presence of left ventricular failure may be associated with perioperative mortality as high as 10–25%, and the need for emergency aortic valve replacement with operative mortality as high as 40%. Surgical risk is increased in the elderly patient, and may be increased severalfold with the need for concomitant bypass or multiple valve surgery. Although advanced age remains a strong predictor of operative death for aortic valve replacement even in recent studies, age alone is not a contraindication to aortic valve replacement in patients with aortic stenosis.[16] The Society of Thoracic Surgeons National Cardiac Surgery Database identified risk factors in nearly 50 000 patients who had valve surgery between 1994 and 1997: for patients with isolated aortic valve replacement, age was not a strong predictor of risk.[17] Fremes and colleagues[18] at the University of Toronto described the result of valve surgery in 469 consecutive patients over 70 years of age, and found that the predicted probability of operative mortality ranged from 0·9 to 76%, depending on the presence of other risk factors, including urgent operation, double valve surgery, coronary artery disease, female gender and left ventricular dysfunction. The authors suggested that elderly patients in good risk categories should be offered surgical intervention for the correction of valvular lesions, whereas alternative therapy might be indicated in patients with multiple risk factors in whom surgical mortality was prohibitively high. Levinson and colleagues at the Massachusetts General Hospital reported on aortic valve replacement for aortic stenosis in octogenarians.[19] In their cohort of 64 patients, serious comorbid non-cardiac conditions were infrequent. In-hospital mortality was 9·4%. An additional 10% of patients had permanent severe neurologic deficits and an additional 38% had a "complicated" course, marked by temporary encephalopathy, discharge to a rehabilitation facility or some combination thereof, albeit with ultimately good results. Although most survivors were ultimately free of cardiac symptoms, there was a high price to pay in terms of perioperative mortality and morbidity to achieve these results. However, recent series suggest that surgical results may be improving in very elderly patients. Rosengart and colleagues[20] compared results in 100 consecutive patients age 85 years or older who underwent open heart surgery between 1994 and 1997 with results obtained in the prior decade, and noted improvement in 30 day mortality and risk of major complications.

Therefore, while surgical aortic valve replacement has clearly improved the outcome in most patients with critical aortic stenosis, the higher risk in some patient subgroups, including the elderly, often leads to physician or patient deferral of aortic valve replacement. In an attempt to define the natural history of such patients, O'Keefe and colleagues[21] at the Mayo Clinic performed a case comparison study of 50 patients with severe, symptomatic aortic stenosis in whom surgery was declined by the patient ($n = 28$) or the physician ($n = 22$). The actuarial survival at 1, 2 and 3 years was 57, 37 and 25%, respectively. The survival of age- and sex-matched control subjects was 93, 85 and 77%, respectively ($P < 0 \cdot 0001$ at each 1 year interval) (Figure 54.2). This study suggested that the natural history of untreated aortic stenosis remains dismal and has not improved in the modern era, and confirmed the necessity of evaluating alternative non-surgical therapy, such as balloon aortic valvuloplasty, in patients likely to decline aortic valve replacement, or for whom surgery is not an option.

Development of balloon aortic valvuloplasty

Grade C Children and adolescents with congenital aortic stenosis generally have non-calcified valves with commissural fusion. Because aortic valve replacement is not desirable in

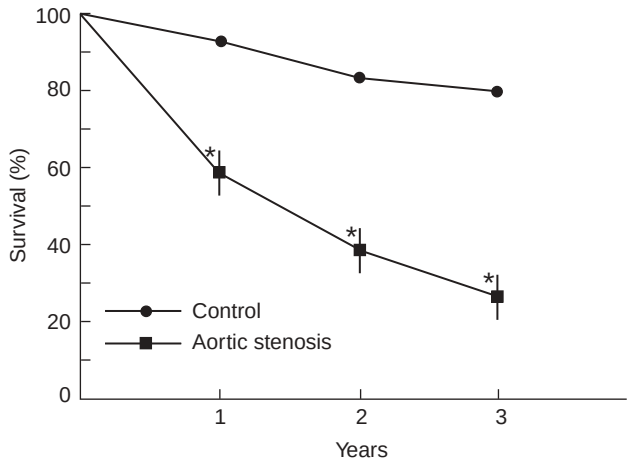


Figure 54.2 Survival among 50 patients with severe aortic stenosis who did not undergo surgical treatment, in comparison with an age- and sex-matched control group from the US population. Asterisks denote significant differences ($P < 0.0001$) between the two groups. Standard errors are shown as vertical lines. (Reproduced with permission from O'Keefe *et al.*[21])

this age group, commissural incision under direct vision is the preferred surgical procedure, and has been shown to confer significant hemodynamic improvement at low risk.[22] The contribution of commissural fusion to the etiology of valvular stenosis and mechanism of surgical improvement in this patient group led to the consideration of balloon aortic valvuloplasty as an alternative, non-surgical therapy.

In 1984 Lababidi and colleagues[23] reported the first series of 23 children and young adults with congenital aortic stenosis treated with percutaneous balloon aortic valvuloplasty. The patients ranged in age from 2 to 17 years. Balloon valvuloplasty was performed by the retrograde approach from the femoral artery, utilizing balloons of 10–20 mm in diameter. Percutaneous balloon dilation resulted in a decrease in the peak aortic valve gradient from 113 to 32 mmHg, with no change in cardiac output. The excellent initial results of percutaneous balloon valvuloplasty for aortic valve stenosis were confirmed by Rosenfeld and colleagues in young adults with congenital aortic stenosis. Long-term follow-up appeared to be excellent, with a 58% event-free rate at mean follow-up of 38 months,[24] although a recent multicenter study from Japan reported that progressive aortic insuffiency and recurrence of pressure gradient was not uncommon by 4 years after balloon valvuloplasty.[25]

The excellent results of balloon valvuloplasty in pediatric patients with congenital aortic stenosis led to consideration of this technique in adult patients with acquired calcific aortic stenosis. Two reports in 1986 described the first successful balloon valvuloplasty procedures in adult patients. Cribier and colleagues in France performed percutaneous balloon dilation in three elderly patients with calcific aortic stenosis.[26] The peak aortic gradient decreased from 75 to 33 mmHg, with an increase in calculated aortic valve area from 0·5 to 0·8 cm^2. All patients had symptomatic improvement. McKay and colleagues[27] at the Beth Israel Hospital in Boston described two elderly patients (aged 93 and 85 years) with calcific aortic stenosis treated with balloon valvuloplasty with 12–18 mm balloons. This report likewise described a substantial reduction in the transaortic pressure gradient and a significant increase in aortic valve area, with symptomatic improvement in both patients and significant improvement in left ventricular function in one. Despite initial concern regarding the possibility of valve disruption or embolization in the calcific valves present in adult patients, no patient in either report developed emboli or a significant increase in aortic regurgitation.

Mechanism of balloon aortic valvuloplasty

Grade B To assess the safety, efficacy and mechanism of balloon aortic valvuloplasty, Safian and colleagues[28] performed balloon dilation of stenotic aortic valves in 33 postmortem specimens and in six patients undergoing aortic valve replacement, prior to removal of the stenotic valve. The cause of aortic stenosis was degenerative nodular calcification in 28 cases, calcific bicuspid aortic stenosis in eight cases, and rheumatic heart disease in three. The distribution of the etiology of aortic stenosis in this report is in concordance with the observation that degenerative calcific aortic stenosis is now the most common cause of aortic stenosis in adults presenting for aortic valve replacement.[1]

Safian and colleagues performed balloon dilation with 15–25 mm balloons in the postmortem specimens, and with 18–20 mm balloons in the surgical patients. Balloon dilation resulted in increased leaflet mobility and increased valve orifice dimensions in all patients. The mechanism of successful dilation included fracture of calcified nodules within the leaflets in 16 valves, separation of fused commissures in five valves, both in six valves, and "grossly inapparent microfractures" (or stretching) in 12 valves. Liberation of calcific debris, valve ring disruption and midleaflet tears did not occur in any valve, although valve leaflet avulsion was produced in one postmortem specimen after inflation with a clearly oversized balloon. The authors concluded that there were several mechanisms for successful balloon aortic valvuloplasty, with the predominant mechanism in a given patient depending on the etiology of the stenosis. Furthermore, it appeared that embolic phenomena and acute regurgitation were not likely to be frequent complications following valvuloplasty.

The study by Safian and colleagues suggested that the most common etiology of aortic stenosis in the balloon valvuloplasty population is degenerative nodular calcification, and that the predominant mechanism of valve dilation is fracture of calcified nodules within leaflets and leaflet

stretching. Considered in conjunction with the disappointing surgical experience when stenotic aortic valves were dilated or cracked, the results of this mechanistic study predicted that there might be only mild improvement in aortic valve orifice area in patients treated with balloon aortic valvuloplasty, and that any such improvement might be short-lived. As will be seen, these implications were subsequently borne out in clinical trials.

Technical aspects

In the original reports by Cribier[26] and McKay,[27] balloon valvuloplasty was performed via the retrograde femoral approach. The most common balloon size used with the single-balloon retrograde approach is 20 mm, although smaller balloons can be used initially in small or frail patients. If no waist is produced in the inflated balloon, or if the aortic valve gradient is not sufficiently decreased by a given balloon size, a larger balloon may produce a better result.

Several modifications of the percutaneous retrograde femoral approach have been described. Block and Palacios[29] described an antegrade transseptal technique which they advocated for patients with severe iliac occlusive disease, tortuous iliac vessels or abdominal aortic aneurysm. This approach has recently been reported using the Inoue balloon, which may provide a greater increase in aortic valve area than conventional balloons[30] and which allows combined mitral and aortic valvuloplasty using a single catheter and access site.[31] A retrograde brachial approach may also be useful in such situations, although care must be taken to avoid injury to the brachial artery by the large valvuloplasty balloon. Dorros and colleagues[32] described a double-balloon technique, using both femoral arteries or a combined brachial and femoral approach. The combined diameter of the balloons used in this approach usually exceeds the diameter of the largest balloon used with single-balloon techniques. While initial results with double-balloon aortic valvuloplasty showed a greater enlargement of aortic valve area, follow-up studies showed no reduction in subsequent restenosis compared to single-balloon valvuloplasty.[33] An important recent technical advance is management of the femoral access site with preloaded suture closure devices, which may significantly reduce the incidence of vascular complications following balloon valvuloplasty.[34,35]

Initial results of balloon aortic valvuloplasty

Single center studies

Grade B Within several years of the initial reports of balloon valvuloplasty in adult patients with aortic stenosis, several centers reported large single-center experiences.[36–39] Cribier *et al*[36] reported their initial experience with 92 adult patients with symptomatic aortic stenosis and a mean age of 75 years. The aortic valve gradient was reduced from 75 to 30 mmHg, with an increase in calculated aortic valve area from 0·5 to 0·9 cm^2. The left ventricular ejection fraction rose from 48% at baseline to 51% immediately following the procedure. The majority of patients had marked symptomatic improvement. There were three in-hospital deaths and eight late deaths.

Safian *et al*[37] reported their initial experience with balloon aortic valvuloplasty in 170 consecutive patients treated at the Beth Israel Hospital in Boston. The procedure was completed successfully in 168 patients and resulted in significant increases in mean aortic valve area (0·6–0·9 cm^2) and cardiac output (4·6–4·8 l/min) and a significant decrease in aortic valve pressure gradient (71–36 mmHg) ($P < 0·01$ for all comparisons). There were six in-hospital deaths and five patients required early aortic valve replacement. The majority of patients had marked symptomatic improvement following the procedure. The most common complication was vascular, involving the femoral access site: 40 patients required transfusion and 17 required surgical repair. Transient dysrhythmias, most commonly left bundle branch block, occurred in 28 patients. Left ventricular perforation and tamponade occurred in three patients, a marked increase in aortic regurgitation in two patients, and a non-Q wave myocardial infarction in one patient. No patient suffered a stroke.

The hemodynamic results and complications of balloon aortic valvuloplasty in several large single-center studies are summarized in Tables 54.1 and 54.2, respectively. The results are remarkable for their similarity across study sites.

Table 54.1 Acute hemodynamic results of balloon aortic valvuloplasty

Author	Patients (*n*)	Aortic valve gradient (mmHg)		Aortic valve area (cm^2)	
		Pre	Post	Pre	Post
Cribier[26]	92	75	30	0.5	0.9
Safian[28]	170	71	36	0.6	0.9
Block[29]	162	61	27	0.5	0.9
Lewin[39]	125	87	32	0.6	1.0

Table 54.2 Complications of balloon aortic valvuloplasty

Author	Patients (*n*)	Complications (%)					
		Death	CVA	Perforation	MI	AI	Vascular
Safian[28]	170	3·5	0	1·8	0·6	1·2	10·0
Block[29]	162	7·0	2·0	0	0	0	7·0
Lewin[39]	125	10·4	3·2	0	1·6	1·6	9·6
Total	457	6·6	1·5	0.7	0·7	0·9	8·8

Abbreviations: AI, aortic insufficiency; CVA, cerebrovascular accident; MI, myocardial infarction

In general, balloon aortic valvuloplasty resulted in a 50–70% decrease in aortic valve gradient and a 50–70% increase in aortic valve area, resulting in early symptomatic improvement in most patients. The most common complication was vascular at the access site; there was a low incidence of life-threatening procedural complications. Death during the periprocedural period occurred in about 6% of patients.

Multicenter studies

Grade B Two large multicenter studies reported the initial results of balloon valvuloplasty in adult patients with symptomatic aortic stenosis.[40,41] The Mansfield Balloon Aortic Valvuloplasty Registry[40] evaluated data from 27 clinical centers in the United States and included 492 patients treated with balloon aortic valvuloplasty between December 1986 and October 1987. The mean age of patients was 79 years. All had severe symptoms, with 92% reporting congestive heart failure. Balloon aortic valvuloplasty was performed via the femoral approach in 92% of patients, by the brachial approach in 6%, and by the transseptal approach in 2%. A single-balloon technique was used in 72% of patients. The largest balloon size was 20 mm in over half of patients.

In the Mansfield Registry, balloon aortic valvuloplasty resulted in a decrease in mean aortic valve gradient from 60 to 30 mmHg, an increase in cardiac output from 3·9 to 4·0 l/min and an increase in aortic valve area from 0·5 to 0·8 cm^2. Most patients had significant symptomatic improvement. Death occurred during the procedure in 4·9% of patients, and within 7 days of the procedure in an additional 2·6%. The most common complication (11%) was local vascular injury, requiring surgical repair in 5·7% of patients. Embolic complications, ventricular perforation resulting in tamponade, and significant increase in aortic insufficiency each occurred in 1–2% of patients, and significant arrhythmia or myocardial infarction in less than 1%. Emergency aortic valve replacement was required in 1% of patients following balloon valvuloplasty.

The National Heart Lung and Blood Institute (NHLBI) Balloon Valvuloplasty Registry enrolled 674 elderly (average age 78 years) patients at 24 centers between November 1987 and November 1989.[41] Heart failure was the most common presenting symptom, occurring in 92% of patients; 45% of patients had angina and 35% had syncope. A single-balloon retrograde valvuloplasty technique was used in 94% of patients; the largest balloon used was 20 mm in over half. The mean gradient decreased from 55 to 29 mmHg and the aortic valve area increased from 0·5 to 0·8 cm^2, associated with symptomatic improvement in most patients. Procedural mortality was 3%; other major complications associated with the valvuloplasty procedure included cardiac arrest (5%), emergency aortic valve replacement (1%), left ventricular tamponade (2%), cerebral vascular accident (1%), systemic embolus (1%), emergency temporary pacing (5%), and ventricular arrhythmia requiring countershock (3%).

In summary, the initial results of the multicenter studies were similar to each other, and to the results of the previously described single-center studies, and suggested that balloon aortic valvuloplasty resulted in modest hemodynamic improvement and significant symptomatic improvement in many patients considered to be at high risk for aortic valve surgery.

Left ventricular function

Grade B Aortic valve replacement has been shown to improve left ventricular function in many patients with aortic stenosis and left ventricular dysfunction.[9–11] Safian and colleagues[42] at Beth Israel Hospital examined the effect of balloon aortic valvuloplasty on left ventricular performance in 28 patients with a low left ventricular ejection fraction (mean 37%), severe aortic stenosis and a mean age of 79 years. Balloon valvuloplasty resulted in significant increases in aortic valve area (0·5–0·9 cm^2), systolic pressure (120–135 mmHg), and cardiac output (4·2–4·8 l/min) ($P < 0·01$ for all comparisons), and significant decreases in transaortic pressure gradient (69–35 mmHg) and pulmonary capillary wedge pressure (24–20 mmHg) ($P < 0·01$ for both comparisons). All patients were symptomatically improved at the time of discharge.

Serial radionuclide ventriculography showed an increase in left ventricular ejection fraction from 37% prior to

valvuloplasty to 44% 48 hours post procedure and 49% at 3 month follow up. However, there was substantial heterogeneity of response, with 13 patients showing progressive increases in left ventricular ejection fraction (34% to 49% to 58%, $P < 0 \cdot 001$), whereas 15 patients showed no significant change in ejection fraction (41% to 40% to 41%, $P =$ NS) over 3 months. There was no difference between the groups with respect to age, extent of coronary disease, history of myocardial infarction, or baseline or postprocedure aortic valve area. However, peak systolic wall stress and left ventricular dimensions were higher in those patients who showed no improvement in ejection fraction. It may be that the failure to increase ejection fraction in this group is due to irreversible impairment in myocardial contractile function, secondary to previous infarction or long-standing aortic stenosis. Davidson and colleagues at Duke University also found that fewer than half of patients with a baseline left ventricular ejection fraction less than 45% showed sustained improvement following percutaneous balloon aortic valvuloplasty, even at short-term follow up.[43]

Follow up

Grade B Despite the moderate hemodynamic improvement and significant symptomatic improvement initially achieved in most patients with aortic stenosis following percutaneous balloon valvuloplasty, this technique is severely limited by the high incidence of restenosis. The Beth Israel group reported follow-up results in 170 patients (mean age 77 years) with symptomatic aortic stenosis who underwent balloon aortic valvuloplasty between October 1985 and April 1988.[37] The procedure was completed successfully in 168 patients, with significant improvement in aortic valve area and gradient. There were six in-hospital deaths and five patients required early aortic valve replacement. Follow up averaging 9·1 months was available for all 157 patients discharged from the hospital after successful valvuloplasty. In 44 patients (28%), recurrent symptoms developed a mean of 7·5 months after the procedure: 16 were treated by repeat valvuloplasty, 17 by aortic valve replacement and 11 with medical therapy. Two patients had a second restenosis, treated by aortic valve replacement in one case and by a third valvuloplasty procedure in the other. At latest follow up 103 patients (66%) were symptomatically improved, including 15 with restenosis who successfully underwent redilation. Twenty-five patients died after discharge, a mean of 6 months after balloon valvuloplasty. The most common cause of death was progressive congestive heart failure.

Repeat cardiac catheterization was performed in 35 patients in the Beth Israel follow-up cohort, including 21 with recurrent symptoms, a mean of 6 months after valvuloplasty. Significant aortic valve restenosis was found in all 21 patients with recurrent symptoms, and in eight of the 14 patients without symptoms. If restenosis was assumed to have occurred in all 25 patients who died, and in all 44 patients with recurrent symptoms, then the "clinical" rate of restenosis following valvuloplasty was 44% at only 9 months. The probability of survival at 1 year was 74% for the entire study population. However, if both recurrent symptoms and death were considered as events, the probability of event-free survival at 1 year was only 50%.

Similarly poor long-term results with high rates of early restenosis were reported by both of the multicenter studies of balloon aortic valvuloplasty. Among the 492 patients treated with balloon valvuloplasty in the Mansfield Registry the 1 year survival rate was 64%, with an event-free survival rate of only 43%.[44] Among the 674 patients reported in the National Heart, Lung and Blood Institute Balloon Valvuloplasty Registry, survival at 1, 2 and 3 years was 55, 35 and 23%, respectively.[45] Lieberman and colleagues[46] reported long-term follow up in 165 patients undergoing balloon aortic valvuloplasty. The median duration of follow up was 3·9 years, with follow up achieved in 99% of patients. Ninety-three per cent of patients died or underwent aortic valve replacement, and 60% died of cardiac-related causes. The probability of event-free survival, defined as freedom from death, aortic valve replacement or repeat balloon aortic valvuloplasty at 1, 2 and 3 years after balloon valvuloplasty, was 40%, 19% and 6%, respectively. By contrast, the probability of survival 3 years after balloon aortic valvuloplasty in a subset of 42 patients who underwent subsequent aortic valve replacement was 84%.

Mechanism of restenosis

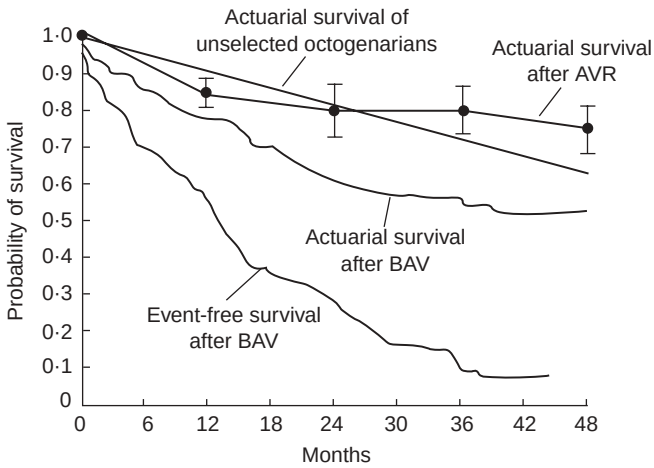
Because the mechanism by which balloon aortic valvuloplasty increases aortic valve area appears to consist chiefly of fracture of calcified nodules within leaflets and leaflet stretching, and only rarely involves separation of commissural fusion,[28] it is not surprising that the initial improvement in aortic valve area is modest at best, and that significant and early restenosis occurs in most patients. Any element of improvement in the aortic valve area due to leaflet stretching is likely to be rapidly compromised by elastic recoil, and in fact postprocedure echocardiographic follow up suggests early loss of initial valve area in many patients.[47] Histologic examination in patients who underwent balloon aortic valvuloplasty and had subsequent valve tissue examined at the time of aortic valve replacement or necropsy, showed evidence of closing of fractures in calcified nodules by granulation tissue that may lead to valvular scarring.[48,49] The more rapid time course of this type of inflammatory response, compared to the slowly developing valvular calcification that initially led to the aortic stenosis, may explain the relatively rapid progression to symptomatic restenosis following initially successful balloon valvuloplasty.

Results of balloon aortic valvuloplasty

- Initial hemodynamic and symptomatic improvement
- Early restenosis, with recurrent symptoms
- No improvement in long-term survival or event-free survival.

Predictors of outcome following balloon aortic valvuloplasty

Grade B Following recognition of the high incidence of restenosis after balloon aortic valvuloplasty, attempts were made to identify patient subsets more likely to derive long-term benefit. Kuntz and colleagues[50] analyzed event-free survival in 205 patients who underwent balloon valvuloplasty for symptomatic critical aortic stenosis. They evaluated 40 demographic and hemodynamic variables as univariate predictors of event-free survival by Cox regression analysis, and attempted to identify independent predictors of event-free survival by stepwise multivariate analysis. The rate of event-free survival, defined as survival without recurrent symptoms, repeat balloon valvuloplasty or subsequent aortic valve replacement, was 18% over a mean follow-up period of 24 months (Figure 54.3). Direct predictors of long-term event-free survival in the univariate analysis included female gender, left ventricular ejection fraction, and left ventricular and aortic systolic pressure. Inverse



Event-free survival:	205	137	103	70	51	32	16	14
Total survival:	205	172	154	135	123	115	109	107

Figure 54.3 Actuarial total and event-free survival among 205 patients treated by balloon aortic valvuloplasty (BAV). Shown for comparison are the actuarial survival rates among unselected octogenarians in the United States and among octogenarians who undergo aortic-valve replacement (AVR). The numbers below the figure show how many patients were alive or alive without an event at each follow-up. (Reproduced with permission from Kuntz *et al.*[50])

predictors of event-free survival included pulmonary capillary wedge and pulmonary artery pressures. Although the pre- and postvalvuloplasty aortic valve area and aortic valve gradient were not associated with event-free survival, the per cent reduction in the peak aortic valve gradient was a strong predictor of long-term event-free survival. For patients with a left ventricular ejection fraction of less than 40% at baseline, improvement in the ejection fraction was also directly associated with event-free survival. Notably, when patients aged 80 or older were analyzed as a subgroup, univariate analysis indicated that the predictors of long-term event-free survival were the same in elderly patients as in the entire patient cohort.

In the stepwise multivariate analysis the only independent predictors of event-free survival following balloon aortic valvuloplasty were the baseline aortic systolic pressure, the baseline pulmonary capillary wedge pressure (inversely related), and the per cent reduction in the peak aortic valve gradient. A baseline aortic systolic pressure less than 110 mmHg was associated with a relative risk of late events of 2·03, and a baseline pulmonary capillary wedge pressure greater than 25 mmHg was associated with a relative risk of 1·73, compared to the risk in patients with a baseline aortic systolic pressure greater than or equal to 140 mmHg and a pulmonary capillary wedge pressure less than 18 mmHg, respectively. Furthermore, a reduction of less than 40% in the peak aortic valve gradient was associated with a relative risk of late events of 1·75, compared to the risk in patients in whom valvuloplasty produced a reduction of 55% or more in the peak aortic valve gradient.

To facilitate prediction of outcome following aortic valvuloplasty, using only information available *prior* to the procedure, Kuntz and colleagues utilized the two independent baseline hemodynamic predictors in the Cox model, and estimated the probability of event-free survival at 6, 12, 18 and 24 months for all patients (Table 54.3). According to this two-variable predictive model, patients with baseline pulmonary capillary wedge pressure less than 18 mmHg and aortic systolic pressure greater than or equal to 140 mmHg (the most favorable patient subgroup) had event-free survival rates of 65% at 1 year and 41% at 2 years. On the other hand, patients with baseline pulmonary capillary wedge pressure greater than 25 mmHg and aortic systolic pressure less than 110 mmHg had event-free survival rates of only 23% at 1 year and 4% at 2 years.

In summary, Kuntz and colleagues found that the most important predictors of event-free survival following balloon aortic valvuloplasty were factors related to baseline left ventricular performance, a finding confirmed by analysis of long-term outcome in both large multicenter balloon aortic valvuloplasty registries.[44,45] The best long-term results following valvuloplasty were observed in patients who would also have been expected to have excellent long-term results after aortic valve replacement. In fact, comparison with the

Table 54.3 Estimated event-free survival according to baseline hemodynamic variables

Pre PCWP (mmHg)	Pre AOSP (mmHg)	Event-free survival (%)			
		6 mth	12 mth	18 mth	24 mth
<18	≥140	79	65	51	41
<18	110–139	73	58	42	31
<18	<110	64	46	30	19
18–25	≥140	74	59	43	32
18–25	110–139	68	50	34	23
18–25	<110	58	38	22	13
>25	≥140	63	44	28	18
>25	110–139	55	35	19	10
>25	<110	43	23	10	4

Abbreviations: AOSP, aortic systolic pressure; PCWP, pulmonary capillary wedge pressure
Reproduced with permission from Kuntz *et al.*[50]

surgical data on aortic valve replacement in octogenarians suggests that patients with good hemodynamic performance have better survival after aortic valve replacement than after balloon aortic valvuloplasty.[19] Among patients with poor left ventricular performance or advanced heart failure, event-free survival following balloon aortic valvuloplasty was dismal and did not appear to improve the natural history of untreated aortic stenosis.[21] Therefore, even in elderly patients with advanced heart failure and higher perioperative risk,[13] aortic valve replacement may increase the likelihood of long-term survival compared to balloon aortic valvuloplasty. In such high-risk patients, however, balloon aortic valvuloplasty may have a role in providing transient hemodynamic improvement, perhaps decreasing the risk of subsequent aortic valve replacement.

Repeat balloon aortic valvuloplasty

Grade B/C In patients who are not candidates for surgery the development of restenosis following balloon aortic valvuloplasty can be managed with a repeat procedure. Studies of repeat valvuloplasty have shown that the absolute aortic valve area tends to be slightly smaller both before and after the repeat valvuloplasty, even when larger balloons or balloon combinations are used.[51] The incidence of repeat restenosis remains high: follow up of the 47 patients in the Mansfield Registry who underwent repeat valvuloplasty showed that 66% of patients had died, undergone subsequent valve replacement or required a third valvuloplasty at a mean follow up of 5 months.[52] Histologic study of valves treated with balloon valvuloplasty, and excised prior to subsequent surgery or examined at autopsy, has shown active cellular proliferation within the splits in calcified nodules, as well as foci of ossification.[48] These findings suggest an active scarring process in response to balloon valvuloplasty, which may explain the failure to achieve better results with the use of larger balloons, and raises the possibility that balloon-induced injury to the aortic valve may accelerate the natural history of aortic stenosis.

Aortic valve surgery after balloon aortic valvuloplasty

Grade B Most surviving patients who have undergone balloon aortic valvuloplasty develop clinically significant restenosis within 1–2 years of the procedure. Many of these patients are subsequently treated with aortic valve replacement. Johnson and colleagues at the Beth Israel Hospital reported 45 patients (25% of the initial balloon valvuloplasty cohort) subsequently treated with aortic valve replacement.[53] Three patients required emergency operation immediately after unsuccessful valvuloplasty, and the remaining 42 had an elective operation at a mean of 8 months following valvuloplasty, primarily for the development of symptomatic restenosis. Despite the fact that the majority of these patients had initially undergone balloon valvuloplasty because they were considered to be at high risk for surgery, there were only four hospital deaths among the 45 patients. Three additional patients died a mean of 11 months following surgery. All surviving patients had persistent symptomatic improvement following surgery.

Lieberman and colleagues at Duke reported 40 patients (24% of the initial balloon valvuloplasty treatment group) who subsequently underwent aortic valve replacement.[54] Only one patient (2·5%) suffered a perioperative death. The probability of survival 3 years from the date of the last mechanical intervention was 75% for patients treated with balloon valvuloplasty and subsequent aortic valve

replacement, compared to only 20% for patients whose restenosis was treated with repeat balloon valvuloplasty, and 13% for patients who had no further mechanical intervention after developing restenosis. The majority of surgically treated patients remained asymptomatic at last follow up. It is important to note that this study is not a randomized comparison of treatment strategies for restenosis, and the results must be interpreted in light of the probable selection bias with regard to choice of management strategy for aortic valve restenosis. Nevertheless, it appears that in this group of patients initially felt to be at high risk for aortic valve replacement, surgery could be performed with an acceptable operative risk. Furthermore, as opposed to balloon valvuloplasty, aortic valve replacement appears to offer a reasonable chance of long-term freedom from symptoms. Although these reports do not specifically address potential reduction in the risk of subsequent surgery by prior performance of balloon valvuloplasty, a beneficial effect cannot be excluded.

Balloon aortic valvuloplasty *v* aortic valve surgery

Grade B There are no randomized trials comparing balloon aortic valvuloplasty with aortic valve replacement in adult patients with critical aortic stenosis. However, Bernard and colleagues in France compared two non-randomized matched series of patients with aortic stenosis treated with either balloon aortic valvuloplasty or aortic valve replacement at the same institution between January 1986 and March 1989.[55] Forty-six patients were treated with balloon aortic valvuloplasty and 23 with aortic valve replacement with a bioprosthesis. Baseline clinical and hemodynamic parameters were similar in both groups; all patients were at least 75 years old. Follow-up was 22 months for the aortic valvuloplasty patients and 28 months for those having surgery. Among patients treated with balloon aortic valvuloplasty, three patients (6·5%) died within 5 days of the procedure, and an additional 24 (42%) died during subsequent follow up, with 16 deaths being due to recurrent heart failure. Sixteen patients (35%) underwent subsequent aortic valve replacement at a mean of 16 months following balloon valvuloplasty. At last follow up, only three valvuloplasty patients (6·5%) remained alive without subsequent aortic valve replacement. Of the patients treated with initial aortic valve replacement, two (8·7%) died in the perioperative period and an additional three (13%) died during the follow up period. All remaining patients (78%) were alive and in New York Heart Association functional class I or II at last follow up. The overall survival rate following balloon valvuloplasty was 75% at 1 year, 47% at 2 years and 33% at 5 years. By contrast, survival following surgery was 83% at 1 and 2 years and 75% at 3 and 4 years. Although selection bias cannot be excluded in this non-randomized case comparison study, nevertheless the results strongly suggest that percutaneous balloon aortic valvuloplasty does not compare favorably with aortic valve surgery in elderly patients with aortic stenosis.

Specific indications for balloon valvuloplasty

Aortic valvuloplasty prior to non-cardiac surgery

Grade B/C Patients with severe aortic stenosis are at increased risk for significant cardiac complications during non-cardiac surgery.[56] Three studies described the role of balloon aortic valvuloplasty in the management of patients with critical aortic stenosis requiring major non-cardiac surgery.[57–59] In these studies, 29 patients with critical aortic stenosis underwent balloon aortic valvuloplasty which was complicated by procedural death due to ventricular perforation and tamponade in one patient. Valvuloplasty resulted in a significant improvement in aortic valve gradient and aortic valve area. Twenty-eight of the 29 patients underwent the planned surgical procedure under general or epidural anesthesia. All but one patient had uncomplicated non-cardiac surgery, with no significant congestive heart failure, hypotension, myocardial infarction, arrhythmia or conduction abnormality either during or immediately after surgery. One patient developed marked hypotension requiring transient intravenous pressor support during surgery for bowel carcinoma, resulting in interruption of surgery. This patient subsequently underwent aortic valve replacement and coronary artery bypass graft surgery, followed by repeat bowel resection. Procedures performed successfully following palliative balloon aortic valvuloplasty included aortic aneurysm repair, repair of hip fracture, exploratory laparotomy and thoracotomy. However, the cited reports are not randomized or case–control comparisons of preoperative balloon aortic valvuloplasty versus aortic valve replacement or medical therapy, and do not test the hypothesis that routine balloon valvuloplasty reduces the risk of non-cardiac surgery in patients with critical aortic stenosis. O'Keefe and colleagues[60] at the Mayo Clinic described 48 patients with severe aortic stenosis who underwent non-cardiac surgery (including vascular, orthopedic and abdominal procedures) without preoperative balloon valvuloplasty. There were no major perioperative complications in this group, who were managed with careful monitoring of systemic and pulmonary artery pressure during anesthesia. Therefore, the available evidence suggests that balloon valvuloplasty prior to urgent non-cardiac surgery may have greatest benefit in those patients with critical aortic stenosis and poor ventricular function, heart failure or hypotension, in whom transient hemodynamic improvement may decrease the risk of perioperative complications.

Aortic valvuloplasty as a bridge to aortic valve replacement

Grade B/C As noted earlier, many patients treated with balloon aortic valvuloplasty subsequently undergo aortic valve replacement. Early series of such patients demonstrated an acceptable operative risk and excellent surgical outcome, with long-term freedom from symptoms in most survivors.[53,54] In contrast, recent reports of cardiac surgery in octogenarians identified previous percutaneous aortic valvuloplasty as an independent predictor of hospital death following valve replacement.[61,62] However, in most patients undergoing surgery in these studies, valve replacement was performed because of failure of the initial balloon aortic valvuloplasty, which was not specifically used to stabilize the patient for subsequent surgery.

Smedira and colleagues[63] studied critically ill patients with aortic stenosis in whom balloon aortic valvuloplasty was specifically used as a bridge to aortic valve replacement. They reported five patients with severe aortic stenosis, multiple organ failure and severe hemodynamic compromise who were judged to be at excessive risk for aortic valve surgery. Balloon aortic valvuloplasty was used in these patients to provide transient hemodynamic improvement, to improve organ function, and to decrease the risk of subsequent definitive surgical correction. Following successful balloon aortic valvuloplasty and clinical stabilization, subsequent elective valve replacement was performed in all patients without complications. This report suggests that balloon aortic valvuloplasty may have a role as a bridge to subsequent aortic valve replacement for patients in whom heart failure or hypotension is so severe that the risk of primary aortic valve surgery is unacceptable.

Aortic valvuloplasty in cardiogenic shock

Grade C Of the 674 patients in the multicenter NHLBI Balloon Valvuloplasty Registry, 39 (6%) had cardiogenic shock. The largest reported series specifically describing the role of balloon aortic valvuloplasty in cardiogenic shock is that of Moreno and colleagues from the Massachusetts General Hospital.

Moreno[64] studied 21 patients with critical aortic stenosis and cardiogenic shock treated with balloon aortic valvuloplasty. All patients had major associated comorbid conditions precluding the use of emergency aortic valve replacement. The hemodynamic results were excellent, with an increase in systolic aortic pressure from 77 to 116 mmHg and an increase in aortic valve area from 0·5 to 0·8 cm^2 ($P = 0·0001$ for both comparisons). Cardiac index increased from 1·84 to 2·24 l/min/m^2 ($P = 0·06$). Nine treated patients died in hospital, two during the procedure and seven following successful valvuloplasty. Procedural complications were frequent, with five patients suffering vascular complications and one patient each developing stroke, cholesterol embolus and aortic regurgitation requiring aortic valve replacement. Twelve patients (57%) survived and were discharged from the hospital. During follow up of 15 months, five additional patients died. Actuarial survival was 38% at 27 months. The only predictor of improved survival was the postprocedure cardiac index.

In summary, the limited published data suggest that emergency percutaneous balloon aortic valvuloplasty can be successfully performed in patients with critical aortic stenosis and cardiogenic shock. Morbidity and mortality remain high even after hemodynamically successful procedures. Given the poor long-term outcome in patients treated with balloon aortic valvuloplasty, its use in patients with cardiogenic shock should be considered a bridge to subsequent aortic valve replacement in those patients who improve sufficiently to undergo surgery at reasonable risk.

Aortic valvuloplasty in patients with low output, low gradient

Grade B Patients with left ventricular dysfunction and aortic stenosis in the presence of low cardiac output and low aortic valve gradient present a complex diagnostic and therapeutic challenge. Aortic valve surgery is associated with increased morbidity and mortality in such patients, a subset of whom have irreversible myocardial dysfunction.[10–12] Balloon aortic valvuloplasty has been proposed as a diagnostic tool in patients with aortic stenosis and low-output low-gradient hemodynamics, to distinguish those with reversible myocardial dysfunction due to abnormal loading conditions from those with irreversible myocardial dysfunction. It has been suggested that patients with low-output low-gradient hemodynamics who have a significant improvement in either ventricular function or symptoms following successful balloon aortic valvuloplasty are more likely to improve following aortic valve replacement than those patients in whom the former produces no significant benefit.

Safian and colleagues studied 28 patients with a low left ventricular ejection fraction (mean 37%) and severe aortic stenosis who underwent balloon aortic valvuloplasty.[42] On the basis of response to balloon valvuloplasty they were able to separate patients into a subset with progressive improvement in left ventricular ejection fraction, and a subset which showed no significant change in left ventricular function. Nishimura and colleagues, utilizing data from the multicenter Mansfield Aortic Valvuloplasty Registry, compared 67 patients with low-output low-gradient hemodynamics against 200 patients with a low cardiac index but not a low aortic valve gradient.[65] Patients with low-output low-gradient hemodynamics had less of a decrease in aortic valve gradient after valvuloplasty, but a similar improvement in estimated aortic valve area. However, actuarial survival at 12 months was 46% for these patients, as against 64% in the comparison cohort ($P < 0·05$). Furthermore, patients with

low-gradient hemodynamics were less likely to show sustained symptomatic improvement. Therefore, as long-term outcome after balloon valvuloplasty is poor in these patients aortic valve replacement may be indicated in those in whom balloon aortic valvuloplasty produces an initial favorable response. Although these reports suggest that it may be possible to identify a subset of patients with aortic stenosis and low-output low-gradient hemodynamics likely to benefit from subsequent aortic valve replacement, the hypothesis that response to aortic valvuloplasty predicts subsequent outcome following surgery has not been tested.

Other indications

Grade C Case reports have described the use of balloon aortic valvuloplasty for the management of critical aortic stenosis in pregnancy, documenting its safe performance during pregnancy with subsequent normal births.[66] Given their age range, pregnant patients are more likely to have congenital or rheumatic aortic stenosis and therefore to have valve stenosis due to commissural fusion, which responds more favorably to balloon dilation than does the more frequently encountered degenerative calcific valvular disease. Use of balloon aortic valvuloplasty as a bridge to subsequent cardiac transplant in a patient with aortic stenosis and end-stage heart failure has also been described.[67]

Indications for balloon aortic valvuloplasty

- Symptomatic critical aortic stenosis in patients who are not candidates for aortic valve replacement
- Bridge to aortic valve replacement in patients with severe hemodynamic compromise
- Prior to urgent non-cardiac surgery
- Aortic stenosis with low-output low-gradient hemodynamics.

Conclusions

The development and analysis of balloon aortic valvuloplasty as a treatment strategy for adult patients with critical aortic stenosis offers a paradigm for the investigation of new therapeutic techniques. The initial enthusiasm for new treatment modalities, often based on arguments of physiology, first principles or small case series, is often replaced by a sobering realization of limitations and complications, revealed by careful prospective multicenter clinical trials, ultimately resulting in the development of appropriate clinical indications for the new treatment strategy. The development and investigation of balloon aortic valvuloplasty for aortic stenosis followed just such a course and illustrates the impact of careful, early prospective clinical trial data on the evolution and rapid development of appropriate indications for new therapeutic techniques.

Although valve replacement clearly improves morbidity and mortality in patients with symptomatic aortic stenosis, concern regarding the higher morbidity in high-risk subgroups led to the investigation of balloon aortic valvuloplasty as an alternative. Early evidence from both single- and multicenter series showing hemodynamic and symptomatic improvement in most patients treated with balloon valvuloplasty, led to initial widespread enthusiasm for this new technique. However, this enthusiasm was quickly tempered as subsequent follow up in these high-quality case series demonstrated a high rate of hemodynamic and clinical restenosis, and failure of balloon valvuloplasty to improve long-term or event-free survival.

Critical evaluation of the data from these large case series provided further understanding of the appropriate role of balloon valvuloplasty in the management of patients with aortic stenosis. When patients were stratified by the independent predictors of event-free survival, it became clear that those who did best with balloon aortic valvuloplasty were acceptable candidates for valve surgery and had an even better event-free survival following surgery. On the other hand, patients with baseline profiles that indicated a high risk for surgery also did extremely poorly with balloon valvuloplasty, with event-free survival that did not appear to differ from the natural history of untreated aortic stenosis. The rapid accumulation and careful analysis of clinical trial data on patients treated with balloon valvuloplasty quickly established that the treatment of choice for adult patients with symptomatic aortic stenosis is valve replacement, with balloon valvuloplasty being reserved for those in whom surgery is not possible or practical. Further refinement of the appropriate therapeutic niche for balloon aortic valvuloplasty has been aided by small case series targeted at specific indications for non-surgical therapy of aortic stenosis.

The following guidelines on appropriate utilization of balloon aortic valvuloplasty in adult patients with symptomatic critical aortic stenosis are based on case series and case–control studies, and therefore should be considered as Grade B recommendations.

Based on the available evidence, balloon aortic valvuloplasty should be considered:

1. For patients with symptomatic aortic stenosis who are not operable, or who are poor candidates for aortic valve replacement owing to severe comorbid illness or advanced age in the presence of other significant predictors of surgical risk. It should be emphasized that advanced age alone in a patient without other significant surgical risk factors is not a contraindication to aortic valve replacement. It must be further stressed that the goal of balloon aortic valvuloplasty in this patient group is transient symptomatic relief, as there is no evidence that valvuloplasty improves survival or provides long-term freedom from symptoms. **Grade B**

2. As a bridge to subsequent aortic valve replacement in patients with advanced heart failure, hypotension or cardiogenic shock, when clinical presentation suggests excessive risk for an initial surgical strategy. The goal of balloon aortic valvuloplasty in this cohort is transient hemodynamic improvement, leading to stabilization of the patient for subsequent aortic valve replacement, the only treatment shown to ultimately improve long-term survival. **Grade B**
3. For patients with critical aortic stenosis and poor ventricular function, heart failure or hypotension who require urgent or emergency non-cardiac surgery. The goal of balloon aortic valvuloplasty in this patient subset is successful completion of the required non-cardiac surgical procedure, with subsequent aortic valve replacement for the underlying aortic stenosis. **Grade B**
4. For patients with aortic stenosis, diminished left ventricular function and low-output low-gradient hemodynamics, in whom the response to initial "diagnostic" balloon valvuloplasty may help identify those likely to benefit from subsequent aortic valve replacement. **Grade B**

Given the disparity in outcome between aortic valve replacement and balloon aortic valvuloplasty in large high-quality case series and non-randomized case–control studies, it is unreasonable to pursue randomized clinical trials comparing these treatment strategies. However, the high-quality case series rapidly performed and reported in patients treated with balloon aortic valvuloplasty not only established the appropriate role for balloon valvuloplasty in the treatment of aortic stenosis, but also confirmed the value of prompt clinical investigation in the rapid development of appropriate indications for new therapeutic techniques. When the *goal* of therapy is long-term or symptom-free survival, the available clinical trial data clearly support valve replacement as the treatment of choice for aortic stenosis. However, in patients who are not candidates for or who refuse surgery, the trial data have demonstrated a role for balloon aortic valvuloplasty, albeit with the more limited goal of transient, palliative symptomatic relief, without improvement in survival or long-term symptomatic benefit.

References

1. Passik CS, Ackermann DM, Pluth JR, Edwards WD. Temporal changes in the causes of aortic stenosis: a surgical pathologic study of 646 cases. *Mayo Clin Proc* 1987;**62**:119–23.
2. Frank S, Johnson A, Ross J. Natural history of valvular aortic stenosis. *Br Heart J* 1973;**35**:41–6.
3. Ross J, Braunwald E. Aortic stenosis. *Circulation* 1968;**38** (Suppl. V):61–7.
4. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;**15**:1012–17.
5. Otto CM, Burwash IG, Legget ME *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70.
6. Carabello BA. Timing of valve replacement in aortic stenosis. Moving closer to perfection. *Circulation* 1997;**95**:2241–3.
7. Hsieh K, Keane JF, Nadas AS, Bernhard WF, Castaneda AR. Long-term follow-up of valvotomy before 1968 for congenital aortic stenosis. *Am J Cardiol* 1986;**58**:338–41.
8. McBride LR, Nannheim KS, Fiore AC *et al.* Aortic valve decalcification. *J Thorac Cardiovasc Surg* 1990;**100**:36–42.
9. Kennedy JW, Doces J, Stewart DK. Left ventricular function before and following aortic valve replacement. *Circulation* 1977;**56**:944–50.
10. Smith N, McAnulty JH, Rahimtoola SH. Severe aortic stenosis with impaired left ventricular function and clinical heart failure: results of valve replacement. *Circulation* 1978;**58**: 255–64.
11. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis. *Circulation* 1990;**82**:124–39.
12. Magovern JA, Pennock JL, Campbell DB *et al.* Aortic valve replacement and combined aortic valve replacement and coronary artery bypass grafting: predicting high risk groups. *J Am Coll Cardiol* 1987;**9**:38–43.
13. Edmunds LH, Stephenson LW, Edie RN, Ratcliffe MB. Open-heart surgery in octogenarians. *N Engl J Med* 1988;**319**: 131–6.
14. Verheul HA, Van Den Brink RBA, Bouma BJ *et al.* Analysis of risk factors for excess mortality after aortic valve replacement. *J Am Coll Cardiol* 1995;**26**:1280–6.
15. Gehlot A, Mullany CJ, Ilstrup D *et al.* Aortic valve replacement in patients aged eighty years and older: early and long-term results. *J Thorac Cardiovasc Surg* 1996;**111**:1026–36.
16. Asimakopoulos G, Edwards M, Taylor K. Aortic valve replacement in patients 80 years of age and older. Survival and cause of death based on 1100 cases: collective results from the UK Heart Valve Registry. *Circulation* 1997;**96**:3403–8.
17. Edwards FH, Peterson ED, Coombs LP *et al.* Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol* 2001;**37**:885–92.
18. Fremes SE, Goldman BS, Ivanou J, Weisel RD, David TE, Salerno T. Valvular surgery in the elderly. *Circulation* 1989; **80**(Suppl. I):177–90.
19. Levinson JR, Akins CW, Buckley MJ *et al.* Octogenarians with aortic stenosis. Outcome after aortic valve replacement. *Circulation* 1989;**80**(Suppl. I):149–56.
20. Rosengart TK, Finnin EB, Kim DY *et al.* Open heart surgery in the elderly: results from a consecutive series of 100 patients aged 85 years or older. *Am J Med* 2002;**112**:143–77.
21. O'Keefe JH, Vlietstra RE, Bailey KR, Holmes DR. Natural history of candidates for balloon aortic valvuloplasty. *Mayo Clin Proc* 1987;**62**:986–91.
22. Kirklin JW, Barratt-Boyes BG. Congenital aortic stenosis. In: *Cardiac Surgery*, 2nd edn. New York: Churchill Livingstone, 1993.

23.Lababidi Z, Wu JR, Walls JT. Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 1984; **53**:194–7.
24.Rosenfeld HM, Landzberg MJ, Perry SB, Colan SD, Keane JF, Lock JE. Balloon aortic valvuloplasty in young adults with congenital aortic stenosis. *Am J Cardiol* 1994;**73**:1112–17.
25.Tomita H, Echigo S, Kimura K *et al.* Balloon aortic valvuloplasty in children: a multicenter study in Japan. *Jpn Circ J* 2001;**65**:599–602.
26.Cribier A, Savin T, Saondi N, Rocha P, Berland J, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet* 1986;**i**:63–7.
27.McKay RG, Safian RD, Lock JE *et al.* Balloon dilatation of calcific aortic stenosis in elderly patients: postmortem, intraoperative, and percutaneous valvuloplasty studies. *Circulation* 1986;**74**:119–25.
28.Safian RD, Mandell VS, Thurer RE *et al.* Postmortem and intraoperative balloon valvuloplasty of calcific aortic stenosis in elderly patients: mechanisms of successful dilation. *J Am Coll Cardiol* 1987;**9**:655–60.
29.Block PC, Palacios IF. Comparison of hemodynamic results of anterograde versus retrograde percutaneous balloon aortic valvuloplasty. *Am J Cardiol* 1987;**60**:659–62.
30.Eisenhauer AC, Hadjipetrou P, Piemonte TC. Balloon aortic valvuloplasty revisited: the role of the Inoue balloon and transseptal antegrade approach. *Cathet Cardiovasc Interv* 2000;**50**:484–91.
31.Bahl VK, Chandra S, Goswami KC. Combined mitral and aortic valvuloplasty by the antegrade transseptal approach using the Inoue balloon catheter. *Int J Cardiol* 1998;**63**:313–15.
32.Dorros G, Lewin RF, King JF, Janke LM. Percutaneous transluminal valvuloplasty in calcific aortic stenosis: the double balloon technique. *Cathet Cardiovasc Diagn* 1987;**13**:151–6.
33.Fields CD, Lucas A, Desnoyers M *et al.* Dual balloon aortic valvuloplasty, despite augmenting acute hemodynamic improvement, fails to prevent post-valvuloplasty restenosis. *J Am Coll Cardiol* 1989;**13**:148A.
34.Solomon LW, Fusman B, Jolly N, Kim A, Feldman T. Percutaneous suture closure for management of large French size arterial puncture in aortic valvuloplasty. *J Invas Cardiol* 2001;**13**:592–6.
35.Michaels AD, Ports TA. Use of a percutaneous arterial suture device (Perclose) in patients undergoing percutaneous balloon aortic valvuloplasty. *Cathet Cardiovasc Interv* 2001;**53**:445–7.
36.Cribier A, Savin T, Berland J *et al.* Percutaneous transluminal balloon valvuloplasty of adult aortic stenosis: report of 92 cases. *J Am Coll Cardiol* 1987;**9**:381–6.
37.Safian RD, Berman AD, Diver DJ *et al.* Balloon aortic valvuloplasty in 170 consecutive patients. *N Engl J Med* 1988;**319**: 125–30.
38.Block PC, Palacios IF. Clinical and hemodynamic follow-up after percutaneous aortic valvuloplasty in the elderly. *Am J Cardiol* 1988;**62**:760–3.
39.Lewin RF, Dorros G, King JF, Mathiak L. Percutaneous transluminal aortic valvuloplasty: acute outcome and follow-up of 125 patients. *J Am Coll Cardiol* 1989;**14**:1210–17.
40.McKay RG, for the Mansfield Scientific Aortic Valvuloplasty Registry. Balloon aortic valvuloplasty in 285 patients: initial results and complications. *Circulation* 1988;**78**(Suppl. II): II–594.
41.McKay RG, for the NHLBI Aortic Valvuloplasty Registry. Clinical outcome following balloon aortic valvuloplasty for severe aortic stenosis. *J Am Coll Cardiol* 1989;**13**:1218.
42.Safian RD, Warren SE, Berman AD *et al.* Improvement in symptoms and left ventricular performance after balloon aortic valvuloplasty in patients with aortic stenosis and depressed left ventricular ejection fraction. *Circulation* 1988;**78**:1181–91.
43.Davidson CJ, Harrison JK, Leithe ME, Kisslo KB, Bashore TM. Failure of balloon aortic valvuloplasty to result in sustained clinical improvement in patients with depressed left ventricular function. *Am J Cardiol* 1990;**65**:72–7.
44.O'Neill WW, for the Mansfield Scientific Aortic Valvuloplasty Registry Investigators. Predictors of long-term survival after percutaneous aortic valvuloplasty: report of the Mansfield Scientific Aortic Valvuloplasty Registry. *J Am Coll Cardiol* 1991;**17**:193–8.
45.Otto CM, Mickel MC, Kenedy JW *et al.* Three year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation* 1994;**89**:642–50.
46.Lieberman EB, Bashore TM, Hermiller JB *et al.* Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol* 1995;**26**:1522–8.
47.Nishimura RA, Holmes DR, Reeder GS *et al.* Doppler evaluation of results of percutaneous aortic balloon valvuloplasty in calcific aortic stenosis. *Circulation* 1988;**78**:791–9.
48.Feldman T, Glagov S, Carroll JD. Restenosis following successful balloon valvuloplasty: bone formation in aortic valve leaflets. *Cathet Cardiovasc Diagn* 1993;**29**:1–7.
49.Isner JM. Aortic valvuloplasty: are balloon-dilated valves all they are "cracked" up to be? *Mayo Clin Proc* 1988;**63**: 830–4.
50.Kuntz RE, Tosteson AN, Berman AD *et al.* Predictors of event-free survival after balloon aortic valvuloplasty. *N Engl J Med* 1991;**325**:17–23.
51.Kuntz RE, Tosteson AN, Maitland LA *et al.* Immediate results and long-term follow-up after repeat balloon aortic valvuloplasty. *Cathet Cardiovasc Diagn* 1992;**25**:4–9.
52.Ferguson JJ, Garza RA, and the Mansfield Scientific Aortic Valvuloplasty Registry Investigators. Efficacy of multiple balloon aortic valvuloplasty procedures. *J Am Coll Cardiol* 1991;**17**:1430–5.
53.Johnson RG, Dhillon JS, Thurer RL, Safian RD, Wientraub RM. Aortic valve operation after percutaneous aortic balloon valvuloplasty. *Ann Thorac Surg* 1990;**49**:740–5.
54.Lieberman EB, Wilson JS, Harrison JK *et al.* Aortic valve replacement in adults after balloon aortic valvuloplasty. *Circulation* 1994;**90**(Suppl. II):II205–8.
55.Bernard Y, Etievent J, Mourand JL *et al.* Long-term results of percutaneous aortic valvuloplasty compared with aortic valve replacement in patients more than 75 years old. *J Am Coll Cardiol* 1992;**20**:796–801.
56.Goldman L, Caldera DL, Nussbaum SR. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;**297**:845–56.
57.Levine MJ, Berman AD, Safian RD, Diver DJ, McKay RG. Palliation of valvular aortic stenosis by balloon valvuloplasty as preoperative preparation for noncardiac surgery. *J Am Coll Cardiol* 1988;**62**:1309–10.

58.Roth RB, Palacios IF, Block PC. Percutaneous aortic balloon valvuloplasty: its role in the management of patients with aortic stenosis requiring major noncardiac surgery. *J Am Coll Cardiol* 1989;**13**:1039–41.
59.Hayes SN, Holmes DR, Nishimura RA, Reeder GS. Palliative percutaneous aortic balloon valvuloplasty before noncardiac operations and invasive diagnostic procedures. *Mayo Clin Proc* 1989;**64**:753–7.
60.O'Keefe JH, Shub C, Pettke SR. Risk of noncardiac surgical procedures in patients with aortic stenosis. *Mayo Clin Proc* 1989;**64**:400–5.
61.Kohl P, Lahaye L, Gerard P, Limet R. Aortic valve replacement in octogenarians: perioperative outcome and clinical follow-up. *Eur J Cardiovasc Surg* 1999;**16**:68–73.
62.Kolh P, Kerzmann A, Lahaye L, Gerard P, Limet R. Cardiac surgery in octogenarians: peri-operative outcome and long-term results. *Eur Heart J* 2001;**22**:1235–43.
63.Smedira NG, Ports TA, Merrick SH, Rankin JS. Balloon aortic valvuloplasty as a bridge to aortic valve replacement in critically ill patients. *Ann Thorac Surg* 1993;**55**: 914–16.
64.Moreno PR, Ik-Kyung J, Block PC, Palacios IF. The role of percutaneous aortic balloon valvuloplasty in patients with cardiogenic shock and critical aortic stenosis. *J Am Coll Cardiol* 1994;**23**:1071–5.
65.Nishimura RA, Holmes DR, Michela ME *et al.* Follow-up of patients with low output, low gradient hemodynamics after percutaneous balloon aortic valvuloplasty: the Mansfield Scientific Aortic Valvuloplasty Registry. *J Am Coll Cardiol* 1991;**17**:828–33.
66.Banning AP, Pearson JF, Hall RJ. Role of balloon dilatation of the aortic valve in pregnant patients with severe aortic stenosis. *Br Heart J* 1993;**70**:544–5.
67.Vaitkus PT, Mancini D, Herrman HC. Percutaneous balloon aortic valvuloplasty as a bridge to heart transplantation. *J Heart Lung Transplant* 1993;**12**:1062–4.

55 Balloon valvuloplasty: mitral valve

Zoltan G Turi

Introduction

Percutaneous balloon mitral valvuloplasty is the latest technique in an evolution that began with Elliot Cutler advancing a knife retrograde through the apex of the left ventricle of a beating heart in 1923.[1] Neither he nor Henry Suttar, who performed a similar procedure in England two years later received the expected accol ades,[2] and there has been continuing dispute about the relative role of mitral obstruction in defining the spectrum of mitral stenosis. Sir Thomas Lewis' statement that valvotomy was based on an erroneous idea, namely that the valve is the chief source of the trouble[3] has few proponents in the modern era and relieving mitral obstruction is the *de facto* standard of care.

After a 20 year hiatus, the battlefield experience with closed heart procedures in the second world war led to the application of these techniques outside the trauma arena. Although early results were confounded by significant morbidity and mortality, closed mitral valvotomy became a routine procedure for severe mitral stenosis, and is still the treatment of choice in many parts of the world where the disease is endemic and medical facilities limited. Large series[4,5] have claimed good long-term results, but lack of systematic follow up or comprehensive objective data obscure the actual restenosis rate and survival. In a Mayo Clinic retrospective analysis[6] there was 79% 10 year and 55% 20 year survival rate with reoperation in 34% by 10 years; however nearly a quarter of patients were lost to follow up and severity of disease at baseline could only be estimated. Open commissurotomy with the potential advantages of direct vision has supplanted closed procedures in industrialized nations. Controversy remains as to its superiority[7–9] with the advantages of direct vision favoring cases where thrombus is present.

The percutaneous approach

A pediatric cardiac surgeon, Kanji Inoue, developed a double lumen atrial septostomy balloon catheter made of latex, with a mesh weave used to constrain the balloon during inflation into the classic wishbone shape depicted in Figure 55.1.[10] He then adapted the device for percutaneous balloon mitral valvuloplasty, demonstrated under direct vision in the operating room its ability to split fused mitral commissures[11] and performed the first procedure in 1982.[12]

Mechanisms of valvuloplasty

The mechanisms responsible for the benefits of balloon mitral valvuloplasty[13] arise from the substantial radial force exerted by the enlarging balloon.[14] This stretches the mitral annulus, has the capacity to split fused commissures, and occasionally results in the cracking of calcifications. The stretching mechanism has been observed intraoperatively,[15] whereas the splitting of commissures[16] and cracking of

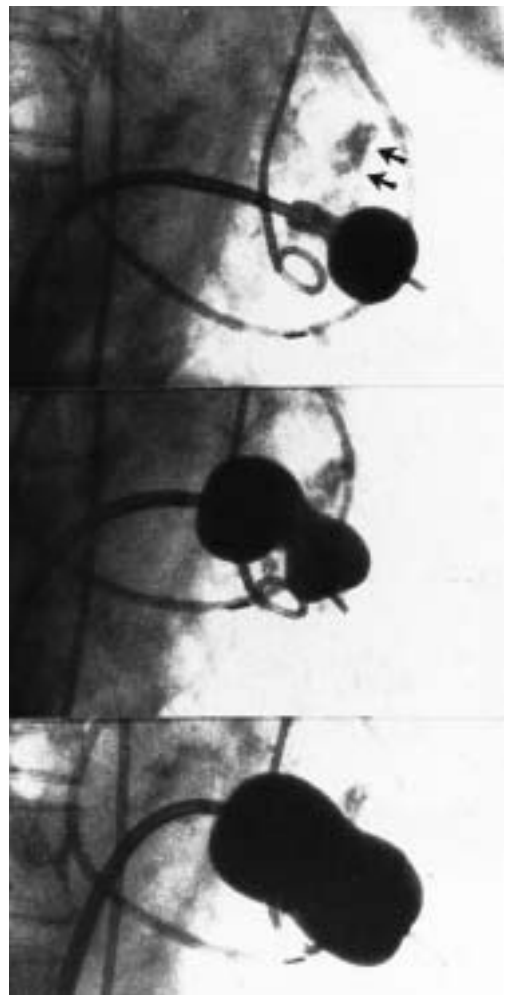


Figure 55.1 The Inoue balloon during staged deployment. From top to bottom: distal inflation with pullback against the valve; proximal inflation; full deployment. (Reprinted with permission of the American Heart Association, Inc.[38])

calcifications have been demonstrated by direct observation in excised valves.[17] The largely successful nature of balloon mitral valvuloplasty is derived from commissural splitting; balloon dilatation procedures where the other two mechanisms predominate, such as balloon valvuloplasty for calcific aortic stenosis, have less impressive short- and long-term results.

Preprocedure evaluation

The most common reason for exclusion of patients is unsuitable valve anatomy. Specific relevant physical examination findings are diminution of the first heart sound (often indicative of extensive subvalvular disease) and a hyperdynamic ventricle, suggestive of volume loading secondary to mitral or aortic regurgitation, both of which are relative contraindications to the procedure.

Non-invasive methods

The echocardiographic findings of greatest predictive value have been debated at length. The standard,[18] the Wilkins-Weyman score, incorporates a scoring system for mitral valve leaflet thickening, mobility and calcification, and severity of subvalvular disease (Table 55.1), with a score of <8 described as an "ideal" patient population, and echo scores over 12 potentially predicting poorer results. The correlation between this echo score and initial as well as long-term results is only fair, perhaps because it is a semiquantitative system based on partly subjective assessments and because other factors not included in the system have predictive value. Thus studies have alternately confirmed[19–21] or refuted the predictive value of the Wilkins-Weyman score.[22–25] One element of the score, leaflet mobility, correlates more strongly with outcome (r value $= 0{\cdot}67$) than the complete score,[26] while another element, severe calcification of the valve,[27] alone predicts a fourfold increase in cardiac complications and a 26% increase in 6 year mortality. In addition important anatomic features that predict outcome, such as eccentricity of commissural fusion and a funnel shaped subvalvular apparatus[28] (both negative predictors) are not included. Neither are presence of moderate or severe mitral regurgitation or left atrial thrombus, both relative contraindications. In univariate analysis, the scoring system does predict long-term results,[20] but so do age, presence of atrial fibrillation,[27] and severity of stenosis before and after the procedure.[29] Further, multivariate analyses that included the echo score *but not its individual components*, failed to demonstrate a single preprocedure predictor of event free survival.[30] Multivariate analysis that *includes* commissural calcification did reveal this to be a strong predictor of death, restenosis, and mitral valve replacement.[31] Perhaps the most compelling reason for routinely deriving the echo score is to allow for comparison with known data; most mitral valvuloplasty trials incorporate this or similar scoring systems. However, no absolute predictors of short- and long-term outcome have been developed.

Routine, preprocedure, transesophageal echocardiography has been recommended because of its superiority for detection of left atrial thrombus,[32] as well as other structural

Table 55.1 Grading of mitral valve characteristics from the echocardiographic examination

Grade	Mobility	Subvalvar thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	Midleaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the midportion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Note. The total echocardiographic score was derived from an analysis of mitral leaflet mobility, valvar and subvalvar thickening, and calcification which were graded from 0 to 4 according to the above criteria. The total possible score ranges from 0 to 16.

Reprinted with permission from Wilkins GT, Weyman AE, Abascal VM *et al.* Percutaneous balloon dilation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilation. *Br Heart J* **60**:299–309. © 1988 by the BMJ Publishing Group.[18]

abnormalities including vegetations or ruptured chordae. The case is most compelling in patients predisposed to clot formation such as those with spontaneous echo contrast ("smoke") on surface echocardiography and those with atrial fibrillation. The former was an independent predictor of left atrial thrombus in a prospective study of 100 patients.[33]

Cardiac catheterization

Cardiac catheterization prior to balloon commissurotomy is rarely necessary in young patients, but can be beneficial to exclude coronary artery disease in older subjects. The gradient alone is a poor proxy for assessment of severity of disease pre-valvuloplasty since it can lead to overestimation of disease with poor heart rate control or underestimation in patients who have not had fluids for many hours prior to catheterization.

Contraindications

While the usually cited contraindications are left atrial thrombus, greater than mild mitral regurgitation and severe calcification or subvalvular disease, these were largely empirically derived and can be challenged.

Thrombus

Hung[34] and others have described at least three series exceeding 90 patients total with apparent organized left atrial appendage clot who underwent uncomplicated balloon commissurotomy. However, valvuloplasty is not attempted when there is left atrial thrombus along the septum, free in the cavity, or on the surface of the valve. Using the conservative approach preferred by most interventionalists, Kang reports successful resolution of left atrial thrombi with warfarin therapy followed by balloon commissurotomy.[35]

Mitral regurgitation

The general presumption that valvuloplasty in patients with moderate or greater mitral regurgitation carried a high risk has not been prospectively tested; however, there have been two retrospective evaluations. A comparison of 25 patients with moderate mitral regurgitation and 25 age and gender matched patients with mild or no regurgitation did indeed demonstrate an increase in severe insufficiency post procedure; however, these patients had much higher echo scores and twice as frequently had severe calcification.[36] Further, while 20% of those with initially moderate mitral regurgitation developed severe regurgitation, hemodynamic improvement overall was similar, as was the incidence of post procedure mitral valve replacement. Similarly, patients with mild mitral regurgitation also had less favorable anatomy at baseline and had lower event free survival but a similar success rate.[37] Thus, the evidence suggests that balloon commissurotomy can still be considered for these patients if they are poor risks for heart surgery. Nevertheless, a theoretical disadvantage is additional volume loading of the left ventricle when antegrade flow is improved after balloon commissurotomy, a concern in the presence of aortic regurgitation as well.

Severe calcification

Patients with symmetrical severe calcification may not respond at all to balloon commissurotomy;[22,38] those with asymmetric calcification are prone to leaflet tearing or rupture.[28] While high echo score alone does not predict the occurrence of severe mitral regurgitation,[39] one component, severe calcification, does.[40] Nevertheless, when the risk of surgery is prohibitive, growing experience with predominantly elderly patients with high echo scores and poor overall morphology has shown moderate improvement in hemodynamics and palliation of symptoms at the cost of high morbidity and mortality.[41]

Procedure

Antegrade *v* retrograde approaches

The predominant approach to percutaneous balloon mitral valvuloplasty is the antegrade transseptal approach. The techniques include single cylindrical balloon, Inoue, double and trefoil balloons, as well as monorail and metal valvulotomes. Inoue and the double cylindrical balloon methods account for virtually all mitral valvuloplasties performed. The procedure has also been performed retrograde.[42–44] The advantages include avoidance of transseptal puncture; however large devices are introduced into the femoral artery and balloons are passed across the submitral apparatus without balloon flotation (increasing the risk of catheter entrapment). There are no direct comparison studies between antegrade and retrograde techniques.

Inoue technique

The Inoue balloon's principal features are: a modifiable distal tip with reduced profile for transseptal passage, a nylon mesh covering that allows the balloon to straddle the mitral valve, and a compliance curve that allows the balloon to dilate over at least a 4 mm range of sizes (Figure 55.1). A stepwise approach involves evaluating the patient, typically by echocardiography, between each balloon inflation to assess for improvement and detect presence of increasing mitral regurgitation. If improvement is suboptimal and regurgitation has not occurred/increased, the size is typically increased by 1 mm increments. In reviewing 19 series reporting results of Inoue

valvuloplasty, we noted a reported early success rate of 93% in a total of 7091 patients.[45,46] Success was variably defined and in some reports overlapped with severe mitral regurgitation, atrial septal defect or embolic events, but included a doubling of the valve area in most studies.

Cylindrical balloon techniques

The cylindrical balloon technique, introduced in 1985,[47] did not uniformly result in adequate gradient reduction and gave way to a double balloon method.[48] A stepwise dilation technique is also used with progressively larger balloons placed side by side until adequate gradient reduction is obtained or an increase in mitral regurgitation is noted. The results of 12 studies incorporating 1864 patients reported a 90% overall success rate.

Long-term follow up

In an extraordinary series of 4832 patients across 120 centers in China, Chen and colleagues have claimed that 98·8% of patients were in NYHA functional class I or II at a mean 32 months follow up, 99·3% success rate, and virtually no complications.[49] Restenosis was reported as 5·2% over a mean 32 months follow up. While there were likely problems with data gathering, the evidence from multiple studies of high success and low complication rates in patients with favorable anatomy is consistent.[20,50] Less favorable long-term results were reported by Cohen *et al*[51] for 145 patients followed for a mean of 3 years. Their 5 year event free survival was only 51% (freedom from mitral valve replacement, redilation, or death); however, a high percentage of their patients had unfavorable anatomic features. In general, these descriptive series have suffered from incomplete follow up, non-overlapping end points, and lack of serial hemodynamic measurements for assessing hemodynamics and restenosis.

Single *v* double cylindrical balloons

The disadvantages of single balloons are related to the conundrum of a round balloon in an elliptical orifice – resulting in lower gradient reduction. Although no randomized comparisons were made, and much of the data are from sequential individual operator series, or sequential inflations with single followed by double balloons, the latter appears to be superior in retrospective comparisons (Figure 55.2)[52–54] as well as in an *in vitro* study.[55] The increased lateral force exerted by two balloons is one presumed mechanism for the superior splitting of the laterally directed commissures. However, a comparison of effective balloon dilating area to body surface area showed that a large single balloon could have similar hemodynamic benefits as two smaller balloons. Thus, geometry is not the sole determinant.

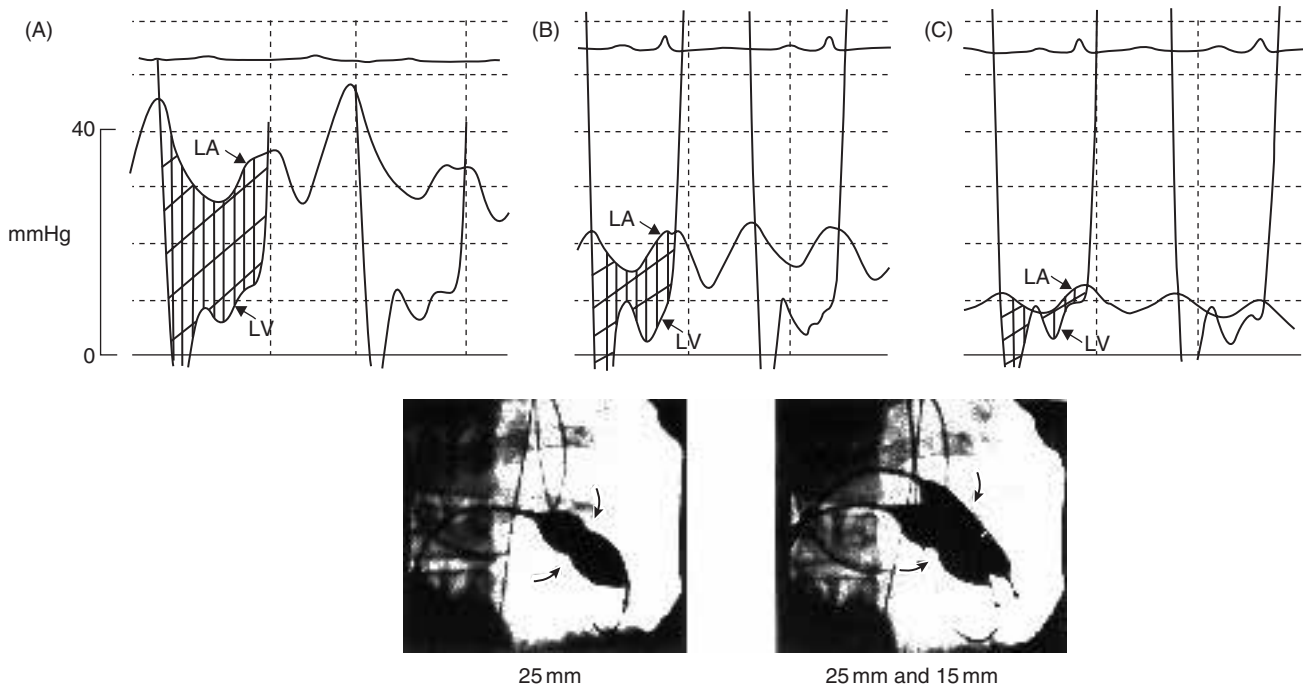


Figure 55.2 Single *v* double balloon mitral valvotomy. Note the initial modest reduction of gradient from baseline (A) after single balloon commissurotomy (B), with near complete resolution of gradient after double balloon inflation (C). (Reprinted with permission of the American Heart Association, Inc.[115])

Inoue *v* double balloon (Table 55.2)

The Inoue technique's principal advantages are simplicity and short procedure times. The Inoue balloon differs from cylindrical single balloons because of the unique balloon design. The slenderizing feature that facilitates septal passage and the dumb-bell shape of the inflated balloon have been reported by some to result in a lower incidence of atrial septal defect ($\leqslant 2{\cdot}5\%$ *v* up to 10% for the double balloon technique)[56] and a much lower likelihood of catastrophic apical perforation.

In a prospective randomized comparison between Inoue and double balloon valvotomy, no significant differences were noted in immediate results, including complications.[57] A trend toward fewer atrial septal defects with the Inoue balloon was not significant. Because of a lack of other prospective randomized comparisons by physicians equally experienced at both techniques, questions remain unanswered. It is likely that an easier procedure with lower complication rates (the Inoue technique) is a trade off for slightly greater mitral regurgitation,[25,58] possibly because the distal portion of the balloon is oversized and may traumatize the subvalvular apparatus. There are also suggestive data that the double balloon technique, by virtue of the lateralization of forces, is advantageous in less favorable anatomy. One example is the result of dilation of asymmetrically fused commissures – where the Inoue technique has been used this led to significant risk of severe mitral regurgitation,[59] whereas with double balloon technique use this appeared to be less of a problem.[60] The disadvantages of the two balloon technique include longer procedure times, and higher risk of left ventricular apical perforation[61–64] although the higher complication rates reported[61,65] may also reflect operator experience with this more complex procedure. **Grade B**

Other techniques

Percutaneous metal mitral commissurotomy is a promising new technique being adopted primarily in a number of developing countries; a series of 153 patients was described by its inventor, Alain Cribier.[66] The device, essentially a Tubbs dilator mounted on a cable, is introduced via the right femoral venous approach and can be opened to a maximum of 40 mm. Initial results are encouraging; in particular, what appear to be relatively high postprocedure valve areas ($2{\cdot}2 \pm 0{\cdot}4\,cm^2$) and low rates of mitral regurgitation (severe mitral regurgitation in 1%). Randomized trials comparing this technique to balloon dilatation have not yet been published although several smaller studies have been completed. The metallic head of the device, the most expensive component, is theoretically resterilizable by autoclaving: a potential advantage in parts of the world where mitral stenosis is endemic and the cost of disposables prohibitive. **Grade B**

Additional data on the retrograde non-transseptal technique previously described by Stefanadis and colleagues have been reported[67] for the first time from multiple investigational sites. Long-term (up to 9 years) results are relatively comparable to antegrade techniques. However, significant rates of severe mitral regurgitation (3·4%) and of femoral artery injury (1·1%), as well as a relatively modest success rate (88%) in the setting of favorable echocardiography scores ($7{\cdot}7 \pm 2{\cdot}0$), suggest that this procedure might best be reserved for patients where transseptal puncture has

Table 55.2 Comparative results of valvuloplasty techniques

	Inoue		Double balloon		Single balloon	
	MVA (mean ± SD)	*n*	MVA (mean ± SD)	*n*	MVA (mean ± SD)	*n*
Abdullah[117]	1·9 ± 0·4	60	2·1 ± 0·5	60		
Arora[57]	2·1 ± 0·4	310	2·2 ± 0·4	290		
Bassand[64]	2·0 ± 0·5	71	2·0 ± 0·5	161		
Kasper[118]	1·7 ± 0·7	23	2·2 ± 0·8	22		
Ortiz[119]	1·8 ± 0·4	100	2·0 ± 0·5	36		
Park[56a]	1·9 ± 0·5	59	2·0 ± 0·5	61		
Rothlisberger[120]	1·6 ± 0·6	145	1·8 ± 0·7	90		
Ruiz[121]	1·9 ± 0·3	85	2·0 ± 0·6	322		
Sharma[25]	2·2 ± 0·4	120	2·1 ± 0·5	230		
Trevino[60]	2·0 ± 0·4	157	2·1 ± 0·5	56		
Zhang[61]	1·8 ± 0·3	43	1·8 ± 0·4	43		
NHLBI[122]			2·0 ± 0·8	591	1·7 ± 0·7	114

[a]Study by Park *et al* was randomized.
Abbreviation: MVA, mitral valve area in cm^2

unique contraindications. Because of the learning curve associated with this procedure, and the fact that most patients are amenable to the antegrade approach, the long-term role of this technique is uncertain. Similarly, a series of antegrade Inoue balloon valvuloplasties via a jugular venous route had a significant associated complication rate, but represents another alternative approach.[68] Finally, Bonhoeffer and colleagues have described a monorail double balloon technique that has potential cost advantages and simplifies the standard double balloon technique; no formal comparison to other techniques has been performed.[69]

Intraprocedural transesophageal echocardiography

Use of transesophageal echocardiography during balloon mitral valvuloplasty has been recommended for early detection of major complications (severe mitral regurgitation, tamponade, and large atrial septal defect).[70] In addition, transesophageal echo can confirm needle location during transseptal puncture.[71] Finally, decreased procedure time, mitral regurgitation, and residual atrial septal defects have been described in a randomized study of fluoroscopy plus transesophageal echo versus fluoroscopy without echo during balloon commissurotomy.[72] The evidence provided by these three studies is not compelling. The latter included a 60% rate of major complications in the non-echo group, suggesting limited experience. Surface two-dimensional echocardiography is sensitive enough to detect increasing mitral regurgitation in most patients, and is an excellent tool for early appreciation of tamponade. Atrial septal defects are becoming substantially less common and are largely limited to 5 mm or smaller and resolve post procedure. Finally, transseptal puncture in experienced hands has limited risk; arguably the procedure should not be performed by those who need transesophageal echo guidance. Intracardiac echo using a transducer placed via the femoral vein may be an alternative but has not yet been tested systematically in this setting.

Complications

The learning curve is steep, which has had a major effect both on success and complication rates,[73] as well as skewing data in the literature.[56] The National Heart Lung Blood Institute (NHLBI) registry reported substantially lower rates of all major complications except acute mitral regurgitation at centers performing more than 25 cases and in the second year that sites enrolled patients; a willingness to attempt balloon commissurotomy in higher-risk subsets in the second year may explain the mitral regurgitation. A recent report compares the first 100 cases of Inoue balloon dilatation versus a subsequent 133 cases, all by the same high volume operator with extensive prior double balloon experience. The postprocedure valve area, overall success rate and complication rates were significantly improved beyond 100 cases.[74] It is likely that the best interests of patients undergoing the procedure would be served by having relatively few centers perform higher volumes.

Overall mortality has been approximately 1%, most commonly related to tamponade not only from transseptal catheterization[75] but also from fenestration of the left ventricular apex, in particular by the cylindrical balloon technique. The incidence of tamponade has ranged from 2% to 4%, severe mitral regurgitation from 1% to 6%, and cerebral vascular accident and/or thromboembolism in up to 4%. Disturbingly, magnetic resonance imaging detected new hyperintensitivity foci suggestive of cerebral infarcts in 11 of 27 patients.[76] All had been evaluated before their procedure by transesophageal echocardiography without detection of clot. Thus, embolization may be common even if not clinically apparent. The probable sources are intracavitary clot, catheter induced thrombus formation and showers of calcium.

Atrial septal defects were a significant source of early complications,[76] arising from transseptal tearing secondary to inadvertent proximal deployment of cylindrical balloons, withdrawal of winged balloons retrograde, or trauma to the septum from 5 or 8 mm balloons used to dilate the septum. Theoretically these problems should be avoidable by use of a dilator and a shorter balloon system, both features of the Inoue technique, and indeed this has been the finding.[77] It should be noted that decompression of the left atrium by a significant sized post procedure atrial septal defect may have influenced the results of some balloon valvuloplasty series and may lead operators to overestimate the mitral valve area post procedure.[78]

Predictors of outcome

Predictors of outcome were addressed in a number of non-randomized prospective and retrospective analyses. Factors predicting poorer functional class, hemodynamics, overall and event free survival were found to include age, presence of atrial fibrillation, valvular calcification, and postprocedure results, with event free survival at 6–7 years ranging from 15% (unfavorable baseline anatomy) to 83%.[79–81] Although these studies were not randomized, they incorporate a broader spectrum of patients with mitral stenosis than the randomized trials, and may represent a more "real world" assessment of results to be expected in the overall population.

Additional attention was focused on predictors of adverse outcome, in particular mitral regurgitation. Age and severity of mitral stenosis,[82] and degree of anterior leaflet retraction[83] correlated with postprocedure insufficiency. The nature of pre- and postprocedure mitral regurgitation was carefully studied in 50 patients.[84] As previously noted,

severe mitral regurgitation is typically due to leaflet tearing, while most new mitral regurgitation is typically pericommissural in origin. In addition to anatomic predictors, the steep compliance curve of the Inoue balloon was reported as a likely culprit for severe mitral regurgitation.[85] Use of balloon sizes in the upper portion of the pressure-volume curve was associated with increased mitral regurgitation; whether this finding, based on retrospective observation, is truly causal is unproven, but has been the subject of numerous anecdotal reports and several abstracts. Previous observations that patients with prior surgical commissurotomy have satisfactory but inferior results were again confirmed.[86,87]

Perhaps the most comprehensive analysis of outcome was a recently published follow up of up to 15 years in 879 patients. Severe postprocedure mitral regurgitation, echo score >8, age, prior surgical commissurotomy, NYHA functional class IV, moderate preprocedure mitral regurgitation, and elevated pulmonary artery pressures postprocedure were identified as independent predictors of adverse events at long-term follow up.[88]

Valvuloplasty for mild mitral stenosis

Several studies have looked retrospectively at the results of balloon valvuloplasty for patients with valve areas of 1·3–1·5 cm^2.[89,90] While historical comparisons suggest greater valve area increase than in patients with severe mitral stenosis, there is no evidence that the risk of occasional mortality, need for mitral valve replacement or other major morbidity warrants this approach. The possibility that early commissurotomy may adversely affect the course of the disease, including progression to pulmonary hypertension, atrial fibrillation and stroke remains a hypothesis in need of prospective investigation.[91] **Grade C**

Pregnancy

There have been multiple reports of successful balloon commissurotomy during pregnancy.[92–94] The procedure has been performed with echo guidance and without fluoroscopy[95] to avoid radiation exposure to the fetus. **Grade B**

Dilation for restenosis

Reoperation for mitral valve stenosis has long been associated with increased morbidity and mortality.[96] Several large balloon commissurotomy series have reported inferior overall results compared to *de novo* dilatation. Davidson reported less symptomatic improvement[97] while Jang described a 20% lower success rate (only 51% having valve area >1·5 cm^2) and nearly 20% requiring mitral valve replacement by 4 years.[98] Cohen described twice the frequency[99] and Medina described a 10-fold increase in restenosis rates at 5 years for patients with prior commissurotomy[100] (both to approximately 20%). Most significant is the finding by Jang and colleagues that stratification by echo score resulted in nearly superimposable results for *de novo* and repeat commissurotomy procedures, suggesting that results are defined by valve morphology rather than history of prior commissurotomy.[98] **Grade B**

Bioprosthesis

Several case reports have described successful balloon dilatation of bioprosthetic mitral valves, although both the hemodynamic and longer term benefits were obscure in all but one.[101–103] However, bioprosthetic valves are typically similar histologically to those seen in calcific aortic stenosis: severe leaflet thickening, immobility and calcification, without commissural fusion.[104,105] **Grade B** Thus, a formal intraoperative study, examining the morphology of severely stenosed bioprosthetic valves before and after balloon dilation, revealed "completely ineffectual" dilation[106] with substantial leaflet tearing and cuspal perforation. Although the need for a percutaneous approach to the problem is great, the data do not support bioprosthetic mitral valve dilation.

Balloon *v* surgical commissurotomy

Randomized trials comparing balloon and surgical commissurotomy were begun early in the development phase of the percutaneous technique. Because both use blind dilation of the valve with blunt instruments, and because closed commissurotomy was the predominant procedure in countries where mitral stenosis was prevalent, the early randomized trials compared balloon and closed commissurotomy. In these studies, surgeons were typically more experienced than the operators performing balloon valvuloplasty. In 1988 we randomized 40 patients with relatively ideal anatomy and severe mitral stenosis;[107] these patients have been followed with serial catheterization and echocardiography over a 7 year period; there were similar hemodynamic improvements in both groups, sustained through 7 years (Figure 55.3), with one late death in each group and need for repeat commissurotomy in 20%.[108] The actual restenosis rate (26% in the balloon group and 35% in the surgical group) as defined by a 50% loss of the gain and a valve area <1·5 cm^2 is significantly higher than the repeat commissurotomy rate because restenosis and functional class do not correlate strongly. Thus it is likely that restenosis rates in trials that have not done formal follow up hemodynamics underestimated the true severity of disease during follow up. Two other studies have compared balloon and closed commissurotomy with shorter, non-invasive follow

up only; these have demonstrated balloon results superior to[73] or similar to closed commissurotomy.[109] However closed commissurotomy in the former study resulted in only a 1·3 cm^2 mean valve area, suggesting relatively unaggressive dilation. Finally, a randomized comparison by Ben Farhat and colleagues described superior acute results ($2·2 \pm 0·4\ cm^2$ *v* $1·6 \pm 0·4\ cm^2$) for balloon valvuloplasty and 4 year restenosis rate of 7% *v* 37%.[110] Thus balloon commissurotomy is at least equal and probably superior to closed surgical commissurotomy. **Grade A**

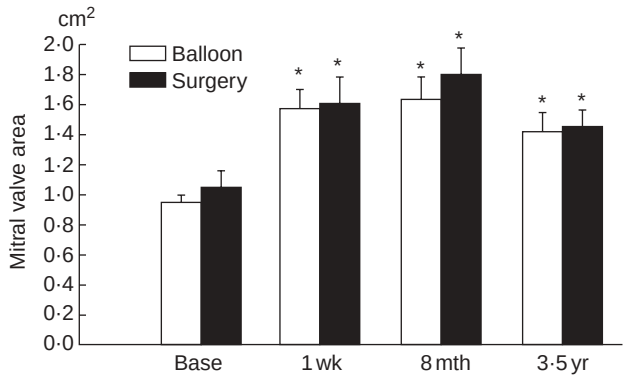


Figure 55.3 Mitral valves areas at baseline and each follow up interval over $3\frac{1}{3}$ years in patients randomized to percutaneous balloon or surgical closed mitral commissurotomy.[108] Asterisk denotes $P < 0·001$ compared with baseline.

Open commissurotomy *v* balloon

The hypothesis that open commissurotomy would be superior to balloon valvuloplasty was based on the potential benefits of direct vision, including surgical splitting and remodeling of the subvalvular apparatus, neither of which are features of closed or balloon commissurotomy. A prospective series of 100 open commissurotomy patients gathered data specifically for historical comparison to the then reported results of balloon valvuloplasty and concluded that open commissurotomy was distinctly superior.[111] The results of surgery, mean valve area 2·9 cm^2, exceeds expectations and may be related to technique of measurement[112] or patient selection, while mitral regurgitation was absent in all but eight cases (where it was reported to be mild), results also testimony to great operator skill but in excess of prior reports.[8] **Grade A** On the contrary, the more compelling evidence from prospective randomized studies is for similar or superior results with balloon commissurotomy. In 1989 we randomized 60 patients to a prospective comparison of balloon versus open commissurotomy.[113] Patients had near identical baseline hemodynamics but those undergoing balloon commissurotomy had superior mitral valve areas at 3 years (Figure 55.4). A possible explanation for superior results in balloon commissurotomy patients is the direct and

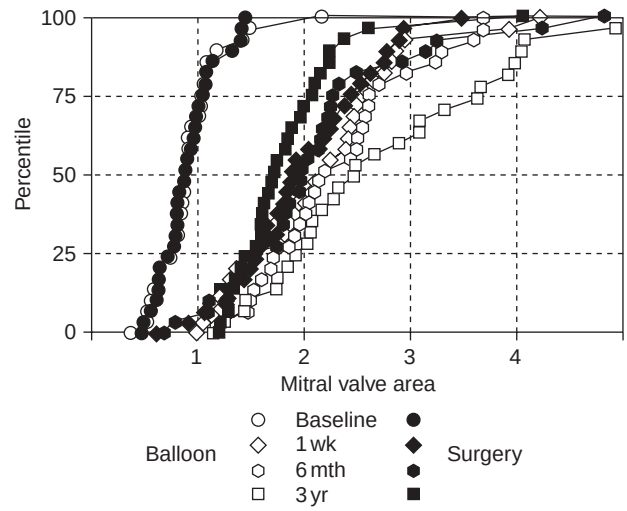


Figure 55.4 Mitral valve areas at baseline and at each follow up interval in patients randomized to balloon or open surgical commissurotomy. The values represent the percentile of patients whose valve areas are ≤ the valve areas on the abscissa. The baseline values overlap, but a shift to the right (representing higher valve areas) is seen for the balloon group at each time point. (Reprinted by permission of the *New England Journal of Medicine*. Copyright © 1994, Massachusetts Medical Society.[113])

continuous feedback to the operator of hemodynamics during catheterization laboratory procedures, which even with the advent of transesophageal monitoring in the operating room is not available to the same degree to the surgeon.

In the trial referred to earlier, Ben Farhat and colleagues report a three-way randomized comparison of balloon, closed and open surgical commissurotomy in 90 patients.[110] Most of the objective information is through 6 month follow up, although clinical status/events and valve areas are described through 7 years. Their results, which include an absence of mortality, NYHA class I function in 90% of the balloon and open mitral commissurotomy (OMC) patients, and residual valve area of 1·8 cm^2 in these two groups at 7 years with only 7% restenosis, are exceptionally optimistic. The results of closed commissurotomy were distinctly inferior. Because functional class correlates poorly with hemodynamics in mitral stenosis and because planimetry, the technique used here for mitral valve area assessment beyond 6 months, is subjective when the commissures are open (and was not performed by blinded investigators), the findings of this study need to be confirmed. Less optimistic data, utilizing hemodynamics and blinded interpretation, suggest that restenosis rates may be 25% by 7 years even in patients with relatively ideal valve anatomy preprocedure.[114] Nevertheless, this paper confirms that balloon valvuloplasty is at least as effective as open commissurotomy for patients with severe mitral stenosis and ideal valve anatomy.

The study's optimistic findings may perhaps in part be due to a distinguishing feature of all of the randomized comparisons of balloon versus surgical commissurotomy: single site studies that depend to a significant degree on individual physician practices and small patient populations. **Grade A**

Cost

Although formal cost comparison studies have not been reported, charges and costs at hospitals in India and in the United States have been estimated. Lau and Ruiz described cost to a United States hospital of $3000 for balloon valvuloplasty and $6000 for closed commissurotomy (assuming a hospital could be found that still performs this procedure). We published 1991 charges for balloon and closed commissurotomy in the United States and India (Figure 55.5) and demonstrated a sixfold greater expense for balloon valvuloplasty in India. However, our calculations did not include the extensive reuse of disposables in developing countries, where balloons can account for a much higher portion of the charges than physicians' fees or operating room billings. Percutaneous metallic commissurotomy, as referred to earlier, may also have a significant impact on cost considerations.

The results of the randomized trials offer compelling evidence that balloon valvuloplasty is an effective alternative to surgery for patients with good valve anatomy. Even with a number of anatomic features predicting less favorable outcome, balloon commissurotomy, at the cost of higher risk in patients with unfavorable anatomy, still has the potential for palliation. The safety and efficacy of Inoue and double balloon valvuloplasty are not compellingly different in experienced hands and the selection of techniques should be based on operator preference, experience, and equipment availability. Low cost, avoidance of thoracotomy scar and discomfort, shorter hospitalization and excellent follow up results to date mandate consideration of balloon valvuloplasty in most patients with rheumatic mitral valve stenosis without significant contraindications. Since balloon as well as surgical commissurotomy are largely palliative procedures, percutaneous balloon valvuloplasty has the added benefit of delaying the time until eventual thoracotomy. **Grade A**

In summary, percutaneous balloon mitral valvuloplasty is a superior alternative to surgical commissurotomy for a significant subset of patients with rheumatic mitral stenosis. Careful case selection and performance of the procedure by experienced teams will have a significant impact on outcome. Both clinical and financial considerations suggest that balloon valvuloplasty is the procedure of choice for rheumatic mitral stenosis in patients with suitable anatomy. **Grade A**

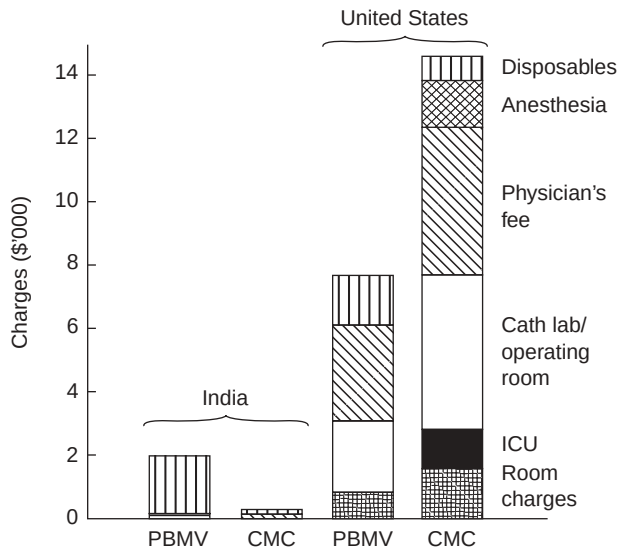


Figure 55.5 Charges for percutaneous balloon mitral valvuloplasty (PBMV) and closed surgical commissurotomy (CMC) at the Nizam's Institute of Medical Sciences in Hyderabad, India and at Harper Hospital in Detroit, MI in 1991. With the extensive reuse of disposables in developing countries, the cost of balloon valvuloplasty more closely approximates that for closed commissurotomy. (© 1993, F.A. Davis Co. Reprinted with permission.[116])

Key points

- Ideal patients have severe mitral stenosis without:
  - >mild mitral regurgitation, severe subvalvular disease, or severe calcification
  - eccentric commissural fusion, clot in left atrium, volume loaded left ventricle
- Procedure may be of benefit in:
  - <critical mitral stenosis, but evidence for favorable long-term risk–benefit ratio is lacking
  - patients with unfavorable anatomy, including moderate mitral regurgitation, but with less favorable results and higher morbidity/mortality
  - patients with mitral restenosis, dependent on anatomic features
  - pregnant patients
- Balloon valvuloplasty is superior to closed commissurotomy and is equivalent or superior to open commissurotomy in ideal patients

References

1. Cutler EC, Levine SA. Cardiotomy and valvulotomy for mitral stenosis. Experimental observations and clinical notes concerning an operated case with recovery. *Boston Med Surg J* 1923;**188**:1023–7.
2. Suttar HS. The surgical treatment of mitral stenosis. *BMJ* 1925;**2**:603–6.
3. Lewis T. *Diseases of the heart. 3rd edn.* London: Macmillan, 1943.
4. John S, Bashi VV, Jairaj PS *et al.* Closed mitral valvotomy: early results and long-term follow-up of 3724 consecutive patients. *Circulation* 1983;**68**:891–6.

5. Toumbouras M, Panagopoulos F, Papakonstantinou C *et al.* Long-term surgical outcome of closed mitral commissurotomy. *J Heart Valve Dis* 1995;**4**:247–50.
6. Rihal CS, Schaff HV, Frye RL, Bailey KR, Hammes LN, Holmes DR Jr. Long-term follow-up of patients undergoing closed transventricular mitral commissurotomy: a useful surrogate for percutaneous balloon mitral valvuloplasty? *J Am Coll Cardiol* 1992;**20**:781–6.
7. Scalia D, Rizzoli G, Campanile F *et al.* Long-term results of mitral commissurotomy. *J Thorac Cardiovasc Surg* 1993; **105**:633–42.
8. Villanova C, Melacini P, Scognamiglio R *et al.* Long-term echocardiographic evaluation of closed and open mitral valvulotomy. *Int J Cardiol* 1993;**38**:315–21.
9. Hickey MS, Blackstone EH, Kirklin JW, Dean LS. Outcome probabilities and life history after surgical mitral commissurotomy: implications for balloon commissurotomy. *J Am Coll Cardiol* 1991;**17**:29–42.
10. Inoue K, Kitamura F, Chikusa H, Miyamoto N. Atrial septostomy by a new balloon catheter. *Jpn Circ J* 1981;**45**:730–8.
11. Inoue K, Nakamura T, Kitamura F. Nonoperative mitral commissurotomy by a new balloon catheter. [Abstract] *Jpn Circ J* 1982;**46**:877.
12. Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984; **87**:394–402.
13. Block PC, Palacios IF, Jacobs ML, Fallon JT. Mechanism of percutaneous mitral valvotomy. *Am J Cardiol* 1987;**59**: 178–9.
14. Matsuura Y, Fukunaga S, Ishihara H *et al.* Mechanics of percutaneous balloon valvotomy for mitral valvular stenosis. *Heart Vessels* 1988;**4**:179–83.
15. Nabel E, Bergin PJ, Kirsh MM. Morphological analysis of balloon mitral valvuloplasty; intra-operative results. [Abstract] *J Am Coll Cardiol* 1990;**15**:97A.
16. Kaplan JD, Isner JM, Karas RH *et al. In vitro* analysis of mechanisms of balloon valvuloplasty of stenotic mitral valves. *Am J Cardiol* 1987;**59**:318–23.
17. McKay RG, Lock JE, Safian RD *et al.* Balloon dilation of mitral stenosis in adult patients: postmortem and percutaneous mitral valvuloplasty studies. *J Am Coll Cardiol* 1987;**9**: 723–31.
18. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;**60**:299–308.
19. Desideri A, Vanderperren O, Serra A *et al.* Long-term (9 to 33 months) echocardiographic follow-up after successful percutaneous mitral commissurotomy. *Am J Cardiol* 1992;**69**:1602–6.
20. Palacios IF, Tuzcu ME, Weyman AE, Newell JB, Block PC. Clinical follow-up of patients undergoing percutaneous mitral balloon valvotomy. *Circulation* 1995;**91**:671–6.
21. Abascal VM, Wilkins GT, O'Shea JP *et al.* Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation* 1990;**82**:448–56.
22. Fatkin D, Roy P, Morgan JJ, Feneley MP. Percutaneous balloon mitral valvotomy with the Inoue single-balloon catheter: commissural morphology as a determinant of outcome. *J Am Coll Cardiol* 1993;**21**:390–7.
23. Levin TN, Feldman T, Bednarz J, Carroll JD, Lang RM. Transesophageal echocardiographic evaluation of mitral valve morphology to predict outcome after balloon mitral valvotomy. *Am J Cardiol* 1994;**73**:707–10.
24. Herrmann HC, Ramaswamy K, Isner JM *et al.* Factors influencing immediate results, complications, and short-term follow-up status after Inoue balloon mitral valvotomy: a North American multicenter study. *Am Heart J* 1992;**124**:160–6.
25. Sharma S, Loya YS, Desai DM, Pinto RJ. Percutaneous mitral valvotomy using Inoue and double balloon technique: comparison of clinical and hemodynamic short term results in 350 cases. *Cathet Cardiovasc Diagn* 1993;**29**:18–23.
26. Reid CL, Chandraratna PA, Kawanishi DT, Kotlewski A, Rahimtoola SH. Influence of mitral valve morphology on double-balloon catheter balloon valvuloplasty in patients with mitral stenosis. Analysis of factors predicting immediate and 3-month results. *Circulation* 1989;**80**:515–24.
27. Zhang HP, Allen JW, Lau FY, Ruiz CE. Immediate and late outcome of percutaneous balloon mitral valvotomy in patients with significantly calcified valves. *Am Heart J* 1995;**129**: 501–6.
28. Miche E, Fassbender D, Minami K *et al.* Pathomorphological characteristics of resected mitral valves after unsuccessful valvuloplasty. *J Cardiovasc Surg* 1996;**37**:475–81.
29. Ruiz CE, Zhang HP, Gamra H, Allen JW, Lau FY. Late clinical and echocardiographic follow up after percutaneous balloon dilatation of the mitral valve. *Br Heart J* 1994;**71**:454–8.
30. Orrange SE, Kawanishi DT, Lopez BM, Curry SM, Rahimtoola SH. Actuarial outcome after catheter balloon commissurotomy in patients with mitral stenosis. *Circulation* 1997;**95**:382–9.
31. Cannan CR, Nishimura RA, Reeder GS *et al.* Echocardiographic assessment of commissural calcium: a simple predictor of outcome after percutaneous mitral balloon valvotomy. *J Am Coll Cardiol* 1997;**29**:175–80.
32. Kronzon I, Tunick PA, Glassman E, Slater J, Schwinger M, Freedberg RS. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. *J Am Coll Cardiol* 1990;**16**:1320–2.
33. Rittoo D, Sutherland GR, Currie P, Starkey IR, Shaw TR. A prospective study of left atrial spontaneous echo contrast and thrombus in 100 consecutive patients referred for balloon dilation of the mitral valve. *J Am Soc Echocardiogr* 1994;**7**:516–27.
34. Hung JS. Cheng TO, eds. *Percutaneous balloon valvuloplasty.* Mitral stenosis with left atrial thrombi: Inoue balloon catheter technique. New York: Igaku-Shoin, 1992.
35. Kang DH, Song JK, Chae K *et al.* Comparison of outcomes of percutaneous mitral valvuloplasty versus mitral valve replacement after resolution of left atrial appendage thrombi. *Am J Cardiol* 1998;**81**:97–100.
36. Zhang HP, Gamra H, Allen JW, Lau FY, Ruiz CE. Balloon valvotomy for mitral stenosis associated with moderate mitral regurgitation. *Am J Cardiol* 1995;**75**:960–3.
37. Alfonso F, Macaya C *et al.* Early and late results of percutaneous mitral valvuloplasty for mitral stenosis associated with mild mitral regurgitation. *Am J Cardiol* 1993;**71**:1304–10.
38. Tuzcu EM, Block PC, Griffin B, Dinsmore R, Newell JB, Palacios IF. Percutaneous mitral balloon valvotomy in patients with calcific mitral stenosis: immediate and long-term outcome. *J Am Coll Cardiol* 1994;**23**:1604–9.

39. Feldman T, Carroll JD, Isner JM *et al.* Effect of valve deformity on results and mitral regurgitation after Inoue balloon commissurotomy. *Circulation* 1992;**85**:180–7.
40. Herrmann HC, Lima JA, Feldman T *et al.* Mechanisms and outcome of severe mitral regurgitation after Inoue balloon valvuloplasty. North American Inoue Balloon Investigators. *J Am Coll Cardiol* 1993;**22**:783–9.
41. Tuzcu EM, Block PC, Griffin BP, Newell JB, Palacios IF. Immediate and long-term outcome of percutaneous mitral valvotomy in patients 65 years and older. *Circulation* 1992; **85**:963–71.
42. Bahl VK, Juneja R, Thatai D, Kaul U, Sharma S, Wasir HS. Retrograde nontransseptal balloon mitral valvuloplasty for rheumatic mitral stenosis. *Cathet Cardiovasc Diagn* 1994; **33**:331–4.
43. Stefanadis C, Stratos C, Kallikazaros I *et al.* Retrograde nontransseptal balloon mitral valvuloplasty using a modified Inoue balloon catheter. *Cathet Cardiovasc Diagn* 1994;**33**: 224–33.
44. Stefanadis C, Stratos C, Pitsavos C *et al.* Retrograde nontransseptal balloon mitral valvuloplasty. Immediate results and long-term follow-up. *Circulation* 1992;**85**:1760–7.
45. Lau KW, Hung JS, Ding ZP, Johan A. Controversies in balloon mitral valvuloplasty: the when (timing for intervention), what (choice of valve), and how (selection of technique). *Cathet Cardiovasc Diagn* 1995;**35**:91–100.
46. Glazier JJ, Turi ZG. Percutaneous balloon mitral valvuloplasty. *Prog Cardiovasc Dis* 1997;**40**:5–26.
47. Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;**313**:1515–18.
48. al Zaibag M, Ribeiro PA, Al Kasab S, al Fagih MR. Percutaneous double-balloon mitral valvotomy for rheumatic mitral-valve stenosis. *Lancet* 1986;**1**:757–61.
49. Chen CR, Cheng TO. Percutaneous balloon mitral valvuloplasty by the Inoue technique: a multicenter study of 4832 patients in China. *Am Heart J* 1995;**129**:1197–203.
50. Iung B, Cormier B, Ducimetiere P *et al.* Functional results 5 years after successful percutaneous mitral commissurotomy in a series of 528 patients and analysis of predictive factors. *J Am Coll Cardiol* 1996;**27**:407–14.
51. Cohen DJ, Kuntz RE, Gordon SP *et al.* Predictors of long-term outcome after percutaneous balloon mitral valvuloplasty. *N Engl J Med* 1992;**327**:1329–33.
52. Shrivastava S, Mathur A, Dev V, Saxena A, Venugopal P, SampathKumar A. Comparison of immediate hemodynamic response to closed mitral commissurotomy, single-balloon, and double-balloon mitral valvuloplasty in rheumatic mitral stenosis. *J Thorac Cardiovasc Surg* 1992;**104**:1264–7.
53. Al Kasab S, Ribeiro PA, Sawyer W. Comparison of results of percutaneous balloon mitral valvotomy using consecutive single (25 mm) and double (25 mm and 12 mm) balloon techniques. *Am J Cardiol* 1989;**64**:1385–7.
54. Chen CG, Wang YP, Qing D, Lin YS, Lan YF. Percutaneous mitral balloon dilatation by a new sequential single- and double-balloon technique. *Am Heart J* 1988;**116**:1161–7.
55. Ribeiro PA, al Zaibag M, Rajendran V *et al.* Mechanism of mitral valve area increase by *in vitro* single and double balloon mitral valvotomy. *Am J Cardiol* 1988;**62**:264–9.
56. Complications and mortality of percutaneous balloon mitral commissurotomy. A report from the National Heart, Lung, and Blood Institute Balloon Valvuloplasty Registry. *Circulation* 1992;**85**:2014–24.
57. Park SJ, Kim JJ, Park SW, Song JK, Doo YC, Lee SJ. Immediate and one-year results of percutaneous mitral balloon valvuloplasty using Inoue and double-balloon techniques. *Am J Cardiol* 1993;**71**:938–43.
58. Arora R, Kalra GS, Murty GS *et al.* Percutaneous transatrial mitral commissurotomy: immediate and intermediate results. *J Am Coll Cardiol* 1994;**23**:1327–32.
59. Miche E, Bogunovic N, Fassbender D *et al.* Predictors of unsuccessful outcome after percutaneous mitral valvulotomy including a new echocardiographic scoring system. *J Heart Valve Dis* 1996;**5**:430–5.
60. Rodriguez L, Monterroso VH, Abascal VM *et al.* Does asymmetrical mitral valve disease predict an adverse outcome after percutaneous balloon mitral valvotomy? An echocardiographic study. *Am Heart J* 1992;**123**:1678–82.
61. Trevino AJ, Ibarra M, Garcia A *et al.* Immediate and long-term results of balloon mitral commissurotomy for rheumatic mitral stenosis: comparison between Inoue and double-balloon techniques. *Am Heart J* 1996;**131**:530–6.
62. Zhang HP, Gamra H, Allen JW, Lau FY, Ruiz CE. Comparison of late outcome between Inoue balloon and double-balloon techniques for percutaneous mitral valvotomy in a matched study. *Am Heart J* 1995;**130**:340–4.
63. Fu XY, Zhang DD, Schiele F, Anguenot T, Bernard Y, Bassand JP. Complications of percutaneous mitral valvuloplasty; comparison of the double balloon and the Inoue techniques. *Arch Mal Coeur Vaiss* 1994;**87**:1403–11.
64. Rihal CS, Nishimura RA, Reeder GS, Holmes DR Jr. Percutaneous balloon mitral valvuloplasty: comparison of double and single (Inoue) balloon techniques. *Cathet Cardiovasc Diagn* 1993;**29**:183–90.
65. Bassand JP, Schiele F, Bernard Y *et al.* The double-balloon and Inoue techniques in percutaneous mitral valvuloplasty: comparative results in a series of 232 cases. *J Am Coll Cardiol* 1991;**18**:982–9.
66. Cribier A, Eltchaninoff H, Koning R *et al.* Percutaneous mechanical mitral commissurotomy with a newly designed metallic valvulotome. *Circulation* 1999;**99**:793–9.
67. Stefanadis CI, Stratos CG, Lambrou SG *et al.* Retrograde nontransseptal balloon mitral valvuloplasty: immediate results and intermediate long-term outcome in 441 cases – a multicenter experience. *J Am Coll Cardiol* 1998;**32**:1009–16.
68. Joseph G, Baruah DK, Kuruttukulam SV, Chandy ST, Krishnaswami S. Transjugular approach to transseptal balloon mitral valvuloplasty. *Cathet Cardiovasc Diagn* 1997;**42**: 219–26.
69. Bonhoeffer P, Esteves C, Casal U *et al.* Percutaneous mitral valve dilatation with the Multi-Track System. *Catheter Cardiovasc Interv* 1999;**48**:178–83.
70. Goldstein SA, Campbell A, Mintz GS, Pichard A, Leon M, Lindsay J, Jr. Feasibility of on-line transesophageal echocardiography during balloon mitral valvulotomy: experience with 93 patients. *J Heart Valve Dis* 1994;**3**:136–48.
71. Ballal RS, Mahan EF, Nanda NC, Dean LS. Utility of transesophgeal echocardiography in interatrial septal puncture

during percutaneous mitral balloon commissurotomy. *Am J Cardiol* 1990;**66**:230–2.
72. Ramondo A, Chirillo F, Dan M *et al.* Value and limitations of transesophageal echocardiographic monitoring during percutaneous balloon mitral valvotomy. *Int J Cardiol* 1991; **31**:223–33.
73. Rihal CS, Nishimura RA, Holmes DR, Jr. Percutaneous balloon mitral valvuloplasty: the learning curve. *Am Heart J* 1991;**122**:1750–6.
74. Sanchez PL, Harrell LC, Salas RE, Palacios IF. Learning curve of the Inoue technique of percutaneous mitral balloon valvuloplasty. *Am J Cardiol* 2001;**88**:662–7.
75. Schoonmaker FW, Vijay NK, Jantz RD. Left atrial and ventricular transseptal catheterization review: losing skills. *Cathet Cardiovasc Diagn* 1987;**13**:233–8.
76. Rocha P, Mulot R, Lacombe P, Pilliere R, Belarbi A, Raffestin B. Brain magnetic resonance imaging before and after percutaneous mitral balloon commissurotomy. *Am J Cardiol* 1994; **74**:955–7.
77. Yoshida K, Yoshikawa J, Akasaka T *et al.* Assessment of left-to-right atrial shunting after percutaneous mitral valvuloplasty by transesophageal color Doppler flow-mapping. *Circulation* 1989;**80**:1521–6.
78. Thomas MR, Monaghan MJ, Metcalfe JM, Jewitt DE. Residual atrial septal defects following balloon mitral valvuloplasty using different techniques. A transthoracic and transoesophageal echocardiography study demonstrating an advantage of the Inoue balloon. *Eur Heart J* 1992;**13**: 496–502.
79. Petrossian GA, Tuzcu EM, Ziskind AA, Block PC, Palacios I. Atrial septal occlusion improves the accuracy of mitral valve area determination following percutaneous mitral balloon valvotomy. *Cathet Cardiovasc Diagn* 1991;**22**:21–4.
80. Lau KW, Ding ZP, Quek S, Kwok V, Hung JS. Long-term (36–63 month) clinical and echocardiographic follow-up after Inoue balloon mitral commissurotomy. *Cathet Cardiovasc Diagn* 1998;**43**:33–8.
81. Meneveau N, Schiele F, Seronde MF *et al.* Predictors of event-free survival after percutaneous mitral commissurotomy. *Heart* 1998;**80**:359–64.
82. Zhang HP, Yen GS, Allen JW, Lau FY, Ruiz CE. Comparison of late results of balloon valvotomy in mitral stenosis with versus without mitral regurgitation. *Am J Cardiol* 1998;**81**:51–5.
83. Matsubara T, Yamazoe M, Tamura Y *et al.* Progression to moderate or severe mitral regurgitation after percutaneous transvenous mitral commissurotomy using stepwise inflation technique. *J Cardiol* 1998;**31**:289–95.
84. Mueller UK, Sareli P, Essop MR. Anterior mitral leaflet retraction – a new echocardiographic predictor of severe mitral regurgitation following balloon valvuloplasty by the Inoue technique. *Am J Cardiol* 1998;**81**:656–9.
85. Rittoo D, Sutherland GR, Shaw TR. A prospective echocardiographic study of the effects of balloon mitral commissurotomy on pre-existing mitral regurgitation in patients with mitral stenosis. *Cardiology* 1998;**89**:202–9.
86. Goel PK, Garg N, Sinha N. Pressure zone used and the occurrence of mitral regurgitation in Inoue balloon mitral commissurotomy. *Cathet Cardiovasc Diagn* 1998;**43**:141–6.
87. Ito T, Suwa M, Hirota Y *et al.* Comparison of immediate and long-term outcome of percutaneous transvenous mitral commissurotomy in patients who have and have not undergone previous surgical commissurotomy. *Jpn Circ J* 1997;**61**: 218–22.
88. Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. *Circulation* 2002;**105**: 1465–71.
89. Pan M, Medina A, Suarez De Lezo J *et al.* Balloon valvuloplasty for mild mitral stenosis. *Cathet Cardiovasc Diagn* 1991; **24**:1–5.
90. Herrmann HC, Feldman T, Isner JM *et al.* Comparison of results of percutaneous balloon valvuloplasty in patients with mild and moderate mitral stenosis to those with severe mitral stenosis. The North American Inoue Balloon Investigators. *Am J Cardiol* 1993;**71**:1300–3.
91. Turi ZG. Mitral balloon valvuloplasty [letter; comment]. *Cathet Cardiovasc Diagn* 1992;**25**:343–4.
92. Glantz JC, Pomerantz RM, Cunningham MJ, Woods JR Jr. Percutaneous balloon valvuloplasty for severe mitral stenosis during pregnancy: a review of therapeutic options. *Obstet Gynecol Surg* 1993;**48**:503–8.
93. Patel JJ, Mitha AS, Hassen F *et al.* Percutaneous balloon mitral valvotomy in pregnant patients with tight pliable mitral stenosis. *Am Heart J* 1993;**125**:1106–9.
94. Ribeiro PA, Fawzy ME, Awad M, Dunn B, Duran CG. Balloon valvotomy for pregnant patients with severe pliable mitral stenosis using the Inoue technique with total abdominal and pelvic shielding. *Am Heart J* 1992;**124**: 1558–62.
95. Kultursay H, Turkoglu C, Akin M, Payzin S, Soydas C, Akilli A. Mitral balloon valvuloplasty with transesophageal echocardiography without using fluoroscopy. *Cathet Cardiovasc Diagn* 1992;**27**:317–21.
96. Harken DE, Black H, Taylor WJ, Thrower WB, Ellis LB. Reoperation for mitral stenosis. A discussion of postoperative deterioration and methods of improving initial and secondary operation. *Circulation* 1961;**23**:7–12.
97. Davidson CJ, Bashore TM, Mickel M, Davis K. Balloon mitral commissurotomy after previous surgical commissurotomy. The National Heart, Lung, and Blood Institute Balloon Valvuloplasty Registry participants. *Circulation* 1992;**86**: 91–9.
98. Jang IK, Block PC, Newell JB, Tuzcu EM, Palacios IF. Percutaneous mitral balloon valvotomy for recurrent mitral stenosis after surgical commissurotomy. *Am J Cardiol* 1995; **75**:601–5.
99. Cohen JM, Glower DD, Harrison JK *et al.* Comparison of balloon valvuloplasty with operative treatment for mitral stenosis. *Ann Thorac Surg* 1993;**56**:1254–62.
100. Medina A, de Lezo JS, Hernandez E *et al.* eds. *Percutaneous balloon valvuloplasty*. Mitral restenosis: the Cordoba-Las Palmas experience. New York: Igaku-Shoin, 1992.
101. Calvo OL, Sobrino N, Gamallo C, Oliver J, Dominguez F, Iglesias A. Balloon percutaneous valvuloplasty for stenotic bioprosthetic valves in the mitral position. *Am J Cardiol* 1987;**60**:736–7.
102. Cox DA, Friedman PL, Selwyn AP, Lee RT, Bittl JA. Improved quality of life after successful balloon valvuloplasty of a stenosed mitral bioprosthesis. *Am Heart J* 1989;**118**:839–41.

103.Babic UU, Grujicic S, Vucinic M. Balloon valvoplasty of mitral bioprosthesis. *Int J Cardiol* 1991;**30**:230–2.
104.Waller BF, McKay C, VanTassel J, Allen M. Catheter balloon valvuloplasty of stenotic porcine bioprosthetic valves: Part II: Mechanisms, complications, and recommendations for clinical use. *Clin Cardiol* 1991;**14**:764–72.
105.Waller BF, McKay C, Van Tassel J, Allen M. Catheter balloon valvuloplasty of stenotic porcine bioprosthetic valves: Part I: Anatomic considerations. *Clin Cardiol* 1991;**14**:686–91.
106.Lin PJ, Chang JP, Chu JJ, Chang CH, Hung JS. Balloon valvuloplasty is contraindicated in stenotic mitral bioprostheses. *Am Heart J* 1994;**127**:724–6.
107.Turi ZG, Reyes VP, Raju BS *et al.* Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis. A prospective, randomized trial. *Circulation* 1991;**83**:1179–85.
108.Raju BS, Turi ZG, Raju R *et al.* Three and one-half year follow-up of a randomized trial comparing percutaneous balloon and surgical closed mitral commissurotomy. [Abstract] *J Am Coll Cardiol* 1993;**21**:429A.
109.Arora R, Nair M, Kalra GS, Nigam M, Khalilullah M. Immediate and long-term results of balloon and surgical closed mitral valvotomy: a randomized comparative study. *Am Heart J* 1993;**125**:1091–4.
110.Ben Farhat M, Ayari M, Maatouk F *et al.* Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation* 1998;**97**:245–50.
111.Antunes MJ, Nascimento J, Andrade CM, Fernandes LE. Open mitral commissurotomy: a better procedure? *J Heart Valve Dis* 1994;**3**:88–92.
112.Acar J. Open mitral commissurotomy or percutaneous mitral commissurotomy? [editorial]. *J Heart Valve Dis* 1994;**3**:133–5.
113.Reyes VP, Raju BS, Wynne J *et al.* Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med* 1994;**331**:961–7.
114.Turi ZG. Percutaneous balloon valvuloplasty versus surgery: randomized comparisons. *J Interv Cardiol* 2000;**13**:395–401.
115.Palacios I, Block PC, Brandi S *et al.* Percutaneous balloon valvotomy for patients with severe mitral stenosis. *Circulation* 1987;**75**:778–84.
116.Turi ZG. Frankel W, Brest A, eds. *Valvular heart disease: comprehensive evaluation and treatment. 2nd edn.* Valvuloplasty. Philadelphia: F.A. Davis, 1993.
117.Abdullah M, Halim M, Rajendran V, Sawyer W, al Zaibag M. Comparison between single (Inoue) and double balloon mitral valvuloplasty: immediate and short-term results. *Am Heart J* 1992;**123**:1581–8.
118.Kasper W, Wollschlager H, Geibel A, Meinertz T, Just H. Percutaneous mitral balloon valvuloplasty – a comparative evaluation of two transatrial techniques. *Am Heart J* 1992;**124**:1562–6.
119.Ortiz FA, Macaya C, Alfonso F. Mono- versus double-balloon technique for commissural splitting after percutaneous mitral valvotomy. *Am J Cardiol* 1992;**69**:1100–1.
120.Rothlisberger C, Essop MR, Skudicky D, Skoularigis J, Wisenbaugh T, Sareli P. Results of percutaneous balloon mitral valvotomy in young adults. *Am J Cardiol* 1993;**72**:73–7.
121.Ruiz CE, Zhang HP, Macaya C, Aleman EH, Allen JW, Lau FYK. Comparison of Inoue single-balloon versus double-balloon technique for percutaneous mitral valvotomy. *Am Heart J* 1992;**123**:942–7.
122.Multicenter experience with balloon mitral commissurotomy. NHLBI Balloon Valvuloplasty Registry Report on immediate and 30-day follow- up results. The National Heart, Lung, and Blood Institute Balloon Valvuloplasty Registry Participants. *Circulation* 1992;**85**:448–61.

56 Valve repair and choice of valves

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Introduction

Changes in treatment of mitral regurgitation provide a classic example of how advances in surgical technique influence the overall strategy of medical management of valvular heart disease, including both the indications for and timing of operation. In North America, degenerative diseases such as floppy valves and ruptured chordae tendineae are the most common causes of non-ischemic mitral valve regurgitation.[1–3]

Previously, clinicians observed patients with mitral regurgitation until symptoms developed or until there was evidence of left ventricular failure. Usually, operation resulted in replacement of the valve with a prosthesis. This left the patient with ventricular dysfunction, irreversible in some cases, and also the attendant prosthesis-related risks such as thromboembolism, hemorrhage caused by systemic anticoagulation, infection, and risks of mechanical failure. The advent of mitral valve repair, with its predictability and safety, lead to new criteria for intervention. Indeed, early operation for valve repair should be considered for all patients with severe mitral regurgitation.[4,5]

Timing of operation for mitral valve regurgitation

Grade B Mitral valve regurgitation often progresses slowly and because of favorable loading conditions, left ventricular dysfunction can develop even though systolic indices of left ventricular performance are maintained. Indeed, with severe mitral valve regurgitation, normal ventricular function should result in a hyperdynamic left ventricle with a supranormal ejection fraction. When the ejection fraction falls below 60% in the presence of severe mitral regurgitation, the prognosis of patients after surgical correction worsens (Figure 56.1).[4] However, the relative insensitivity of ejection fraction in gauging ventricular performance in patients with mitral regurgitation has led to the development of indices of

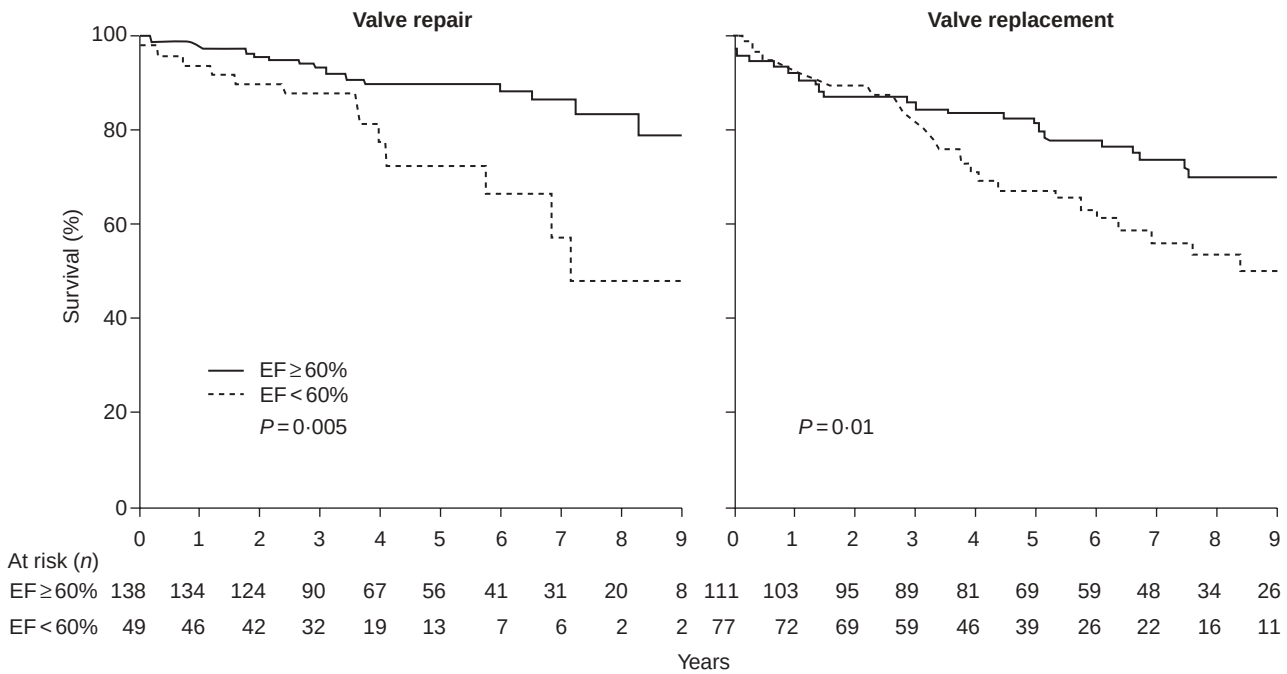

Figure 56.1 Graphs of late survival according to preoperative ejection fraction (EF) after valve repair (left) and valve replacement (right). (From Enriques-Sarano *et al.*[4])

left ventricular function that are less dependent on preload, such as end systolic dimension. Again, prognosis after valve repair or replacement is poor when preoperative left ventricular end systolic dimension exceeds 45 mm.[4] Thus, even in an asymptomatic patient with an ejection fraction greater than 60%, if left ventricular end systolic diameter approaches 45 mm, valve repair should be seriously considered.[4]

Valve repair *v* replacement

Grade A There are no prospective, randomized studies comparing outcomes after mitral valve repair with replacement for mitral regurgitation. In addition, it is often difficult to compare these two modes of surgical treatment by review of the literature because of heterogeneous patient populations.[6] Patients with anatomy favorable for valve repair may have less advanced disease when compared to those patients in whom valve replacement is necessary.[7]

However, even with these confounding factors, some generalizations can be made. First, analysis based upon adjustment for baseline differences in patient populations indicates that patients undergoing mitral valve repair have improved survival and better postoperative left ventricular function than patients undergoing mitral valve replacement (Figure 56.2).[7] In addition, patients undergoing valve repair have a lower operative mortality than their counterparts having prosthetic replacement (Table 56.1).[6] These good results following valvuloplasty are, at least in part, due to maintenance of normal left ventricular geometry and function through preservation of the valve-chordal-papillary muscle complex.[8–11]

Table 56.1 Operative mortality for mitral valve replacement *v* repair

	Replacement	Repair	*P*
Overall	*n* = 214 (10·3%)	*n* = 195 (2·6%)	0·002
Age ≤75 years	*n* = 39 (30·8%)	*n* = 44 (6·8%)	0·0005
Age ≥75 years	*n* = 175 (5·7%)	*n* = 151 (1·3%)	0·036

From Enriquez-Sarano *et al*[7]

Importantly, valve repair and replacement have similar low rates of reoperation. A study from our clinic comparing the outcomes of 195 patients undergoing valve repair with 214 who underwent valve replacement for organic mitral regurgitation demonstrated that freedom from reoperation was 90% and 93% (repair and replacement) at 5 years and 75% and 80% at 10 years respectively ($P = 0{\cdot}47$)[7] (Figure 56.3).

Valve repair can even be undertaken in some patients with calcification of the leaflets and annulus. Although this

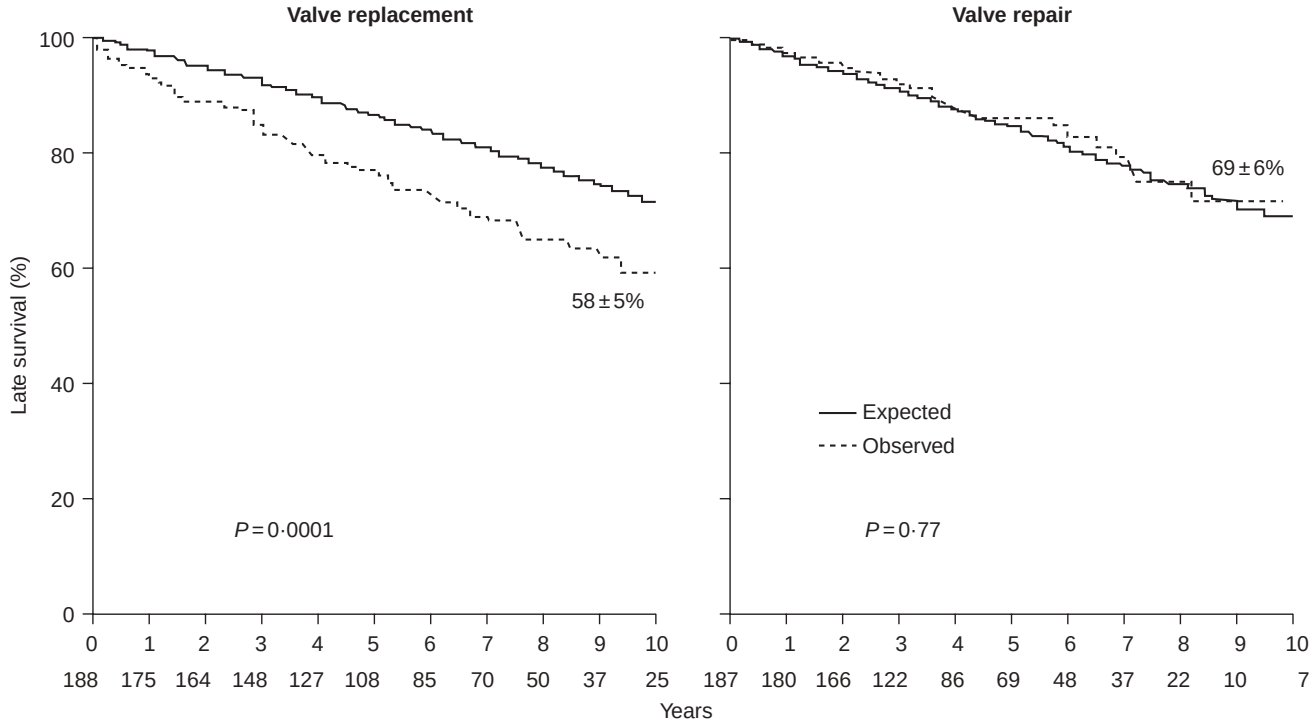

Figure 56.2 Plots of late survival (in operative survivors) of patients with valve replacement (left) and valve repair (right) compared with their expected survival. Note that in patients with valve repair, there is no difference in the expected survival, whereas in patients with valve replacement, the survival is significantly lower than expected. (From Enriquez-Sarano *et al.*[7])

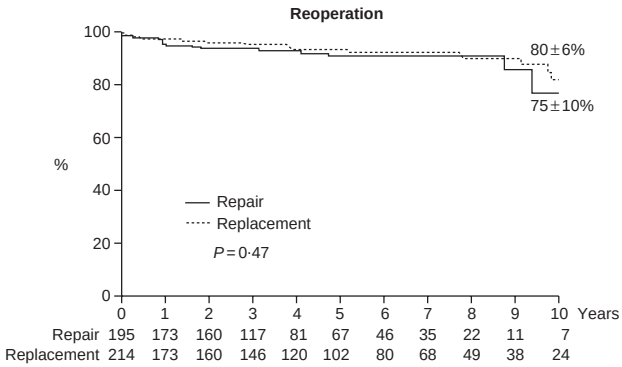

Figure 56.3 Plot of freedom from reoperation in valve repair and replacement groups. No significant difference is observed. (From Enriquez-Sarano *et al.*[7])

presents a challenge to the surgeon, repair utilizing standard techniques after tissue decalcification and debridement does not adversely affect surgical outcome.[12,13] Mitral valve repair rather than replacement is also possible in the setting of native valve endocarditis, as this results in lower hospital mortality and improved long-term outcome when compared to valve replacement.[14] Thus, valve repair for mitral regurgitation, whatever the etiology, should be the first choice of surgical correction.

Freedom from reoperation for structural valve-related degeneration has been reported as high as 90% at 10 years and 85% at 15 years following valve repair.[15] In patients who exhibit valve failure following repair, successful re-repair can be undertaken in 16–21% of patients.[16,17] Thus, the ultimate likelihood of requiring a mitral prosthesis following surgical repair of mitral regurgitation is very low.

Basic concepts of repair

Prolapse of a segment of the posterior leaflet is treated by triangular or quadrangular resection of the unsupported portion or by plication of the redundant leaflet tissue.[18,19] In patients with anterior leaflet prolapse, with or without chordal rupture, we favor chordal replacement with Gore-Tex suture.[20]

Dilation of the valve annulus almost always accompanies mitral regurgitation.[21] Progressive annular enlargement worsens regurgitation by further decreasing the area of leaflet coaptation. The dilation tends to be asymmetrical, in that it affects the mural leaflet up to the commissures.[22] Dilation changes annular shape so that the anteroposterior diameter of the valve becomes greater than the transverse diameter. Because of this, an annuloplasty procedure is an integral part of mitral valve repair. The goals of an annuloplasty are fourfold:

1. decrease annulus diameter, thereby decreasing the area that the leaflets must seal;
2. prevent further dilation of the annulus;
3. allow coaptation of the leaflets along several millimeters from their free margins, thus decreasing the probability of tears in areas where segments of leaflets or chordae were repaired;
4. restoration of normal annulus shape.

Annuloplasty is typically performed with a prosthetic ring;[23,24] we favor a partial posterior ring[25] to reorient the anterior or posterior leaflets for adequate coaptation (Figure 56.4). Postoperative valve function as assessed by degree of regurgitation, transvalvular gradient, and valve area is comparable, irrespective of which technique is utilized.[25] It should be noted that the normal mitral annulus changes size and shape during the cardiac cycle.[26–29] This "sphincter-like" function results in a reduction in valve area by 26% during systole, which is associated with a change in shape from circular to elliptical.[30] If a flexible annuloplasty is utilized for repair rather than a rigid ring, superior left ventricular systolic function can be demonstrated early and late following valve repair.[31,32]

Valve replacement

Grade B Choice of a valve prosthesis requires consideration of the qualities of the valve weighed against the patient's needs. Durability of the prosthesis is often the primary concern of the patient. Indeed, when discussing valve replacement with a patient, the most commonly asked question is "How long will it [the prosthesis] last?" For currently available mechanical valves in the United States, the answer is a qualified "forever", qualified in the sense that intrinsic material failure of mechanical valves is now extremely rare.[33] However, this does not mean that a valve might not need to be replaced because of extrinsic mechanical failure (for example, pannus ingrowth inhibiting proper function of the closure mechanism), and the patient should understand these differences. Durability of biologic valves is not so well

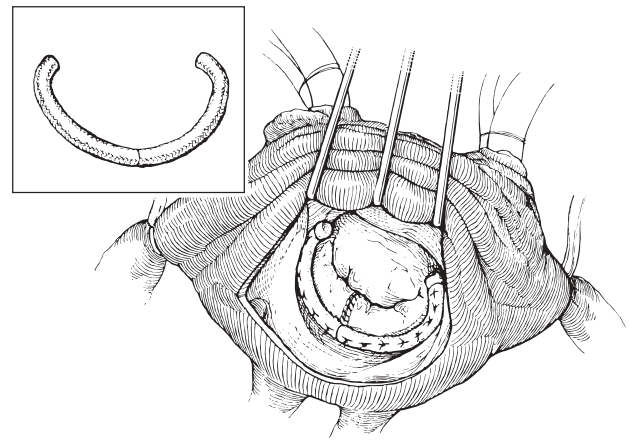

Figure 56.4 An annuloplasty ring

defined for the individual patient. Indeed, as outlined below, by their very nature, tissue valves have a limited lifespan and their use must be matched to a patient's needs.

Anticoagulation and thrombogenicity are the other major issues with prosthetic valves. Mechanical valves offer excellent durability that clearly surpasses that of currently available tissue valves, but thrombus formation and thromboembolism are recognized hazards. Anticoagulation to prevent thromboembolism introduces an incremental risk to a patient. Indeed, taken together, anticoagulant-related hemorrhage and thrombosis account for up to 75% of complications following mechanical valve replacement.[34]

Finally, when evaluating different types of cardiac valve prostheses, one must understand the concepts of valvular hemodynamics. These are directly related to valve design and determine the work the heart must expend to pump blood through the prosthesis. All currently approved prosthetic valves have a sewing ring which, with the housing of the valve, takes up a certain cross-sectional area in the path of blood flow. This "sewing ring area" is larger for the tissue valves than for the mechanical valves. The effective orifice area (EOA) of a valve is the actual area of the valve available for blood flow. If one divides the EOA by the sewing ring area, one can calculate the performance index of a given valve. The performance index of currently available porcine valves ranges from 0·35 to 0·4, pericardial valves 0·65, and tilting disc valves from 0·67 to 0·70, so that all stent mounted prosthetic valves are, by definition, stenotic compared to normal native valves. The potential for residual outflow obstruction when a small prosthetic valve is used in a large patient gives rise to the condition termed valve-prosthesis patient mismatch.[35,36] For most patients, the transvalvular gradient is small and of little clinical significance. It should be noted, however, that as the valve size decreases and the EOA concomitantly decreases, there can be a precipitous rise in the transvalvular gradient, which could cancel out the clinical improvement anticipated from valve replacement.

Two other aspects of valve function are often overlooked: dynamic and static prosthetic valve regurgitation. Dynamic regurgitant fraction is the amount of regurgitation that occurs through a valve before the occluder has a chance to close fully. This is lowest for the tilting disc valves, followed by the bileaflet prostheses; the greatest dynamic regurgitation is associated with the ball and cage prostheses.[37] Static regurgitation occurs through a valve after the valve has closed. Some static regurgitation is engineered into most valves to wash the valve components and eliminate microemboli. Bileaflet valves and Medtronic-Hall tilting disc valves have greater static regurgitation than ball and cage valves.[37] Although regurgitant volume through a normally functioning prosthesis is not important in a patient with adequate ventricular function, in the face of decreased ejection fraction, large regurgitant volumes may attenuate the hemodynamic improvement produced by valve replacement.

Mechanical valves

Grade B Currently in the United States, there are five categories of mechanical valves approved for implication by the Food and Drug Administration. These include the St Jude (St Jude Medical, Minneapolis, MN) bileaflet prosthesis, the Medtronic-Hall (Medtronic Inc, Minneapolis, MN) tilting disc valve, the CarboMedics (CarboMedics, Austin, TX) bileaflet prosthesis, the Starr-Edwards ball valve (Baxter Healthcare, Santa Ana, CA), and the Omnicarbon tilting disc valve, which evolved from the Omniscience valve. There are few prospective, randomized studies comparing outcomes between these categories of valves in the same patient populations.

Non-randomized studies and informal comparisons of published series show little difference in late patient outcome, either in morbidity or mortality, following implantation of currently approved mechanical prostheses (for review, see reference[37]). Several prospective, randomized studies comparing specific valves bear out this assertion. Schulte and associates randomized 150 consecutive patients to receive a tilting disc prosthesis or Starr-Edwards valve or mitral valve replacement; there was no significant difference in late patient survival (mean follow up 14·8 years) between the two tilting disc valves (Bjork-Shiley, Lillehei-Kaster) and a ball and cage prosthesis (Starr-Edwards).[38]

In another randomized study of 102 patients, Fiore and colleagues found no significant difference in linearized rates of valve-related events and 3 year actuarial survival between a tilting disc (Medtronic-Hall) and bileaflet (St Jude) prosthesis (Figure 56.5).[39] Even when comparing an early model tilting disc prosthesis (Bjork-Shiley) with a bileaflet prosthesis (St Jude), no significant difference in early and late survival or major bleeding complications could be demonstrated in 178 patients in a prospectively randomized, European study (mean follow up of 52 months or 778 patient-years).[40] Thus, with regard to clinical performance and hemodynamic data, there are no large randomized studies that definitively demonstrate the superiority and thus preferential selection of one mechanical prosthesis over another.

Bioprosthetic valves

Grade B The three most commonly used bioprostheses are the Hancock porcine valve (Medtronic Inc) and the Carpentier-Edwards porcine and bovine pericardial valves (Baxter Healthcare). The main drawback of the bioprosthetic valves is structural deterioration which is not a simple linear function of time as the rate of structural dysfunction steadily accelerates after 5–6 years of implantation.[41–43] Regurgitation through cusp tears associated with calcific nodules is the most frequent form of bioprosthesis failure; pure stenosis due to calcified leaflets occurs infrequently. Structural dysfunction of bioprostheses is markedly accelerated in children, adolescents, and young adults, but is attenuated in very elderly

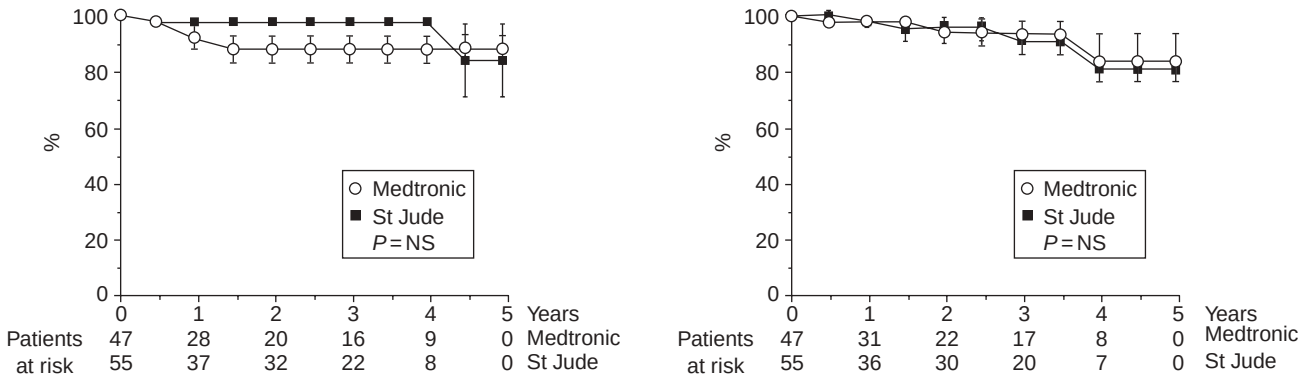

Figure 56.5 Actuarial freedom from thromboembolism (left) and hemorrhage (right) after mitral valve replacement with the St Jude and Medtronic-Hall valves (NS=not significant). (From Fiore *et al.*[39])

patients. For aortic bioprostheses, patients younger than 39–44 years of age have structurally related, event free estimates ranging from 58% to 70% at 10 years;[43–45] this drops to 33% at 15 years.[46] This is in contrast to patients over 70 years of age, who have event free estimates of 95% and 93% at 10 and 15 years following implantation.[46] Event free estimates for patients between 60 and 69 years of age, 10 years following implantation, range from 92% to 95%.[45–47]

Many investigators have compared the performance of the Hancock and the Carpentier-Edwards porcine bioprostheses. In general, no significant differences in the short- and long-term performance of these valves have been demonstrated.[48–51] Indeed, at 10 year follow up of 174 patients undergoing mitral or aortic valve replacement who were prospectively randomized to receive either a Hancock or Carpentier-Edwards porcine bioprosthesis, there were no significant differences in patient survival, durability of the prosthesis or valve-related complications.[48] These findings were confirmed in another study of 147 patients randomized to receive either the Carpentier-Edwards or Hancock porcine bioprosthesis in the mitral position. At 10 years, no significant differences in survival or valve-related complications were apparent.[52]

Previously, all commercially available bioprostheses were mounted on a stent or frame to give the relatively flaccid tissue valve a fixed base to facilitate implantation. The stent and sewing ring, however, significantly decrease the EOA and make tissue valves relatively obstructive when compared with mechanical prostheses. There has been considerable interest recently in stentless bioprosthetic valves that are inserted in much the same fashion as homografts. Hemodynamic performance of stentless bioprostheses is good and like other tissue valves, no anticoagulation is required.[53–56] In one report, 254 patients with the Toronto SPV stentless valve (St Jude Medical) were followed for 3 years and the initially favorable EOAs and transvalvular gradients were said to improve with time.[53] In addition, left ventricular mass decreased by 14·3% in the study period.

The primary mode of failure of stentless valves, like all bioprostheses, is valvular regurgitation. Indeed, 27% of 200 patients were found to have aortic insufficiency 1 year following implantation of a stentless aortic valve (PRIMA Edwards; Baxter Healthcare); however, only one patient exhibited grade 3 insufficiency.[55] In addition, in a non-randomized study of 150 patients receiving either a stentless bioprosthesis (PRIMA Edwards), a traditional bioprosthesis or a homograft, no difference in morbidity or mortality was noted between the groups after 1 year.[57] While the initial data on stentless bioprostheses in the aortic position are encouraging, further long-term studies will be needed to establish their ultimate role in the management of aortic valve disease.

Development of stentless valves for the mitral position has been difficult. Because the mitral valve annulus changes shape during the cardiac cycle, a stentless prosthesis in this location requires additional external support to maintain competence. This engineering challenge has been met by using artificial chordae to anchor the stentless valve to native papillary muscle.[58] Short-term success has been reported, but a stentless prosthesis for the mitral position should be considered as experimental.

An additional category of tissue valves currently available for implantation are homografts. These are human tissue valves (either aortic or pulmonic) that have been harvested from cadavers, sterilized antibiotically, and cryopreserved.[59,60] Homografts have many attractive features including minimal gradients, low thrombogenicity without need for anticoagulation, and low risk of infection, even when used in patients with active endocarditis.[61,62] Implantation of a homograft is considered more difficult than implantation of a stent mounted bioprosthesis and both experience of the surgeon and surgical technique appear to influence late results.[63] Freedom from reoperation due to structural deterioration of homografts has been reported to range from 83% at 8 years[64] to 86% at 14 years.[60] When valve failure occurs, it is due to the gradual development of insufficiency.

The other homograft available for aortic valve replacement is the pulmonary valve autograft (termed the Ross procedure). The Ross procedure involves excision of a patient's normal pulmonic valve (autograft) and utilizing it to replace the diseased aortic valve.[65,66] A cryopreserved human pulmonary artery homograft (allograft) is then implanted to replace the native pulmonic valve. There are many positive aspects of the operation. First, as both of the valves are tissue valves, no anticoagulation is required. Second, since the pulmonic valve autograft is not exposed to the antibiotic sterilization or cryopreservation process, it is viable and has potential for growth and long-term durability.[67,68] In one series of 195 patients, the freedom from reoperation (autograft or allograft) was reported to be 89% at 5 years.[69] Compared to allograft replacement of the aortic valve, patients receiving the pulmonary autograft have comparable hemodynamics and early- to medium-term postoperative recovery.[70]

However, there are three potential drawbacks to the pulmonary autograft. First, the operation converts single valve disease to a double valve replacement. And even if the pulmonary autograft functions perfectly, there is potential for tissue degeneration and obstruction of the pulmonary allograft; in fact, the need for right-sided valve re-replacement may be underestimated. In the best of hands and in carefully selected patients, cumulative risk of reoperation for pulmonary valve substitute approaches 20% at 20 years postoperatively.[65,71] In addition, there is a 10–20% incidence of autograft aortic insufficiency, grade 2+, following operation.[72] Long-term follow up from multiple institutions is necessary to define the safety and durability of the pulmonary autograft for aortic valve replacement.

Comparative studies of mechanical *v* bioprosthetic valves

Grade A In a prospective, randomized study in which 262 patients received either a mechanical (Bjork-Shiley) or porcine bioprosthesis (initially Hancock and subsequently Carpentier-Edwards) in the mitral position, actuarial survival and incidence of thromboembolism was comparable at 7 years follow up.[73] Another prospective, randomized study also demonstrated comparable survival following valve replacement with either a mechanical valve or bioprosthesis.[74] Five hundred and seventy-five men, scheduled to undergo either aortic or mitral valve replacement, were randomized either to receive a mechanical valve (Bjork-Shiley) or porcine bioprosthesis (Hancock). After 11 years, survival rates and freedom from all valve-related complications were similar for both patient groups. However, the profile of valve-related complications was different in that structural failure was only observed with the bioprosthetic valves, whereas bleeding complications were more frequent in patients with mechanical valves. Thus, while the types of complications might differ between patients with either a bioprosthesis or mechanical valve, the actual incidence of the complications is comparable and survival is similar. As such, the choice between a bioprosthesis and a mechanical valve should be based on other factors.

Matching the patient to the prosthesis: factors in selecting a valve for implantation

Grade B Because patient survival following valve replacement is independent of the type of prosthesis used and dependent on other factors, one needs to focus on patient variables when selecting a valve. First, one must assess a patient's life expectancy after valve replacement. For patients aged 65–69 years undergoing aortic and/or mitral valve replacement, survival is approximately 53% at 10 years and 25% at 15 years; for patients 70 years of age or older, survival is 30–38% at 10 years and 25% at 15 years.[47] Coronary artery disease requiring bypass grafting at the time of valve replacement further decreases long-term survival.[75]

All other factors being equal, it has been our practice to suggest a mechanical valve to patients 70 years or younger and a bioprosthesis to those 75 years and older. In the "gray area" between 70 and 75 years, recommendations are made based upon a patient's general health and personal preference.

The other major issue related to the choice of a valve prosthesis is anticoagulation. Obviously, a mechanical valve, with its obligatory need for lifelong oral anticoagulation, would be contraindicated in a patient who:

- has bleeding tendencies
- because of geography or psychosocial issues, would be unable to monitor the level of anticoagulation
- has an occupation with a high risk of trauma
- is a female of childbearing age who desires a future pregnancy.

In these situations, one of the tissue valves would be indicated. However, if a patient is likely to require anticoagulation for some other condition such as atrial fibrillation, a large left atrium, chronic deep venous thrombosis or a mechanical prosthesis in another location, then a mechanical valve is chosen for its durability. In addition, if for some reason a patient would be at great risk for reoperation and valve re-replacement, a mechanical valve is favored.

References

1. Dare AJ, Harrity PJ, Tazelaar HD, Edwards WD, Mullany CJ. Evaluation of surgically excised mitral valves: revised recommendations based on changing operative procedures in the 1990s. *Hum Pathol* 1993;**24**:1286–93.
2. Olson LJ, Subramanian R, Ackermann DM, Orszulak TA, Edwards WD. Surgical pathology of the mitral valve: a study of 712 cases spanning 21 years. *Mayo Clin Proc* 1987;**62**:22–34.

3. Waller BF, Morrow AG, Maron BJ *et al.* Etiology of clinically isolated, severe, chronic, pure mitral regurgitation: an analysis of 97 patients over 30 years of age having mitral valve replacement. *Am Heart J* 1982;**104**:276–88.
4. Enriquez-Sarano M, Tajik AJ, Schaff HV *et al.* Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation* 1994;**90**:830–7.
5. Ling LH, Enriquez-Sarano M, Sewrad JB *et al.* Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;**355**:1417–23.
6. Perier P, Deloche A, Chauvaud S *et al.* Comparative evaluation of mitral valve repair and replacement with Starr, Bjork, and porcine valve prostheses. *Circulation* 1984;**70**:187–92.
7. Enriquez-Sarano M, Schaff HV, Orszulak TA *et al.* Valve repair improves the outcome of surgery for mitral regurgitation: a multivariate analysis. *Circulation* 1995;**91**:1022–8.
8. Goldman ME, Mora F, Guarino T, Fuster V, Mindich BP. Mitral valvuloplasty is superior to mitral valve replacement for preservation of left ventricular function: an intraoperative two-dimensional echocardiographic study. *J Am Coll Cardiol* 1987; **10**:568–75.
9. Rozich JD, Carabello BA, Usher BW *et al.* Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation. Mechanisms for differences in postoperative ejection performance. *Circulation* 1992; **86**:1718–26.
10. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. *Circulation* 1983;**68**:1176–83.
11. David TE, Burns RJ, Bacchus CM, Druck MN. Mitral regurgitation with and without preservation of chordae tendineae. *J Thorac Cardiovasc Surg* 1984;**88**:718–25.
12. Grossi EA, Galloway AC, Steinberg BM *et al.* Severe calcification does not affect long-term outcome of mitral valve repair. *Ann Thorac Surg* 1994;**58**:685–8.
13. Carpentier AF, Pellerin M, Fuzellier JF, Relland JYM. Extensive calcification of the mitral valve annulus: pathology and surgical management. *J Thorac Cardiovasc Surg* 1996;**111**:718–30.
14. Muehrcke DD, Cosgrove DM, Lytle BW *et al.* Is there an advantage to repairing infected mitral valves? *Ann Thorac Surg* 1997;**63**:1718–24.
15. Alvarez JM, Deal CW, Loveridge K *et al.* Repairing the degenerative mitral valve: ten to fifteen year follow-up. *J Thorac Cardiovasc Surg* 1996;**112**:238–47.
16. Cerfolio RJ, Orszulak TA, Pluth JR, Harmsen WS, Schaff HV. Reoperation after valve repair for mitral regurgitation: early and immediate results. *J Thorac Cardiovasc Surg* 1996;**111**: 1177–84.
17. Gillinov AM, Cosgrove DM, Lytle BW *et al.* Reoperation for mitral valve repair. *J Thorac Cardiovasc Surg* 1997;**113**: 467–75.
18. Carpentier A. Cardiac valve surgery: the French connection. *J Thorac Cardiovasc Surg* 1983;**86**:323–37.
19. McGoon DC. Repair of mitral insufficiency due to ruptured chordae tendinae. *J Thorac Cardiovasc Surg* 1960;**39**: 357–62.
20. David TE, Armstrong S, Sun Z. Replacement of chordae tendineae with Gore-Tex sutures: a ten-year experience. *J Heart Valve Dis* 1996;**5**:352–5.
21. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. II. Abnormalities in mitral valve prolapse. *Circulation* 1982;**65**:713–19.
22. Carpentier A. Plastic and reconstructive mitral valve surgery. In Kalmanson D, ed. *The mitral valve, a pluridisciplinary approach*. London: Publishing Science Group, 1976.
23. Carpentier A, Deloche A, Dauptain J *et al.* A new reconstructive operation for correction of mitral and tricuspid insufficiency. *J Thorac Cardiovasc Surg* 1971;**61**:1–13.
24. Duran CMG, Umbago JL. Clinical and hemodynamic performance of a totally flexible prosthetic ring for atrioventricular valve reconstruction. *Ann Thorac Surg* 1976;**22**:458–63.
25. Odell JA, Schaff HV, Orszulak TA. Early results of a simplified method of mitral valve anuloplasty. *Circulation* 1995;**92** (Suppl. II):II-150–4.
26. David TE, Strauss HD, Mesher E *et al.* Is it important to preserve the chordae tendineae and papillary muscles during mitral valve replacement? *Can J Surg* 1981;**24**:236–9.
27. Hansen DE, Cahill PD, DeCampli WM *et al.* Valvular ventricular interactions: importance of the mitral apparatus in canine left ventricular systolic performance. *Circulation* 1986;**73**: 1310–20.
28. Hansen DE, Cahill PD, Derby GC, Miller DC. Relative contributions of the anterior and posterior mitral chordae tendineae to canine global left ventricular systolic performance. *J Thorac Cardiovasc Surg* 1987;**93**:45–55.
29. Sarris GE, Cahill PD, Hansen DE *et al.* Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of the valvular-ventricular interaction. *J Thorac Cardiovasc Surg* 1988;**95**:969–79.
30. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral annulus in man: a two-dimensional echocardiographic method and findings in normal subjects. *Circulation* 1981;**64**:113–20.
31. David TE, Komeda M, Pollick C, Burns RJ. Mitral valve annuloplasty: the effect of the type on left ventricular function. *Ann Thorac Surg* 1989;**47**:524–8.
32. Duran CG, Revuelta JM, Gaite L, Alonso C, Fleitas MG. Stability of mitral reconstructive surgery at 10–12 years for predominantly rheumatic valvular disease. *Circulation* 1988; **78**:191–6.
33. Grunkemeier GL, Rahimtoola SH. Artificial heart valves. *Annu Rev Med* 1990;**41**:251–63.
34. Edmonds LH. Thrombotic and bleeding complications of prosthetic heart valves. *Ann Thorac Surg* 1987;**44**:430–45.
35. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. *Circulation* 1978;**58**:20–4.
36. Rahimtoola SH, Murphy E. Valve prosthesis-patient mismatch. A long-term sequela. *Br Heart J* 1981;**45**:331–5.
37. Akins CW. Results with mechanical cardiac valvular prostheses. *Ann Thorac Surg* 1995;**60**:1836–44.
38. Schulte HD, Horstkotte D, Bircks W, Strauer BE. Results of a randomized mitral valve replacement with mechanical prostheses after 15 years. *Int J Artif Organs* 1992;**15**:611–16.
39. Fiore AC, Naunheim KS, d'Orazio S *et al.* Mitral valve replacement: randomized trial of St. Jude and Medtronic-Hall prostheses. *Ann Thorac Surg* 1992;**54**:68–73.
40. Vogt S, Hoffmann A, Roth J *et al.* Heart valve replacement with the Bjork-Shiley and St. Jude Medical

prostheses: a randomized comparison in 178 patients. *Eur Heart J* 1990; **11**:583–91.
41. Jamieson WRE, Murno AI, Miyagishima RT *et al.* Carpentier-Edwards standard porcine bioprosthesis: clinical performance to seventeen years. *Ann Thorac Surg* 1995;**60**:999–1007.
42. Glower DD, White WD, Hatton AC *et al.* Determinants of reoperation after 960 valve replacements with Carpentier-Edwards prostheses. *J Thorac Cardiovasc Surg* 1994;**107**: 381–93.
43. Pelletier LC, Carrier M, Leclerc Y *et al.* Influence of age on late results of valve replacement with porcine bioprostheses. *J Cardiovasc Surg* 1992;**33**:526–33.
44. Cohn LH, Collins JJ Jr, DiSesa V *et al.* Fifteen-year experience with 1,678 Hancock porcine bioprosthetic heart valve replacements. *Ann Surg* 1989;**210**:435–43.
45. Jones EL, Weintraub WS, Craver JM *et al.* Ten-year experience with the porcine bioprosthetic valves; interrelationship of valve survival and patient survival in 1,050 valve replacements. *Ann Thorac Surg* 1990;**49**:370–84.
46. Burdon TA, Miller DC, Oyer PE *et al.* Durability of porcine valves at fifteen years in a representative North American population. *J Thorac Cardiovasc Surg* 1992;**103**:238–52.
47. Burr LH, Jamieson WRE, Munro AI *et al.* Porcine bioprostheses in the elderly: clinical performance by age groups and valve positions. *Ann Thorac Surg* 1995;**60**:S264–9.
48. Sarris GE, Robbins RC, Miller DC *et al.* Randomized, prospective assessment of bioprosthetic valve durability: Hancock verses Carpentier-Edwards valves. *Circulation* 1993;**88** (pt 2):55–64.
49. Bolooki H, Kaiser GA, Mallon SM, Palatianos GM. Comparison of long-term results of Carpentier-Edwards and Hancock bioprosthetic valves. *Ann Thorac Surg* 1986;**42**:494–9.
50. Hartz RS, Fisher EB, Finkelmeier B *et al.* An eight-year experience with porcine bioprosthetic cardiac valves. *J Thorac Cardiovasc Surg* 1986;**91**:910–17.
51. McDonald ML, Daley RC, Schaff HV *et al.* Hemodynamic performance of a small aortic valve bioprostheses: is there a difference? *Ann Thorac Surg* 1997;**63**:362–6.
52. Perier P, Deloche A, Chauvaud S *et al.* A ten-year comparison of mitral valve replacement with Carpentier-Edwards and Hancock porcine bioprostheses. *Ann Thorac Surg* 1989; **48**:54–9.
53. Del Rizzo DF, Goldman BS, Christakis GT, David TE. Hemodynamic benefits of the Toronto Stentless Valve. *J Thorac Cardiovasc Surg* 1996;**112**:1431–45.
54. Sintek CF, Fletcher AD, Khonsari S. Small aortic root in the elderly: use of a stentless bioprosthesis. *J Heart Valve Dis* 1996;**5**(Suppl. 3):S308–13.
55. Dossche K, Vanermen H, Daenen W, Pillai R, Konertz W. Hemodynamic performance of the PRIMA Edwards stentless aortic xenograft: early results of a multicenter clinical trial. *Thorac Cardiovasc Surg* 1996;**44**:11–14.
56. Wong K, Shad S, Waterworth PD *et al.* Early experience with the Toronto stentless porcine valve. *Ann Thorac Surg* 1995;**60**(Suppl. 2):S402–5.
57. Dossche K, Vanermen H, Wellens F *et al.* Free-hand sewn allografts, stentless (Prima Edwards) and stented (CESA) porcine bioprostheses. A comparative hemodynamic study. *Eur J Cardiothorac Surg* 1995;**9**:562–6.
58. Deac RF, Simionescu D, Deac D. New evolution in mitral physiology and surgery: mitral stentless pericardial valve. *Ann Thorac Surg* 1995;**60**(Suppl. 2):S433–8.
59. McGriffin DC, O"Brien MF, Stafford EG *et al.* Long-term results of the viable cryopreserved allograft valve: continuing evidence for superior valve durability. *J Cardiac Surg* 1988; **3**(Suppl.):289.
60. O'Brien MF, McGriffin DC, Stafford EG *et al.* Allograft aortic valve replacement: long-term comparative clinical analysis of the viable cryopreserved and antibiotic 4 C stored valves. *J Cardiac Surg* 1991;**6**(Suppl. 4):534.
61. Tuna IC, Orszulak TA, Schaff HV, Danielson GK. Results of homograft aortic valve replacement for active endocarditis. *Ann Thorac Surg* 1990;**49**:619–24.
62. Dearani JA, Orszulak TA, Schaff HV *et al.* Results of allograft aortic valve replacement for complex endocarditis. *J Thorac Cardiovasc Surg* 1997;**113**:285–91.
63. Dearani JA, Orszulak TA, Daly RC *et al.* Comparison of techniques for implantation of aortic valve allografts. *Ann Thorac Surg* 1996;**62**:1069–75.
64. Kirklin JK, Naftel DC, Novick W *et al.* Long-term function of cryopreserved aortic valve homografts: a ten year study. *J Thorac Cardiovasc Surg* 1993;**106**:154–66.
65. Ross D, Jackson M, Davies J. Pulmonary autograft aortic valve replacement: long-term results. *J Cardiac Surg* 1991;**6**: 529–53.
66. Elkins RC, Santangelo K, Stelzer P, Randolph JD, Knott-Craig CJ. Pulmonary autograft replacement of the aortic valve: an evolution of technique. *J Cardiac Surg* 1992;**7**:108–16.
67. Gerosa G, McKay R, Ross DN. Replacement of the aortic valve or root with an autograft in children. *Ann Thorac Surg* 1991;**51**:424.
68. Walls JT, McDaniel WC, Pope ER *et al.* Documented growth of autogenous pulmonary valve translocated to the aortic valve position (letter). *J Thorac Cardiovasc Surg* 1994;**107**:1530.
69. Elkins RC, Lane MM, McCue C. Pulmonary autograft reoperation: incidence and management. *Ann Thorac Surg* 1996; **62**:450–5.
70. Santini F, Dyke C, Edwards S *et al.* Pulmonary autograft versus homograft replacement of the aortic valve: a prospective randomized trial. *J Thorac Cardiovasc Surg* 1997;**113**:894–900.
71. Ross D. Replacement of the aortic valve with a pulmonary autograft: the "switch" operation. *Ann Thorac Surg* 1991;**52**:1346.
72. Elkins RC. Editorial: pulmonary autograft – the optimal substitute for the aortic valve? *N Engl J Med* 1994;**330**:59.
73. Bloomfield P, Kitchin AH, Wheatley DJ *et al.* A prospective evaluation of the Bjork-Shiley, Hancock, and Carpentier-Edwards heart valve prostheses. *Circulation* 1993;**88**:1155–64.
74. Hammermeister KE, Sethi GK, Henderson WG *et al.* A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. *N Engl J Med* 1993;**328**:1289.
75. Jones EL, Weintraub WS, Craver JM *et al.* Interaction of age and coronary disease after valve replacement: implications for valve selection. *Ann Thorac Surg* 1994;**58**:378–85.

57 Diagnosis and management of infective endocarditis

David T Durack, Michael L Towns

The diagnosis and management of infective endocarditis (IE) raises many questions and clinical decisions which invite application of the principles of evidence-based medicine. Most of these have not been formally asked or answered by means of controlled clinical studies. Current practice is based upon an extensive accumulation of uncontrolled clinical experience, rather than upon validated clinical trials.

Here we will discuss common issues that arise during diagnosis and management of IE. Recommendations will be offered, along with an evidence-based grading (on an A, B, C scale) of the basis for each recommendation.

Background

Pathophysiology

Endocarditis refers to inflammation of the endocardial lining of the heart. The heart valves are most often involved, or less commonly the lining of the heart chambers (mural endocarditis). When the lesions of endocarditis (vegetations) contain micro-organisms, the associated disease is termed infective endocarditis. This general term covers the various clinical subcategories of the disease (for example, acute, subacute, prosthetic valve infection) and also the various etiologic agents (bacteria, yeasts or fungi).

The pathophysiology of this disease often begins with the formation of non-bacterial thrombotic endocarditis (NBTE). This lesion, which is sometimes called a "fibrin-platelet plug", is a receptive precursor site which may become infected by circulating organisms during the course of a bacteremia or fungemia.[1–3] NBTE is not normally found in healthy hearts, but it may develop on an endocardial lining which has been damaged by one of several mechanisms. One of the most common pathogenic mechanisms is that of a cardiac valvular lesion, such as scarring or stenosis, leading to high velocity turbulent flow across the valve, with resultant damage to the endothelial lining.[4,5] The damaged area may become a locus for deposition of fibrin and platelets, resulting in NBTE. The type of underlying cardiac valvular lesion determines where a vegetation is most likely to form on the endocardial surface. A bacteremia caused by organisms that have the capacity to adhere to this lesion, mediated by surface factors such as adhesins, may seed the NBTE and lead to development of an infected vegetation.[1–3,6]

Vegetations are the pathologic hallmark of IE.[1,2,6] They are composed of masses of organisms enmeshed with fibrin, platelets, and a variable (often scanty) inflammatory infiltrate. The vegetations may be of various sizes, and may or may not progress to cause further valvular, perivalvular, or extracardiac complications. Valvular complications may include valvular dysfunction, destruction, or obstruction. Perivalvular complications include extension of infection into adjacent structures, which may result in formation of a perivalvular abscess. Extracardiac complications most commonly result from embolic phenomena such as embolization into the coronary arteries or the systemic arterial tree, resulting in ischemia, infarcts, and sometimes secondary bleeding. Less commonly, abscesses or mycotic aneurysms may develop in various organs. Other extracardiac complications may include immune complex mediated disease such as glomerulonephritis.

Epidemiology

IE has been variously categorized in the past as acute, subacute, chronic, native valve, prosthetic valve, culture-negative, and intravenous drug abuse associated endocarditis. These terms have some value, but they may overlap. It is useful to specify the infecting organism because this allows prediction of the likely natural history, treatment requirements, and prognosis for an individual patient. Here we will briefly discuss the epidemiology of IE in the context of three main categories: native valve, prosthetic valve, and culture-negative endocarditis.[7–9]

Table 57.1 shows the etiologic agents that are most commonly isolated in native valve IE. Cases caused by virulent pathogens such as *Streptococcus pneumoniae* or *Staphylococcus aureus* may develop on previously normal valves. More often, native valve endocarditis develops in association with predisposing congenital or acquired valvular lesions, especially when caused by less virulent organisms such as the viridans streptococci.

Prosthetic valve endocarditis can be subcategorized into early (onset up to 60 days after valve replacement),

Table 57.1 Frequency of various organisms isolated in native value infective endocarditis

Organism	NVE (%)	IV drug abusers (%)	Early PVE (%)	Late PVE (%)
Streptococci	65	15	5	35
Viridans, alpha-hemolytic	35	5	<5	25
Strep. bovis (group D)	15	<5	<5	<5
Strep. faecalis (group D)	10	8	<5	<5
Other streptococci	<5	<5	<5	<5
Staphylococci	25	50	50	30
Coagulase-positive	23	50	20	10
Coagulase-negative	<5	<5	30	20
Gram-negative aerobic bacilli	<5	5	15	10
Fungi	<5	5	10	5
Miscellaneous bacteria	<5	5	5	5
Diphtheroids, propionibacteria	<1	<5	5	<5
Other anaerobes	<1	<1	<1	<1
Rickettsia	<1	<1	<1	<1
Chlamydia	<1	<1	<1	<1
Polymicrobial infection	<1	5	5	5
Culture-negative endocarditis	5–10	<5	<5	<5

These are representative figures collated from the literature; wide local variations in frequency are to be expected.
Abbreviations: NVE, native valve endocarditis; PVE, prosthetic valve endocarditis
Reproduced with permission, from Durack[7]

intermediate (onset from 2 to 12 months) or late cases (onset after one year). The observed spectrum of etiologic agents is different for the two categories, with the organisms causing late onset prosthetic valve endocarditis more closely resembling native valve subacute endocarditis, except that coagulase-negative staphylococci remain important (Table 57.1).

Culture-negative IE remains fairly common (3–30% of cases in recent series), despite improvements in blood culture techniques and culture media. Organisms that previously were difficult to recover, such as nutritionally variant streptococci and the fastidious Gram-negatives (HACEK group: *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp, and *Kingella kingae*) are now routinely isolated from modern, optimized blood culture media, usually within 3–5 days. An exception to this is *Bartonella* spp which have recently been found in association with endocarditis among homeless individuals, and as a rare opportunistic infection in patients with AIDS.[10,11]

Diagnosis

Clinical manifestations

Patients with acute IE typically present with an accelerated course typified by high fever, chills, and prostration, whereas those with subacute endocarditis present more insidiously. These patients often have a "flu-like illness" consisting of fever, chills, myalgias/arthralgias, and weakness, but there is great variability in the clinical presentation.[7]

Cardiac manifestations may dominate the clinical presentation in either acute or subacute disease, with the presence of new or worsened murmurs, or development of cardiac failure due to valvular damage. The patient may present with chest pain due to pleuritis, pericarditis or myocardial infarction resulting from coronary arterial embolism.

Extracardiac clinical manifestations consist of embolic as well as vascular phenomena. The patient may present with a headache without any definable neurologic abnormalities, or may have focal abnormalities such as areas of cerebritis, infarcts, hemorrhages or mycotic aneurysms. A cellular reaction in the cerebrospinal fluid (with or without meningismus) may also be present, although only a minority of patients have positive cerebrospinal fluid cultures. The patient may present with focal pain such as flank or left-sided upper quadrant abdominal pain due to embolic infarcts, which may at times be complicated by the formation of abscesses, especially in the spleen. There are many other potential sites for embolization with associated clinical findings, although autopsy findings show that many emboli go undetected during life.

Various other vascular phenomena may occur, including petechiae, splinter hemorrhages, Osler's nodes, Janeway lesions, or clubbing of the fingernails.

Laboratory tests

Anemia is commonly present, usually of mild to moderate severity with a normochromic, normocytic film typical of the anemia of chronic disease. Although many patients with acute or subacute endocarditis have some degree of leukocytosis, this is not a reliable laboratory finding. In approximately 90% of patients with infective endocarditis the erythrocyte sedimentation rate (ESR) is elevated; the median value is about 65 mm/h, but the range is wide and about 10% are within the normal range. Urinalysis may show microscopic hematuria and/or mild proteinuria in approximately 50% of cases, with occasional red blood cell casts and heavy proteinuria in those patients who develop immune-complex glomerulonephritis. Non-specific serologic abnormalities are common, especially positive rheumatoid factor which is seen in 30–40% of cases of the subacute form of the disease. A polyclonal increase in gammaglobulins is characteristic of active endocarditis.

Microbiology

Blood cultures remain the definitive microbiologic procedure for diagnosis of infective endocarditis.[12–15] The microorganisms isolated from blood cultures may provide the clinician with clues to the diagnosis, given the clinical setting. For example, patients who present from the community with a fever of unknown origin who have multiple positive blood cultures for viridans group streptococci, enterococci, or the HACEK organisms, should be considered to have IE until proven otherwise.[12,16,17] In addition, the temporal pattern of positive cultures may assist in the diagnosis. If three or more blood culture sets drawn at least one hour apart all are positive for the same micro-organism, this is termed "persistent bacteremia", which indicates that an endovascular infection may be present. Table 57.1 shows the leading organisms isolated from patients with acute, subacute, and prosthetic valve infective endocarditis.

What are the optimal blood culture techniques required to diagnose infective endocarditis?

Background

A positive blood culture is one of the two major diagnostic criteria for IE.[13] Therefore, blood cultures should be obtained from every patient in whom this diagnosis is suspected. Optimal techniques are required in order to minimize the number of patients with infective endocarditis that fall into the "culture-negative" category, without resorting to an excessive number of costly blood cultures.[14,15]

Evidence

Typically, the bacteremia associated with endocarditis is continuous, with 10–200 colony-forming units per milliliter of blood.[18] If this were true in every case, it would only be necessary to draw one single sample of about one milliliter of venous blood in order to make the diagnosis. In practice, however, some patients with IE have intermittent or fluctuating bacteremia, and some have less than one organism per milliliter of blood. Therefore, the number of positive culture results is directly correlated with the number of blood samples drawn and the volume of blood in each individual sample.

Single samples should not be drawn because the most common contaminants of blood cultures, coagulase-negative staphylococci from the skin, can cause IE.[12,19–21] Therefore, a single sample drawn from a patient who might have IE, which is positive for a coagulase-negative staphylococcus, is uninterpretable.

Overall, about two thirds of all samples drawn from patients with IE are positive. This figure represents the combined results from two patient populations. The first group includes the "classical" untreated IE patient with continuous bacteremia in whom all or nearly all cultures will be positive.[22] In such patients, more than 90% will be diagnosed by the first sample drawn, rising to more than 95% from three cultures.[19–22] The second population is a mixed group in whom the proportion of positive cultures is much lower. Many of these patients have received some antibiotic treatment, such as empirical oral ampicillin or cephalosporin, which has temporarily or permanently suppressed the bacteremia and turned the blood cultures negative without curing the underlying endocarditis. Others may have difficult-to-culture organisms, fungal infections or culture-negative IE.[14]

In order to decrease the number of "culture-negative" endocarditis episodes, investigators have tried to improve the yield by drawing blood during fever spikes, or by culturing arterial instead of venous blood.[23] These practices are of marginal or no value.

The majority of clinical microbiology laboratories routinely hold their blood culture bottles for 5–7 days before issuing a negative report. Because some of the etiologic agents, for example, HACEK group organisms,[24,25] have been traditionally regarded as slow-growers, some laboratories have adopted the policy of prolonging incubation times for blood cultures to 14–21 days in cases of suspected infective endocarditis. Recent data, however, suggest that with modern, improved blood culture media this practice may be unnecessary for all but a very few organisms, such as *Bartonella* spp.[10,12,26,27]

Should transesophageal echocardiography be performed in all patients with suspected infective endocarditis?

Background

Transthoracic M-mode echocardiography (TTE) was first used for the detection of vegetations associated with endocarditis

Conclusions	Grading	Comments/references
Draw at least two sets (two separate venepunctures, with each sample divided equally between two bottles) for each blood culture ordered	**Grade A**	This helps to identify contaminants and increases yield of positives[12,14,15,19]
Inoculate 8–12 ml blood into each bottle	**Grade B**	This maximizes yield of positives[12,14,15,19]
Hold the culture bottles for 14–21 days before issuing the final negative report in order to minimize "culture-negative" episodes (not recommended)	**Grade C**	The yield is very low after 5 days[12,27]
Draw an arterial blood sample for culture if venous blood samples are negative but the diagnosis of IE still seems likely (not recommended)	**Grade C**	The benefit of culturing arterial blood is none or very small[23,28]

in 1973. Several years later a report describing two dimensional transthoracic echocardiographic findings of vegetations was published. Since then there have been many reports on the use of this technology to assist in the diagnosis of endocarditis.[29–45] The sensitivity of the procedure for detection of vegetations is 60–75%.[29–32]

Transesophageal echocardiography (TEE) was initially described in the late 1980s, and has proved especially valuable in evaluating patients with suspected endocarditis. TEE is more sensitive than TTE for detection of vegetations, abscesses, valve perforations, and other complications of IE.[30,35] Because a TEE examination is more costly than a TTE examination, many comparative studies have been undertaken to determine which technology should be used in the initial diagnostic evaluation of a patient with suspected IE.

Evidence

Multiple studies have demonstrated the superior sensitivity of TEE when compared to TTE. However, this fact does not resolve the question of which is the most appropriate and cost effective test for IE in patients with different pretest probabilities of having that disease.

Transthoracic echocardiography (TTE) has an overall sensitivity for detection of intracardiac vegetations of 60–75%.[32] Transesophageal echocardiography (TEE) has greater sensitivity – 95% or better overall, although the sensitivity in an individual case varies depending upon factors such as the location and size of the vegetations.[30,35–40]

TEE is far superior to TTE in detecting abscesses in patients with both native and prosthetic valve endocarditis (PVE), with a sensitivity of detection of 87%, as compared to 28% with TTE in one study.[41] Because patients with PVE are more likely than those with native valve endocarditis (NVE) to have perivalvular abscesses, it is now accepted that TEE is the technique of choice in evaluating a patient with suspected PVE. TEE should also be applied in cases of NVE where there is a prolonged clinical course of infection, as well as those patients who do not respond to adequate medical therapy.

The need for TEE in the initial evaluation of patients with NVE, however, is not so clear. In a retrospective analysis of 180 patients referred for echocardiography for suspected infective endocarditis, in whom both TTE and TEE were done, the TTE was reported as technically inadequate in 46 patients (25%). In the remaining 134 patients, there was an almost equal distribution of patients who had a positive TTE (41 patients), a negative TTE (46 patients), and an abnormal but non-diagnostic TTE (47 patients). All patients who had a positive TTE were subsequently found to have a positive TEE, while only two patients with a negative TTE were found to have a positive TEE, yielding a sensitivity of 100% and a specificity of 96%. The principal value of the TEE was in the non-diagnostic group, as well as those with a technically inadequate TTE. In the non-diagnostic group, 9 patients (41%) were found to have positive TEE results for vegetations or abscesses. The study concluded that for initial evaluation of suspected native valve endocarditis, a TTE should be the first echocardiographic study. If the TTE is technically inadequate, then a TEE should be performed. If the TTE is clearly positive, or clearly negative, no additional echocardiographic study should be performed, as there was no incremental diagnostic value with TEE. A TEE, however, should be routinely performed if the TTE is abnormal but non-diagnostic.

Another study analyzed the diagnostic value of echocardiography in suspected infective endocarditis, based on the pretest probability of disease.[42] In this study, both TTE and TEE were performed on 105 consecutive patients with suspected endocarditis. On the basis of clinical criteria and (separately) echocardiography, patients were classified as having either low, intermediate, or high probability of endocarditis. Echocardiography had low diagnostic value in patients with a low clinical probability of endocarditis, using either TTE or TEE. The authors concluded that echocardiography

Conclusions	Grading	Comments/references
Echocardiography should not be used routinely as a screening test to "rule out endocarditis" in patients with fever and murmur	**Grade B**	Not cost effective unless there is other evidence of IE, raising the pretest probability[30,32,42]
For suspected native valve infective endocarditis, TTE should be the initial echocardiographic study	**Grade A**	This is the most cost effective approach[32,42]
If the TTE is technically inadequate in a patient with intermediate or high clinical probability of IE, then TEE should be performed	**Grade A**	Otherwise the diagnosis may be missed[32,42]
If the TTE is abnormal but non-diagnostic in a patient with intermediate or high pretest clinical probability of IE, then TEE should be performed	**Grade B**	TEE is more sensitive[32,42]
If the TTE is negative or abnormal but non-diagnostic in a patient with high pretest clinical probability of IE, then TEE should be performed	**Grade B**	TEE is more sensitive[32,42]
If the TTE is technically adequate and positive, no additional echocardiographic studies are warranted initially – that is, it is not necessary to "confirm" a positive TTE with a TEE study	**Grade B**	Note however that TEE may be performed for other reasons, such as to detect abscesses[32,42]
In patients with suspected prosthetic valve endocarditis, TEE should be performed	**Grade A**	TEE is best for detection of abscesses[30,32,41,42]

should not be used to make a diagnosis of IE in patients with a low clinical probability of disease. In addition, for those patients with an intermediate or high clinical probability of IE, TTE should be the initial echocardiographic procedure, reserving TEE for those patients with prosthetic valves and those with either a technically inadequate TTE, or a TTE which indicates an intermediate probability of endocarditis.[42]

How can the diagnosis of suspected IE be confirmed?

Background

The vegetations of IE are located in an inaccessible site, and can be visualized directly only at surgery or autopsy. Therefore, for purposes of initial diagnosis of IE they must be visualized indirectly, usually by means of echocardiography. Positive findings on echocardiography are a major criterion for diagnosis of IE, but they are not definitive because of possible false positive or false negative results.[43–45] Likewise, blood cultures, which constitute the second major criterion for diagnosis of IE, also can yield false positive or false negative results.

Evidence

In 1981, von Reyn and colleagues[46] published a paper on infective endocarditis in which they proposed a set of diagnostic criteria which designated cases as definite, probable, possible, or rejected. These criteria, however, contained some confusingly worded definitions and did not utilize findings from echocardiography, which had only recently come into general use. In 1994, Durack and colleagues from the Duke Endocarditis Service published improved criteria which introduced the concept of major and minor diagnostic criteria and included echocardiographic findings.[13] (Tables 57.2 and 57.3). Subsequently, multiple studies have analyzed cases diagnosed by the gold standard of pathologic confirmation at surgery or autopsy, comparing both sets of criteria. In each of these studies the Duke criteria were found to be notably more sensitive than the von Reyn criteria.[47–51] In most of these studies, it was felt that the inclusion of echocardiographic data was the primary factor resulting in the increased sensitivity, although even when compared with a modified von Reyn classification with addition of echocardiographic data, there still was an increase in sensitivity. Often increased sensitivity is associated with a concomitant decrease in specificity, but two studies indicate that the Duke criteria have good specificity.[52,53] These criteria

Table 57.2 Criteria for diagnosis of infective endocarditis

Definite infective endocarditis

Pathologic criteria

Micro-organisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess, *or*

Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical criteria (use specific definitions listed in Table 57.3)

2 major criteria, *or*

1 major and 3 minor criteria, *or*

5 minor criteria

Possible infective endocarditis

Findings consistent with infective endocarditis that fall short of "Definite," but not "Rejected"

Rejected

Firm alternative diagnosis for manifestations of endocarditis, *or*

Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*

No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

Adapted from Durack *et al*[13] with permission

Conclusions	Grading	Comments/references
The diagnosis of IE is certain only if confirmed by suitable pathologic specimens and/or cultures obtained at surgery or autopsy	**Grade A**	Echocardiography can yield false positives[13]
A "definite" diagnosis of IE (more than 95% confidence) can be made without surgical or autopsy specimens if defined major and minor criteria (the Duke criteria) are properly applied	**Grade A**	13,47–50
The diagnosis of IE can be rejected with high specificity if defined clinical criteria are properly applied, but this usually requires some delay to allow a period of observation	**Grade A**	52,53
The decision as to whether or not to begin antibiotics should be made on the overall clinical assessment as to the likelihood of IE, not based solely upon the Duke criteria	**Grade B**	Treatment decisions often need to be made before all diagnostic information is available[13,53]

should be useful to specify patient entry criteria for epidemiologic studies and clinical trials involving IE.

Can IE be cured with bacteriostatic antimicrobials?

Background

Antimicrobial agents are traditionally classified as bactericidal or bacteriostatic, according to whether they kill or inhibit growth, respectively. In fact, this classification is an oversimplification because an antimicrobial drug may be partially bactericidal, or may be bacteriostatic for one species of bacteria and bactericidal for another. There is a widely quoted "general rule" that IE should be treated only with bactericidal drugs. The rationale often given to support this "rule" is that colonies of bacteria within a vegetation are protected from host defenses, especially neutrophils, which in other sites would usually eliminate organisms that had been inhibited by bacteriostatic antibiotics.

Table 57.3 Definitions of terminology used in the diagnostic criteria for endocarditis

Major criteria

Positive blood culture for infective endocarditis

Typical micro-organism for infective endocarditis from two separate blood cultures:
Viridans streptococci,[a] *Streptococcus bovis*, HACEK group, or community acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, *or*

Persistently positive blood culture, defined as recovery of a micro-organism consistent with infective endocarditis from:
(i) Blood cultures drawn more than 12 hours apart, *or*
(ii) All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart

Evidence of endocardial involvement

Positive echocardiogram for infective endocarditis
(i) Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jet, *or* on implanted material, in the absence of an alternative anatomic explanation, *or*
(ii) Abscess, *or*
(iii) New partial dehiscence of prosthetic valve, *or*

New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

Minor criteria

- Predisposition: predisposing heart condition *or* injection drug use
- Fever: ≥ 38·0 °C (100·4 °F)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- Microbiologic evidence: positive blood culture, but not meeting major criterion as previously defined[b] *or* serologic evidence of active infection with organism consistent with infective endocarditis[c]
- Echocardiogram: consistent with infective endocarditis but not meeting major criterion as previously defined

[a] Including nutritional variant strains.
[b] Excluding single positive cultures for coagulase-negative staphylococci or organisms that do not cause endocarditis.
[c] Positive serology for *Coxiella burnetii* or *Bartonella* spp may be used as a major criteria.
HACEK, *Haemophilus* spp, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp, and *Kingella kingae*
Source: adapted from Durack *et al*[13]

Evidence

In the early days of antimicrobial therapy before penicillin was available, patients with IE were often treated with prolonged courses of sulfonamides. This nearly always failed. For example, in one study none of 42 patients with streptococcal IE treated with sulfonamides survived.[54] On the other hand, sulfonamide therapy occasionally cured a fortunate patient.[55] Sulfonamides were most likely to succeed in the small subgroup of cases of IE caused by *Haemophilus* spp, which are especially susceptible to sulfonamides. In the special case of IE caused by *Coxiella burnetii* (the organism causing Q fever) bacteriostatic antibiotics such as tetracyclines are generally used for lack of better alternatives. In most cases they suppress but do not cure the endocardial infection; valve replacement surgery is required to increase the likelihood of cure. Similarly, few antibiotics are available to treat IE caused by resistant Gram-negative bacilli such as *Pseudomonas cepacia* or *Stenotrophomonas maltophilia*, in these the combination of a (bacteriostatic) sulfonamide plus trimethoprim has been used with some success.[56]

Should combinations of antimicrobials be used to treat IE?

Background

IE is generally regarded as being difficult and/or slow to cure. Therefore, many attempts have been made to improve cure rates by using optimal antimicrobial regimens, even more so than in most other infections. In the course of this effort, many combinations of antibiotics have been tried,

Conclusions	Grading	Comments/references
Bacteriostatic antibiotics often fail when used to treat IE	**Grade A**	There are animal data and case reports to show this[54,55]
Bacteriostatic antibiotics may be used to treat IE in a few special cases, for example, Q fever, resistant organisms like *Pseudomonas cepacia* or *Stenotrophomonas maltophilia*, or suppressive therapy for organisms not likely to be curable, such as *Pseudomonas* on a prosthetic valve	**Grade B**	Uncontrolled case reports show that cure or useful suppression can be achieved in some patients[56,57]

and a general impression exists that combination therapy is optimal for treatment of IE. This is only partly true.

Evidence

There is excellent documentation that enterococcal endocarditis usually is best treated with a combination of two antibiotics. The primary reason for this is that most strains of *Enterococcus faecalis* are relatively resistant to antibiotics, but are killed synergistically by a combination of a penicillin and an aminoglycoside.[58] This does not hold true, however, if the strain shows high level resistance to aminoglycosides (defined as resistance to 2000 micrograms/ml of streptomycin or 500 micrograms/ml of gentamicin). In the latter case, vancomycin should be substituted,[59] except for strains that are vancomycin resistant.[60] Ample documentation for the value of combination therapy has been published, based upon *in vitro* studies, and *in vivo* treatment of both animals and humans. Unfortunately, the frequency of high level resistance among enterococci has greatly increased over the past 15 years, making the choice of optimal therapy more difficult.[65]

Even when streptococci are fully sensitive to penicillin, combinations of a penicillin and an aminoglycoside or vancomycin act synergistically against them, so long as the strain is not vancomycin resistant (VRE) or has high level resistance to aminoglycosides.[61] This has been convincingly demonstrated both *in vitro* and in experimental animals.[62,63] The human correlate is found in the fact that combination therapy cures more than 97% of cases caused by penicillin-sensitive viridans streptococci within 2 weeks, whereas penicillin alone cures only 80–85% in the same interval, and requires 4 weeks to reach 97% cure or better. This fact has been well proven.[54,64]

What is the optimal duration of treatment for IE?

Background

Early experience established that endocarditis could not be cured by short courses of antibiotics (7–10 days) that would have been adequate to cure other common infections such as pneumonia or gonorrhea. Trials of longer duration were more successful, eventually leading to the widely followed practice of treating IE for 6 weeks. This remains common practice today, despite the fact that more than half of all cases of IE could be reliably cured by 2–4 weeks of treatment.

Evidence

Before 1950 it was reported that IE could not be cured with 10 days of treatment, even when the organisms were highly susceptible to penicillin and/or high doses were given.[56,74,75] Subsequently, high cure rates were achieved by extending treatment to 4–6 weeks. For many years, 6 weeks of therapy was regarded as the standard duration for treatment of IE. In fact, this "rule" often led to overtreatment because 4 weeks would have been adequate for the majority of these cases.[55] Because of number preferencing for even numbers, 3 and 5 week regimens have not been studied, even though intuitively it seems likely that these durations would work as well as 4 and 6 week regimens, respectively.

Some cases of endocarditis can be cured with treatment for only 2 weeks. This is well supported by clinical experience for two important groups of patients: uncomplicated penicillin sensitive streptococcal native valve endocarditis,[55,76] and intravenous drug addicts with right-sided *S. aureus* endocarditis.[70]

It should be noted that outpatient parenteral antibiotic therapy (OPAT) is appropriate for selected patients with IE.[76–79] In most cases, these will be patients without serious complications who have responded promptly to standard therapy begun in hospital. When OPAT is employed for treatment of IE, the total duration of therapy should normally be the same as if the patient had been hospitalized throughout the course of treatment.

The **B** ratings listed in the conclusions below could be improved by publication of larger numbers of cases or by randomized controlled studies.

Conclusions	Grading	Comments/references
Combination therapy should be used for IE caused by enterococci	**Grade A**	60, 66
A combination of at least two antibiotics (a β lactam plus an aminoglycoside) should be used for IE caused by coagulase-negative staphylococci	**Grade A**	67, 68
A combination of three antibiotics (a β lactam plus an aminoglycoside plus rifampin) should be used for IE caused by coagulase-negative staphylococci	**Grade C**	Limited number of patients reported; no comparative trials[67,68]
An aminoglycoside should be added to a β lactam for the first few days of therapy for IE caused by *S. aureus*	**Grade C**	A definitive outcome study has not been done[68,69]
Combination therapy should be used for right-sided IE caused by *S. aureus* if a short course (2 week) regimen is used	**Grade B**	Only one major study available[70,71,72]
Addition of an aminoglycoside for IE caused by penicillin sensitive streptococci is beneficial and cost effective if a short course (2 week) regimen is used	**Grade A**	73
Addition of an aminoglycoside for IE caused by penicillin sensitive streptococci is beneficial and cost effective if a standard (4 week) regimen is used	**Grade C**	No modern cost effectiveness study has been done[73]

Conclusions	Grading	Comments/references
Penicillin sensitive IE can be cured in 2 weeks by combined penicillin plus aminoglycoside, or in 4 weeks by penicillin alone	**Grade A**	73, 80
Enterococcal endocarditis should be treated for at least 4 weeks	**Grade B**	59, 73, 81, 82
Most cases of HACEK endocarditis can be cured in 3–4 weeks (*Haemophilus, Actinobacilllus, Cardiobacterium, Eikenella*, *Kingella* spp)	**Grade B**	Total number of reported cases is small[73,83,84]
Most cases of tricuspid valve *S. aureus* IE in intravenous drug users can be cured in 2 weeks	**Grade B**	Only one major study done[70]
Results of treatment for IE in HIV infected patients with >200 CD4 lymphocytes/mm^3 are similar to results in non-HIV patients	**Grade B**	72
HIV infected patients with <200 CD4 lymphocytes and IE have a worse prognosis, and therefore should not receive short-course (2 week) antibiotic therapy for IE	**Grade C**	This has not been formally studied[72]
Most cases of left-sided native valve *S. aureus* IE can be cured in 4 weeks	**Grade B**	Controlled study not done[73]

What are the main indications for surgical intervention during management of IE?

Background

The introduction of valve replacement, valve repair, and other surgical procedures has revolutionized the management of IE, being second in importance only to the advent of antibiotic therapy for IE. Many studies have indicated that surgical intervention improves the prognosis of IE over medical therapy alone.[85–87] The benefits of early rather than late surgical intervention have been appropriately emphasized.[86–88] However, surgical placement of artificial cardiac valves is associated with high costs, significant morbidity, especially in the form of late complications, and some mortality. Furthermore, about two thirds of all patients with IE can be cured without any surgical intervention. Therefore, correct selection of the

subgroup of about one third of patients who will benefit from surgery becomes of critical importance.

Evidence

Many hundreds of publications have reported on experience with surgery for IE, beginning in 1965[89] and continuing unabated today. The cumulative experience is based upon thousands of patients. However, this extensive experience does not include randomized studies of medical versus surgical therapy, primarily because selection bias (that is, choosing more seriously ill patients for surgery) is virtually impossible to overcome. Therefore, the conclusions which have emerged, although often well supported by case studies, can only be rated **B** in terms of evidence-based analyses.

What is the correct timing for valve replacement during management of IE?

Background

In the past, it was often stated on empirical grounds that valve replacement surgery should be postponed until the patient had been cured by antibiotics. If the patient could not survive until cure, it was believed that surgery should be delayed as long as possible to allow suppression of the number of remaining bacteria to the lowest possible level to reduce the risk of relapse or infection of the new prosthetic valve. The available evidence does not support these widely held views.

Evidence

Actual experience showed that the frequency of relapse and/or infection of the prosthesis after surgery for IE is low,

Conclusions I: Strong indications for surgical intervention during IE	Grading	Comments/references
Heart failure unresponsive to medical therapy	**Grade B**	7, 8, 87, 90
Presence of a valve ring abscess	**Grade B**	7, 8, 90, 91, 92
Early prosthetic valve infection (onset within 60 days of surgery)	**Grade B**	7, 8, 90, 93
Prosthetic valve infection caused by *S. aureus*	**Grade B**	7, 8, 68, 71, 92, 93
Prosthetic valve infection caused by Gram-negative bacilli (not HACEK group)	**Grade B**	7, 8, 93
Endocarditis caused by filamentous fungi (not yeasts)	**Grade B**	94, 95
Prosthetic valve infection caused by yeasts	**Grade B**	93, 96
Development of a sinus of Valsalva aneurysm	**Grade B**	97
Occlusion of valves by very large vegetations	**Grade B**	7, 8, 98

Conclusions II: Relative (less strong) indications for surgical intervention during IE	Grading	Comments/references
Recurrent arterial emboli	**Grade C**	7, 8, 99, 100
Native left-sided valve infection caused by *S. aureus*	**Grade C**	7, 8, 68, 71
Apparent failure of medical therapy (persistent bacteremia, persistent fever, increase in size of vegetation during treatment)	**Grade C**	7, 8, 90
Native valve infection caused by Gram-negative bacilli (not HACEK)	**Grade C**	7, 8
Large-sized left-sided vegetations by echo (greater than 15–20 mm)	**Grade C**	7, 8
Native valve infection caused by yeasts	**Grade C**	95, 96, 101–103
Late onset prosthetic valve infection	**Grade C**	7, 8, 93
Development of cardiac conduction abnormality during IE, but no abscess identified by TEE	**Grade C**	7, 8, 91

whether or not antibiotics had been given for long periods before operation. For patients with a good indication for valve replacement early in the course of active endocarditis, many authors have strongly advocated early surgery, before antibiotics have cured the patient, to avoid deaths and complications that might occur during antibiotic treatment.[85–88]

Can IE be prevented?

Background

IE sometimes develops as a complication of bacteremias associated with medical and dental procedures, such as urinary catheterizations or tooth extractions. Although these cases represent only a small proportion – about 5% – of all cases of IE, much effort has been made to prevent them because IE carries high associated morbidity and mortality. Soon after antibiotics became available, various attempts were made to prevent bacteremias and/or IE by giving antibiotics before dental extractions or other procedures.[104–108] Subsequently, the American Heart Association[109] and many other groups[110–112] have issued recommendations for prevention of IE by this means.

Evidence

The evidence that bacteremias induced by medical and dental procedures can cause IE in patients with predisposing heart lesions consists of many uncontrolled case reports. There are sufficient numbers of these to support the conclusion that there is a real risk after tooth extractions and procedures involving an infected genitourinary tract.[113–115] The evidence that lower-risk procedures such as gastrointestinal endoscopy, procedures on the uninfected urinary tract, and biopsies and other minor surgical procedures cause a significant number of cases of IE is sketchy.[108,116–114]

Prophylaxis of IE has been proven unequivocally to be effective in experimental animal models of endocarditis by giving antibiotics before injecting bacteria intravenously.[125–132] However, there has been no definitive study to demonstrate efficacy of antibiotic prophylaxis for infective endocarditis in humans.[116] One review of patients with prosthetic heart valves indicated that antibiotic prophylaxis before dental and urogenital procedures was effective,[133] but this study was retrospective, unrandomized, and unblinded. Analysis of prospectively collected cases in the Netherlands indicated that prophylaxis was either ineffective or, at best, only

Conclusions	Grading	Comments/ references
If there is no indication for early surgery, complete a standard course of antibiotic treatment before valve replacement.	**Grade B**	No randomized studies available[90]
If there is an adequate indication for early surgery, proceed to valve replacement without regard to the duration of antibiotic treatment already given. Delay can result in avoidable complications or death.	**Grade A**	Many uncontrolled reports support early surgery[85–88,90]

Conclusions	Grading	Comments/ references
Bacteremias following tooth extraction or surgical procedures involving an infected genitourinary tract can cause endocarditis	**Grade B**	137
Bacteremias following gastrointestinal endoscopy or surgical procedures involving an uninfected genitourinary tract can cause endocarditis	**Grade C**	124, 137, 138
Prevention of IE by giving antibiotics before medical and dental procedures that cause bacteremia is an empiric practice which has been proven effective in animal models but not in humans	**Grade A**	116, 129
Attempted prevention of IE in selected high-risk groups undergoing high-risk procedures such as tooth extraction is probably effective	**Grade C**	133
Attempted prevention of IE in selected high-risk groups undergoing high-risk procedures such as tooth extraction is recommended	**Grade B**	110–112
Extensive practice of attempted prophylaxis for IE is probably not cost effective	**Grade B**	139, 140

marginally effective.[134] Other analyses have indicated that even if prophylaxis is effective, it would probably not be cost effective as a general strategy.[135,136] Despite all this uncertainty, most authorities continue to recommend selective use of prophylaxis for patients with higher risk cardiac lesions undergoing higher risk procedures.[109,116]

References

1. Durack DT, Beeson PB. Experimental bacterial endocarditis. I. Colonization of a sterile vegetation. *Br J Exp Pathol* 1972;**53**:44–9.
2. Angrist A, Oka M, Nakao K. Vegetative endocarditis. *Pathol Ann* 1967;**2**:155–212.
3. Blanchard DG, Ross RS, Dittrich HC. Nonbacterial thrombotic endocarditis. *Chest* 1993;**102**:954–6.
4. Rodbard S, Yamamoto C. Effect of stream velocity on bacterial deposition and growth. *Cardiovasc Res* 1969;**3**:68–74.
5. Grant RT, Wood JE, Jr, Jones TD. Heart valve irregularities in relation to subacute bacterial endocarditis. *Am Heart J* 1928; **14**:247–61.
6. Moreillon P, Que YA, Bayer AS. Pathogenesis of streptococcal and staphylococcal endocarditis. *Infect Dis Clin North Am* 2002;**16**:297–318.
7. Durack DT. Infective and noninfective endocarditis. In: Hurst JW, ed. *The heart, arteries and veins, 7th edn*. New York: McGraw-Hill, 1990.
8. Scheld WM, Sande MA. Endocarditis and intravascular infections. In: Mandell GL, Douglas RG, Jr, Dolin R, eds. *Principles and practice of infectious diseases, 4th edn*. New York: Churchill Livingstone, 1995.
9. Cabell CH, Abruytn E. Progress toward a global understanding of infective endocarditis: early lessons from the International Collaboration on Endocarditis investigation. *Infect Dis Clin North Am* 2002;**16**:255–72.
10. Houpikian P, Raoult D. Diagnostic methods: current best practices and guidelines for identification of difficult-to-culture pathogens in endocarditis. *Infect Dis Clin North Am* 2002;**16**:377–92.
11. Schwartzman WA, Marchevsky A, Meyer RD. Epithelioid angiomatosis or cat scratch disease with splenic and hepatic abnormalities in AIDS: case report and review of the literature. *Scand J Infect Dis* 1990;**22**:121–33.
12. Towns ML, Reller LB. Diagnostic methods: current best practices and guidelines for isolation of bacteria and fungi. *Infect Dis Clin North Am* 2002;**16**:363–76.
13. Durack DT, Bright DK, Lukes AS, Duke Endocarditis Service. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med* 1994;**96**:200–9.
14. Washington JA, II. The role of the microbiology laboratory in the diagnosis and antimicrobial treatment of infective endocarditis. *Mayo Clin Proc* 1982;**57**:22–32.
15. Washington JA. The microbiological diagnosis of infective endocarditis. *J Antimicrob Chemother* 1987;**20**:29–39.
16. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. *Medicine* 1988;**67**:248–69.
17. Gullberg RM, Homann SR, Phair JP. Enterococcal bacteremia: analysis of 75 episodes. *Rev Infect Dis* 1989;**11**:74–85.
18. Beeson PB, Brannon ES, Warren JV. Observations of the sites of removal of bacteria from the blood in patients with bacterial endocarditis. *J Exp Med* 1945;**81**:9–23.
19. Weinstein M, Reller L, Murphy J, Lichtenstein K. Clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. *Rev Infect Dis* 1983;**5**:35–53.
20. Towns M, Quartey S, Weinstein M *et al.* Clinical significance of positive blood cultures: a prospective, multicenter investigation. ASM 1993; Abstract No. C232: Abstract.
21. Weinstein M, Murphy J, Reller L, Lichtenstein K. Clinical significance of positive blood cultures: A comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. *Rev Infect Dis* 1983;**5**:54–70.
22. Belli J, Waisbren BA. The number of blood cultures necessary to diagnose most cases of bacterial endocarditis. *Am J Med Sci* 1956;**232**:284–8.
23. Mallen MS, Hube EL, Brenes M. Comparative study of blood cultures made from artery, vein, and bone marrow in patients with subacute bacterial endocarditis. *Am Heart J* 1946;**XX**: 692–5.
24. Geraci JE, Wilson WR. Endocarditis due to gram-negative bacteria: report of 56 cases. *Mayo Clin Proc* 1982;**57**:145–8.
25. Chen YC, Chang SC, Luh KT, Hsieh WC. *Actinobacillus actinomycetemcomitans* endocarditis: a report of four cases and review of the literature. *QJM* 1992;**81**:871–8.
26. Drancourt M, Birtles R, Chaumentin G, Vandenesch F, Etienne J, Raoult D. New serotype of *Bartonella henselae* in endocarditis and cat-scratch disease. *Lancet* 1996;**347**: 441–3.
27. Doern GV, Davaro R, George M, Campognone P. Lack of requirement for prolonged incubation of Septi-Chek blood culture bottles in patients with bacteremia due to fastidious bacteria. *Diagn Microbiol Infect Dis* 1996;**24**:141–3.
28. Murray M, Moosnick F. Arterial vs venous blood cultures. *J Lab Clin Med* 1940;**26**:382–7.
29. Gilbert BW, Haney RS, Crawford F *et al.* Two-dimensional echocardiographic assessment of vegetative endocarditis. *Circulation* 1977;**55**:346–53.
30. Sachdev M, Peterson G, Jollis JG. Diagnostic methods: imaging techniques for diagnosis of endocarditis. *Infect Dis Clin North Am* 2002;**16**:319–38.
31. Stewart JA, Silimperi D, Harris P, Wise NK, Fraker TD, Jr, Kisslo JA. Echocardiographic documentation of vegetative lesions in infective endocarditis: clinical implications. *Circulation* 1980;**61**:374–80.
32. Irani WN, Grayburn PA, Afridi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. *Am J Cardiol* 1996;**78**: 101–3.
33. Jaffe WM, Morgan DE, Pearlman AS, Otto CM. Infective endocarditis, 1983–1988: echocardiographic findings and factors influencing morbidity and mortality. *J Am Coll Cardiol* 1990;**15**:1227–33.

34.Martin RP. The diagnostic and prognostic role of cardiovascular ultrasound in endocarditis: bigger is not better. *J Am Coll Cardiol* 1990;**15**:1234–7.
35.Taams MA, Gussenhoven EJ, Bos E *et al.* Enhanced morphological diagnosis in infective endocarditis by transesophageal echocardiography. *Br Heart J* 1990;**63**:109–13.
36.Rohmann S, Erbel R, Gorge G *et al.* Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. *Eur Heart J* 1992;**12**:446–52.
37.Shapiro SM, Bayer AS. Transesophageal and Doppler echocardiography in the diagnosis and management of infective endocarditis. *Chest* 1991;**100**:1125–30.
38.Pedersen WR, Walker M, Olson JD *et al.* Value of transesophageal echocardiography as an adjunct to transthoracic echocardiography in evaluation of native and prosthetic valve endocarditis. *Chest* 1991;**100**:351–6.
39.Morguet AJ, Werner GS, Andreas S, Kreuzer H. Diagnostic value of transesophageal compared with transthoracic echocardiography in suspected prosthetic valve endocarditis. *Herz* 1995;**20**:390–8.
40.Anders K, Foley K, Stern WE, Brown WJ. Intracranial sparganosis: an uncommon infection. Case report. *J Neurosurg* 1984;**60**:1282–6.
41.Daniel WG, Mugge A, Martin RP *et al.* Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med* 1991;**324**: 795–800.
42.Lindner JR, Case RA, Dent JM *et al.* Diagnostic value of echocardiography in suspected endocarditis. An evaluation based on the pretest probability of disease. *Circulation* 1996;**93**:730–6.
43.Hickey AJ, Wolfers J. False positive diagnosis of vegetations on a myxomatous mitral valve using two-dimensional echocardiography. *Aust NZ J Med* 1982;**12**:540–2.
44.Mintz GS, Kotler MN. Clinical value and limitations of echocardiography. Its use in the study of patients with infectious endocarditis. *Arch Intern Med* 1980;**140**:1022–7.
45.Sokil AB. Cardiac imaging in infective endocarditis. In: Kaye D, ed. *Infective endocarditis. 2nd edn.* New York: Raven Press, 1992.
46.von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. *Ann Intern Med* 1981;**94**:505–17.
47.Bayer AS, Ward JI, Ginzton LE, Shapiro SM. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. *Am J Med* 1994;**96**:211–19.
48.Del Pont JM, De Cicco LT, Vartalitis C *et al.* Infective endocarditis in children: clinical analyses and evaluation of two diagnostic criteria. *Pediatr Infect Dis* 1995;**14**:1079–86.
49.Fournier PE, Casalta JP, Habib G, Messana T, Raoult D. Modification of the diagnostic criteria proposed by the Duke Endocarditis Service to permit improved diagnosis of Q fever endocarditis. *Am J Med* 1996;**100**:629–33.
50.Cecchi E, Parrini I, Chinaglia A *et al.* New diagnostic criteria for infective endocarditis. A study of sensitivity and specificity. *Eur Heart J* 1997;**18**:1149–56.
51.Olaison L, Hogevik H. Comparison of the von Reyn and Duke criteria for the diagnosis of infective endocarditis: a critical analysis of 161 episodes. *Scand J Infect Dis* 1996;**28**: 399–406.
52.Hoen B, Beguinot I, Rabaud C *et al.* The Duke criteria for diagnosing infective endocarditis are specific: analysis of 100 patients with acute fever or fever of unknown origin. *Clin Infect Dis* 1996;**23**:298–302.
53.Dodds GA, Sexton DJ, Durack DT, Bashore TM, Corey GR, Kisslo J. Negative predictive value of the Duke criteria for infective endocarditis. *Am J Cardiol* 1996;**77**:403–7.
54.Galbreath WR, Hull E. Sulfonamide therapy of bacterial endocarditis: results in 42 cases. *Ann Intern Med* 1943;**18**:201–3.
55.Durack DT. Review of early experience in treatment of bacterial endocarditis, 1940–1955. In: Bisno AL, ed. Treatment of infective endocarditis. New York: Grune & Stratton, 1981.
56.Speller DCE. *Pseudomonas cepacia* endocarditis treated with co-trimazole and kanamycin. *Br Heart J* 1972;**35**:47–8.
57.Street AC, Durack DT. Experience with trimethoprim-sulfamethoxazole in treatment of infective endocarditis. *Rev Infect Dis* 1988;**10**:915–21.
58.Wilson WR, Wilkowske CJ, Wright AJ, Sande MA, Geraci JE. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. *Ann Intern Med* 1984; **100**:816–23.
59.Watanakunakorn C, Bakie C. Synergism of vancomycin–gentamicin and vancomycin–streptomycin against enterococci. *Antimicrob Agents Chemother* 1973;**4**:120–4.
60.Caron F, Lemeland JF, Humbert G, Klare I, Gutmann L. Triple combination penicillin–vancomycin–gentamicin for experimental endocarditis caused by a highly penicillin- and glycopeptide-resistant isolate of *Enterococcus faecium. J Infect Dis* 1993;**168**:681–6.
61.Watanakunakorn C, Glotzbecker C. Synergism with aminoglycosides of penicillin, ampicillin and vancomycin against non-enterococcal group-D streptococci and viridans streptococci. *J Med Microbiol* 1976;**10**:133–8.
62.Sande MA, Irvin RG. Penicillin-aminoglycoside synergy in experimental *Streptococcus viridans* endocarditis. *J Infect Dis* 1974;**129**:572–6.
63.Fantin B, Carbon C. *In vivo* antibiotic synergism: contribution of animal models. *Antimicrob Agents Chemother* 1992;**36**: 907–12.
64.Geraci JE. The antibiotic therapy of infective endocarditis: therapeutic data on 172 patient seen from 1951 through 1957: additional observations on short-term therapy (two weeks) for penicillin-sensitive streptococcal endocarditis. *Med Clin North Am* 1958;**42**:1101–48.
65.Hoen B. Special issues in the management of infective endocarditis caused by gram-positive cocci. *Infect Dis Clin N Am* 2002;**16**:437–52.
66.Rice LB, Calderwood SB, Eliopoulos GM, Farber BF, Karchmer AW. Enterococcal endocarditis: a comparison of prosthetic and native valve disease. *Rev Infect Dis* 1991; **13**:1–7.
67.Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. *Ann Intern Med* 1983;**98**:447–55.
68.Karchmer AW. Staphylococcal endocarditis. In: Kaye D, ed. *Infective endocarditis, 2nd edn.* New York: Raven Press, 1992.
69.Sande MA, Courtney KB. Nafcillin-gentamicin synergism in experimental staphylococcal endocarditis. *J Lab Clin Med* 1976;**88**:118–24.

70. Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med* 1988;**109**:619–24.
71. Petti CA, Fowler VG. *Staphylococcus aureus* bacteremia and endocarditis. *Infect Dis Clin North Am* 2002;**16**: 419–36.
72. Miro JM, del Rio A, Mestres CA. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. *Infect Dis Clin North Am* 2002;**16**:273–96.
73. Wilson WR, Karchmer A, Dajani A *et al.* Antibiotic treatment of adults with infective endocarditis due to viridans streptococci, enterococci, staphylococci and HACEK microorganisms. *JAMA* 1995;**274**:1706–13.
74. King FH, Schneierson SS, Sussman ML, Janowitz HD, Stollerman GH. Prolonged moderate dose therapy versus intensive short term therapy with penicillin and caronamide in subacute bacterial endocarditis. *J Mt Sinai Hosp* 1949; **16**:35–46.
75. Bloomfield AL, Armstrong CD, Kirby WMM. The treatment of subacute bacterial endocarditis with penicillin. *J Clin Invest* 1945;**24**:251–67.
76. Kwon-Chung KJ, Hill WB. Studies on the pink, adenine-deficient strains of *Candida albicans*. I. Cultural and morphological characteristics. *Sabouraudia* 1970;**8**:48–59.
77. Francioli P, Etienne J, Hoigne R, Thys J, Gerber A. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks. Efficacy and outpatient treatment feasibility. *JAMA* 1992;**267**:264–7.
78. Francioli P, Ruch W, Stamboulian D, International Infective Endocarditis Study Group. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. *Clin Infect Dis* 1995;**21**:1406–10.
79. Stamboulian D, Bonvehi P, Arevalo C *et al.* Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. *Rev Infect Dis* 1991;**13**:S160–S3.
80. Wilson WR, Geraci JE, Wilkowske CJ, Washington JA. Short-term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci. *Circulation* 1978;**57**:1158–61.
81. Geraci JE, Martin WJ. Antibiotic therapy of bacterial endocarditis. VI. Subacute enterococcal endocarditis: clinical, pathologic and therapeutic consideration of 33 cases. *Circulation* 1954;**10**:173–94.
82. Moellering RC, Jr, Wennersten C, Weinstein AJ. Penicillin–tobramycin synergism against enterococci: a comparison with penicillin and gentamicin. *Antimicrob Agents Chemother* 1973;**3**:526–9.
83. Shorrock PJ, Lambert PA, Aitchison EJ, Smith EG, Farrell ID, Gutschik E. Serological response in *Enterococcus faecalis* endocarditis determined by enzyme-linked immunosorbent assay. *J Clin Microbiol* 1990;**28**:195–200.
84. Bieger RC, Brewer NS, Washington JA, II. *Haemophilus aphrophilus*: a microbiologic and clinical review and report of 42 cases. *Medicine* 1978;**57**:345–55.
85. Bogers AJJC, van Vreeswijk H, Verbaan CJ *et al.* Early surgery for active infective endocarditis improves early and late results. *Thorac Cardiovasc Surg* 1991;**39**:284–7.
86. Aranki SF, Adams DH, Rizzo RJ *et al.* Determinants of early mortality and late survival in mitral valve endocarditis. *Circulation* 1995;**92**:143–9.
87. Middlemost S, Wisenbaugh T, Meyerowitz C *et al.* A case for early surgery in native left-sided endocarditis complicated by heart failure: results in 203 patients. *J Am Coll Cardiol* 1991;**18**:663–7.
88. Jubair KA, Al Fagih MR, Ashmeg A, Belhaj M, Sawyer W. Cardiac operations during active endocarditis. *J Thorac Cardiovasc Surg* 1992;**104**:487–90.
89. Wallace AG, Young G, Jr, Osterhout S. Treatment of acute bacterial endocarditis by valve excision and replacement. *Circulation* 1965;**31**:450–3.
90. Olaison L, Pettersson G. Current best practices and guidelines: indications for surgical intervention in infective endocarditis. *Infect Dis Clin North Am* 2002;**16**:453–76.
91. DiNubile MJ, Calderwood SB, Steinhaus DM, Karchmer AW. Cardiac conduction abnormalities complicating native valve active endocarditis. *Am J Cardiol* 1986;**58**:1213–17.
92. Tucker KJ, Johnson JA, Ong T, Mullen WL, Mailhot J. Medical management of prosthetic aortic valve endocarditis and aortic root abscess. *Am Heart J* 1993;**125**:1195–7.
93. Karchmer AW, Longworth DL. Infections of intracardiac devices. *Infect Dis Clin North Am* 2002;**16**:477–506.
94. Woods GL, Wood P, Shaw BW, Jr. *Aspergillus* endocarditis in patients without prior cardiovascular surgery: report of a case in a liver transplant recipient and review. *Rev Infect Dis* 1989;**II**:263–72.
95. Fowler VG, Durack DT. Infective endocarditis. *Curr Opin Cardiol* 1994;**9**:389–400.
96. Guzman F, Cartmill I, Holden MP, Freeman R. Candida endocarditis: report of four cases. *Int J Cardiol* 1987;**16**: 131–6.
97. Scully RE, Mark EJ, McNeely WF, McNeely BU. Case records of the Massachussetts General Hospital. *N Engl J Med* 1996;**334**:105–11.
98. Khan SS, Gray RJ. Valvular emergencies. *Cardiol Clin* 1991; **9**:689–709.
99. Steckelberg JM, Murphy JG, Ballard D *et al.* Emboli in infective endocarditis: the prognostic value of echocardiography. *Ann Intern Med* 1991;**114**:635–40.
100. Sexton DJ, Spelman D. Current best practices and guidelines: assessment and management of complications of infective endocarditis. *Infect Dis Clin North Am* 2002;**16**:507–22.
101. Kawamoto T, Nakano S, Matsuda H, Hirose H, Kawashima Y. Candida endocarditis with saddle embolism: a successful surgical intervention (abstract). *Ann Thorac Surg* 1989; **48**:723–4.
102. Tanka M, Toshio A, Hosokawa S, Suenaga Y, Hikosaka H. Tricuspid valve *Candida* endocarditis cured by valve-sparing debridement. *Ann Thorac Surg* 1989;**48**:857–8.
103. Isalska BJ, Stanbridge TN. Fluconazole in the treatment of candidal prosthetic valve endocarditis. *BMJ* 1988;**297**:178–9.
104. Rhoads PS, Schram WR, Adair D. Bacteremia following tooth extraction: prevention with penicillin and N U 445. *J Am Dent Assoc* 1950;**41**:55–61.
105. Pressman RS, Bender IB. Antibiotic treatment of the gingival sulcus in the prevention of bacteremia. *Antibiotics Annual* 1954;92–104.

106.Northrop PM, Crowley MC. Further studies on the effect of the prophylactic use of sulfathiazole and sulfamerazine on bacteremia following extraction of teeth. *J Oral Surg* 1944;**2**:134.
107.Budnitz E, Nizel A, Berg L. Prophylactic use of sulfapyridine in patients susceptible to subacute bacterial endocarditis following dental surgical procedures. *J Am Dent Assoc* 1942;**29**:346.
108.Camara DS, Gruber M, Barde CJ, Montes M, Caruana JA, Jr, Chung RS. Transient bacteremia following endoscopic injection sclerotherapy of esophageal varices. *Arch Intern Med* 1983;**143**:1350–2.
109.Dajani AS, Taubert KA, Wilson WR *et al.* Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation* 1997;**96**:358–66.
110.Delaye J, Etienne J, Feruglio A *et al.* Prophylaxis of infective endocarditis for dental procedures. Report of a working party of the European Society of Cardiology. *Eur Heart J* 1985;**6**:826–8.
111.Michel MF, Thompson J, Boering G, Hess J, Van Putten PL. Revision of the guidelines of the Netherlands Heart Foundation for the prevention of endocarditis. *Geneesmiddelen-bull* 1986;**20**:53–6.
112.Shanson DC. Antibiotic prophylaxis of infective endocarditis in the United Kingdom and Europe. *J Antimicrob Chemother* 1987;**20**:119–31.
113.Meneely JK. Bacterial endocarditis following urethral manipulation. *N Engl J Med* 1948;**239**:708–9.
114.Slade N. Bacteriaemia and septicaemia after urological operations. *Proc R Soc Med* 1958;**51**:331–4.
115.Sullivan NM, Sutter VL, Mims MM, Marsh VH, Finegold SM. Clinical aspects of bacteremia after manipulation of the genitourinary tract. *J Infect Dis* 1973;**127**:49–55.
116.Durack D. Prevention of infective endocarditis. *N Engl J Med* 1995;**332**:38–44.
117.Shorvon PJ, Eykyn SJ, Cotton PB. Gastrointestinal instrumentation, bacteraemia, and endocarditis. *Gut* 1983;**24**: 1078–93.
118.Edson RS, Van Scoy RE, Leary FJ. Gram-negative bacteremia after transrectal needle biopsy of the prostate. *Mayo Clin Proc* 1980;**55**:489–91.
119.Livengood CH, III, Land MR, Addison WA. Endometrial biopsy, bacteremia, and endocarditis risk. *Obstet Gynecol* 1985;**65**:678–81.
120.Mellow MH, Lewis RJ. Endoscopy-related bacteremia. Incidence of positive blood cultures after endoscopy of upper gastrointestinal tract. *Arch Intern Med* 1976;**136**:667–9.
121.Yin TP, Dellipiani AW. Bacterial endocarditis after Hurst bougienage in a patient with a benign oesophageal stricture. *Endoscopy* 1983;**15**:27–8.
122.Giglio JA, Rowland RW, Dalton HP, Laskin DM. Suture removal-induced bacteremia: a possible endocarditis risk. *J Am Dent Assoc* 1992;**123**:65–70.
123.Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. *Gastroenterology* 1991;**101**:1642–8.
124.Low DE, Shoenut JP, Kennedy JK *et al.* Prospective assessment of risk of bacteremia with colonoscopy and polypectomy. *Dig Dis Sci* 1987;**32**:1239–43.
125.Glauser MP, Bernard JP, Morceillon P, Francioli P. Successful single-dose amoxicillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection. *J Infect Dis* 1983;**147**:568–75.
126.Bernard J, Francioli P, Glauser MP. Vancomycin prophylaxis of experimental *Streptococcus sanguis*; inhibition of bacterial adherence rather than bacterial killing. *J Clin Invest* 1981;**68**:1113–16.
127.Moreillon P, Francioli P, Overholser P, Meylan P, Glauser MP. Mechanisms of successful amoxicillin prophylaxis of experimental endocarditis due to *Streptococcus intermedius*. *J Infect Dis* 1986;**154**:801–7.
128.Malinverni R, Overholser CD, Bille J, Glauser MP. Antibiotic prophylaxis of experimental endocarditis after dental extractions. *Lab Invest* 1988;**77**:182–7.
129.Glauser MP, Francioli P. Relevance of animal models to the prophylaxis of infective endocarditis. *J Antimicrob Chemother* 1987;**20**(Suppl. A):87–93.
130.Durack DT, Petersdorf RG, Beeson PB. Penicillin prophylaxis of experimental *S. viridans* endocarditis. *Trans Assoc Am Phys* 1972;**85**:222–30.
131.Durack DT, Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. I. Comparison of commonly prophylactic regimens. *J Clin Invest* 1973;**52**:592–8.
132.Pelletier LL, Durack DT, Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. IV. Further observations on antimicrobial prophylaxis. *J Clin Invest* 1975; **56**:319–30.
133.Horstkotte D, Friedrichs W, Pippert H, Bircks W, Loogen F. Benefits of endocarditis prevention in patients with prosthetic heart valves. [German]. *Z Kardiol* 1986;**75**:8–11.
134.Van Der Meer JTM, Van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet* 1992;**339**:135–40.
135.Patton JP. Infective endocarditis: economic considerations. In: Kaye D, ed. *Infective endocarditis*, *2nd edn*. New York: Raven Press, 1992.
136.Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. *Am J Med* 1990;**88**:131–6.
137.Everett ED, Hirschmann JV. Transient bacteremia and endocarditis prophylaxis. A review. *Medicine* 1977;**56**: 61–77.
138.Biorn CL, Browning WH, Thompson L. Transient bacteremia immediately following transurethral prostatic resection. *J Urol* 1950;**63**:155–61.
139.Clemens JD, Ransohoff DF. A quantitative assessment of predental antibiotic prophylaxis for patients with mitral-valve prolapse. *J Chron Dis* 1984;**37**:531–44.
140.Bor DH, Himmelstein DU. Endocarditis prophylaxis for patients with mitral valve prolapse: a quantitative analysis. *Am J Med* 1984;**76**:711–17.

58 Antithrombotic therapy after heart valve replacement

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Introduction

Despite improvements in prosthetic materials and valve design, thromboembolism remains a serious complication in patients following heart valve replacement. It is generally agreed that lifelong oral anticoagulants are indicated in patients with mechanical prosthetic valves and in patients with tissue valves, if they have atrial fibrillation or a history of thromboembolism.[1–3] In the absence of antithrombotic therapy, systemic embolism and stroke have been reported in between 5% and 50% of patients, depending upon the valve site, the type of valve replacement and the presence of comorbid conditions.[2,3] With the use of anticoagulants, the rate of systemic embolism has been reduced to 1–3% per year.[4] Antithrombotic therapy, however, carries an important risk of bleeding, which is related to the level of anticoagulation used.[5] Studies of long-term oral anticoagulant therapy for deep vein thrombosis have shown that a less intense regimen (INR 2·0–3·0) is as effective but safer than the more intense regimen (INR 3·0–4·5) that was standard until recently.[6–8] Subsequently, studies in patients following either bioprosthetic or mechanical heart valve replacement have shown reduced bleeding with a lower intensity of anticoagulants without loss of efficacy,[9–11] and based on these studies there has been marked improvement in the safety of the long-term anticoagulant regimens used following heart valve replacement.

Bioprosthetic heart valves

The risk of thromboembolism is less with uncomplicated bioprosthetic valves than with mechanical valves.[12–15] Oral anticoagulants, including warfarin, have been shown to be effective and safe when used at a targeted INR of 2·0–3·0 in such patients based on the results of one prospective clinical trial.[9] This study compared two intensities of anticoagulation to determine the safety and efficacy of a less intense anticoagulant regimen in patients following tissue valve replacement. One hundred and eight patients were randomized to standard anticoagulant control (INR 3·0–4·5), and 102 patients to a less intensive regimen (INR 2·0–2·5). Treatment was continued for 3 months. In this study there was no difference in the frequency of major systemic emboli (1·8% *v* 1·8%) between the two treatment groups, but there were significantly fewer major hemorrhagic complications (0·0% *v* 4·5%; $P = 0·034$) and total hemorrhagic complications (5·4% *v* 14·6%; $P = 0·042$) in the low intensity group (INR 2·0–3·0) compared to the high intensity group, respectively. This level of anticoagulation (INR 2·0–3·0) is now recommended by the American College of Chest Physicians (ACCP) for patients with tissue valve replacement.[4] **Grade A1a**

The risk of thromboembolism is limited mainly to the first 3 months postoperatively in uncomplicated patients with tissue valves, but is present indefinitely in patients with atrial fibrillation.[16] A low ejection fraction, an enlarged left atrium, previous history of venous thromboembolism, and the presence of a pacemaker also increase the risk of thromboembolic complications.[17,18] Consequently, in uncomplicated patients with mitral bioprosthetic valves, anticoagulant therapy is recommended for 3 months while long-term therapy is indicated in patients with atrial fibrillation, those with an atrial thrombus detected at echocardiography, and those who develop a systemic embolus.[4] **Grade B3** Patients with uncomplicated bioprosthetic valves in the aortic position are at very low risk of systemic embolism and some authorities therefore suggest they do not require anticoagulant therapy, although this recommendation remains controversial.[4,19] Long-term treatment with aspirin 80 mg/day following 3 months of oral anticoagulant therapy is likely to be beneficial to prevent subsequent thromboembolic events in patients with uncomplicated bioprosthetic valves.[4] **Grade B4** The current recommendations by the ACCP for patients with tissue valves are shown below.

Mechanical prosthetic heart valves

Patients with mechanical heart valve prostheses require lifelong anticoagulation therapy. The optimal level of anticoagulation in patients with mechanical heart valve replacements has been placed on a scientific footing based on the results of recent studies. Randomized trials have shown that oral anticoagulants are effective in reducing the risk of systemic embolism in patients with mechanical prosthetic valves

Antithrombotic therapy in bioprosthetic heart valve replacement: recommendations

	INR	Duration	Grade of recommendation
Mitral	2·0–3·0	3 mth	**Grade B3**
Aortic	2·0–3·0	3 mth	**Grade B3**
Atrial fibrillation	2·0–3·0	Long-term	**Grade B3**
Left atrial thrombosis	2·0–3·0	Long-term (duration uncertain)	**Grade B3**
Permanent pacemaker	2·0–3·0	Optional	**Grade B4**
Systemic embolism	2·0–3·0	3–12 mth	**Grade B4**
Normal sinus rhythm	Long-term aspirin (80 mg/day)		**Grade B4**

From Stein *et al.*[4]

when given at lower intensity than has been used in the past. The 2001 guidelines of the ACCP[4] recommend two intensity regimens of long-term oral anticoagulant treatment according to the site of the mechanical prosthesis and the presence of concomitant risk factors. A lower INR range between 2·0 and 3·0 is now recommended for patients with a bileaflet valve (St Jude Medical or Carbomedics) or a tilting disc valve (Medtronic–Hall) in the aortic position who are in normal sinus rhythm and have a left atrium of normal size. These newer recommendations, which are levels of evidence **Grade A2** for the St Jude Medical valves and **Grade B2** for Carbomedics and Medtronic–Hall, are based on the results of long-term follow up studies.[20–23] In particular, a study from France[20] has confirmed the efficacy of a less intense level of anticoagulation following mechanical heart valve replacement. In this study 433 patients with mechanical prostheses were randomized to anticoagulant therapy monitored to achieve an INR of 2·0–3·0 or 3·0–4·5 and followed for 2·2 years. Thromboembolic outcome events, either clinical events or asymptomatic CNS abnormalities proven on CT scan, occurred in 10 of 185 (5·3%) patients in the low intensity group and 9 of 192 (4·7%) patients in the high intensity group ($P = 0{\cdot}78$). Importantly, there was a statistically significant difference in the rate of bleeding complications between the two groups. Bleeding events occurred in 34 patients (18·1%) in the low intensity group compared with 56 patients (29·2%) in the high intensity group ($P < 0{\cdot}01$). The majority of patients in this trial, however, had aortic valve replacements and were in sinus rhythm, which limits the generalizability of the results.

An INR range between 2·5 and 3·5 is still recommended for mechanical valves in the mitral position.[4] This recommendation was based on two prospective studies that demonstrated that anticoagulant therapy maintained within this target INR range was as effective as a more intense level of anticoagulation, but with less bleeding. In the first study[10] there was no difference in the frequency of major embolic events in the patients treated with a high intensity regimen (INR 9·0) compared with patients treated with a less intense (INR 2·65) anticoagulant regimen (4·0 *v* 3·7 embolic episodes per 100 patient years, respectively). However, there was significantly less bleeding in the less intense group (6·2 *v* 12·1 hemorrhagic episodes per 100 patient years; $P < 0{\cdot}02$). The second study[11] compared low intensity (INR 2·0–2·99) with high intensity (INR 3·0–4·5) oral anticoagulants in patients with mechanical valves, all of whom were treated with aspirin (330 mg twice per day) in combination with dipyridamole (75 mg per day). In this study one transient ischemic attack occurred in the low intensity group and two in the high intensity group. There were significantly fewer bleeding events in the low intensity group, in which three episodes occurred compared with 12 in the high intensity group ($P < 0{\cdot}02$).

Although these studies form the basis for the recommendations for a less intense level of anticoagulation, they have a number of limitations. In the first study a very high intensity anticoagulant regimen was compared with a moderately high intensity anticoagulant regimen. The mean daily dose of warfarin in the high intensity group was 8·5 mg and in the low intensity group the mean daily dose of 5·9 mg was similar to the average daily dose of 5·4 mg used in the high intensity group in three venous thrombosis studies,[6–8] and in the randomized study in patients with tissue valves.[9] This suggests that the low intensity group in the first mechanical valve study[10] may have been equivalent to the standard intensity group in the venous thromboembolism studies.[8] The second study[11] was small, and therefore the claim that the two regimens were identical in efficacy is questionable. This latter study does, however, confirm the marked difference in bleeding between high intensity and low intensity anticoagulant regimens. The ACCP recommendations for mechanical valves are shown below.

The ACCP recommendation of an INR target of 2·5–3·5 is lower than that reported in a study conducted in Europe which has recommended a target range of 3·0–4·0.[24] However, the European recommendation is based on retrospective data and largely on events that occurred in patients with older caged ball valve prostheses. Thus recommendations based on these data are unlikely to be applicable for use in patients with the modern bileaflet and tilting disc valves that are currently in use.

Of interest, two recent studies have reported a high sensitivity to warfarin in the immediate postoperative phase during oral anticoagulation induction and suggested the

Antithrombotic therapy in mechanical heart valve replacement: recommendations

	INR	Grade of recommendation
Uncomplicated bileaflet aortic	2·0–3·0	**Grade A1a**
Uncomplicated tilting disc aortic	2·0–3·0	**Grade B3**
Bileaflet aortic and atrial fibrillation	2·5–3·5 or 2·0–3·0 + aspirin 80 mg to 100 mg/day	**Grade B3/4**
Uncomplicated bileaflet mitral	2·5–3·5	**Grade B3**
Uncomplicated tilting disc mitral	2·5–3·5	**Grade B2**
Additional risk factors	2·5–3·5 + aspirin 80 mg to 100 mg/day	**Grade B2**
Systemic embolism	2·5–3·5 + aspirin 80 mg to 100 mg/day	**Grade B2**
Caged ball or caged disc valve	2·5–3·5 + aspirin 80 mg to 100 mg/day	**Grade A/C**

From Stein *et al.*[4]

need for lower starting doses of warfarin to regularly achieve the therapeutic range (that is, 2·5–3·0 mg instead of 5·0 mg) in most patients.[25,26]

Combination antithrombotic therapy

A major limitation to the current approach used to treat high-risk patients with prosthetic heart valves is that systemic embolism, which may result in disabling stroke, still occurs at a rate of approximately 2–3% per year, despite the use of anticoagulants.[4] The addition of antiplatelet agents to oral anticoagulants has been advocated as an improved approach to the treatment of patients with mechanical valves, or high-risk patients with tissue valves, to reduce further the risk of major systemic embolism. In an early study[27] the combination of dipyridamole and oral anticoagulants significantly reduced mortality in patients with early models of the Starr–Edwards prosthesis compared with anticoagulants alone. A subsequent study from the Mayo Clinic[28] reported that the addition of dipyridamole to oral anticoagulants significantly reduced the risk of thromboembolic events in patients with mechanical heart valve prostheses. A recent meta-analysis of the dipyridamole studies (Table 58.1) has confirmed improved outcomes with combined therapy compared with anticoagulants alone.[29] The routine use of dipyridamole in combination with oral anticoagulants is, however, not widely accepted for the treatment of patients with mechanical valves or high-risk patients with tissue valves, because of the frequency of adverse effects, including intractable headache, dizziness, nausea, flushing, and syncope.

The combination of aspirin and oral anticoagulants has also been used in the treatment of patients with heart valve replacement with a significant reduction in embolic complications, but with an increased risk of bleeding complications.[30] In the early studies reported to date, aspirin was used in high doses (approximately 1 g/day), and in most cases the bleeding with the combination of high-dose aspirin and high-dose oral anticoagulants was gastrointestinal.[31] There is good evidence that gastrointestinal irritation and hemorrhage is dose-dependent over a range of 100–1000 mg of aspirin per day and that the antithrombotic effects of aspirin are independent of the dose over this range.

One completed study[32] compared low-dose aspirin combined with warfarin in the treatment of patients with mechanical heart valve replacements to determine whether low-dose aspirin would result in an improved antithrombotic effect, without the same high risk of bleeding that has

Table 58.1 Dipyridamole plus anticoagulants following heart valve replacement

	Oral A/C alone	Oral A/C + dipyridamole	% RR	2*P*
Thromboembolism	69/582 (11·9%)	31/559 (5·5%)	56	0·007
Non-fatal T/E	48/582 (8·2%)	24/559 (4·3%)	50	0·005
Fatal T/E	21/582 (3·6%)	7/559 (1·3%)	64	0·008
Death	67/582 (11·5%)	40/559 (7·2%)	40	0·013
Hemorrhage	87/539 (16·1%)	80/501 (16·0%)	−1	0·94

Abbreviations: A/C, anticoagulants; T/E, thromboembolism
From Pouleur and Buyse[29]

Table 58.2 Effect of aspirin combined with antithrombotic therapy following heart valve replacement

	Aspirin + warfarin ($n = 186$)	Placebo + warfarin ($n = 184$)	RR% (95% CI)	2*P*
Systemic embolism	1·6	4·6	65·0 (1·8–37·5)	0·037
Vascular death	0·6	4·4	85·5 (36·0–96·7)	0·003
Death	2·8	7·4	61·7 (16·8–82·3)	0·009

Figures represent % annualized rates.
From Turpie *et al.*[32]

been reported for the combination of oral anticoagulants with high-dose aspirin. This was a double-blind, randomized trial to compare the relative efficacy and safety of aspirin (100 mg per day) with placebo in the prevention of systemic embolism or vascular death in patients with mechanical heart valve replacement or high-risk patients with tissue valves who had atrial fibrillation or a history of thromboembolism. Three hundred and seventy patients were treated with oral anticoagulant therapy (warfarin: INR 3·0–4·5) and randomized to receive aspirin (186 patients) or placebo (184 patients) and followed for up to 4 years (average 2·5 years). The outcomes of the study were systemic embolism, valve thrombosis, vascular death, and hemorrhage. Systemic embolism or vascular death occurred in 6 (3·2%) of the aspirin-treated patients and 24 (13·0%) of the placebo-treated patients (RR 77·2%; 90% CI 51·7–89·2; $P = 0·0002$). The corresponding rates for systemic embolism or death from any cause were 13 (7·0%) and 33 (17·9%), respectively (RR 64·7%; 90% CI 39·6–79·5; $P = 0·0005$); for vascular death 2 (1·1%) and 13 (7·1%), respectively (RR 85·4%; 90% CI 49·8–95·9; $P = 0·0015$); and for death from any cause 9 (4·8%) and 22 (12·0%), respectively (RR 62·7%; 90% CI 44·5–80·5; $P = 0·0048$). Major bleeding events occurred in 24 (12%) of the aspirin-treated patients compared with 19 (10·3%) in the placebo-treated patients (absolute difference 2·6%; 90% CI −8·3–3.4; $P = 0·2710$).

The results of this study, the annualized rates of which are summarized in Table 58.2, demonstrated that in patients with mechanical valve replacement or high-risk patients with tissue valve replacement, the addition of aspirin (100 mg per day) to oral anticoagulation therapy (warfarin: INR 3·0–4·5) reduced mortality, vascular mortality, and systemic embolism, but with some increase in minor bleeding. In a recent study in patients with mechanical prostheses,[33] it was shown that low-dose aspirin (100 mg/day) was as effective as high-dose aspirin (650 mg/day) in combination with oral anticoagulants at a target INR of 2·0–3·0, but with a reduced risk of bleeding. Therefore, the addition of low-dose aspirin (80–100 mg/day) is now recommended for patients with concomitant atrial fibrillation or other additional risk factors and patients who had thromboembolic events despite adequate oral anticoagulant therapy.

Ticlopidine may also be useful as an adjunct to oral anticoagulants, but the data are less solid since the one study in which it has been evaluated was not randomized.[34] There are currently no available data on the association of aspirin and clopidogrel in this setting.

Summary

The demonstration that, for most indications for oral anticoagulant therapy, less intense anticoagulation (INR 2·0–3·0) is as efficacious as standard intensity anticoagulation (INR 3·0–4·5) but with significantly less bleeding is an important advance in antithrombotic therapy. It has greatly improved safety of long-term oral anticoagulant therapy and has resulted in its more widespread use in the prevention and treatment of thromboembolism. It is the level of choice in uncomplicated patients with tissue prostheses. Further evidence is required, however, before this less intense regimen is routinely adopted for patients with mechanical valves and for high-risk patients with tissue valves. The addition of low-dose aspirin to anticoagulants may be more efficacious in the prevention of systemic embolism and vascular death in heart valve replacement patients than anticoagulants alone and may permit a lower intensity of anticoagulation to be used.

References

1. Starr A. Late complications of aortic valve replacement with cloth-covered composite-seat prostheses. *Ann Thorac Surg* 1975;**19**:289.
2. Larsen GL, Alexander JA, Stanford W. Thromboembolic phenomena in patients with prosthetic aortic valves who did not receive anticoagulants. *Ann Thorac Surg* 1977;**12**:323.
3. Limet R, Lepage G, Grondin CM. Thromboembolic complications with the cloth-covered Starr–Edwards aortic prosthesis in patients not receiving anticogulants. *Ann Thorac Surg* 1977;**23**:529.

4.Stein PD, Alpert JS, Bussey HI *et al.* Antithrombotic therapy in patients with mechanical or biological prosthetic heart valves. *Chest* 2001;**119**:220S–7S.
5.Levine MN, Hirsh J, Landefeld S *et al.* Hemorrhagic complications of anticoagulant treatment. *Chest* 1992;**102** (Suppl. 4):352–63.
6.Hull R, Delmore T, Genton E *et al.* Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* 1979;**301**:855–8.
7.Hull R, Hirsh J, Jay R *et al.* Different intensities of oral anticoagulant therapy in the treatment of proximal vein thrombosis. *N Engl J Med* 1982;**307**:1676–81.
8.Hull R, Delmore T, Carter C *et al.* Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. *N Engl J Med* 1982;**306**:189–94.
9.Turpie AGG, Gunstensen J, Hirsh J *et al.* A randomized trial comparing two intensities of oral anticoagulant therapy following tissue heart valve replacement. *Lancet* 1988;**i**: 1242–5.
10.Saour JN, Sieck JO, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med* 1990;**332**:428–32.
11.Altman P, Rouvier J, Gurfinkel E *et al.* Comparison of two levels of anticoagulant therapy in patients with substitute heart valves. *J Thorac Cardiovasc Surg* 1991;**101**:427–31.
12.Cevese PG. Long-term results of 212 xenograft valve replacements. *J Cardiovasc Surg* 1975;**16**:639–42.
13.Pipkin RD, Buch WS, Fogarty TS. Evaluation of aortic valve replacement with a porcine xenograft without long-term anticoagulation. *J Thorac Cardiovasc Surg* 1976;**71**:179–86.
14.Stinson EB, Griepp RB, Oyer PE *et al.* Long-term experience with porcine aortic valve xenografts. *J Thorac Cardiovasc Surg* 1977;**73**:54–63.
15.Ionescu MI, Pakrashi BC, Mary DAS *et al.* Long-term evaluation of tissue valves. *J Thorac Cardiovasc Surg* 1974;**68**: 361–79.
16.Cohn LH, Collins JJ Jr, Rizzo RJ *et al.* Twenty-year follow-up of the Hancock modified orifice porcine aortic valve. *Ann Thorac Surg* 1998;**66**(Suppl):S30–S41.
17.Horstkotte D, Scharf RE, Schulteiss HP. Intracardiac thrombosis: patient-related and device-related risk factors. *J Heart Valve Dis* 1995;**4**:114–20.
18.Lonuagie YA, Jamart J, Enucher P *et al.* Mitral valve Carpentier–Edwards bioprosthetic replacement, thromboembolism, and anticoagulants. *Ann Thorac Surg* 1993;**56**: 931–37.
19.Moinuddeen K, Quin J, Shaw R *et al.* Anticoagulation is unnecessary after biological aortic valve replacement. *Circulation* 1998;**98**:II-95–II-99.
20.Acar J, Iung B, Boissel JP *et al.* AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation* 1996;**94**:2107–12.
21.Horstkotte D, Schulte HD, Birks W *et al.* Lower intensity anticoagulation therapy results in lower complication rates with the St Jude Medical Prosthesis. *J Thorac Cardiovasc Surg* 1994;**107**:1136–45.
22.David TE, Gott VL, Harker LA *et al.* Mechanical valves. *Ann Thorac Surg* 1996;**62**:1567–9.
23.Akins CW. Long term results with the Medtronic–Hall valvular prosthesis. *Ann Thorac Surg* 1996;**61**:806–13.
24.Cannegieter SC, Rosendaal FR, Wintzen AR *et al.* Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;**333**:11–17.
25.Ageno W, Turpie AGG. Exaggerated initial response to warfarin following heart valve replacement. *Am J Cardiol* 1999;**84**:905–8.
26.Ageno W, Turpie AGG, Steidl L *et al.* Comparison of a daily fixed 2·5 mg warfarin dose with a 5 mg, INR adjusted, warfarin dose initially following heart valve replacement. *Am J Cardiol* 2001;**88**:40–4.
27.Sullivan JM, Harken DE, Gorlin R. Pharmacologic control of thromboembolic complications of cardiac valve replacement. *N Engl J Med* 1971;**284**:1391–4.
28.Chesebro JG, Fuster V, Elveback LR *et al.* Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: danger of aspirin compared with dipyridamole. *Am J Cardiol* 1983;**51**:1537–41.
29.Pouleur H, Buyse M. Effects of dipyridamole in combination with anticoagulant therapy on survival and thromboembolic events in patients with prosthetic heart valves. A meta-analysis of the randomized trials. *J Thorac Cardiovasc Surg* 1995; **110**:463–6.
30.Dale J, Myhre E, Storstein O *et al.* Prevention of arterial thromboembolism with acetylsalicylic acid: a controlled clinical study in patients with aortic ball valves. *Am Heart J* 1977;**94**:101–11.
31.Patrono C, Coller B, Dalen JE *et al.* Platelet-active drugs. The relationship among dose, effectiveness and side effects. *Chest* 2001;**119**:39S–63S.
32.Turpie AGG, Gent M, Laupacis A *et al.* A double-blind randomized trial of acetylsalicylic acid (100 mg) versus placebo in patients treated with oral anticoagulants following heart valve replacement. *N Engl J Med* 1991;**329**:1365–9.
33.Altman R, Rouvier J, Gurfinkel E, Scazziota A, Turpie AGG. Comparison of high-dose with low-dose aspirin in patients with mechanical heart valve replacement treated with oral anticoagulant. *Circulation* 1996;**94**:2113–16.
34.Hayashi JI, Nakazawa S, Oguma F, Miyamura H, Eguchi S. Combined warfarin and antiplatelet therapy after St Jude mechanical valve replacement for mitral valve disease. *J Am Coll Cardiol* 1994;**23**:672–7.

Part IIIh

Specific cardiovascular disorders: Other conditions

Bernard J Gersh and Salim Yusuf, Editors

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

59 Treatment of patients with stroke

Craig S Anderson

The increasing burden of stroke

Stroke is a major global healthcare problem.[1] In most Western countries, stroke is the third leading cause of death after heart disease and cancer, and is a major cause of long-term disability and a significant cost to health and social services.[2] The majority (about 75%) of new cases of stroke occur in people over the age of 65 years,[2–4] and about one third of them are dead within one year.[5,6] In addition to concerns about dependency and being a burden to others, survivors hope to remain free of recurrent stroke (and other serious vascular events), estimated at about 30–40% over the first five years after the onset of stroke.[7,8]

After a long period of neglect and an attitude to stroke that has been one of therapeutic nihilism, the past few decades has seen growing interest in the area of stroke medicine and considerable advances in the epidemiology and therapeutics of stroke. This can be explained by a number of factors, such as the ready availability of non-invasive diagnostic technology and an increase in evidence from randomized controlled trials. Computerized tomography (CT) and magnetic resonance imaging (MRI) provide the clinician with the ability to confirm the bedside diagnosis of stroke and transient ischemic attack (TIA), differentiate accurately intracerebral hemorrhage (and subarachnoid hemorrhage) from infarction, and distinguish the cerebral lesions underlying several distinct stroke syndromes in life. In comparison to ischemic heart disease, stroke is a heterogeneous clinical syndrome that encompasses a number of pathological entities that are not necessarily related to atherosclerosis, have different patterns of occurrence and outcome, and may require different management. However, it is often difficult to assign a specific cause for the different types of cerebral infarction (that is, large artery atherothrombosis, cardioembolism, and "small vessel" lacunes) in a particular individual due to the non-specific and overlapping nature of risk factors and other features. Modern neuro-imaging has also allowed a greater awareness of the importance of "silent strokes" and of the broader effects of strokes on the mind and emotion. Depression is an important sequela of stroke,[9] while cerebrovascular disease and Alzheimer's disease often coincide in older people. Indeed, evidence is accumulating that cerebrovascular disease may play a role in the etiology of Alzheimer's disease as well as vascular dementia.[10]

Although the continuous decline in mortality and incidence from stroke in some populations over recent decades is an encouraging trend,[11–17] there is still no general consensus about the factors responsible, or their relative contributions, to these trends. It is unclear, for example, whether there has been a change in the natural history with fewer and less severe strokes, either of which could be related to the better control of blood pressure and other risk factors; or whether there has been an improvement in survival following stroke related to improvements in acute and long-term medical care. It is also uncertain why there has been recent trend of a slowdown in the decline,[15,18,19] or even an increase in mortality rates from stroke in some Eastern European countries.[20] One possible explanation is that this is related to the decline in mortality from coronary artery disease and consequent rising prevalence of chronic ischemic heart disease and heart failure, which increase the pool of persons at high risk of stroke. Other potential candidates include changes in the prevalence of risk factors, in particular diabetes, obesity and smoking, and the recognized failure of hypertension detection and control programs.

Untangling the puzzle of trends in stroke is a matter of pressing importance because the elderly, the most stroke-prone age group, constitute the fastest growing segment of the population. If the incidence of stroke were to stabilize rather than fall, there will soon be an absolute increase in the numbers of disabled survivors of stroke, with major consequences for the health system and informal caregivers. In developed countries, at least, it has been suggested that early death from stroke in patients who were already "handicapped" from other causes may contribute to these communities avoiding an overall increase in the burden of care related to long-term survivors of stroke.[21] Even so, country-specific data on trends in the cause-specific incidence of stroke provide important local feedback on the success (or failure) of preventative strategies, while patterns of case fatality and outcome should bear a closer relationship to the management of acute stroke. Both are required for the planning of services that will inevitably come under increasing pressure from the aforementioned demographic changes. The burden of stroke, in particular, is projected to increase dramatically in developing countries, due to rapid changing population demographics and a shift from traditional, rural

Table 59.1 Summary of effectiveness and costs of acute treatment for stroke each year in a large population. (Modified with permission from Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet* 1999;354:1457–63.)

Intervention	Death or dependency		RRR (95% CI)	ARR	Deaths/ dependents avoided per 1000 treated (*n*)	NNT	Target population (% of all 2400 strokes)	Deaths/ dependents avoided in 1 million population with 2400 strokes (*n*, (%))	Approximate cost per death or dependency avoided (Aus $)
	Control	Intervention							
Stroke unit	62·0%	56·4%	9% (4–14)	5·6%	56	18	1920 (80%)	107 (8·3%)	? Nil additional
Aspirin	47·0%	45·8%	3% (1–5)	1·2%	12	83	1900 (80%)	23 (1·8%)	$83
Thrombolysis	62·7%	56·4%	10% (5–15)	6·3%	63	16	240 (10%)	15 (1·2%)	$36 000 (t-PA) $3200 (streptokinase)

Table 59.2 Summary of secondary stroke prevention strategies and their cost effectiveness for patients with stroke or TIA each year in a large population. (Reproduced with permission from Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet* 1999;354:1457–63.)

Strategy/ intervention	Stroke risk per year		RRR (95% CI)	ARR	Strokes avoided per 1000 treated per year (*n*)	TIA/ stroke patients needed to treat to avoid one stroke per year	Target population (% of all prevalent TIA and stroke survivors)	Strokes avoided per year among target population (*n*)	% of all 2400 strokes avoided each year in population of 1 million	Approximate cost per stroke avoided (Aus $)
	Control	Intervention								
Blood pressure lowering drugs	7·0%	4·8%*	28% (15–38)[a]	2·2%	22	45	6000 (50%)	132	5·5%	1 350 (diuretic) 18 000 (ACE inhibitor)
Smoking cessation	7·0%	4·7%	33% (29–38)	2·3%	23	43	3600 (30%)	84	3·5%	0 (voluntary) <19 600 (patches for all)
Cholesterol lowering drugs	7·0%	5·3%	24% (8–38)	1·7%	17	59	4800 (40%)	81	3·4%	41 000
Antiplatelet drugs							8000 (75% of 10 650 TIA/ischemic strokes)			
Aspirin	7·0%	6·0%	13% (4–21)	1·0%	10	100		80[b]	3·3%[b]	2000
Clopidogrel	7·0%	5·4%	10% (2–17)[b]	1·6%	16	62 (166[b])		128 (48[b])	5·3% (2·0[b])	74 400
Aspirin + dipyridamole	7·0%	5·1%	15% (5–26)[a, b]	1·9%	19	53 (111[b])		152 (72[b])	6·3% (3·0%[b])	18 500
Anticoagulants							2130 (20% of 10 650 TIA/ischemic strokes) but only up to 1065 (50%) realistically			
	12·0%	4·0%	67% (43–80)	8·0%	80	12		85	3·5%	1200
Carotid endarterectomy							850 (8% of 10 650 TIA/ischemic strokes)			
Symptomatic	8·8%	5·0%	44% (21–60)	3·8%	38	26		32	1·3%	182 000

[a] Size of effect remains to be confirmed in ongoing trials.
[b] Compared with aspirin (ie, over and above effect of aspirin).

to urban lifestyles.[1,22] It is imperative, then, that researchers, healthcare providers and policy makers develop appropriate and cost effective interventions for the prevention, treatment and management of stroke. Hankey and Warlow[23] provide an excellent overview of the effectiveness and costs of such strategies, and this is summarized in Tables 59.1 and 59.2.

Stroke units and stroke services

Arguably the single most important therapeutic advance during the past decade in the treatment of patients with acute stroke has been the development of stroke services and stroke units. Strong evidence exists from pooled clinical trial data that well coordinated multidisciplinary, inpatient, stroke unit care can significantly improve the likelihood of returning home and retaining independence after stroke.[24] **Grade A1c**

Compared with conventional care in a general medical ward, stroke units are associated with a relative risk reduction (RRR) of 9% and an absolute risk reduction (ARR) of 5·6%. Thus, the number of patients with stroke that need to be treated (NNT) on a stroke unit to prevent one from dying or becoming dependent is an impressive 18.[23] The benefit of stroke units applies across all subgroups of patients including those who are old, severely disabled, or are admitted late to hospital.[24] While it is uncertain which part of this expert care is important, there is broad consensus that stroke services, both in the acute and rehabilitation phases, need to be well coordinated and include a multidisciplinary team approach, active participation of family, and special education and training of staff (see Table 59.3). In common with coronary care units, stroke units also facilitate the conduct of randomized trials and allow the development of protocols and practices to facilitate rapid, early and thorough evaluation, treatment and rehabilitation.

There is much interest in extending the "black box" package of stroke unit care into the community. In the past decade, there have been an increasing number of trials of specialist domiciliary (home-based) stroke care and rehabilitation schemes, with the aim of either avoiding the need for admission to hospital, or enabling earlier and more effective discharge and follow up. Although there may be scope to prevent some admissions to hospital after stroke, it is not an easy task, not least because stroke is a frightening illness, with most patients disabled at onset. In most countries, hospitals offer a safe and secure environment for intensive nursing care and rehabilitation. Patients with stroke, therefore, conventionally receive a substantial part of their acute care and rehabilitation in hospitals or in other institutions that offer a 24 hour stay. This emphasis on hospital care, together with greater public and professional education on acute symptoms and the need to regard stroke as an emergency,[25,26] mean that it is probably unrealistic to anticipate major service development to the area of "hospital avoidance" for patients with stroke in the future.

Conversely, there is much interest in the development of services that allow patients with stroke to be sent home from hospital earlier than usual and receive domiciliary rehabilitation. Advocates of early discharge schemes suggest several advantages: satisfying patient choice, reducing risks associated with prolonged inpatient care, the home setting

Table 59.3 Organization of stroke services – evidence grades

Recommendation	Evidence grade
1. Every health care organization involved in the care of patients with acute stroke should ensure that the there are specialty service(s) responsible for the management of these patients which comprise the following factors: • A geographically defined unit as the inpatient service base • A well coordinated multidisciplinary team • Staff with special training and expertise in stroke care and rehabilitation • Educational programs for staff, patients and caregivers • Agreed-on protocols for common problems	**Grade A1c**
2. Specialist stroke services can be delivered to patients, following the acute phase, equally effectively in hospital or the community	**Grade A1c**
3. Rehabilitation can be provided to patients within a specialist outpatient or domiciliary setting with equal effect	**Grade A1c**
4. Patients with acute stroke who are not admitted to hospital can benefit from a domicilary rehabilitation team that includes an occupational therapist.	**Grade A1c**

being more focused toward rehabilitation outcomes, and savings in costs.[27] Since 1997, several randomized trials of early hospital discharge and domiciliary stroke rehabilitation have been published.[28] These data are consistent with regard to no adverse impact on patient outcomes and a reduction in hospital length of stay, and the limited economic analyses available indicate potential cost-savings with such schemes.[29,30] There is high quality evidence that allows some broad recommendations to be made regarding the organization of stroke care[31] (see Table 59.1).

Treatment of ischemic stroke

Another major therapeutic landmark in the management of stroke is the use of thrombolytic therapy for acute ischemic stroke. Most acute strokes are due to cerebral infarction following occlusion of arterial blood vessels. The pathogenesis of resulting brain damage can be separated into two sequential processes:

1. the vascular and hematological events that produce occlusion and reduce blood flow in the affected area
2. ischemic necrosis of brain cells.

Surrounding blood vessels in the brain may partly maintain blood flow into the damaged area and therefore, the outer regions of the damaged area are less severely affected than within the core. This process produces an area of irreversible severe ischemia surrounded by an area of moderate ischemia, known as the "penumbra". The recognition that further death of neurons in the penumbra may be prevented has focused attention on treatments to minimize, or even reverse, the damaging effects of ischemia provided they can be initiated within a short period of time after the onset of stroke. This "therapeutic window" may be divided into two partly overlapping components: the "reperfusion window" related to the restoration of blood flow and the "neuroprotective window" related to damaging effects within brain cells. Studies in various animal models and clinical trials suggest that the reperfusion window is very short, perhaps only a few hours, while the neuroprotective window may be much longer, maybe up to 48 hours. While an effective neuroprotective agent for acute stroke has yet to be identified, considerable progress has been made in therapies aimed at restoring blood flow to prevent or lessen the spreading ischemia within the penumbra.

In 1996, the United States Food and Drug Administration (FDA) approved intravenous recombinant tissue plasminogen activator (rt-PA) in selected patients with acute ischemic stroke, provided treatment can begin within 3 hours of the onset of symptoms. The approval was based largely on the results of two combined, National Institute of Neurologic Disease and Stroke (NINDS) Acute Stroke Studies, where all patients were treated within 3 hours of the onset of symptoms and half of the patients were treated within 90 minutes.[32] Subsequent individual trials of rt-PA (and streptokinase) with time windows extending up to 6 hours after the onset of stroke have failed to show a definite positive benefit on their own, but several meta-analyses of the trials indicate a large beneficial effect of treatment, albeit with significant risk, mainly intracerebral hemorrhage.[33,34] Risk of intracerebral hemorrhage is estimated to be 5–10%, and appears more likely to occur in patients with evidence of a large visible infarct on CT, and concurrent use of aspirin among other factors. Despite this risk, use of intravenous rt-PA appears to result in at least a 30% RRR in disability from stroke. The benefits (about 65 patients per 1000 treated avoid "death or long-term dependence") appear to be several times greater than for aspirin, the only other proven effective medical treatment used early after the onset of stroke.[35,36] **Grade A1a**

Although licenses have been granted for the use of rt-PA in several countries and subsequent consensus statements from lead professional organizations such as the American Heart Association[37] endorsing the use of intravenous rt-PA. The uptake of this therapy in clinical practice is extremely limited, even despite intensive community and professional awareness campaigns.[38] In addition, there has been criticism of editorial format of certain consensus statements[39] and concerns raised about the randomization process in the NINDS trial and failure to adjust for imbalance in baseline variables (J Wardlow, personal communication). Thus, there is a long way to go before we can use thrombolysis *widely* in patients with acute ischemic stroke. Despite the published data, consensus statements, and guidelines, only a very small minority of patients with acute ischemic stroke currently receive intravenous rt-PA, mainly due to various educational barriers and delays in getting people to hospital quickly after the onset of symptoms. Much more data is required to establish reliably the balance of benefits and risks of thrombolysis across different groups of patients, even those patients treated after the 3 hour time window.[33,34] A large multicenter trial (International Stroke Trial (IST) – 3) has commenced to address these issues and influence clinical practice.

Apart from rt-PA, two very large trials have established that aspirin 300 mg, administered within the first 48 hours after the onset of ischemic stroke, reduce the risk of death or dependency at 6 months by 1·3%, mainly by reducing early recurrent ischemic stroke.[35,36] **Grade A1a**

Despite a long history of use as standard therapy for established or threatened acute ischemic stroke, a large number of trials individually, and when combined in a meta-analysis,[35,40] have established beyond doubt that heparin in any form, dose or route of administration has no benefit. Even among patients with presumed cardio-embolic stroke, the modest potential benefit is counterbalanced by a significant

excess risk of symptomatic hemorrhage, of which the most lethal is intracerebral hemorrhage.[35,40,41] **Grade A1a**

Prevention of stroke

The most realistic approach to lessen the burden of stroke is prevention, with both population-based strategies and the targeting of high-risk individuals being advocated. Epidemiologic studies suggest that significant reductions in the incidence of stroke, as with coronary heart disease, can be expected by reducing the prevalence or shifting the distribution of risk factors across the entire population.[42] Thus, identifying risk factors and intervening to control or modify them remains the most important means of reducing the burden of stroke. Favorable lifestyle behaviors, including weight reduction, diets that are high in fish, fruit and vegetables, and increased physical activity, are based on sound epidemiologic data. Although direct evidence is lacking, observational studies suggest that stopping smoking decreases the risk of stroke by at least 30%.[43] A substantial reduction in the incidence of stroke has been noted following cessation of smoking, even in older people and in those who have been heavy smokers for many years.[44] **Grade B2**

The "high risk" strategy involves the identification and management of people at high risk of developing stroke. Therapies of proven benefit in the prevention of stroke among certain individuals are blood pressure lowering therapy, antiplatelet therapy, cholesterol lowering therapy, anticoagulation, and carotid endarterectomy. Evidence is mounting that aggressive treatment of hyperglycemia among patients with diabetes mellitus is also effective in reducing the risk of stroke.[45] The absolute benefits of these interventions appear to be greater in subjects in whom the absolute risk is particularly high, notably older people. Effective prevention of stroke in individuals depends on the efficient identification and management of these subjects, particularly in primary care.

Blood pressure reduction strategies

Blood pressure is the single most important reversible risk factor for stroke. Pivotal data about the relationship between blood pressure and stroke comes from both prospective observational studies and clinical trials. Observational studies provide information from which the effects of prolonged blood pressure differences can be estimated,[46] while trials provide data about the effects of short-term blood pressure reduction.[47] Four major overviews of observational studies on blood pressure and stroke have been conducted to date. Such analysis overcomes many of the limitations of individual studies, which have frequently failed to adjust the size of the association for measurement error, in particular regression dilution bias.[46,48–50] A consistent finding of these overviews is a continuous, approximately log linear relationship between usual levels of blood pressure and the primary incidence of stroke, with no evidence of an upper or lower threshold level of blood pressure and stroke risk. On the basis of this relationship, it is estimated that a 5 mmHg lower diastolic blood pressure (or 10 mmHg lower systolic blood pressure) is associated with a 30–40% lower risk of stroke, and there is no evidence that these associations differ between men and women.

Most of the trial data is on the primary prevention of stroke, confirming beyond doubt the benefits of blood pressure lowering in preventing first-ever stroke in middle-aged men and women. Several meta-analyses of trials[51–53] demonstrate that lowering blood pressure in this age group is effective in preventing stroke, with risk reductions commensurate with predictions based on non-experimental epidemiologic studies of 30–40%. **Grade A1a**

Moreover, the Heart Outcomes Prevention Evaluation (HOPE) trial[54] results suggest that activation of the renin–angiotensin system is an independent risk factor for stroke. In this study of 9297 patients with a history of symptomatic vascular disease (mainly coronary artery disease), who were randomized to either ramipril 10 mg daily or placebo on top of best medical therapy, there was a significant reduction in the rate of the combined end point cluster of stroke, myocardial infarction, or death from vascular causes in the patients allocated ramipril (14·0%) compared with those given placebo (17·8%). This RRR of 22% (95% CI 14–30) and an ARR of 3·8% over about 5 years of follow up was much greater than could be expected from the size of the reductions in blood pressure (3 mmHg systolic, 1 mmHg diastolic). The effects of treatment on the end point of any stroke, a RRR of 32% (95% CI 16–44), were consistent across baseline blood pressures, concurrent medication use, and important patient subgroups including those with and without a history of hypertension.[55] Moreover, these data support the hypothesis that angiotensin converting enzyme (ACE) inhibition has beneficial effects independent of blood pressure reduction.

Existing data from randomized controlled trials and a systematic review including patients with cerebrovascular disease suggested that blood pressure lowering therapy may reduce the risk of recurrent stroke by an equivalent amount to that of primary stroke prevention.[56] However, this evidence has not been compelling enough to influence clinical practice. In fact, the approach to blood pressure control among clinicians involved in the care of patients with stroke, and particularly those who are old and normotensive, has been conservative, due in part to concerns about the adverse effects of aggressive blood pressure lowering in this setting. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) undertaken in over 6000 patients was designed to address this issue by determining the effects of a flexible ACE-inhibitor based blood pressure lowering regimen (perindopril with or without the addition of the diuretic,

indapamide) on the risks of stroke and other major vascular events in patients with a history of stroke or TIA.[57] Overall, blood pressure was reduced by an average of 9·0/4·0 mmHg (SE 0·3/0·2) among patients assigned active treatment compared with those assigned placebo during the trial. Compared with those assigned to placebo, the blood pressure reductions among those treated with combination therapy (12·3/5·0 mmHg, SE 0·5/0·3) were about twice as high as those treated with single-drug therapy (4·9/2·8 mmHg, SE 0·6/0·3). The study showed that treatment reduced the incidence of stroke, coronary events and major vascular events by 28%, 26% and 26%, respectively. Active treatment reduced the risks of ischemic stroke by around one quarter and hemorrhagic stroke by one half, and was equally effective in patients with and without a history of hypertension. Combination perindopril and indapamide provided even greater benefits.

Thus, blood pressure lowering therapy should now be regarded as the most important measure for both the primary and secondary prevention of stroke. **Grade A1a**

Although the choice of therapy will depend on the degree of acceptance of direct evidence, as well as on regulations and prescribing patterns, the evidence is strong for therapy that includes an ACE inhibitor and maximizes the degree of blood pressure reduction, such as a combination of perindopril and indapamide. Moreover, effective implementation of such therapy in high-risk groups in combination with population-wide blood pressure lowering strategies, provides one of the most meaningful, practical, and effective ways of controlling the looming epidemic of cardiovascular disease and stroke, worldwide.

Antiplatelet therapy

In the late 1950s and mid-1960s two research paths converged. The first involved the identification of platelet fibrin thrombogenesis as a cause of retinal and hemispheric TIAs. The other involved investigators in Toronto, New York, and Oxford who coincidently determined that several drugs – sulfinpyrazone, aspirin, and dipyridamole – altered platelet responsiveness both in the test tube and in experimentally injured arteries.[58–60] Clinical trials of platelet inhibitors were subsequently undertaken for the prevention of stroke, interestingly before being tested in other vascular diseases. The first was a small trial of dipyridamole involving only 169 patients, which showed no benefit.[61] Next, the Canadian Cooperative Study was undertaken using a factorial study design in which patients received aspirin 1300 mg daily, sulfinpyrazone 800 mg, both or neither in patients with a recognizable arterial origin for their TIA or nondisabling stroke.[62] After 585 patients, two thirds male and one third female, had been followed for an average of 28 months, the investigators reported that patients in the two arms of the trial containing aspirin compared with those not on aspirin had a RRR of 31% for the combined end point of stroke and death. No benefit was detected in the sulfinpyrazone arm. A subgroup analysis reported no benefit for the 200 women in the trial and when the results for men alone were analyzed in a data generated subgroup, a 48% benefit in stroke and death was observed in the aspirin containing groups.

Since the publication of that important study there has been a flurry of activity. Most importantly, the mode of action and effectiveness of aspirin has been well elucidated, and several new antiplatelet agents identified and tested. Aspirin inhibits thromboxane A_2 formation by irreversibly acetylating the platelet enzyme cyclo-oxygenase. Thromboxane A_2 is an important stimulus for platelet aggregation and release. Platelet aggregation is thus inhibited for up to 10 days after exposure to aspirin. Absorption of aspirin occurs rapidly and peak plasma concentrations are reached within 1–3 hours. Even though the plasma half life of aspirin is short, antiplatelet activity is prolonged, but bleeding times return to normal within two days of cessation of aspirin. In a meta-analysis of 145 randomized trials of antiplatelet therapy, aspirin was shown to be associated with a RRR of all vascular events (including stroke) of about 22%.[63] **Grade A1a**

Aspirin is, therefore, appropriate for all patients with ischemic stroke unless there is specific contraindication, such as aspirin sensitivity. Aspirin given to patients with a history of stroke or TIA reduces the relative risk of stroke and other important vascular events by about 14% (95% CI 4–21),[64] from about 7% to 6% per year. This equates to an ARR of 1·0% and an NNT of 100. Aspirin is also beneficial in such patients who also have atrial fibrillation (AF). The annual risk of stroke has been shown to be reduced from 12% to 10%, a RRR of 14% (95% CI 15–36) and an ARR of 2·0%.[65]

In the mid-1990s, there was much controversy over the most effective dose of aspirin.[66–68] The optimal dose for efficacy and tolerability is low dose aspirin (100–300 mg daily). Gastrointestinal side effects such as gastritis and hemorrhage are more common in older people and are dependent on the dose and duration of treatment. The small risk of intracerebral hemorrhage with prolonged use of aspirin is outweighed by the benefits in high-risk patients.

Among the other antiplatelet agents, dipyridamole, ticlopidine and clopidogrel have all been shown to be beneficial in the secondary prevention of stroke. Compared with aspirin, clopidogrel reduces the relative risk of stroke and other major vascular events by about 10% (95% CI 3–17)[69,70] from about 6·0% (aspirin) to 5·4% (clopridogrel) per year, which is an ARR of 0·6% compared with aspirin, and equates to about a NNT of 166 compared with aspirin, and probably 62 compared with aspirin. **Grade A1a**

Although expensive, clopidogrel is as safe as aspirin and, unlike the closely related agent ticlopidine, is not known to

cause an excess of neutropenia and thrombocytopenia.[70,71] In the European Stroke Prevention Study 2 (ESPS 2),[72] 6602 patients were given aspirin (25 mg twice daily), modified-release dipyridamole (200 mg twice daily), the combination or placebo. The RRR for the combined end points of stroke and death were 13·2% for aspirin, 15·4% for dipyridamole, and 24·4% for the combination of aspirin and dipyridamole. An update of the data indicates that compared with aspirin, the combination of aspirin and modified-release dipyridamole reduces the risk of stroke by about 23% (95% CI 7–37), and that this effect is greater for stroke than other serious vascular events.[73,74] **Grade A1c**

Anticoagulants

AF is a major risk factor for stroke. It predisposes to the formation of intracardiac thrombi, mainly within the atria, that may embolize to the brain and other organs. The prevalence of AF increases with age, from 0·5% in patients aged 50–59 years to about 9% in patients over the age of 70 years.[75] With an aging population, it is likely that AF will become an increasingly important public health problem. Overall, the annual risk of stroke is about 5%, but rates vary from less than 2% to more than 10% according to the presence of one or more clinical characteristics such as congestive cardiac failure, hypertension, older age (≥75 years), diabetes and previous history of stroke or TIA.[76] **Grade A1a**

There is good evidence that warfarin and aspirin are both highly efficacious in preventing stroke (and other vascular and embolic events) in patients with AF. Six randomized trials have evaluated warfarin with placebo,[77–82] two other trials have compared warfarin with aspirin,[83,84] and a meta-analysis[85] indicates a 64% RRR of stroke favoring warfarin over placebo and a 48% RRR favoring warfarin over aspirin. Aspirin is associated with a RRR of 22%.[86,87] Given the consistency of the treatment effects across subgroups of patients, the absolute benefits of antithrombotic therapy is high in those patients who are at highest risk of stroke. Thus, the decision to commence warfarin anticoagulation therapy is usually based on an evaluation of the risks and benefits in an individual patient. Bleeding is the main risk associated with warfarin. Results of the pooled analyses of the major studies show a slightly higher frequency of major bleeding events in warfarin treated groups compared with placebo (1·3% *v* 1·0% per year). On the basis of these data, a target international normalized ratio (INR) of between 2·0 and 3·0 is generally recommended as a safe and effective level of anticoagulation.[88] These recommendations are further supported by the results of the Stroke Prevention in Reversible Ischemic Trial (SPIRIT),[89] which involved 1316 patients with TIA or minor stroke in which aspirin (30 mg daily) was compared with warfarin and a target INR of 3·0 to 4·5. The trial was stopped after the first scheduled interim analysis due to an excess of major bleeding in the warfarin group, and no significant difference between groups in the incidence of the non-hemorrhagic end points (hazard ratio 1·03, 95% CI 0·6–1·75).

Based on small studies only, warfarin (or heparin) appears to reduce the incidence of stroke in patients with recent anterior myocardial infarction.[90] Patients who have had a recent stroke or TIA in conjunction with a recent myocardial infarction should be given heparin therapy followed by 3–6 months of warfarin therapy.[91] In the setting of acute ischemic stroke attributed to cardio-embolism, though, it is often advisable to wait at least a week before commencing anticoagulation, in order to prevent hemorrhagic transformation of the infarct. **Grade B2**

In the absence of a potential cardiac source for the stroke, such as AF, recent transmural, anterior, myocardial infarction, dilated cardiomyopathy, valvular heart disease, there are presently no other clear indications for warfarin therapy for the prevention of stroke. In the recently completed Warfarin-Aspirin Recurrent Stroke Study (WARSS), there was no significant difference in the prevention of recurrent ischemic stroke, death or intracranial hemorrhage between the groups, although there was a slight trend for aspirin superiority.[92] **Grade A1a**

There may be benefit of warfarin in certain other subgroups of patients with vascular disease. On the basis of retrospective observational data, the Warfarin-Aspirin Symptomatic Intracranial Disease study[93] a clinical trial has commenced comparing warfarin with aspirin in patients with severe intracranial arterial stenosis.

Cholesterol lowering therapy

The relation between diet, serum cholesterol levels and ischemic heart disease is relatively well understood but the evidence is less reliable and more complex for stroke. This reflects, in part, the diversity of stroke pathogenesis, with qualitatively different associations of serum cholesterol with the risks of ischemic and hemorrhagic stroke.[94–98] High serum cholesterol is considered an important risk factor for ischemic stroke, more so in Western societies than in Asian populations,[99] whereas a weak inversion association is apparent between serum cholesterol and the risk of intracerebral hemorrhage. Although there have been no completed randomized trials of cholesterol lowering therapy in patients with stroke or TIA alone, several large scale, randomized trials have established that long-term use of certain 3-hydrozy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) results in significant reductions in the risk of major cardiovascular events in patients with a wide range of lipid levels, both[100] with[101–103] and without,[104,105] a history of coronary artery disease. The evidence suggests that lowering serum cholesterol with statins can reduce the risk of stroke by about 25% (95% CI 14–41) over just a few years of therapy.[106] **Grade A1a**

Carotid endarterectomy

Symptomatic disease

Atherosclerotic disease of the carotid artery is an important cause of stroke. The risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over 2 years. The introduction of carotid artery surgery in 1954 by Eastcott, Pickering, and Rob heralded a new era in stroke prevention. In 1967 a randomized trial was launched to evaluate this exciting prospect of carotid endarterectomy, with results published in 1970.[107] The trial, despite its merits, was not supportive of the procedure due to a number of problems including the small sample size of only 316 randomized patients and relatively high perioperative complication rate of 11%. In addition, almost half of the patients had symptoms only in the vertebral basilar vascular territory and too many patients were lost to follow up (12% in the surgical and 1·3% in the medical group). A second small trial conducted at the same time but reported much later, was overwhelmingly negative due to a high perioperative complication rate.[108]

These negative trials did not reduce the enthusiasm for the procedure. By 1985 a total of 107 000 endarterectomies were being carried out annually in the United States and it was estimated that a cumulative total of one million endarterectomies had been conducted for both symptomatic and asymptomatic disease. The appropriateness of patient selection and the awareness that in many centers, a forbiddingly high level of operative morbidity and mortality existed, led to a requirement for high quality clinical trials.

The two major trials for symptomatic disease are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), which between them included nearly 6000 patients, and they have demonstrated convincingly the benefits of carotid endarterectomy.[109,110] A third smaller trial, when stopped, had a trend towards the same result but involved only 189 patients.[111] NASCET and ECST required angiography for entry and demanded focal hemisphere or retinal minor stroke or TIAs within 180 days. Both stopped the randomization of patients with severe stenosis because of compelling evidence on interim analyses demonstrating a clear reduction in ipsilateral strokes with endarterectomy. Both trials also showed no net benefit of surgery for all patients with mild-moderate grades of stenosis.[112,113] NASCET and ECST used measurements of the narrowest diameter of the stenosed segment as the numerator based on angiographic criteria. The results from NASCET demonstrated a 2 year 65% relative and a 17% absolute risk reduction favoring endarterectomy (Table 59·2). When the ECST angiograms were remeasured by the NASCET method and the results calculated for the reduced number of patients who would be "severe" by NASCET criteria, the favorable results in the survival curves for surgery were very similar.[114] **Grade A1a**

The compelling results in favor of endarterectomy for severe stenosis in NASCET and ECST are dependent on two important caveats. First, the surgical complication rate undertaken by experienced surgeons was low. In NASCET the occurrence of any stroke, disabling or mild, lasting more than 24 hours or death in the 30 day period was 5·8%. For disabling stroke and perioperative death, the complication rate was 2·1%. The long-term benefits of endarterectomy are abolished as the complication rate exceeds 10%. Surgeons must therefore be highly skilled.

Second, the results relate to a measurement of the degree of stenosis from conventional carotid angiograms. Conventional angiography carries a 1% risk of stroke; one stroke in five is disabling.[115] In NASCET, from 2929 angiograms performed in 100 centers, the minor and non-disabling stroke rate was 0·6%, the disabling stroke rate 0·1%. While this rate was high, it was only one tenth the risk of stroke from

Table 59.4 Risk of ipsilateral stroke or any perioperative stroke or perioperative death – NASCET. (Reproduced with permission from *Neurology* 1996;46:605)

Study time	Risk (%) medical	Risk (%) surgical	Risk (%) difference	RRR (%)	NNT
30 days	3·3	5·8	−2·5	–	–
1 year	17·3	7·5	9·8	57	10
2 years	26·0	9·0	17·0	65	6

From the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the risk of stroke for 331 medically treated and 328 surgically treated patients with symptoms appropriate to severe stenosis are given at 30 days, 1 and 2 years. To prevent one stroke in 2 years, six patients need to have endarterectomy.
Abbreviations: NNT, number needed to treat by endarterectomy to prevent one stroke within the specified study time; RRR, relative risk reduction

endarterectomy: 5·8% for any stroke or death and 2·1% for disabling stroke or death. Modern non-invasive carotid imaging such as MRI, spiral CT and duplex and Doppler ultrasound avoids the risk associated with conventional intra-arterial catheter carotid angiography. However, it is important that the reliability of images obtained are well established in order to avoid operating on patients with false-positive scans, or denying benefits of the intervention in those with false-negative scans.[116] Moreover, carotid ultrasound alone will not identify important lesions of the intracranial arteries. Aneurysms and stenosis of intracranial vessels exists in about 2% and 5% of patients symptomatic with extracranial stenosis, respectively. If such lesions are identified, the benefit:risk ratio of endarterectomy will be reduced.

Although endarterectomy remains the standard treatment for a well defined group of high-risk patients, there is growing interest in the use of percutaneous, transluminal angioplasty (PTA) and stenting for carotid stenosis to avoid the significant risk of stroke or death of between 6% and 8% associated with surgery. In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) involving over 500 patients, almost all with symptomatic carotid stenosis, randomized to PTA and surgery, the 30 day outcomes were almost identical for the groups.[117] The rate of death or any major stroke was 9·9% after surgery and 10·0% after angioplasty. Analysis of the other risks of treatment confirmed that PTA was safer than surgery in terms of minor morbidity, reduced hospital length of stay, but was associated with a higher rate of (asymptomatic) restenosis during follow up. Stents suitable for carotid use have only been available in recent years and few were used in CAVATAS. Given advances in technology in this area, further clinical trials are underway to evaluate whether primary carotid stenting should be the surgical procedure of choice for carotid stenosis based on effectiveness, lower risks and reduced costs.

Asymptomatic disease

Design flaws in early trials prevented conclusive evidence being gained about the benefit of endarterectomy in patients with asymptomatic carotid stenosis. In the Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) trial, patients with greater than 90% stenosis were excluded and crossovers were common between the medical and surgical groups, while in the Mayo Asymptomatic Carotid Endarterectomy (MACE) trial, standard medical care including use of aspirin, was not extended to the surgical arm. The United States Veterans Administration (VA) trial was small, with only 444 patients, and reported a perioperative complication rate of 4·4%, but the stroke-free survival curves were similar in patients receiving endarterectomy to those given best medical care alone.[118] A fourth trial, the Asymptomatic Carotid Atherosclerosis Study (ACAS), used a more robust design and randomized 1662 patients. A significant benefit was demonstrated in favor of endarterectomy with a RRR of 53% after 2·7 years of average follow up.[119] However, there are reservations about the clinical significance of this result (see Table 59.5). The absolute benefits of the procedure in this setting are small, RRR of 1% per year, so that 67 patients are required to undergo endarterectomy to prevent one stroke in 2 years. This is in contrast to the six symptomatic patients required to derive benefit with similarly severe disease. When the perioperative complication rate exceeds 3%, the benefits are negated. A higher figure is known to be common. Thus, endarterectomy for all patients with asymptomatic carotid stenosis is not a cost effective procedure. **Grade A1c**

All of the symptomatic trials and major observational case-series studies have observed a worsening of prognosis with increasing degrees of carotid stenosis.[120,121] However, there is also a strong association between cardiovascular risk

Table 59.5 Risk of ipsilateral stroke or any perioperative stroke or perioperative death (based upon 825 patients randomized to CEA) — ACAS. (Reproduced with permission from *Neurology* 1996;46:605)

Study time	Risk (%) medical	Risk (%) surgical	Risk (%) difference	RRR (%)	NNT
30 days	0·4	2·3	−1·9	–	–
1 year	2·4	3·0	−0·6	–	–
2 years	5·0	3·5	1·5	30	67
5 years	11·0	5·1	5·9	53	17

From the Asymptomatic Carotid Atherosclerosis Study (ACAS), the risk of stroke is compared between the medically and surgically treated patients. To prevent one stroke in 2 years, 67 patients need to have endarterectomy. Adjusting the surgical arm to include only the patients who had endarterectomy, the 30 day surgical risk becomes 2·6% and the 1, 2 and 5 year risks rise to 3·3%, 3·8% and 5·4% respectively. The number needed to treat to prevent one stroke in 2 years becomes 83.
Abbreviations: NNT, number needed to treat by endarterectomy to prevent one stroke within the specified study time; RRR, relative risk reduction

factors and carotid stenosis in all age groups.[122] Thus, although the reduction in strokes after endarterectomy is found to be greatest in those with the most severe stenosis, there remains uncertainty about the benefits of endarterectomy in the elderly, including those with asymptomatic disease.[123] In view of this uncertainty, a fifth and largest trial is being conducted in Europe, the Asymptomatic Carotid Surgery Trial (ACST).[124] It is possible that a high-risk patient subgroup, for example those with high grade stenosis (85–99%) and a high vascular risk profile, will be identified in which endarterectomy is definitely cost effective for asymptomatic carotid disease. In the meantime, only carefully selected high risk patients should be recommended for endarterectomy, conducted by the most expert of surgeons.

Conclusions

Four decades of clinical observation and randomized controlled trials in stroke prevention have provided very positive and promising results. Several key points emerge:

- Modifiable risk factors for stroke have been identified. From a public health viewpoint, risk factors of greatest importance in the prevention of stroke are those that carry a high population-attributable risk, such as high blood pressure, obesity, high cholesterol levels, physical inactivity, and cigarette smoking. Stroke prevention in the community requires manipulation of these risk factors in individuals at high risk and in the whole population.
- Given the continuous relationship between levels of risk factors and stroke risk, effective prevention of stroke involves the management of the patient as a *whole* person defined by their absolute risk of future major vascular events rather than by a single variable such as the level of blood pressure or serum cholesterol.
- On the basis of a large body of direct and indirect evidence, clinicians should now consider blood pressure lowering therapy as pivotal to the prevention of recurrent stroke in all patients with cerebrovascular disease, irrespective of blood pressure levels, age and other characteristics. Although there is no evidence at present to guide the timing of blood pressure lowering therapy after the onset of stroke, pragmatically it is probably wise to wait until patients are clinically stable. The evidence is strong for therapy that maximizes the degree of blood pressure reduction using an ACE inhibitor-based regimen.
- Aspirin is cheap, safe, familiar and acceptable as the antiplatelet agent of first choice for patients with vascular disease. The optimal dose of aspirin is 100–300 mg. Aspirin is also the first choice for patients with acute ischemic stroke, commencing within 48 hours of onset. Clopidogrel is more expensive and combination aspirin and modified-release dypridamole is less well tolerated but both agents offer modest benefits over aspirin.
- Warfarin is indicated only for patients with a proven or potential, cardiac (embolic) source of stroke. Warfarin is favored when the risk of stroke is high and aspirin is favored when the risk of stroke is low. Various clinical parameters have been well identified that allow clinical stratification of risk.
- Carotid endarterectomy is indicated for patients with severe carotid artery stenosis who have had symptoms of retinal or brain ischemia appropriate to the stenosis, and are willing to undergo a small but definite risk of death or disability related to the procedure undertaken by an experienced surgeon. PTA may be undertaken as an alternative to carotid endarterectomy in experienced hands. There remains uncertainty about the cost effectiveness of endarterectomy in patients with high grade asymptomatic stenosis and that of carotid stenting.
- Cholesterol lowering therapy with statins is safe, well tolerated and cost effective in preventing major vascular events including stroke in all high-risk individuals irrespective of baseline cholesterol levels.
- Well organized care and rehabilitation within stroke units or services has been shown to save lives and reduce long-term dependency. The key components of such care should include multidisciplinary team approach, active participation of family, special education and training of staff, and early commencement of rehabilitation.
- The primary focus of thrombolytic therapy is to restore, preserve and improve circulation to acute focal brain ischemia. Although rt-PA remains the only approved hyperacute stroke therapy, all other data suggest that other thrombolytic or neuroprotective approaches are likely to have very short time-windows for efficacy and safety. While the risk of bleeding is significant, it is comparable with the risks associated with other procedures such as carotid endarterectomy. Effective community and professional education, motivation and training are likely to be important for more widespread application as acute stroke treatment.

References

1. Murray CJL, Lopez AD. *Global Health Statistics*. Geneva: World Health Organization, 1996.
2. Warlow CP. Epidemiology of stroke. *Lancet* 1998;**352** (Suppl. 3):SIII 1–4.
3. Bonita R, Anderson C, Broad J, Jamrozik K, Stewart-Wynne E, Anderson N. Stroke incidence and case-fatality in Australasia: a comparison of the Auckland and Perth population-based stroke registers. *Stroke* 1994;**25**:552–7.
4. Bonita R, Broad J, Beaglehole R, Anderson N. Changes in incidence and case-fatality in Auckland, New Zealand, 1981–1991. *Lancet* 1993;**342**:1470–3.

5. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke* 1994;**25**:1935–44.
6. Bonita R, Stewart AWS, Ford M. Predicting survival after stroke: a three-year follow up. *Stroke* 1988;**19**:669–73.
7. Hankey G, Jamrozik K, Broadhurst R *et al.* Long-term risk of recurrent stroke in the Perth Community Stroke Study. *Stroke* 1998;**29**:2491–500.
8. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke: The Oxfordshire Community Stroke Project. *Stroke* 1994; **25**:333–7.
9. House A. Mood disorders after stroke: a review of the evidence. *Int J Geriatric Psychiatry* 1987;**2**:211–21.
10. De la Torre JC. Alzheimer Disease as a vascular disorder: nosological evidence. *Stroke* 2002;**33**:1152–62.
11. Thom JT. Stroke mortality trends: an international perspective. *Ann Epidemiol* 1993;**3**:509–18.
12. Bonita R, Beaglehole R. Monitoring stroke: an international challenge. *Stroke* 1995;**26**:541–2.
13. Bonita R, Broad JB, Beaglehole R. Changes in stroke incidence and case-fatality Auckland, New Zealand in 1981–1991. *Lancet* 1993;**342**:1470–2.
14. Stegmayr B, Asplund K, Wester PO. Trends in incidence, case fatality rate, and severity of stroke in Northern Sweden, 1985–1991. *Stroke* 1994;**25**:1738–45.
15. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;**27**: 373–80.
16. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in Perth, Western Australia. *Stroke* 1999;**30**:2105–11.
17. Thorvaldsen P, Davidsen M, Brønnum-Hansen H, Schroll M, for the Danish MONICA Study Group. Stable stroke occurrence despite incidence reduction in an aging population: stroke trends in the Danish Monitoring trends and determinants in cardiovascular disease (MONICA) population. *Stroke* 1999;**30**:2529–34.
18. Gillum RF, Sempos CT. The end of the long-term decline in stroke mortality in the United States. *Stroke* 1997; **28**: 1527–9.
19. Sarti C, Tuomilehto J, Sivenious J *et al.* Declining trends in incidence, case-fatality and mortality of stroke in three geographical areas of Finland during 1983–1989: results from the FINMONICA stroke register. *J Clin Epidemiol* 1994; **47**: 1259–69.
20. Ryglewicz D, Polakowska M, Lechowicz W *et al.* Stroke mortality rates in Poland did not decline between 1984 and 1992. *Stroke* 1997;**28**:752–7.
21. Malmgren R, Bamford J, Warlow C, Sandercock P, Slattery J. Projecting the number of patients with first ever strokes and patients newly-handicapped by stroke in England and Wales. *BMJ* 1989;**298**:656–60.
22. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998;**97**: 596–601.
23. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet* 1999;**354**:1457–63.
24. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised in-patient (stroke unit) care after stroke. *BMJ* 1997;**314**:1151–9.
25. The European Ad Hoc Consensus Group. European strategies for early intervention in stroke. A report of an ad hoc consensus group meeting. *Cerebrovasc Dis* 1996;**6**:315–24.
26. Organising Committees. Asia Pacific Consensus Forum on Stroke Management. *Stroke* 1998;**29**:1730–6.
27. Young J. Is stroke better managed in the community? *BMJ* 1994;**309**:1356–8.
28. Langhorne P, Dennis MS and collaborators. Services for reducing duration of hospital care for acute stroke patients (Cochrane Review). In: The Cochrane Library, 1, 1999. Oxford: Update Software.
29. Beech R, Rudd AG, Tilling K, Wolfe CDA. Economic consequences of early inpatient discharge to community-based rehabilitation for stroke in an inner-London teaching hospital. *Stroke* 1999;**30**:729–35.
30. Anderson C, Ni Mhurchu C, Rubenach S, Clark M, Spencer C, Winsor A. Home or hospital for stroke rehabilitation? Results of a randomised controlled trial. II: Cost minimisation analysis at 6 months. *Stroke* 2000;**31**:1032–7.
31. Intercollegiate Working Party for Stroke. *National Clinical Guidelines for Stroke*. London, England: Royal College of Physicians; 2000.
32. National Institute of Neurological Disorders and Stroke r-tPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–7.
33. Wardlaw J, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischemic stroke (Cochrane review). Cochrane Database Syst Rev. 2000;(2):CD000213.
34. Ringleb PA, Schellinger PD, Schranz C, Hacke W. Thrombolytic therapy within 3 to 6 hours after onset of ischemic stroke: useful or harmful? *Stroke* 2002;**33**:1437–41.
35. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischemic stroke. *Lancet* 1997;**349**: 1569–14.
36. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomized placebo-controlled trial of early aspirin use in 20 000 patients with acute ischemic stroke. *Lancet* 1997;**349**:1641–9.
37. Adams HP, Brott TG, Furlan AJ *et al.* Guidelines for thrombolytic therapy for acute stroke: a supplement for the guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Circulation* 1996;**94**:1167–74.
38. Morgenstern LB, Staub L, Chan E *et al.* Improving delivery of acute stroke therapy: the TLL Temple Foundation Stroke Project. *Stroke* 2002;**33**:160–6.
39. Caplan LR, Moht JP, Kistler JP, Koroshetz W. Should thrombolytic therapy be the first-line treatment of acute ischemic stroke? Thrombolysis: not a panacea for ischemic stroke. *N Engl J Med* 1997;**337**:1309–10.

40.Gubitz G, Counsell C, Sandercock P. Anticoagulants for acute ischemic stroke (Cochrane Review). In The Cochrane Library. Issue 4. Oxford, UK: Update Software, 2001.
41.Adams HP. Emergent use of anticoagulation for treatment of patients with ischemic stroke. Stroke 2002;**33**:856–61.
42.Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985;**14**:32–8.
43.Hankey GJ. Smoking and risk of stroke. *J Cardiovasc Risk* 1999;**5**:207–11.
44.Wolf PA. Epidemiology and risk factor management. In: Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B, eds. *Primer on cerebrovascular diseases*. San Diego: Academic Press, 1997.
45.The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**:977–86.
46.MacMahon S, Peto R, Cutler J, Collins R, Sorlie Pea. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. *Lancet* 1990;**335**:765–74.
47.Collins R, Peto R, MacMahon S *et al.* Blood pressure, stroke, coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;**336**:827–38.
48.Prospective Studies Collaboration. Cholesterol, diastolic blood pressure and stroke; 13 000 strokes in 45 000 people in 45 prospective cohorts. *Lancet* 1995;**346**:1647–53.
49.Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol and stroke in Eastern Asia. *Lancet* 1998;**352**:1801–7.
50.Asia Pacific Cohort Studies Collaboration. Determinants of Cardiovascular Disease in the Asia Pacific region: Protocol for a Collaborative Overview of Cohort Studies. *CVD Prevention* 1999;**2**:281–9.
51.MacMahon S, Rodgers A. The effects of antihypertensive treatment on vascular disease: reappraisal of the evidence in 1994. *J Vasc Med Biology* 1993;**4**:265–71.
52.Insua JT, Sacks HS, Lau TS *et al.* Drug treatment of hypertension in the elderly: a meta-analysis. *Ann Int Med* 1994;**121**: 355–62.
53.Staessen JA, Gasowski J, Wang JG *et al.* Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;**355**:865–72.
54.The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
55.Bosch J, Yusuf S, Progue J *et al.* on behalf of the HOPE Investigators. Use of ramipril in preventing stroke: double blind randomized trial. *BMJ* 2002;**324**:1–5.
56.Rodgers A, Neal B, MacMahon S. The effects of blood pressure lowering in cerebrovascular disease: an overview of randomized controlled trials. *Neurol Rev Int* 1997; **12**:12–15.
57.PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet* 2001;**358**:1033–41.
58.Mustard JF, Rowsell HC, Smythe HA, Senyi A, Murphy EA. The effect of sulfinpyrazone on platelet economy and thrombus formation in rabbits. Blood 1967;**29**:859–66.
59.Weiss HJ, Aledort LM. Impaired platelet/connective-tissue reaction in man after aspirin ingestion. *Lancet* 1967;**ii**:495–7.
60.Emmons PR, Harrison MJ, Honour AJ, Mitchell JR. Effect of a pyrimido pyrimidine derivative on thrombus formation in the rabbit. *Nature* 1965;**208**:255.
61.Acheson J, Danta G, Hutchinson EC. Controlled trial of dipyridamole in cerebral vascular disease. *BMJ* 1969;**1**:614–5.
62.The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978;**299**:53–9.
63.Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81–106. [Published erratum appears *BMJ* 1994;**308**:1540.]
64.Alga A, van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin. *J Neurol Neurosurg Psychiatry* 1999;**66**:255.
65.European Atrial Fibrillation Trial Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993; **342**: 1255–62.
66.Barnett HJM, Kaste M, Meldrum HE, Eliasziw M. Aspirin dose in stroke prevention: beautiful hypotheses slain by ugly facts. *Stroke* 1996;**27**:588–92.
67.Hart RG, Harrison MJG. Aspirin wars: the optimal dose of aspirin to prevent stroke. *Stroke* 1996;**27**:585–7.
68.Patrono C, Roth GJ. Aspirin in ischemic cerebrovascular disease: how strong is the case for a different dosing regimen? *Stroke* 1996;**27**:756–60.
69.CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
70.Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease. *Stroke* 2000; **31**:1779–84.
71.Hankey GJ. Clopidogrel and thrombotic thrombocytopenic purpura. *Lancet* 2000;**356**:269–270.
72.Diener HC, Cunha L, Forbes C *et al.* European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;**143**:1–13.
73.Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999;**56**:1087–92.
74.De Schryver ELLM on behalf of the European. Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) Group. Design of ESPRIT: an international randomized trial for secondary prevention after non-disabling cerebral ischaemia of arterial origin. *Cerebrovasc Dis* 2000;**10**: 147–50.
75.Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983;**106**:389–96.
76.Cage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for

predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–70.
77. Petersen P, Godtfredsen J, Boysen G. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;**i**:175.
78. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–11.
79. Connolly SJ, Laupacis A, Gent M *et al.* Canadian atrial fibrillation anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991; **18**:349–55.
80. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation* 1991;**84**:527–39.
81. Ezekowitz MD, Bridgers SL, James KE *et al.* Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;**327**:1406–12. (Erratum, *N Engl J Med* 1993;**328**:148.)
82. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993; **342**:1255–62.
83. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;**343**:687–91.
84. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet* 1996;**348**:633–8.
85. The Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomised controlled trials. *Arch Intern Med* 1994;**154**:1449–57. (Published erratum appears in *Arch Intern Med* 1994;**154**:2254.)
86. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**: 492–501.
87. Laupacis A, Boysen G, Connolly S *et al.* The efficacy of aspirin; in patients with atrial fibrillation: analysis of pooled data from 3 randomised trials. *Arch Intern Med* 1997;**157**: 1237–40.
88. Ezekowitz MD, Levine JA. Preventing stroke in patients with atrial fibrillation. *JAMA* 1999;**281**:1830–5.
89. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomised trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol* 1997;**42**:857–65.
90. Cerebral Embolism Task Force. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force. *Arch Neurol* 1989;**86**:727.
91. Turpie AGG, Robinson JG, Doyle DJ *et al.* Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;**320**:352–7.
92. Mohr JP, Thompson JL, Lazar RM *et al.* for the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444–51.
93. Chimowitz MI, Kokkinos J, Strong J *et al.* The Warfarin-Aspirin Symptomatic Intracranial Disease Study. *Neurology* 1995;**45**:1488–51.
94. Neaton JD, Blackburn H, Jacobs D. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. *Arch Int Med* 1992;**152**: 1490–500.
95. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke* 1989;**20**:1460–5.
96. Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. *Stroke* 1996;**27**:1993–8.
97. How Lin C, Shimzu Y, Kato H *et al.* Cerebrovascular diseases in a fixed population of Hiroshima and Nagasaki, with special reference to relationship between type and risk factors. *Stroke* 1984;**15**:653–60.
98. Iso H, Jacobs DRJ, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350 977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med* 1989;**320**:904–10.
99. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998;**352**:1801–7.
100. The Heart Protection Study. Presented at the Scientific Sessions of the American Heart Association; 2001. Available at: http://www.ctsu.ox.ac.uk/~hps/.
101. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
102. Sacks FM, Pfeffer MA, Moyé LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.
103. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
104. Shepherd J, Cobbe SM, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *N Engl J Med* 1995;**333**:1301–7.
105. Downs JR, Clearfield M, Wies S *et al.* Priimary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/Tex CAPS. *JAMA* 1998;**279**:1615–22.
106. Sandercock P. Statins for stroke prevention? *Lancet* 2001; **357**:1548–9.
107. Fields WS, Maslenikov V, Meyer JS *et al.* Joint study of extracranial arterial occlusion. V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA* 1970;**211**:1993–2003.

108.Shaw DA, Venables GS, Cartlidge NEF, Bates D, Dickinson PH. Carotid endarterectomy in patients with transient cerebral ischaemia. *J Neurol Sci* 1984;**64**:45–53.
109.North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445–3.
110.European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;**337**:1235–43.
111.Mayberg MR, Wilson SE, Yatsu F *et al.* Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA* 1991;**266**:3289–94.
112.European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 2000;**351**: 1379–87.
113.North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic, moderate or severe stenosis. *New Engl J Med* 1998;**339**:1415–25.
114.Barnett HJM, Warlow CP. Carotid endarterectomy and the measurement of stenosis. *Stroke* 1993;**24**:1281–4.
115.Hankey GJ, Warlow CP, Molyneuz AJ. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. *J Neurol Neurosurg Psychiatr* 1990;**53**:542–8.
116.Eliasziw M, Rankin RN, Fox AJ, Haynes RB, Barnett HJM, for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. *Stroke* 1995;**26**:1747–52.
117.CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study: a randomised trial. *Lancet* 2001;**357**:1729–37.
118.Hobson RW II, Weiss DG, Fields WS *et al.* Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;**328**:221–7.
119.Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;**273**:1421–8.
120.Hennerici M, Hulsbomer HB, Hefter H, Lemmerts D, Rautenberg W. Natural history of asymptomatic extracranial arterial disease: results of a long-term prospective study. *Brain* 1987;**110**:777–91.
121.Norris JW, Zhu CZ, Bornstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. *Stroke* 1991;**22**: 1485–90.
122.Lernfelt B, Forsberg M, Blomstrand C, Mellström D, Volkmann R. Cerebral atherosclerosis as predictor of stroke and mortality in representative elderly population. *Stroke* 2002;**33**:224–9.
123.Rothwell P. Carotid endarterectomy and prevention of stroke in the very elderly. *Lancet* 2001;**357**:1142–3.
124.Halliday AW, Thomas D, Mansfield A. The Asymptomatic Carotid Surgery Trial (ACST) rationale and design. *Eur J Vasc Surg* 1994;**8**:703–10.

60 Heart disease and pregnancy

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Introduction

Women with heart disease comprise approximately 1% of the population in obstetric referral centers,[1] though they are less frequently seen in general obstetric practice. Current data on pregnancy outcomes of women with heart disease are primarily from studies that were retrospective, focused on a particular cardiac lesion, or examined populations managed at a single institution or from an earlier era. Treatment recommendations are usually based on institutional experience or extrapolation from observational studies.

Pregnancy in most women with heart disease has a favorable outcome for both mother and fetus. With the exception of patients with Eisenmenger syndrome, pulmonary vascular obstructive disease and Marfan syndrome with aortopathy, maternal death during pregnancy in women with heart disease is rare.[1–5] However, pregnant women with heart disease do remain at risk for other complications, including heart failure, arrhythmia and stroke.

Women with congenital heart disease comprise the majority of pregnant women with heart disease seen at referral centers.[1,5] The next largest group includes women with rheumatic heart disease. Other important conditions less frequently encountered include peripartum dilated cardiomyopathy, hypertrophic cardiomyopathy and coronary artery disease. Gestational hypertension, arising de novo or superimposed on pre-existing hypertension, is responsible for around 15% of all maternal mortality and considerable morbidity.[6]

Cardiovascular physiology and pregnancy

Pregnancy is characterized by hormonally mediated changes in blood volume, red cell mass and heart rate, resulting in a 50% increase in cardiac output during the antepartum period.[7] Increases in LV end-diastolic dimension and volume are present by 14 weeks' gestation and reach maximum levels early in the third trimester.[8–12] Preload- and afterload-adjusted indices of contractility remain in the normal range during the antepartum period.[13] LV mass increases during pregnancy as a consequence of increased LV wall thickness. Gestational hormones, circulating prostaglandins and the low-resistance vascular bed in the placenta result in decreases in peripheral vascular resistance and blood pressure (BP). These physiological changes are exacerbated in multifetal gestations. During labor and delivery there are additional increases in cardiac output and oxygen consumption.[7,14] Immediately following delivery, relief of caval compression and autotransfusion from the emptied uterus result in a transient increase in cardiac output. Most of the hemodynamic changes of pregnancy have resolved by the second postpartum week, but complete return to normal does not occur until 6 months after delivery.[15,16] LV diastolic dimension, volume and mass also return to preconception levels by the sixth postpartum month.

Outcomes associated with specific cardiac lesions

Congenital heart lesions

Left to right shunts

The effect of increase in cardiac output on the volume-loaded right ventricle in *atrial septal defect* (ASD), or the left ventricle in *ventricular septal defect* (VSD) and *patent ductus arteriosus* (PDA), is counterbalanced by a decrease in peripheral vascular resistance. Consequently, the increase in volume overload is attenuated. In the absence of pulmonary hypertension, pregnancy, labor and delivery are well tolerated.[1,4,5,17] **Grade B2** However, arrhythmias, ventricular dysfunction and progression of pulmonary hypertension may occur, especially when the shunt is large or when there is pre-existing elevation of pulmonary artery pressure. Infrequently, particularly in ASD, paradoxical embolization may be encountered if systemic vasodilatation and/or elevation of pulmonary resistance promote transient right to left shunting.

Left ventricular outflow tract obstruction

When *aortic stenosis* (AS) complicates pregnancy it is usually due to congenital bicuspid aortic valve, which may also be associated with aortic coarctation and/or ascending aortopathy. Other causes of left ventricular (LV) outflow tract obstruction at, below and above the valve have similar hemodynamic consequences. Women with symptomatic aortic stenosis should delay pregnancy until after surgical correction.[18] **Grade B4** However, the absence of symptoms is not sufficient assurance that pregnancy will be well

tolerated. In a pregnant woman with severe AS the limited ability to augment cardiac output may result in abnormal elevation of LV systolic and filling pressures, which in turn precipitate or exacerbate heart failure or ischemia. In addition the non-compliant, hypertrophied ventricle is sensitive to falls in preload. The consequent exaggerated drop in cardiac output may lead to hypotension. In a compilation of many small retrospective series, 65 patients were followed through 106 pregnancies with a maternal mortality of 11% and a perinatal mortality of 4%.[19] In 25 of the same 65 pregnancies managed more recently there was no maternal mortality, although maternal functional deterioration occurred in 20% of pregnancies.[19] Women with moderate or severe aortic stenosis continue to be at increased risk for pulmonary edema or arrhythmia during pregnancy.[1,5,19] **Grade B2** Intrapartum palliation by balloon valvuloplasty may be helpful in selected cases. **Grade C5**

In the absence of prosthetic dysfunction or residual aortic stenosis, patients with bioprosthetic aortic valves usually tolerate pregnancy well. Although it had been stated that pregnancy might accelerate the rate of degeneration of bioprosthetic or homograft valves, recent studies have shown that this is not the case.[20] **Grade B2** A study of 14 pregnancies in women who underwent pulmonary autograft aortic valve replacement (Ross procedure) reported favorable maternal and fetal outcomes except in one woman who developed postpartum LV dysfunction.[21] **Grade B4** Pregnancy in a woman with a mechanical valve prosthesis carries an increased risk of valve thrombosis as a result of the hypercoagulable state. The magnitude of this increased risk (3–14%) is greater if subcutaneous unfractionated heparin rather than warfarin is used as the anticoagulant agent; this may be the result of inadequate dosing, insufficient monitoring or reduced efficacy of heparin[18,22] **Grade B4** (see anticoagulation section under antepartum management).

Coarctation of the aorta

Maternal mortality with uncorrected coarctation was 3% in an early series; the risk was higher in the presence of associated cardiac defects, aortopathy or long-standing hypertension; aortic rupture accounted for 8 of the 14 reported deaths and occurred in the third trimester as well as in the postpartum period.[23] **Grade B4** The results of recent studies have been more encouraging. In 182 pregnancies reported in three recent studies, the only maternal death occurred in a woman with Turner syndrome who had previously undergone coarctation repair.[1,5,24] **Grade B2** The management of hypertension in uncorrected coarctation is particularly problematic in pregnancy, because satisfactory control of upper body hypertension may lead to excessive hypotension below the coarctation site, thereby compromising the fetus. Intrauterine growth restriction and premature labor and delivery are more common. Following coarctation repair, the risk of dissection and rupture is reduced but not eliminated. Pregnant women with repaired coarctation are at increased risk for pregnancy-induced-hypertension, probably as a result of residual abnormalities in aortic compliance.[1,5,24] **Grade B2**

Pulmonary stenosis

Mild pulmonic stenosis, or pulmonic stenosis that has been alleviated by valvuloplasty or surgery, is well tolerated during pregnancy and fetal outcome is favorable.[1,5] **Grade B2** Although a woman with severe pulmonic stenosis may be asymptomatic, the increased hemodynamic load of pregnancy may precipitate right heart failure or atrial arrhythmias; such a patient should be considered for correction prior to pregnancy. **Grade C5** Even during pregnancy, balloon valvuloplasty may be feasible if symptoms of pulmonary stenosis progress.

Cyanotic heart disease: unrepaired and repaired

In uncorrected or palliated pregnant patients with cyanotic congenital heart disease, such as tetralogy of Fallot, single ventricle etc., the usual pregnancy-associated fall in systemic vascular resistance and rise in cardiac output exacerbate right to left shunting, leading to increased maternal hypoxemia and cyanosis. A study examining the outcomes of 96 pregnancies in 44 women with a variety of cyanotic congenital heart defects reported a high rate of maternal cardiac events (32%, including one death), prematurity (37%) and a low livebirth rate (43%).[25] **Grade B4** The lowest livebirth rate (12%) was observed in mothers with arterial oxygen saturation $\leq$85%.

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease. Pregnancy risk is low in women who have had successful correction of tetralogy.[1,4,5] **Grade B2** However, residua and sequelae, such as residual shunt, right ventricular outflow tract obstruction, arrhythmias, pulmonary regurgitation, right ventricular systolic dysfunction, pulmonary hypertension (owing to the effects of a previous palliative shunt) or LV dysfunction (owing to previous volume overload), increase the likelihood of pregnancy complications and require independent consideration.

Atrial repair (that is Mustard or Senning procedure) was developed for the surgical correction of complete transposition of the great arteries. The anatomic right ventricle supports the systemic circulation. Late adult complications following atrial repair include sinus node dysfunction, atrial arrhythmias and dysfunction of the systemic ventricle. In 43 pregnancies in 31 women described in recent reports, there was one late maternal death.[26,27] **Grade B4** There was a 14% incidence of maternal heart failure, arrhythmias or cardiac deterioration. There have been no studies of

pregnancy outcome in women who received the current repair of choice for complete transposition, the arterial switch procedure. However, in the absence of ventricular dysfunction, coronary obstruction or other important residua or sequelae, a good outcome is expected. **Grade C5**

The Fontan operation eliminates cyanosis and volume overload of the functioning systemic ventricle, but patients have a limited ability to increase cardiac output. In a review of 33 pregnancies in 21 women who were doing well after the Fontan operation there were 15 (45%) term pregnancies with no maternal mortality, although two women had cardiac complications and the incidence of first-trimester miscarriage was high (39%).[28] **Grade B4** As the 10 year survival following the Fontan operation is only 60–80% it is important that information regarding long-term maternal prognosis be discussed during preconception counseling.

Marfan syndrome

Life-threatening aortic complications of Marfan syndrome are due to medial aortopathy resulting in dilatation, dissection and valvular regurgitation. Risk is increased in pregnancy owing to hemodynamic stress and perhaps hormonal effects. Although older case reports suggested a very high mortality risk in the range of 30%, a subsequent study found an overall maternal mortality of 1% and fetal mortality of 22%.[29] A prospective study of 45 pregnancies in 21 patients reported no increase in obstetric complications or significant change in aortic root size in patients with normal aortic roots. Importantly, in the eight patients with a dilated aortic root (>40 mm) or prior aortic root surgery, three of nine pregnancies were complicated by either aortic dissection (2) or rapid aortic dilatation (1).[30] Thus, patients with aortic root involvement should receive preconception counseling emphasizing their risk, and in early pregnancy should be offered termination. In contrast, women with little cardiovascular involvement and with normal aortic root diameter may tolerate pregnancy well, though there remains a possibility of dissection even without prior evidence of aortopathy. **Grade B4** The likelihood of aortic dilatation increases with increasing maternal age, so that advice to complete families at a younger age is appropriate. Serial echocardiography should be used to identify progressive aortic root dilatation during pregnancy and for 6 months postpartum; prophylactic β blockers should be administered.[31] **Grade C5**

Congenitally corrected transposition of the great arteries

Many adult patients will have had surgical interventions, primarily VSD closure and relief of pulmonic stenosis, sometimes requiring a valved conduit from the LV to the pulmonary artery. Potential problems in pregnancy include dysfunction of the systemic right ventricle and/or increased systemic AV valve regurgitation, with heart failure, atrial arrhythmias and AV block. In two recent reports on 41 patients there were 105 pregnancies, with 73% live births and no maternal mortality, although seven patients developed heart failure, endocarditis, stroke or myocardial infarction.[32,33] **Grade B4**

Eisenmenger syndrome and pulmonary vascular obstructive disease

Maternal mortality in Eisenmenger syndrome is approximately 30% in each pregnancy.[34] **Grade B4** The majority of complications occur at term and during the first postpartum week. Preconception counseling should stress the extreme pregnancy-associated risks. Termination should always be offered to such patients, as should sterilization. The vasodilatation associated with pregnancy will increase the magnitude of right to left shunting in patients with Eisenmenger syndrome, resulting in worsening of maternal cyanosis and adverse effects on fetal outcome. Spontaneous abortion is common, intrauterine growth restriction is seen in 30% of pregnancies, and preterm labor is frequent. The high perinatal mortality rate (28%) is due mainly to prematurity.

Pregnancy may accelerate the progression of pulmonary vascular disease by increasing the risk of *in-situ* thrombosis and/or thromboembolism; other mechanisms may be operative as well. **Grade C5**

A recent review of outcome of 125 pregnancies in patients with Eisenmenger syndrome, primary pulmonary hypertension and secondary pulmonary hypertension reported poor outcomes in all three groups.[35] **Grade B4** The maternal mortality observed in the various groups was 36%, 30% and 56%, respectively. The overall neonatal mortality was 13%.

Mitral valve prolapse

Isolated mitral valve prolapse has an excellent outcome in pregnancy[36–38] **Grade B4** and affects management only as a possible indication for endocarditis prophylaxis, or if severe mitral regurgitation has led to symptomatic deterioration or left ventricular dysfunction.

Rheumatic heart disease

Mitral stenosis is the most common rheumatic valvular lesion encountered during pregnancy. The hypervolemia and tachycardia associated with pregnancy exacerbate the impact of mitral valve obstruction. The resultant elevation in left atrial pressure increases the likelihood of atrial fibrillation. Thus, even patients with mild to moderate mitral stenosis who are asymptomatic prior to pregnancy, may develop atrial fibrillation and heart failure during the ante- and peripartum periods. Atrial fibrillation is a frequent precipitant of heart failure in pregnant patients with mitral stenosis,

owing primarily to uncontrolled ventricular rates; equivalent tachycardia of any cause may produce the same detrimental effect. Earlier studies examining a pregnant population comprised predominantly of women with rheumatic mitral disease showed that mortality rate increased with worsening antenatal maternal functional class.[3] More recent studies found no mortality, but described substantial morbidity from heart failure and arrhythmia.[1,5] The risk for complications was especially high in those women with moderate or severe mitral stenosis.[1,5,39] **Grade B2** Percutaneous mitral valvuloplasty should be considered in patients with functional class III or IV symptoms despite optimal medical therapy and hospitalization.[40–42] **Grade B4**

Pregnant women whose dominant lesion is rheumatic aortic stenosis have a similar outcome to those with congenital aortic stenosis. Aortic or mitral regurgitation is generally well tolerated during pregnancy even if severe, although deterioration in maternal functional class has been observed.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a form of idiopathic dilated cardiomyopathy diagnosed by otherwise unexplained LV systolic dysfunction, confirmed echocardiographically, presenting during the last antepartum month or in the first 5 postpartum months.[43] It usually manifests as heart failure, although arrhythmias and embolic events also occur. Many affected women will show improvement in functional status and ventricular function postpartum, but others may have persistent or progressive dysfunction. The relapse rate during subsequent pregnancies is substantial in women with evidence of persisting cardiac enlargement or LV dysfunction. However, pregnancy may not be risk free even in those with recovery of systolic function, as subclinical abnormalities may persist.[44] In a recently published multicenter survey examining the outcomes of 60 pregnancies in women with peripartum cardiomyopathy diagnosed during a prior pregnancy, 44% of women with LV ejection fraction $<0{\cdot}50$ developed symptoms of congestive heart failure during subsequent pregnancies, with an associated mortality rate of 19%. In contrast, symptoms of congestive heart failure developed in 21% of women with LV ejection fraction $\geq 0{\cdot}50$, and none of this group died (Figure 60.1).[45] **Grade B4**

Hypertensive disorders in pregnancy

Hypertensive disorders of pregnancy are the second most common cause of maternal mortality, accounting for 15% of all obstetric deaths.[6] They also predispose to other complications, such as placental abruption, stroke, disseminated intravascular coagulation, renal and/or hepatic failure and congestive heart failure.[46] The fetus is at increased risk for intrauterine growth restriction, prematurity and intrauterine death.

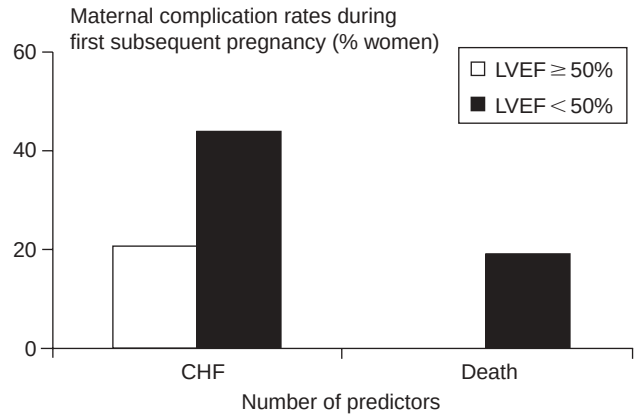

Figure 60.1 The frequency of maternal heart failure (CHF) and death during the first subsequent pregnancy in women with peripartum cardiomyopathy as stratified by preserved (LVEF $\geq$50%) versus reduced left ventricular ejection fraction (LVEF $<$50%). In the group with preserved left ventricular ejection fraction there were no deaths during the first subsequent pregnancy. (From Elkayam *et al.*[45])

Several guidelines and consensus documents have been developed which attempt to standardize definitions and criteria for diagnosis.[46–49] Unfortunately, terminology and definitions vary slightly, but importantly in these documents this compromises clarity. The recommendations of the Canadian Hypertension Society and the Society of Obstetricians and Gynaecologists of Canada define hypertension in pregnancy as *pre-existing hypertension* (elsewhere called chronic hypertension, renal hypertension, underlying hypertension, essential hypertension or secondary hypertension), *gestational hypertension without proteinuria and other adverse conditions* (elsewhere called pregnancy-induced hypertension, transient hypertension) or *gestational hypertension with proteinuria or other adverse conditions* (elsewhere called pre-eclampsia, eclampsia, HELLP [*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets] syndrome, gestational proteinuric hypertension).[46,48,49] The recent American guidelines set criteria for the diagnosis of hypertension in pregnancy as seated systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$90 mmHg (using Korotkoff phase V (disappearance of sound) to determine diastolic pressure).[6] The BP elevation should be noted on repeated measurements. Proteinuria in pregnancy is significant when there is $>0{\cdot}3$ g protein in a 24 hour urine collection. Severe hypertension is defined as a systolic blood pressure $\geq$160 and/or a diastolic blood pressure $\geq$110 mmHg and severe proteinuria as a 24 hour urine protein excretion $>$2 g. Gestational hypertension may be *superimposed* on pre-existing hypertension. In the absence of proteinuria and other adverse conditions, gestational hypertension that resolves postpartum is called *transient hypertension* or *benign gestational hypertension*, whereas if it persists postpartum it is understood as pregnancy-induced unmasking of pre-existing (or chronic) hypertension.

The pathophysiology of gestational hypertension with proteinuria or other adverse conditions (pre-eclampsia) differs from other forms of hypertension. As a result of placental dysfunction, the normal cardiovascular adaptations to pregnancy (increased plasma volume and decreased peripheral resistance) do not occur. There is reduced perfusion to the placenta, liver, kidneys and brain. It is thought that endothelial dysfunction, perhaps a consequence of the decreased perfusion, results in excessive vasoactive toxins, which produce most if not all the manifestations of gestational hypertension. Thus, hypertension is but one effect, not a cause, of the clinical syndrome.

Certain adverse conditions are associated with worse outcomes. Frontal headache, severe nausea and vomiting, visual disturbances, chest pain and shortness of breath, and right upper quadrant pain are significant symptoms. The components of the HELLP syndrome may be found, either individually or combined. Other adverse maternal manifestations are severe hypertension, severe proteinuria, hypoalbuminemia (<18 g/l) oliguria, pulmonary edema and convulsions. Fetal compromise may be revealed by oligohydramnios, absent or reversed umbilical artery end-diastolic flow, and abnormalities in fetal biophysical profile. Intrauterine growth restriction, prematurity and placental abruption are the serious adverse fetoplacental consequences.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a disorder with distinct genetic abnormalities and a diverse clinical profile. Morphologically there is unexplained ventricular hypertrophy, which is usually asymmetric and predominantly involves the interventricular septum. Obstruction to left ventricular outflow is a common but not invariable feature. Diastolic function abnormalities are important determinants of the clinical manifestations.

In patients with dynamic left ventricular outflow tract obstruction, increases in preload tend to reduce the severity of obstruction, whereas increases in contractility and decreases in afterload tend to worsen it. Diastolic dysfunction magnifies the preload dependence on cardiac output. As a consequence, pregnancy may be associated with worsening symptoms. Maternal outcome is often good, although at least two deaths have been reported, and serious complications (congestive heart failure, supraventricular tachyarrhythmias, ventricular tachycardia, syncope) may occur, especially in women who already have symptoms prior to pregnancy, and in those with substantial LV diastolic and/or systolic dysfunction.[50,51] **Grade B4** Fetal outcomes are good. β Blockers may be used, as in the non-pregnant state. Dual chamber pacing may be of value in patients with symptoms refractory to medical therapy. **Grade C5** The role of septal alcohol ablation or surgical myectomy during pregnancy has not been defined.

Coronary artery disease

Symptomatic coronary artery disease (CAD) is an uncommon accompaniment of pregnancy. Major predisposing factors for atherosclerotic CAD include long-standing diabetes mellitus,[52] familial hypercholesterolemia and tobacco abuse. In addition, some non-atherosclerotic causes of CAD, though also rare, are more frequent in or aggravated by pregnancy, such as coronary artery dissection, coronary artery embolism, vascular complications of vasoactive obstetric therapies (for example ergot derivatives, prostaglandins), and collagen vascular diseases. The long-term residua of childhood Kawasaki disease include coronary artery stenoses and aneurysms, which may become symptomatic during pregnancy. Cocaine abuse must be considered in any young person with an acute coronary event.[53]

Diagnosis of infarction may be confounded peripartum because of the release of CK-MB isoenzyme from the uterus.[54] Because of the possibility of unusual causes of ischemia and infarction, coronary angiography should be considered early. Fetal exposure to radiation from routine coronary angiography is <5 mGy (<500 mrad).[55] Adverse fetal consequences of this amount of radiation are extremely small or negligible[55] **Grade B4**, and pregnancy should not be seen as a contraindication to a clinically necessary study.[56] Thromobolysis is not contraindicated,[53] but the diagnosis of coronary thrombosis as opposed to other causes of coronary occlusion cannot be routinely assumed; if immediately available, coronary angiography with the option of primary angioplasty can immediately confirm the diagnosis and thus increase the likelihood of providing appropriate therapy.

Management

Risk stratification and counseling

Risk stratification and counseling of women with heart disease is best accomplished prior to conception. The data required for risk stratification can be readily acquired from a thorough cardiovascular history and examination, 12-lead electrocardiogram (ECG) and transthoracic ECG. In patients with cyanosis, arterial oxygen saturation should be assessed by percutaneous oximetry. In counseling, the following areas should be considered: the underlying cardiac lesion; maternal functional status; the possibility of further palliative or corrective surgery; additional associated risk factors; maternal life expectancy and ability to care for a child; and the risk of congenital heart disease in the offspring.

Defining the *underlying cardiac lesion* is an important part of stratifying risk and determining management. Review of prior catheterization and operative reports may be necessary to clarify the diagnosis. The nature of residua and sequelae should be clarified, especially ventricular function, pulmonary pressure, severity of obstructive lesions, persistence of shunts and the presence of hypoxemia.

Almost all patients can be stratified into low-, intermediate- or high-risk groups (Box 60.1). *Maternal functional status* is widely used as a predictor of outcome, and most often defined by NYHA functional class. In a study of 482 pregnancies in women with congenital heart disease, cardiovascular morbidity was less (8% *v* 30%) and livebirth rate higher (80% *v* 68%) in mothers with NYHA functional class I than in the others.[2] **Grade B2** In two studies examining the outcomes of 851 pregnancies, poor functional status (NYHA > II) or cyanosis, left ventricular systolic dysfunction, left heart obstruction, and history of cardiac events prior to pregnancy (arrhythmia, stroke or pulmonary edema) were independent predictors of maternal cardiac complications.[1,5] **Grade B2** Poor maternal functional class or cyanosis was also predictive of adverse neonatal events.

Box 60.1 Maternal cardiac lesion and cardiac risk during pregnancy

Low risk
- Left to right shunts
- Repaired lesions without residual cardiac dysfunction
- Isolated mitral valve prolapse without significant regurgitation
- Bicuspid aortic valve without stenosis
- Mild–moderate pulmonic stenosis
- Valvular regurgitation with normal ventricular systolic function

Intermediate risk
- Unrepaired or palliated cyanotic congenital heart disease
- Uncorrected coarctation of the aorta
- Mitral stenosis
- Mild or moderate aortic stenosis
- Mechanical prosthetic valves
- Severe pulmonic stenosis
- Moderate to severe systemic ventricular dysfunction
- Systemic right ventricle or single ventricle
- Hypertrophic cardiomyopathy
- History of peripartum cardiomyopathy with no residual ventricular dysfunction
- Symptomatic arrhythmia
- Pre-existing hypertension
- Gestational hypertension without pre-eclampsia
- Stable coronary artery disease

High risk
- New York Heart Association (NYHA) class III or IV symptoms
- Significant pulmonary hypertension with or without right to left shunt
- Marfan syndrome with aortic root or major valvular involvement
- Severe aortic stenosis
- History of peripartum cardiomyopathy with residual ventricular dysfunction
- Recent myocardial infarction or unstable angina
- Gestational hypertension with proteinuria or other adverse conditions (pre-eclampsia)

In a recently published prospective study the four independent risk factors described above (poor functional status or cyanosis, left ventricular systolic dysfunction, left heart obstruction, and history of cardiac events prior to pregnancy) were incorporated into a revised risk index. The risk of a cardiac event (cardiac death, stroke, pulmonary edema or arrhythmia) during pregnancy increased with the number of predictors present during the antepartum evaluation. This risk index was derived using two thirds of the study sample and then validated in the remaining pregnancies. For each risk category there was excellent agreement between the expected and the observed rate of events in both the derivation and the validation set (Figure 60.2).[1] **Grade B2** The above-mentioned predictors were also predictive of the combined likelihood of cardiac event (as defined above), deterioration of maternal functional class during pregnancy, or need for an urgent cardiac intervention during the ante- or postpartum periods (Figure 60.3). This index, together with lesion-specific risk estimates, aids the risk stratification of women with heart disease at preconception counseling, and also during pregnancy.

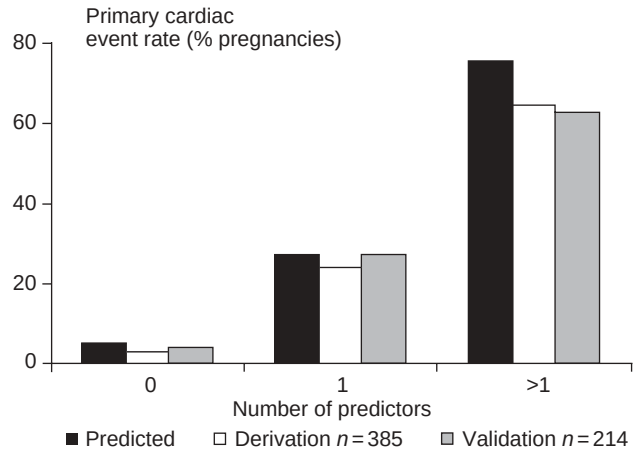

Figure 60.2 The frequency of maternal cardiac complications (pulmonary edema, cardiac arrhythmia, stroke or cardiac death) as predicted by the risk index and observed in the derivation and validation groups, as a function of the number of cardiac predictors (*n* denotes number of pregnancies). (From Siu *et al.*[1])

Further palliative or corrective surgery. Both maternal and fetal outcomes are improved by surgery to correct cyanosis, which should be undertaken prior to conception when possible.[4] **Grade B2** Similarly, patients with symptomatic obstructive lesions should undergo intervention prior to pregnancy.[18] **Grade B4** A systematic overview of the outcome of cardiovascular surgery performed during pregnancy reported a maternal and fetal mortality of 6% and 30%, respectively.[57] **Grade B4** Planning for valve replacement prior to pregnancy requires the need for ongoing anticoagulation with a mechanical valve to be weighed against the likelihood of early reoperation if a tissue valve is used. For aortic stenosis, an attractive alternative is

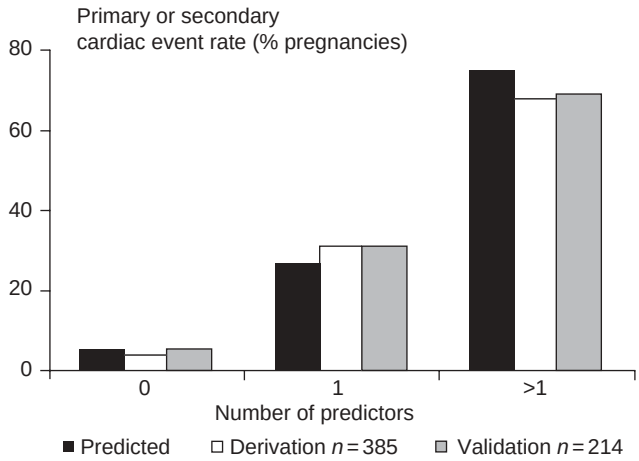

Figure 60.3 The frequency of any primary or secondary cardiac events (deterioration in maternal functional class, need for urgent cardiac interventions during the ante- or postpartum periods, pulmonary edema, cardiac arrhythmia, stroke, death) as predicted by the risk index and observed in the derivation and validation groups, as a function of the number of cardiac predictors (*n* denotes number of pregnancies). (From Siu *et al.*[1])

the pulmonary autograft. The lack of ideal choices once severe valve disease is present argues for completing families earlier, before the age-dependent progression of valve disease necessitates valve replacement surgery.

Additional associated risk factors that may complicate pregnancy include a history of arrhythmia or heart failure, prosthetic valves and conduits, anticoagulant therapy, and the use of teratogenic drugs such as warfarin or angiotensin-converting enzyme inhibitors.

Maternal life expectancy and ability to care for a child. A patient with limited physical capacity or with a condition that may result in premature death should be advised of her potential inability to look after her child. Women whose condition imparts a high likelihood of fetal complications, such as those with cyanosis or on anticoagulants, must be apprised of these added risks.

The *risk of recurrence of congenital heart disease in offspring* should be addressed in the context of a 0·4–0·6% risk in the general population. The risk with an affected first degree relative increases about 10-fold. A multicenter study examining the offspring of patients with major congenital heart defects who survived cardiac surgery described an overall recurrence rate of 4% in the offspring.[58] **Grade B2** Obstructive left heart lesions have a higher recurrence rate. Certain conditions, such as Marfan syndrome and the 22q11 deletion syndromes, are autosomal dominant, conferring a 50% risk of recurrence in an offspring. Patients with congenital heart disease who reach reproductive age should be offered genetic counseling so that they are fully informed of the mode of inheritance and recurrence risk, as well as the prenatal diagnosis options available to them. **Grade C5** Preventative strategies to decrease the incidence of congenital defects, such as preconception use of multivitamins containing folic acid, can be discussed at the time of such counseling.[59] **Grade A1d**

Antepartum management

Pregnant women with heart disease may be at particular risk for one or more of congestive heart failure; arrhythmias; or thrombosis, emboli and adverse effects of anticoagulants. Pre-existing and/or gestational hypertension/pre-eclampsia may also require management.

When ventricular dysfunction is a concern, limitation of activity is helpful, and in severely affected women with class III or IV symptoms hospital admission by mid second trimester may be advisable. Gestational hypertension, hyperthyroidism, infection and anemia should be identified early and treated vigorously. For patients with functionally significant mitral stenosis, β adrenergic blockers should be used to control heart rate. Digitalis, although a time-honored treatment for the same purpose, is often ineffective in blunting pregnancy-induced tachycardia. We also offer empiric therapy with β adrenergic blockers to patients with coarctation and to Marfan patients. **Grade C5**

Arrhythmias

Arrhythmias in the form of premature atrial or ventricular beats are common in normal pregnancy; sustained tachyarrhythmias have also been reported. In those with pre-existing arrhythmias, pregnancy may exacerbate their frequency or hemodynamic severity. Pharmacologic treatment is usually reserved for patients with severe symptoms, or when sustained episodes are poorly tolerated in the presence of ventricular hypertrophy, ventricular dysfunction or valvular obstruction. Sustained tachyarrhythmias, such as atrial flutter or atrial fibrillation, should be treated promptly, avoiding teratogenic antiarrhythmic drugs. Digoxin and β adrenergic blockers are the antiarrhythmic drugs of choice, in view of their known safety profiles.[60] **Grade B4** Quinidine, adenosine, sotalol and lidocaine are also "safe", but published data on their use during pregnancy are more limited. Amiodarone is more problematic and standard texts classify it as contraindicated in pregnancy, although there are case reports describing its successful use with careful follow up; it is not teratogenic, but may impair neonatal thyroid function.[61,62] **Grade B4** Electrical cardioversion is safe in pregnancy. A recent report of 44 pregnancies in women with implantable cardioverter

defibrillators reported favorable maternal and fetal outcomes.[63] **Grade B4**

Anticoagulation

When a pregnant woman with a mechanical heart valve requires anticoagulation heparin and warfarin are used, but controversy continues as to which is better at different stages of pregnancy. Oral anticoagulation with warfarin is better accepted by patients and is effective. However, warfarin embryopathy may be produced during organogenesis, and fetal intracranial bleeding can occur throughout pregnancy. A recent study of 58 pregnancies reported that a daily warfarin dose of ≤5 mg was associated with no cases of embryopathy.[22] **Grade B4** Fetal intracranial hemorrhage during vaginal delivery is a risk with warfarin unless it has been stopped at least 2 weeks prior to labor. Adjusted-dose subcutaneous heparin has no teratogenic effects as the drug does not cross the placenta, but heparin may cause maternal thrombocytopenia and osteoporosis. Claims of inadequate effectiveness of heparin in patients with mechanical heart valves have been countered by arguments that inadequate doses were used. In a systematic overview of prior studies examining the relationship between anticoagulation regimen and pregnancy outcome in women with prosthetic heart valves, the overall pooled maternal mortality was 2·9%.[64] **Grade B4** The use of oral anticoagulants throughout pregnancy was associated with the lowest rate of valve thrombosis/systemic embolism (4%). The use of unfractionated heparin between 6 and 12 weeks' gestation only was associated with an increased risk of valve thrombosis (9%). Recent practice guidelines have favored the use of either warfarin plus low-dose aspirin during the entire pregnancy, or warfarin substituted by heparin only during the peak teratogenic period (6–12 weeks' gestation).[18] **Grade B4** Low molecular weight heparin is easier to administer and has been suggested as an alternative to adjusted-dose unfractionated heparin. The adjunctive use of low-dose acetyl salicylic acid with heparin should also be considered.[65,66] **Grade C5** ASA in low dose is safe for the fetus, even at term[67] **Grade A1a**, although high maternal doses may promote premature duct closure.

Clinical trials are needed to better define the optimal anticoagulation strategy.

Eisenmenger syndrome

If a woman with Eisenmenger syndrome does not accept counseling to terminate, or presents late in pregnancy, meticulous antepartum management is necessary, including early hospitalization, supplemental oxygen, and possibly empiric anticoagulation. **Grade C5** The efficacy of nitric oxide therapy in these patients has yet to be demonstrated.

Hypertension in pregnancy

Mild pre-existing hypertension may not require pharmacotherapy in pregnancy, as fetal outcomes are unaffected, maternal blood pressure falls lower than baseline during the first 20 weeks of gestation, and excessive lowering of maternal blood pressure may compromise placental perfusion, with no proven maternal benefit.[6] Therapy should be initiated or reinstituted if moderate–severe hypertension develops (systolic BP ≥150–160; diastolic BP ≥100–110; or both), or there is target organ damage. It is not clear whether treatment of mild–moderate pre-existing (chronic) hypertension reduces the risk of developing superimposed gestational hypertension with proteinuria (pre-eclampsia). If treatment is indicated, drug therapy established as safe includes methyldopa, hydralazine, labetalol and other β-blockers[68] **Grade B4**, and nifedipine.[69] **Grade B4** Diuretics are indicated for the management of volume overload in renal failure or heart failure, may be used as adjuncts in the management of pre-existing (chronic) hypertension, but should be avoided in gestational hypertension (pre-eclampsia), which is a volume contracted state.[6,70] **Grade A1c** Angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents are contraindicated after the first trimester of pregnancy, and so should be stopped either before conception or in the first trimester as soon as pregnancy is diagnosed.[71,72] **Grade B4**

Gestational hypertension with proteinuria (pre-eclampsia) is treated effectively only by delivery of the fetus and placenta. Delay in delivery to allow maturation of the fetus can often be accomplished if the syndrome is mild, the patient is under very close surveillance in a hospital or obstetric day unit, and pregnancy is terminated as soon as further benefit to the fetus is unlikely or maternal safety is compromised.[6]

Multidisciplinary approach and high-risk pregnancy units

Women with heart disease who are at intermediate or high risk for complications should be managed in a high-risk pregnancy unit by a multidisciplinary team from obstetrics, cardiology, anesthesia and pediatrics (Box 60.2). **Grade C5** When dealing with a complex problem the team should meet early in the pregnancy. At this time the nature of the cardiac lesion, the anticipated effects of pregnancy and potential problems should be explored. As it is often not possible for every member of the team to be at the patient's bedside at a moment of crisis, it is helpful to develop and distribute widely a written management plan for foreseeable contingencies. Women with heart disease in the "low-risk" group can be managed in a community hospital setting. However, if there is doubt about the mother's status or the risk, consultation at a regional referral center should be arranged.

Box 60.2 Management of pregnancy in women with heart disease

All patients

- Define the lesion, the residua and the sequelae
- Assess functional status
- Determine predictors of risk: general and lesion specific
- Eliminate teratogens
- Arrange genetic counseling when relevant
- Consider consultation with a regional center
- Assess need for endocarditis prophylaxis during labor and delivery

Intermediate and high-risk patients

- Arrange management at a regional center for high-risk pregnancy
- Consider antepartum interventions to reduce pregnancy risk
- Engage a multidisciplinary team, as appropriate
- Consider a multidisciplinary case conference
- Develop and disseminate a management plan
- Anticipate vaginal delivery in almost all cases, unless there are obstetric contraindications
- Consider early epidural anesthesia
- Modify labor and delivery to reduce cardiac work
- Plan postpartum monitoring

Labor and delivery

Vaginal delivery is recommended, with very few exceptions. The only cardiac indications for cesarean section are aortic dissection, Marfan syndrome with dilated aortic root, and failure to switch from warfarin to heparin at least 2 weeks prior to labor. **Grade C5** Preterm induction is rarely indicated, but once fetal lung maturity is assured a planned induction and delivery in high-risk situations will ensure the availability of appropriate staff and equipment. Although there is no consensus on the use of invasive hemodynamic monitoring during labor and delivery, we commonly utilize intra-arterial monitoring and often central venous pressure monitoring as well in cases where there are concerns about the interpretation and deleterious effects of a sudden drop in systemic blood pressure (for example in patients with severe aortic stenosis, pulmonary hypertension, or more than moderate systemic ventricular systolic dysfunction). **Grade C5** The need for an indwelling pulmonary artery catheter is contentious and has not been studied during pregnancy. Its value has not been shown in several studies of unselected patients with heart disease monitored through non-cardiac surgical procedures. It may be considered when the information sought is not available otherwise and warrants the risk of the procedure; risk may be increased because of complex anatomy, such as atrial baffles, or in the setting of pulmonary hypertension, because of possible pulmonary infarction or rupture.

Heparin anticoagulation is discontinued at least 12 hours prior to induction, or reversed with protamine if spontaneous labor develops, and can usually be resumed 6–12 hours postpartum.

Endocarditis prophylaxis is initiated at the onset of active labor when indicated. The American Heart Association recommendations state that delivery by cesarean section and vaginal delivery in the absence of infection do not require endocarditis prophylaxis except, perhaps, in patients at high risk.[73] **Grade B2** Although many centers with extensive experience in caring for pregnant women with heart disease utilize endocarditis prophylaxis routinely, there is no evidence to support this common practice.

Epidural anesthesia with adequate volume preloading is the technique of choice. Epidural fentanyl is particularly advantageous in cyanotic patients with shunt lesions as it does not lower peripheral vascular resistance. In the presence of a shunt, air and particulate filters should be placed in all intravenous lines. **Grade C5**

Labor is conducted in the left lateral decubitus position to attenuate hemodynamic fluctuations associated with contractions in the supine position. Forceps or vacuum extraction will shorten the latter part of the second stage of labor and reduce the need for maternal expulsive effort. As hemodynamics do not approach baseline for many days after delivery, those patients at intermediate or high risk may require monitoring for a minimum of 72 hours postpartum. **Grade C5** Patients with Eisenmenger syndrome require longer close postpartum observation, as mortality risk persists for 7 days or more.

References

1. Siu SC, Sermer M, Colman JM *et al.* Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;**104**:515–21.
2. Whittemore R, Hobbins J, Engle M. Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. *Am J Cardiol* 1982;**50**:641–51.
3. McFaul P, Dornan J, Lamki H, Boyle D. Pregnancy complicated by maternal heart disease. A review of 519 women. *Br J Obstet Gynaecol* 1988;**95**:861–7.
4. Shime J, Mocarski E, Hastings D, Webb G, McLaughlin P. Congenital heart disease in pregnancy: short- and long-term implications. *Am J Obstet Gynecol* 1987;**156**:313–22.
5. Siu SC, Sermer M, Harrison DA *et al.* Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997;**96**:2789–94.
6. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;**183**:S1–S22.
7. Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy: Diagnosis and Management of Maternal and Fetal Disease*, 3rd edn. New York: Wiley-Liss, 1998.
8. Rubler S, Damani P, Pinto E. Cardiac size and performance during pregnancy estimated with echocardiography. *Am J Cardiol* 1977;**40**:534–40.

9. Katz R, Karliner J, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978;**58**:434–41.
10. Robson S, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *Br J Obstet Gynaecol* 1987;**94**: 1014–27.
11. Vered Z, Poler S, Gibson P, Wlody D, Perez J. Noninvasive detection of the morphologic and hemodynamic changes during normal pregnancy. *Clin Cardiol* 1991;**14**:327–34.
12. Sadaniantz A, Kocheril A, Emaus S, Garber C, Parisi A. Cardiovascular changes in pregnancy evaluated by two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1992;**5**:253–8.
13. Geva T, Mauer M, Striker L, Kirshon B, Pivarnik J. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J* 1997;**133**:53–9.
14. Robson S, Dunlop W, Boys R, Hunter S. Cardiac output during labour. *BMJ* 1987;**296**:1169–72.
15. Robson S, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. *Br J Obstet Gynaecol* 1987;**94**: 1028–39.
16. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992;**68**:540–3.
17. Zuber M, Gautschi N, Oechslin E, Widmer V, Kiowski W, Jenni R. Outcome of pregnancy in women with congenital shunt lesions. *Heart* 1999;**81**:271–5.
18. Bonow RO, Carabello B, de Leon AC Jr *et al.* ACC/AHA Guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol* 1998;**32**:1486–588.
19. Lao T, Sermer M, MaGee L, Farine D, Colman J. Congenital aortic stenosis and pregnancy – a reappraisal. *Am J Obstet Gynecol* 1993;**169**:540–5.
20. North RA, Sadler L, Stewart AW, McCowan LM, Kerr AR, White HD. Long-term survival and valve-related complications in young women with cardiac valve replacements. *Circulation* 1999;**99**:2669–76.
21. Dore A, Somerville J. Pregnancy in patients with pulmonary autograft valve replacement. *Eur Heart J* 1997;**18**:1659–62.
22. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999;**33**:1637–41.
23. Deal K, Wooley CF. Coarctation of the aorta and pregnancy. *Ann Intern Med* 1973;**78**:706–10.
24. Beauchesne LM, Connolly HM, Ammash NM, Warnes CA. Coarctation of the aorta: outcome of pregnancy. *J Am Coll Cardiol* 2001;**38**:1728–33.
25. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. *Circulation* 1994;**89**:2673–6.
26. Clarkson P, Wilson N, Neutze J, North R, Calder A, Barratt-Boyes B. Outcome of pregnancy after the Mustard operation for transposition of the great arteries with intact ventricular septum. *J Am Coll Cardiol* 1994;**24**:190–3.
27. Genoni M, Jenni R, Hoerstrup SP, Vogt P, Turina M. Pregnancy after atrial repair for transposition of the great arteries. *Heart* 1999;**81**:276–7.
28. Canobbio M, Mair D, van der Velde M, Koos B. Pregnancy outcomes after the Fontan repair. *J Am Coll Cardiol* 1996;**28**:763–7.
29. Pyeritz R. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981;**71**:784–90.
30. Rossiter J, Repke J, Morales A, Murphy E, Pyeritz R. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;**173**:1599–606.
31. Shores J, Berger K, Murphy E, Pyeritz R. Progression of aortic dilatation and the benefit of long-term β-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;**330**:1335–41.
32. Connolly HM, Grogan M, Warnes CA. Pregnancy among women with congenitally corrected transposition of great arteries. *J Am Coll Cardiol* 1999;**33**:1692–5.
33. Therrien J, Barnes I, Somerville J. Outcome of pregnancy in patients with congenitally corrected transposition of the great arteries. *Am J Cardiol* 1999;**84**:820–4.
34. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. *Obstet Gynecol Surv* 1979;**34**: 721–41.
35. Weiss B, Zemp L, Seifert B, Hess O. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *J Am Coll Cardiol* 1998;**31**:1650–7.
36. Rayburn WF, Fontana ME. Mitral valve prolapse and pregnancy. *Am J Obstet Gynecol* 1981;**141**:9–11.
37. Tang LC, Chan SY, Wong VC, Ma HK. Pregnancy in patients with mitral valve prolapse. *Int J Gynecol Obstet* 1985; **23**:217–21.
38. Chia YT, Yeoh SC, Lim MC, Viegas OA, Ratnam SS. Pregnancy outcome and mitral valve prolapse. *Asia Oceania J Obstet Gynaecol* 1994;**20**:383–8.
39. Hameed A, Karaalp IS, Tummala PP *et al.* The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001;**37**:893–9.
40. Mangione JA, Lourenco RM, dos Santos ES *et al.* Long-term follow-up of pregnant women after percutaneous mitral valvuloplasty. *Catheter Cardiovasc Interv* 2000;**50**:413–17.
41. Desai DK, Adanlawo M, Naidoo DP, Moodley J, Kleinschmidt I. Mitral stenosis in pregnancy: a four-year experience at King Edward VIII Hospital, Durban, South Africa. *Br J Obstet Gynaecol* 2000;**107**:953–8.
42. de Souza JAM, Martinez EE, Ambrose JA *et al.* Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. *J Am Coll Cardiol* 2001;**37**:900–3.
43. Pearson GD, Veille JC, Rahimtoola S *et al.* Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA* 2000;**283**:1183–8.
44. Lampert MB, Weinert L, Hibbard J, Korcarz C, Lindheimer M, Lang RM. Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. *Am J Obstet Gynecol* 1997;**176**:189–95.
45. Elkayam U, Tummala PP, Rao K *et al.* Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* 2001;**344**:1567–71.

46.Helewa M, Burrows R, Smith J, Williams K, Brain P, Rabkin S. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *Can Med Assoc J* 1997;**157**:715–25.
47.Brown MA, Hague WM, Higgins J *et al.* The detection, investigation and management of hypertension in pregnancy: full consensus statement. *Aust NZ J Obstet Gynaecol* 2000;**40**:139–55.
48.Moutquin J, Garner P, Burrows R *et al.* Report of the Canadian Hypertension Society Consensus Conference: 2. Non-pharmacologic management and prevention of hypertensive disorders in pregnancy. *Can Med Assoc J* 1997;**157**:907–19.
49.Rey E, LeLorier J, Burgess E, Lange I, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. *Can Med Assoc J* 1997;**157**:1245–54.
50.Elkayam U, Dave R. Hypertrophic cardiomyopathy and pregnancy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*, 3rd edn. New York: Wiley-Liss, 1998.
51.Benitez RM. Hypertrophic cardiomyopathy and pregnancy: maternal and fetal outcomes. *J Maternal–Fetal Invest* 1996; **6**:51–5.
52.Gordon MC, Landon MB, Boyle J, Stewart KS, Gabbe SG. Coronary artery disease in insulin-dependent diabetes mellitus of pregnancy (class H): a review of the literature. *Obstet Gynecol Surv* 1996;**51**:437–44.
53.Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996;**125**:751–62.
54.Leiserowitz GS, Evans AT, Samuels SJ, Omand K, Kost GJ. Creatine kinase and its MB isoenzyme in the third trimester and the peripartum period. *J Reprod Med* 1992;**37**:910–6.
55.Wagner LK, Lester RG, Saldana LR. *Exposure of the pregnant patient to diagnostic radiations: A guide to medical management*, 2nd edn. Madison, WI: Medical Physics Publishing, 1997.
56.Colletti PM, Lee K. Cardiovascular imaging in the pregnant patient. In: Elkayam U, Gleicher N, eds. *Cardiac problems in pregnancy*, 3rd edn. New York: Wiley-Liss, 1998.
57.Weiss BM, von Segesser LK, Alon E, Seifert B, Turina MI. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984–1996. *Am J Obstet Gynecol* 1998;**179**:1643–53.
58.Burn J, Brennan P, Little J *et al.* Recurrence risks in offspring of adults with major heart defects: results from first cohort of British Collaborative study. *Lancet* 1998;**351**:311–16.
59.Czeizel A. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996;**62**:179–83.
60.Chow T, Galvin J, McGovern B. Antiarrhythmic drug therapy in pregnancy and lactation. *Am J Cardiol* 1998;**82**:58I–62I.
61.Magee LA, Downar E, Sermer M, Boulton BC, Allen LC, Koren G. Pregnancy outcome after gestational exposure to amiodarone in Canada. *Am J Obstet Gynecol* 1995;**172**: 1307–11.
62.Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001;**24**:116–30.
63.Natale A, Davidson T, Geiger M, Newby K. Implantable cardioverter-defibrillators and pregnancy: a safe combination? *Circulation* 1997;**96**:2808–12.
64.Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;**160**:191–6.
65.Turpie AG, Gent M, Laupacis A *et al.* A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;**329**:524–9.
66.Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest* 2001;**119**:122S–131S.
67.CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994;**343**:619–29.
68.Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: management of hypertension in pregnancy. *BMJ* 1999; **318**:1332–6.
69.Magee LA, Schick B, Donnenfeld AE *et al.* The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. *Am J Obstet Gynecol* 1996;**174**:823–8.
70.Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. *BMJ (Clin Res)* 1985;**290**:17–23.
71.Hanssens M, Keirse MJ, Vankelecom F, Van Assche FA. Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991; **78**:128–35.
72.Piper JM, Ray WA, Rosa FW. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992;**80**:429–32.
73.Dajani A, Taubert K, Wilson W *et al.* Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;**277**:1794–801.

61 Venous thromboembolic disease

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There are three main aspects to the management of venous thromboembolism (VTE): diagnosis, prevention, and treatment. Prior to focusing on these, relevant aspects of the pathogenesis and natural history of VTE will be reviewed.

Pathogenesis of VTE

Virchow is credited with identifying stasis, vessel wall injury, and hypercoagulability as the pathogenic triad responsible for thrombosis. This classification of risk factors for VTE remains valuable.

- *Venous stasis*. The importance of venous stasis as a risk factor for VTE is demonstrated by the fact that most deep vein thrombosis (DVT), associated with stroke, affect the paralyzed leg,[1] and most DVT which are associated with pregnancy affect the left leg,[2] the iliac veins of which are prone to extrinsic compression by the pregnant uterus and the right common iliac artery.
- *Vessel damage*. Venous endothelial damage, usually as a consequence of accidental injury, manipulation during surgery (for example, hip replacement), or iatrogenic injury, is an important risk factor for VTE. Hence, 75% of proximal DVT complicating hip surgery occur in the operated leg,[3] and thrombosis is common with indwelling venous catheters.[4,5]
- *Hypercoagulability*. A complex balance of naturally occurring coagulation and fibrinolytic factors, and their inhibitors, serve to maintain blood fluidity and hemostasis. Inherited, or acquired, changes in this balance predispose to thrombosis. The most important inherited biochemical disorders associated with VTE are due to defects in the naturally occurring inhibitors of coagulation: deficiencies of antithrombin, protein C or protein S, and resistance to activated protein C caused by factor V Leiden. The first three of these disorders are rare in the normal population (combined prevalence of $<1\%$), have a combined prevalence of about 5% in patients with a first episode of VTE,[6] and are associated with a 10- to 40-fold increase in the risk of VTE.[7] The factor V Leiden mutation is common, occurring in about 5% of Caucasians and about 20% of patients with a first episode of VTE (that is, fourfold increase in VTE risk).[7,8] Hyperhomocysteinemia, owing to hereditary and acquired factors, is also a risk factor for VTE.[9]

  Elevated levels of a number of coagulation factors (I, II, VIII, IX, XI) are associated with thrombosis in a "dose-dependent" manner.[10–12] It is probable that such elevations are often inherited, with strong evidence for this with factor VIII.[10] A mutation in the 3′ untranslated region of the prothrombin gene (G20210A), which is associated with about 25% increase in prothrombin levels, occurs in about 2% of Caucasians and about 5% of those with a first episode of VTE (that is, about a 2·5-fold increase in risk).[7,8,13] Prothrombotic abnormalities of the fibrinolytic system have questionable importance.

  Acquired hypercoagulable states include estrogen therapy, antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulants), systemic lupus erythematosus, malignancy, combination chemotherapy, and surgery.[14] Patients who develop immunologically-related heparin-induced thrombocytopenia also have a very high risk of developing arterial and venous thromboembolism.[15] Unlike the congenital abnormalities, acquired risk factors are often transient, which has important implications for the duration of anticoagulant prophylaxis and treatment.
- *Combinations of risk factors and risk stratification*. The risk of developing VTE depends on the prevalence and severity of risk factors (Box 61.1).[14] Accordingly, by assessment of these factors, surgical patients can be categorized as having a low, moderate, or high risk of VTE (Table 61.1).

Prevalence and natural history of VTE

VTE is rare before the age of 16 years, probably because the immature coagulation system is resistant to thrombosis. However, the risk of VTE increases exponentially with advancing age (1·9-fold per decade), rising from an annual incidence of approximately 30/100 000 at 40 years, to 90/100 000 at 60 years, and 260/100 000 at 80 years.[14,16] Clinically important components of the natural history of VTE are summarized in Box 61.2.[17]

Box 61.1 Risk factors for venous thromboembolism[a]

- *Patient factors*
  - Previous VTE[b]
  - Age over 40
  - Pregnancy, purpureum
  - Marked obesity
  - Inherited hypercoagulable state
- *Underlying condition and acquired factors*
  - Malignancy[b]
  - Estrogen therapy
  - Cancer chemotherapy
  - Paralysis[b]
  - Prolonged immobility
  - Major trauma[b]
  - Lower limb injuries[b]
  - Heparin-induced thrombocytopenia
  - Antiphospholipid antibodies
- *Type of surgery*
  - Lower limb orthopedic surgery[b]
  - General anesthesia >30 min

[a] Combinations of factors have at least an additive effect on the risk of VTE.
[b] Common major risk factors for VTE.
Abbreviation: VTE, venous thromboembolism

Diagnosis of VTE

Objective testing for DVT and pulmonary embolism (PE) is important because clinical assessment alone is unreliable, failure to diagnose VTE is associated with a high mortality, and inappropriate anticoagulation needs to be avoided.

Diagnosis of DVT

Venography is the criterion standard for the diagnosis of DVT.[18,19] However, because of its invasive nature, technical demands, costs, and the risks associated with contrast media, non-invasive tests have been developed, of which venous ultrasound imaging (VUI) and, more recently, D-dimer testing, are the most important (Box 61.3).

Clinical assessment

Although clinical assessment cannot unequivocally confirm or exclude DVT, clinical evaluation with empiric assessment or a structured clinical model (Table 61.2), can stratify patients as having a low (≤10% prevalence), moderate (~25% prevalence) or high (≥60% prevalence) probability

Table 61.1 Risk stratification for postoperative VTE, frequency of VTE without prophylaxis, and recommended methods of prophylaxis.

	Venographic DVT[a]		Pulmonary embolism		Recommended prophylaxis
	Calf (%)	Proximal (%)	Symptomatic (%)	Fatal (%)	
Low risk less than 40 years and uncomplicated surgery and no additional risk factors	2	0·4	0·2	<0·01	Early mobilization
Moderate risk more than 40 years or prolonged/complicated surgery or additional "minor" risk factors	20	5	2	0·5	Low-dose UFH[b] LMWH (~3000 U daily)[c] GC stockings[d]
High risk major surgery for malignancy or previous VTE or knee/hip surgery or heparin-induced thrombocytopenia	50	15	5	2	LMWH (>3000 U per day)[c] Warfarin (INR 2–3)[f] Adjusted-dose UFH[g] IPC devices[e]

[a] Asymptomatic DVT detected by surveillance bilateral venography.
[b] Low-dose UFH: 5000 U of subcutaneous unfractionated heparin preoperatively, and twice or three times daily postoperatively.
[c] LMWH: subcutaneous low molecular weight heparin; higher doses (for example, ~4000 U once daily with a preoperative start [Europe], or ~3000 U twice daily with a postoperative start [North America]) are used in high-risk patients; in moderate-risk patients ~3000 U daily with a preoperative start is used.
[d] GC stockings: graduated compression stockings, alone or in combination with pharmacologic methods.
[e] IPC devices: intermittent pneumatic compression devices, alone or in combination with graduated compression stockings and/or pharmacologic methods.
[f] Warfarin: usually started postoperatively and adjusted to achieve an International Normalization Ratio (INR) of 2·0–3·0.
[g] Adjusted-dose UFH: preoperative start with an adjusted, three times daily, dose to raise the activated partial thromboplastin time to the upper limit of the normal range.
Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism

Box 61.2 Natural history of venous thromboembolism (VTE)

- Clinical factors can identify high-risk patients[14]
- VTE usually starts in the calf veins[112]
- Over 80% of symptomatic DVTs are proximal[19,112]
- Two thirds of asymptomatic DVT detected postoperatively by screening venography are confined to the distal (calf) veins[19]
- About 20% of symptomatic isolated calf DVTs subsequently extend to the proximal veins, usually within a week of presentation[113]
- PE usually arises from proximal DVT[114]
- The majority (~70%) of patients with symptomatic proximal DVT have asymptomatic PE (high probability lung scans in ~40%),[115] and vice versa[43,116]
- Only one quarter of patients with symptomatic PE have symptoms or signs of DVT[117]
- About 50% of untreated symptomatic proximal DVTs are expected to cause symptomatic PE[83]
- About 10% of symptomatic PE are rapidly fatal[118]
- About 30% of untreated symptomatic non-fatal PE will have a fatal recurrence[74,119]
- The risk of recurrent VTE is lower if risk factors are reversible than if there is no apparent, or a persistent, risk factor[90–93,96]

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism

of DVT.[20] **Grade A** Such categorization is useful in guiding the performance and interpretation of objective testing.[20–22]

Venous ultrasound imaging

VUI has a sensitivity for proximal DVT of about 97% and a specificity of 94% in symptomatic patients, which, on average, translates into a positive predictive value of 97% and a negative predictive value of 98% for proximal DVT.[19] The essential component of VUI is assessment of venous compressibility of the common femoral and popliteal veins (down to the calf vein trifurcation), with application of ultrasound probe pressure.[19] **Grade A** VUI is much more difficult to perform and less accurate in the calf (sensitivity of ~70%).[19] For these reasons, and because isolated calf DVT is uncommon and of limited importance, VUI of the calf veins is often not performed. Instead, if DVT cannot be excluded by a normal proximal VUI in combination with other results (for example, low clinical probability or normal D-dimer [see Box 61.3]), a follow up VUI is performed after 1 week to detect extending calf vein thrombosis (~2% of patients).[19] If the second VUI examination is normal, the risk of symptomatic VTE during the next 6 months is less than 2%.[19]

Box 61.3 Test results which effectively confirm or exclude DVT (deep vein thrombosis)

- *Diagnostic for first DVT*
  - Venography: intraluminal filling defect
  - Venous ultrasound: non-compressible proximal veins at two or more of the common femoral, popliteal, and calf trifurcation sites[19]
- *Excludes first DVT*
  - Venography: all deep veins seen, and no intraluminal filling defects[18]
  - D-dimer: normal test, which has a very high sensitivity (≥98%) and at least a moderate specificity (≥40%)[27]
  - Venous ultrasound or impedance plethysmography: normal and
    (a) low clinical suspicion for DVT at presentation,[29,120] or
    (b) normal D-dimer test, which has a moderately high sensitivity (≥85%) and specificity (≥70%) at presentation,[29,120] or
    (c) normal serial testing (venous ultrasound at 7 days; impedance plethysmography at 2 and 7 days)
- Low clinical suspicion for DVT at presentation and a normal D-dimer test, which has a moderately high sensitivity (≥85%) and specificity (≥70%) at presentation[29]
- *Diagnostic for recurrent DVT*
  - Venography: intraluminal filling defect
  - Venous ultrasound:
    (a) a new non-compressible common femoral or popliteal vein segment,[19] or
    (b) a ≥4.0 mm increase in diameter of the common femoral or popliteal vein compared to a previous test[19,37a]
  - Impedance plethysmography:
    (a) conversion of a normal test to abnormal[121,122a]
    (b) an abnormal test 1 year after diagnosis[19a]
- *Excludes recurrent DVT*
  - Venogram: all deep veins seen and no intraluminal filling defects
  - Venous ultrasound or impedance plethysmography: normal, or ≤1 mm increase in diameter of the common femoral or popliteal veins on venous ultrasound compared to a previous test, and remains normal (no progression of venous ultrasound) at 2 and 7 days[19,37,121,122]
  - D-dimer: normal test, which has a very high sensitivity (≥98%) and at least a moderate specificity (≥40%)[27]

[a] If other evidence is not consistent with recurrent DVT (for example, venous ultrasound, impedance plethysmography, clinical assessment, D-dimer), venography should be considered. (Adapted from Kearon *et al.*[19])

Table 61.2 Clinical model for determining clinical suspicion of deep vein thrombosis (Wells *et al.*[20])

Variables	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Dilated superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of DVT	−2
Total points	
Pretest probability calculated as follows:	
High	>2
Moderate	1 or 2
Low	<1

Note: In patients with symptoms in both legs, the more symptomatic leg is used.

The accuracy of VUI is substantially lower if its findings are discordant with the clinical assessment[22,23] and/or if abnormalities are confined to short segments of the deep veins;[24] in about 25% of such cases, the results of venography differ with VUI or reveal calf vein thrombosis.

The accuracy of VUI in asymptomatic postoperative patients who have a high risk for DVT is poor with a sensitivity for proximal DVT of only about 62%,[19] and such screening is not recommended in patients who have received prophylaxis.[25] **Grade A**

D-dimer blood testing

D-dimer is formed when cross-linked fibrin is broken down by plasmin and levels are usually elevated with DVT and/or PE. Normal levels can help to exclude VTE but elevated D-dimer levels are non-specific and have low positive predictive value.[26] D-dimer tests differ markedly as diagnostic tests for VTE. **Grade A** A normal result with a very sensitive (≥98%) D-dimer assay excludes VTE on its own.[26,27] However, very sensitive D-dimer tests have low specificities (~40%), which limits their usefullness because of high false-positive rates.[27] In order to exclude DVT and/or PE, a normal result with a less sensitive D-dimer assay (≥85%) needs to be combined with either a low clinical probability or another objective test that has negative predictive but is also non-diagnostic on its own (see Box 61.4).[28–32] As less sensitive D-dimer assays are more specific (~70%), they yield fewer false-positive results. Specificity of D-dimer decreases with aging[33] and with comorbid illness such as cancer.[34] Consequently, D-dimer testing has limited value as a diagnostic test for VTE in hospitalized patients and is unhelpful in the early postoperative period.

Diagnosis of DVT in pregnancy

Pregnant patients with suspected DVT can generally be managed in the same way as non-pregnant patients, although except for serial impedance plethysmography[19,35,36] diagnostic approaches have not been evaluated in this population. **Grade B** In pregnant patients with normal non-invasive tests who have a high clinical suspicion of isolated iliac or calf DVT, venography (a complete study or a limited study using abdominal shielding, respectively) should be considered. Alternatively, normal magnetic resonance imaging, a normal D-dimer, or normal Doppler ultrasound imaging of the iliac veins, are likely to helpful for excluding DVT.

Diagnosis of recurrent DVT

Persistent abnormalities of the deep veins are common following DVT.[19,37] **Grade B** Therefore, diagnosis of recurrent DVT requires evidence of new clot formation. Tests that can diagnose or exclude recurrent DVT are noted in Box 61.3.[19,37]

Magnetic resonance imaging (MRI)

A recent small but rigorous study suggests that direct MRI of thrombus is very accurate for the diagnosis of DVT, including thrombosis in the calf and pelvis, and in asymptomatic or pregnant patients.[38] The technique does not require radiographic contrast and has the potential to differentiate acute from old thrombus.

Diagnosis of PE

Pulmonary angiography is the criterion standard for the diagnosis of PE, but has similar limitations as venography.[39] As with suspected DVT, clinical assessment is useful for categorizing probability of PE (Table 61.3 and Box 61.4).[40] **Grade A**

Ventilation–perfusion lung scanning

The usual initial investigation in patients with suspected PE is a ventilation–perfusion lung scan. A normal perfusion scan excludes PE,[41] but is found in a minority (10–40%) of patients.[33,42–44] Perfusion defects are non-specific; only about one third of patients with defects have PE.[42,45] The probability that a perfusion defect is due to PE increases

Table 61.3 Model for determining a clinical suspicion of pulmonary embolism (Wells *et al*[123])

Variables	Points
Clinical signs and symptoms of deep vein thrombosis (minimum leg swelling and pain with palpation of the deep veins)	3·0
An alternative diagnosis is less likely than pulmonary embolism	3·0
Heart rate >100 beats/min	1·5
Immobilization or surgery in the previous 4 weeks	1·5
Previous deep vein thrombosis/pulmonary embolism	1·5
Hemoptysis	1·0
Malignancy (treatment ongoing or within previous 6 months or palliative)	1·0
Total points	
Pretest probability calculated as follows:	
High	>6
Moderate	2–6
Low	<2

with size and number, and the presence of a normal ventilation scan ("mismatched" defect).[42,45] A lung scan with mismatched segmental or larger perfusion defects is termed "high probability".[45] A single mismatched defect is associated with a prevalence of PE of about 80%.[46] Three or more mismatched defects are associated with a prevalence of PE of ≥90%.[46] Lung scan findings are highly age dependent with a relatively high proportion of normal scans and a low proportion of non-diagnostic scans in younger patients.[33]

Lung scanning and clinical assessment

Clinical assessment of PE is complementary to ventilation–perfusion lung scanning; a moderate or high clinical suspicion in a patient with a high probability lung scan is diagnostic (prevalence of PE of ≥90%); however, a low clinical suspicion with a high probability defect requires further investigation because the prevalence of PE with these findings is only about 50%.[42,45] **Grade A** The prevalence of PE with subsegmental, matched, perfusion defects ("low probability" scan) and a low clinical suspicion is expected to be less than 10% (see below).[27,30,42]

Helical (spiral) computerized tomography (CT)

Helical CT following intravenous injection of radiographic contrast can be used to visualize the pulmonary arteries. Although widely used to diagnose PE, the technique has yet to be definitively evaluated for this purpose.[47,48] **Grade B**

Current evidence suggests that helical CT can be interpreted as follows:

- Intraluminal filling defects in lobar or main pulmonary arteries are likely to be associated with a probability of PE of at least 85%, similar to a high-probability ventilation–perfusion scan.[48]
- Intraluminal defects confined to segmental or subsegmental pulmonary arteries are non-diagnostic, and patients with such findings require further testing.[48]
- A normal helical CT substantially reduces the probability of PE but does not exclude the diagnosis (that is, similar to a "low probability" ventilation–perfusion scan).[47,48]

Although this statement is largely based on extrapolation from experience with patients who have non-diagnostic lung scans, patients with helical CT scans that are not diagnostic for PE can be managed as outlined in Box 61.4. **Grade C**

Box 61.4 Test results which effectively confirm or exclude pulmonary embolism (PE)

- *Diagnostic for PE*
  - Pulmonary angiography: intraluminal filling defect
  - Helical CT: intraluminal filling defect in a lobar or main pulmonary artery[47,48]
  - Ventilation–perfusion scan: high probability scan and moderate/high clinical suspicion[42,43]
  - Diagnostic for DVT: with non-diagnostic ventilation–perfusion scan or helical CT[124]
- *Excludes PE*
  - Pulmonary angiogram: normal[39]
  - Perfusion scan: normal[41]
  - D-dimer: normal test, which has a very high sensitivity (≥98%) and at least a moderate specificity (≥40%)[27]
  - Non-diagnostic ventilation–perfusion scan, or normal helical CT, and normal proximal VUI and
    (a) low clinical suspicion for PE[30,50 a]
    (b) normal D-dimer test, which has at least a moderately high sensitivity (≥85%) and specificity (≥70%)[30,32 a]
  - Low clinical suspicion for PE and normal D-dimer, which has at least a moderately high sensitivity (≥85%) and specificity (≥70%)[30,32]

[a] If serial VUI (venous ultrasound imaging) is performed it is expected to become abnormal in 1–2% of these patients and reduce the frequency of symptomatic VTE (venous thromboembolism) during 3 months of follow up from ~1.5% to ~0.5%.
(Adapted from Kearon[40])

D-dimer testing

As previously discussed when considering diagnosis of DVT, a normal D-dimer result, alone[27] or in combination with another negative test,[30,32] can be used to exclude PE (Box 61.4). **Grade A**

Box 61.5 Management of patients with non-diagnostic non-invasive tests for PE

- *Serial VUI of the proximal veins after 1 and 2 weeks*
  Suitable for most such patients,[30,44] although pulmonary angiography is preferred for the subgroups outlined below. This approach can be supplemented with bilateral venography (for patients that might otherwise be considered for pulmonary angiography).[116]
- *Pulmonary angiography preferred option if:*
  - segmental intraluminal filling defect on helical CT[a,b]
  - subsegmental intraluminal filling defect and high clinical suspicion
  - high probability ventilation–perfusion scan and low clinical suspicion[b]
  - symptoms are severe, post-test probability is high but non-diagnostic, and PE needs to be excluded from the differential diagnosis
  - serial testing is not feasible (for example, scheduled for surgery, geographic inaccessibility)

[a] A segmental intraluminal filling defect with a high clinical suspicion is likely to have a positive predictive value of ≥85% and could be considered diagnostic for PE.

[b] Ventilation–perfusion scanning can be performed after these findings have been obtained with helical CT; or helical CT may be performed after these findings have been obtained with ventilation–perfusion scanning;[47,48] If the second test is also non-diagnostic for PE, serial ultrasounds may be reconsidered.

Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism; VUI, venous ultrasound imaging, (Adapted from Kearon[40])

Tests for DVT in patients with suspected PE

Testing for DVT is an indirect way to diagnose PE (see Box 61.4).[49] VUI of the proximal veins is the usual method, although bilateral ascending venography, or CT or MRI of the legs at the same time as examination of the pulmonary veins, can also be used. Negative tests for DVT do not rule out PE but they reduce the probability, and suggest that the short-term risk of recurrent PE is low.[49] Because the prevalence of PE is expected to be less than 5% in patients with a non-diagnostic lung scan, a low clinical suspicion of PE, and a normal VUI of the proximal veins, it is reasonable to exclude PE with these findings.[27,30,44,50] **Grade B**

Management of patients with non-diagnostic combinations of non-invasive tests for PE (Box 61.5)

Patients with non-diagnostic test results for PE at presentation have, on average, a prevalence of PE of 20%.[42,49] Two management approaches are reasonable in such patients. The first is the performance of pulmonary angiography, which is usually definitive. The second is the withholding of anticoagulants and performance of serial VUI to detect evolving proximal DVT, the forerunner of recurrent PE. If serial VUI for DVT (two additional tests a week apart) is negative, the subsequent risk of recurrent VTE during the next 3 months is less than 1%,[30,44,51] which is similar to that after a normal pulmonary angiogram.[39] As an additional precaution, patients who have had PE and/or DVT excluded should routinely be asked to return for re-evaluation if symptoms of PE and/or DVT persist or recur.

Diagnosis of PE in pregnancy

Pregnant patients with suspected PE can be managed similarly to non-pregnant patients, with the following modifications: **Grade B**

- VUI can be performed first and lung scanning performed if there is no DVT; patients with unequivocal evidence of DVT can be presumed to have PE.
- The amount of radioisotope used for the perfusion scan can be reduced and the duration of scanning extended.
- If pulmonary angiography is performed, the brachial approach with abdominal screening is preferable.
- In the absence of safety data relating to helical CT in pregnancy, this is discouraged (if it is necessary, abdominal screening should be used). Consistent with other young patients who are suspected of having PE, a high proportion of pregnant patients have normal scans and a small proportion have high probability scans.[33,52] These recommendations are based on a belief that the risk of inaccurate diagnosis of suspected PE during pregnancy is greater than the risk of radioactivity to the fetus.[52,53]

Algorithms for the diagnosis of PE

Local availability of methods of testing and differences among patient presentations influence the diagnostic approach to PE. A number of prospectively validated algorithms have been published, which emphasize the use of different initial non-invasive tests in conjunction with ventilation–perfusion lung scanning including:

- structured clinical assessment and serial VUI;[44]
- sensitive D-dimer assay, empiric clinical assessment, and single bilateral VUI;[27]
- clinical assessment, moderately sensitive D-dimer assay and serial VUI.[30]

Prevention of VTE (Box 61.6)

In a non-randomized trial, oral anticoagulation was shown to prevent PE in patients with fractured hips, without causing an unacceptable increase in bleeding.[54] **Grade A** Subsequently, low-dose unfractionated heparin was shown to reduce postoperative DVT and fatal PE by two thirds.[55,56] Further studies have demonstrated that the efficacy of

Box 61.6 Prevention and treatment of venous thromboembolism

- Primary prophylaxis with anticoagulants and/or mechanical methods should be used in hospitalized patients who have a moderate or high risk of VTE. **Grade A**
- Acute VTE (DVT and/or PE) should be anticoagulated with:
  - Heparin (unfractionated or LMWH) for a minimum of 4–5 days. **Grade A** If unfractionated heparin is used, a dose of at least (a) 30 000 U/day or 18 U/kg/h by intravenous infusion; or (b) 33 000 U/day, by twice daily, subcutaneous, injection, should be administered. **Grade A** Dose of unfractionated heparin should be adjusted to achieve "therapeutic" APTT results. **Grade C**
  - Oral anticoagulation for 3–6 months, **Grade A** with a dose adjusted to achieve an INR of 2.0–3.0. **Grade A** Prolonged unfractionated heparin or LMWH at therapeutic, or near therapeutic, doses is a satisfactory alternative. **Grade A** Anticoagulation should be continued for longer than 3 months in patients with a first episode of idiopathic VTE, **Grade B** and when VTE is associated with a risk factor, for as long as such factors are active. **Grade C**

See Box 61.5 for abbreviations

low-dose unfractionated heparin can be improved either by increasing the dose so as to minimally prolong the activated partial thromboplastin time (APTT),[57] or by combining its use with graduated compression stockings[58] or intermittent pneumatic compression devices.[59]

Meta-analyses support that, at doses that are associated with equivalent efficacy (odds ratio 1·03) following general surgery, low molecular weight heparins (LMWH) are associated with less bleeding (odds ratio 0·68) than low-dose unfractionated heparin.[60] **Grade A** Used at higher dose than for general surgery, LMWH is more effective (odds ratio 0·83) that unfractionated heparin following orthopedic surgery and is associated with a similar frequency of bleeding.[60] An additional 3 or 4 weeks of LMWH after hospital discharge further reduces the frequency of symptomatic VTE after orthopedic surgery (from 3·3% to 1·3%[61]). Warfarin (target INR 2–3 for about 7 to 10 days) is less effective that LMWH at preventing DVT detected by venography soon after orthopedic surgery,[62] but appears to be similarly effective at preventing symptomatic VTE over a 3 month period.[62,63] **Grade A** There is evidence that aspirin reduces the risk of postoperative VTE by one third.[64] **Grade A** A study of over 17 000 patients, mostly following hip fracture repair, confirmed these findings, including a reduction in fatal PE (0·27% *v* 0·65%) during the month following surgery.[65] However, as warfarin and LMWH are expected to be more effective (at least a two thirds reduction in VTE), aspirin alone is not recommended during the initial postoperative period.[62] It may be a reasonable alternative to LMWH or warfarin for the weeks following hospital discharge, particularly if patients do not have additional risk factors for VTE. **Grade B** Recently, hirudin[66] (a direct thrombin inhibitor) and fondaparinux[67,67a,67b] (the pentasaccharide of heparin that binds antithrombin) have been shown to be more effective than LMWH following major orthopaedic surgery; fondaparinux may cause marginally more bleeding. **Grade A**

The evidence that short-term prophylaxis (for example, low-dose unfractionated heparin) prevents clinically important VTE in immobilized medical patients is less convincing, partly because it has been less extensively studied in this population, and because there is concern that medical patients remain at high risk of VTE after prophylaxis is stopped.[62,68]

In addition to augmenting the efficacy of pharmacologic methods of prophylaxis, mechanical methods are effective on their own. Graduated compression stockings prevent postoperative VTE in moderate-risk patients (risk reduction of 68%),[62,69] and intermittent pneumatic compression devices prevent postoperative VTE in high-risk orthopedic patients.[62,70,71] The relative efficacy of graduated compression stockings and intermittent pneumatic compression devices is uncertain. No difference in efficacy was evident in neurosurgical patients;[72] however, pneumatic compression devices are expected to be superior to graduated compression stockings in high-risk patients.[62] Mechanical methods of prophylaxis should be used in patients who have a moderate or high risk of VTE if anticoagulants are contraindicated (for example, neurosurgical patients).[62] **Grade A**

Because postoperative fatal PE is rarely preceded by symptomatic DVT,[55] prophylaxis is the best way to prevent it. Use of primary prophylaxis is strongly supported by cost effectiveness analyses, which indicate that it reduces overall costs in addition to reducing morbidity.[73]

Treatment of VTE

Heparin therapy

In 1960, Barritt and Jordan established that heparin (1·5 days) and oral anticoagulants (2 weeks) reduced the risk of recurrent PE and associated death.[74] Based on expert opinion, 10–14 days of heparin therapy, and 3 months of oral anticoagulation became widely adopted in clinical practice. It was subsequently shown that 4 or 5 days of intravenous heparin is as effective as 10 days of therapy for the initial treatment of VTE.[75,76] Comparatively recently, the need for an initial course of heparin therapy was verified.[77] Many trials have established that weight-adjusted LMWH (without laboratory monitoring) is as safe and effective as adjusted-dose unfractionated heparin for the treatment of acute VTE;[78] it can be used to treat patients without hospital admission[79] and need only be

injected subcutaneously once daily.[80] Danaparoid, hirudin, and argatroban can be used to treat heparin induced thrombocytopenia, with or without associated thrombosis.[81,82]

Oral anticoagulant therapy

A randomized trial of patients with DVT, comparing 3 months of warfarin (International Normalization Ratio (INR) ~3·0–4·0) with low-dose heparin after initial treatment with full-dose intravenous heparin, established the necessity for prolonged oral anticoagulation after initial heparin therapy.[83] **Grade A** Prolonged high-dose subcutaneous heparin[84] and, subsequently, LMWH (50–75% of acute treatment dose) was subsequently shown to be equally effective.[85] **Grade A** In the 1970s it was recognized that, because of differences in the responsiveness of thromboplastins to oral anticoagulants, a prothrombin time ratio of 2·0 reflected a much more intense level of anticoagulation in North America than in Europe. This prompted a comparison of two intensities of warfarin therapy (corresponding to mean INRs of ~2·1 and ~3·2) for the treatment of DVT.[86] This study found that the lower intensity of oral anticoagulation was as effective as the higher intensity but caused less bleeding. The trials showing that heparin therapy could be reduced to 5 days also showed that warfarin could be started at the same time as heparin.[75,76] A recent series of small studies support starting warfarin with the expected daily dose rather than a loading dose (for example, 5 mg *v* 10 mg),[87,88] and managing over-anticoagulation without bleeding (for example, INRs ≥ 6) with small oral rather than subcutaneous doses of vitamin K (for example, 1 mg).[89]

During the last decade, a series of well-designed studies have helped to define the optimal duration of anticoagulation. Their findings can be summarized as follows:

- Shortening the duration of anticoagulation from 3[90,91] or 6[92] months to 4[90,91] or 6[92] weeks results in a doubling of the frequency of recurrent VTE during 1[90,91] to 2[92] years of follow up. **Grade A**
- Patients with VTE provoked by a transient risk factor have a lower (about one third) risk of recurrence than those with an unprovoked VTE or a persistent risk factor.[90–94]
- Three months of anticoagulation is adequate treatment for VTE provoked by a transient risk factor; subsequent risk of recurrence is ≤3% per patient-year.[90,91,94–96] **Grade A**
- Three months of anticoagulation may not be adequate treatment for an unprovoked ("idiopathic") episode of VTE; subsequent early risk of recurrence has varied from 5% to 25% per patient-year.[92,95,97,98]
- After 6 months of anticoagulation, recurrent DVT is at least as likely to affect the contralateral leg; this suggests that "systemic" rather than "local" (including inadequate treatment) factors are responsible for recurrences after 6 months of treatment.[99]
- There is a persistently elevated risk of recurrent VTE after a first episode; this appears to be 5–12% per year after 6 or more months of treatment for an unprovoked episode.[92,95,98]
- Oral anticoagulants targeted at an INR of ~2·5 are very effective (risk reduction ≥90%) at preventing recurrent unprovoked VTE after the first 3 months of treatment.[97,100] **Grade A**
- Indefinite anticoagulation is an option for patients with a first unprovoked VTE who have a low risk of bleeding. **Grade B**
- A second episode of VTE does not necessarily indicate a high risk of recurrence or the need for indefinite anticoagulation.[97]
- Risk of bleeding on anticoagulants differs markedly among patients depending on the prevalence of risk factors (for example, advanced age; previous bleeding or stroke; renal failure; anemia; antiplatelet therapy; malignancy; poor anticoagulant control).[101]
- Risk of recurrence is lower (about half) following an isolated calf (distal) DVT; this favors a shorter duration of treatment.[92,95] **Grade B**
- Risk of recurrence is higher with antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulants),[97,102] homozygous factor V Leiden[103] cancer[93] and, probably, antithrombin deficiency; these favor a longer duration of treatment. **Grade B**
- Heterozygous factor V Leiden and the G20210A prothrombin gene mutations do not appear to be clinically important risk factors for recurrence.[103] **Grade B**
- Other abnormalities, such as elevated levels of clotting factors VIII, IX, XI, and homocysteine, and deficiencies of protein C and protein S, may be risk factors for recurrence; they have uncertain implications for duration of treatment.

Thrombolytic therapy

Systemic thrombolytic therapy accelerates the rate of resolution of DVT and PE at the cost of around a fourfold increase in frequency of major bleeding, and about a 10-fold increase in intracranial bleeding.[104–107] This can be life-saving for PE with hemodynamic compromise.[106,108] **Grade A** Thrombolytic therapy may reduce the risk of the prothrombotic syndrome following DVT but this does not appear to justify its associated risks[104,105] Catheter-based treatments (that is, thrombolytic therapy or removal of thrombus) require further evaluation before they can be recommended.

Inferior vena caval filters

A recent randomized trial demonstrated that a filter, as an adjunct to anticoagulation, reduced the rate of PE (asymptomatic and symptomatic) from 4·5% to 1·0% during the

12 days following insertion, with a suggestion of fewer fatal episodes (0% *v* 2%).[109] However, after 2 years, patients with a filter had a significantly higher rate of recurrent DVT (21% *v* 12%) and a non-statistically significant reduction in the frequency of PE (3% *v* 6%). This study supports the use of vena caval filters to prevent PE in patients with acute DVT and/or PE who cannot be anticoagulated (that is, they are bleeding), but does not support more liberal use of filters. **Grade A** Patients should receive a course of anticoagulation if this subsequently becomes safe.

Treatment of VTE during pregnancy

Unfractionated heparin and LMWH do not cross the placenta and are safe for the fetus, whereas oral anticoagulants cross the placenta and can cause fetal bleeding and malformations.[110,111] Therefore, pregnant women with VTE should be treated with therapeutic doses of subcutaneous heparin (unfractionated heparin or, increasingly, LMWH) throughout pregnancy. **Grade B** Care should be taken to avoid delivery while the mother is therapeutically anticoagulated; one management approach involves stopping subcutaneous heparin 24 hours prior to induction of labor and switching to intravenous heparin if there is a high risk of embolism. After delivery, warfarin, which is safe for infants of nursing mothers, should be given (with initial heparin overlap) for 6 weeks and until a minimum of 3 months of treatment has been completed. **Grade B**

The future

There are many questions relating to currently available antithrombotic agents and diagnostic techniques that need answering, and many new antithrombotic agents under development that will require clinical evaluation. In addition, future studies are expected to focus on clinical and genetic subgroups that may benefit from tailored management, such as different intensities or durations of prophylaxis or treatment. Thrombolytic therapy deserves further evaluation, particularly systemic therapy for severe PE without overt hemodynamic compromise (for example, with echocardiographic right ventricular dysfunction), and catheter-directed therapy for iliofemoral DVT. Safer thrombolytic regimens might also broaden indications. In order to provide clear directions for clinical management, future studies need to focus on clinically important outcomes (that is, symptomatic VTE, major bleeding).

References

1. Turpie AGG, Levine MN, Hirsh J *et al.* Double blind randomised trial of Org 10172 low-molecular-weight heparinoid in the prevention of deep vein thrombosis in thrombotic stoke. *Lancet* 1987;**1**:523–6.
2. Ginsberg J, Brill-Edwards P, Burrows RF *et al.* Venous thrombosis during pregnancy: leg and trimester of presentation. *Thromb Haemost* 1992;**67**:519–20.
3. Cruickshank MK, Levine MN, Hirsh J *et al.* An evaluation of impedance plethysmography and ^{125}I-fibrinogen leg scanning in patients following hip surgery. *Thromb Haemost* 1989;**62**: 830–4.
4. Bern MM, Lokich JJ, Wallach SR *et al.* Very low doses of warfarin can prevent thrombosis in central venous catheters. *Ann Intern Med* 1990;**112**:423–8.
5. Merrer J, De Jonghe B, Golliot F *et al.* Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;**286**: 700–7.
6. Heijboer H, Brandjes PM, Buller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. *N Engl J Med* 1990;**323**:1512–16.
7. Kearon C, Crowther M, Hirsh J. Management of patients with hereditary hypercoagulable disorders. *Ann Rev Med* 2000; **51**:169–85.
8. Emmerich J, Rosendaal FR, Cattaneo M *et al.* Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism – pooled analysis of 8 case–control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. *Thromb Haemost* 2001;**86**:809–16.
9. Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. *Thromb Haemost* 1999;**81**:165–76.
10. Rosendaal FR. High levels of factor VIII and venous thrombosis. *Thromb Haemost* 2000;**83**:1–2.
11. Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000;**342**: 696–701.
12. van Hylckama Vlieg A, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000;**95**:3678–82.
13. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;**88**:3698–703.
14. Kearon C. Epidemiology of venous thromboembolism. *Sem Vasc Med* 2001;**1**:7–25.
15. Warkentin TE, Levine MN, Hirsh J *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;**332**:1330–5.
16. Anderson FA, Wheeler HB, Goldberg RJ *et al.* A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 1991;**151**:933–8.
17. Kearon C. Natural history of venous thromboembolism. *Sem Vasc Med* 2001;**1**:27–37.
18. Hull R, Hirsh J, Sackett DL *et al.* Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. *Circulation* 1981;**64**:622–5.

19. Kearon C, Julian JA, Newman TE, Ginsberg JS, for the McMaster Diagnostic Imaging Practice Guidelines Initiative. Non-invasive diagnosis of deep vein thrombosis. *Ann Intern Med* 1998;**128**:663–77.
20. Wells PS, Hirsh J, Anderson DR *et al.* A simple clinical model for the diagnosis of deep-vein thrombosis combined with impedance plethysmography: potential for an improvement in the diagnosis process. *J Intern Med* 1998;**243**:15–23.
21. Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS. Does this patient have deep vein thrombosis? *JAMA* 1998;**279**:1094–9.
22. Wells PS, Anderson DR, Bormanis J *et al.* Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;**350**:1795–8.
23. Wells PS, Hirsh J, Anderson DR *et al.* Accuracy of clinical assessment of deep-vein thrombosis. *Lancet* 1995;**345**: 1326–30.
24. Wells PS, Hirsh J, Anderson DR *et al.* Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two center paired-design prospective trial. *Thromb Haemost* 1995;**74**:1423–7.
25. Robinson KS, Anderson DR, Gross M *et al.* Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: the Post-Arthoplasty Screening Study. A randomized, controlled trial. *Ann Intern Med* 1997;**127**: 439–45.
26. Lee AYY, Ginsberg JS. Laboratory diagnosis of venous thromboembolism. *Bailliere's Clin Haematol* 1998;**11**:587–604.
27. Perrier A, Desmarais S, Miron MJ *et al.* Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; **353**:190–5.
28. Bernardi E, Prandoni P, Lensing AWA *et al.* D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ* 1998;**317**:1037–40.
29. Kearon C, Ginsberg JS, Douketis J *et al.* Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. *Ann Intern Med* 2001; **135**:108–11.
30. Wells PS, Anderson DR, Rodger M *et al.* Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001;**135**: 98–107.
31. Anderson DR, Wells PS, Stiell I *et al.* Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med* 1999;**159**:477–82.
32. Ginsberg JS, Wells PS, Kearon C *et al.* Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med* 1998; **129**:1006–11.
33. Righini M, Goehring C, Bounameaux H, Perrier A. Effects of age on the performance of common diagnostic tests for pulmonary embolism. *Am J Med* 2000;**109**:357–61.
34. Lee A, Julian J, Levine M *et al.* Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. *Ann Intern Med* 2000;**131**:417–23.
35. Hull RD, Raskob GE, Carter CJ. Serial impedance plethysmography in pregnant patients with clinically suspected deep-vein thrombosis. Clinical validity of negative findings. *Ann Intern Med* 1990;**112**:663–7.
36. de Boer K, Buller HR, ten Cate JW, Levi M. Deep vein thrombosis in obstetric patients: diagnosis and risk factors. *Thromb Haemost* 1992;**67**:4–7.
37. Prandoni P, Cogo A, Bernardi E *et al.* A simple ultrasound approach for detection of recurrent proximal vein thrombosis. *Circulation* 1993;**88**:1730–5.
38. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. *Ann Intern Med* 2002;**136**:89–98.
39. Stein PD, Athanasoulis C, Alavi A *et al.* Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992;**85**:462–8.
40. Kearon C. Diagnosis of pulmonary embolism. *Can Med Ass J* 2002 (in press).
41. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. *Chest* 1990;**97**:23–6.
42. The PIOPED investigators. Value of the ventilation perfusion scan in acute pulmonary embolism. *JAMA* 1990;**263**:2753–9.
43. Hull RD, Hirsh J, Carter CJ *et al.* Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983;**98**:891–9.
44. Wells PS, Ginsberg JS, Anderson DR *et al.* Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;**129**:997–1005.
45. Hull RD, Hirsh J, Carter CJ *et al.* Diagnostic value of ventilation–perfusion lung scanning in patients with suspected pulmonary embolism. *Chest* 1985;**88**:819–28.
46. Stein PD, Henry JW, Gottschalk A. Mismatched vascular defects. An easy alternative to mismatched segmental equivalent defects for the interpretation of ventilation/perfusion lung scans in pulmonary embolism. *Chest* 1993;**104**:468–72.
47. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;**132**:227–32.
48. Perrier A, Howarth N, Didier D *et al.* Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med* 2001;**135**:88–97.
49. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998; **129**:1044–9.
50. Perrier A, Miron MJ, Desmarais S *et al.* Using clinical evaluation and lung scan to rule out suspected pulmonary embolism: Is it a valid option in patients with normal results of lower-limb venous compression ultrasonography? *Arch Intern Med* 2000;**160**:512–16.
51. Hull RD, Raskob GE, Ginsberg JS *et al.* A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. *Arch Intern Med* 1994;**154**:289–97.
52. Chan WS, Ray JG, Murray S, Coady GE, Coates AL, Ginsberg JS. Suspected pulmonary embolism in pregnancy: Clinical presentation, results of lung scan, subsequent materenal and pediatric outcomes. *Arch Intern Med* 2002 (in press).

53. Ginsberg JS, Hirsh J, Rainbow AJ, Coates G. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. *Thromb Haemost* 1989;**61**:189–96.
54. Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients. *Lancet* 1959;**ii**: 981–9.
55. Kakkar VV, Corrigan TP, Fossard DP. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicenter trial. *Lancet* 1975;**ii**:45–51.
56. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. *N Engl J Med* 1988; **318**:1162–73.
57. Leyvraz PF, Richard J, Bachmann F. Adjusted versus fixed dose subcutaneous heparin in the prevention of deep vein thrombosis after total hip replacement. *N Engl J Med* 1983;**309**:954–8.
58. Wille-Jorgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. *Br J Surg* 1985;**72**:579–81.
59. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest* 1996;**109**:82–5.
60. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg* 1997;**84**:750–9.
61. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001;**358**:9–15.
62. Geerts WH, Heit JA, Clagett GP *et al.* Prevention of venous thromboembolism. *Chest* 2001;**119**:132S–75S.
63. Colwell CW Jr, Collis DK, Paulson R *et al.* Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. *J Bone J Surg* 1999;**81-A**:932–40.
64. "Antiplatelet trialists' collaboration". Collaborative overview of randomised trials of antiplatelet therapy-III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;**308**:235–46.
65. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;**355**:1295–302.
66. Eriksson BI, Wille-Jorgensen P, Kalebo P *et al.* A comparison of recombinant hirudin with a low-molecular weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997;**337**:1329–35.
67. Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 2001;**344**:619–25.
67a. Erikssen BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001;**345**:1298–304.
67b. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001;**345**:1305–10.
68. Gårdlund for the Heparin Prophylaxis Group. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. *Lancet* 1996;**347**:1357–61.
69. Wells PS, Lensing AWA, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism: a meta-analysis. *Arch Intern Med* 1994;**154**: 67–72.
70. Hull R, Delmore T, Hirsh J *et al.* Effectiveness of an intermittent pulsatile elastic stocking for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thromb Res* 1979;**16**:37–45.
71. Hull RD, Raskob GE, Gent M *et al.* Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. *JAMA* 1990;**263**: 2313–17.
72. Turpie AGG, Hirsh J, Gent M, Julian DH, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 1989;**149**:679–81.
73. Salzman EW, Davies GC. Prophylaxis of venous thromboembollism: analysis of cost effectiveness. *Ann Surg* 1980;**191**: 207–18.
74. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960;**1**: 1309–12.
75. Gallus AS, Jackaman J, Tillett J, Mills W, Sycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. *Lancet* 1986;**2**:1293–6.
76. Hull RD, Raskob GE, Rosenbloom D *et al.* Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* 1990;**322**:1260–4.
77. Brandjes DPM, Heijboer H, Buller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;**327**:1485–9.
78. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000;**160**:181–8.
79. Koopman MMW, Prandoni P, Piovella F *et al.* Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996;**334**:682–7.
80. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. *Thromb Haemost* 2001;**86**:980–4.
81. Hirsh J, Warkentin TE, Shaughnessy SG *et al.* Heparin and low-molecular-weight heparin: mechanisms of action,

pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;**119**:64S–94S.
82. Chong BH, Gallus AS, Cade JF *et al.* Prospective randomized open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopenia with thrombosis. *Thromb Haemost* 2001;**86**:1170–5.
83. Hull R, Delmore T, Genton E *et al.* Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* 1979;**301**:855–8.
84. Hull R, Delmore T, Carter C *et al.* Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. *N Engl J Med* 1982;**306**:189–94.
85. Hyers TM, Agnelli G, Hull RD *et al.* Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001; **119**:176S–93S.
86. Hull R, Hirsh J, Jay R *et al.* Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982;**307**:1676–81.
87. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; **126**:133–6.
88. Crowther MA, Ginsberg JS, Kearon C *et al.* A randomized trial comparing 5 mg and 10 mg warfarin loading doses. *Arch Intern Med* 1999;**159**:46–8.
89. Crowther MA, Julian J, McCarty D *et al.* Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. *Lancet* 2000;**356**:1551–3.
90. Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. *Lancet* 1992;**340**:873–6.
91. Levine MN, Hirsh J, Gent M *et al.* Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost* 1995;**74**:606–11.
92. Schulman S, Rhedin A-S, Lindmarker P *et al.* A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;**332**:1661–5.
93. Prandoni P, Lensing AWA, Cogo A *et al.* The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;**125**:1–7.
94. Pini M, Aiello S, Manotti C *et al.* Low molecular weight heparin versus warfarin the prevention of recurrence after deep vein thrombosis. *Thromb Haemost* 1994;**72**:191–7.
95. Pinede L, Ninet J, Duhaut P *et al.* Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001;**103**:2453–60.
96. Pinede L, Duhaut P, Cucherat M, Ninet J, Pasquier J, Boissel JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. *J Intern Med* 2000;**247**:553–62.
97. Kearon C, Gent M, Hirsh J *et al.* A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;**340**:901–7.
98. Agnelli G, Prandoni P, Santamaria MG *et al.* Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. *N Eng J Med* 2001;**345**:165–9.
99. Lindmarker P, Schulman S. The risk of ipsilateral versus contralateral recurrent deep vein thrombosis in the leg. The DURAC Trial Study Group. *J Intern Med* 2000;**247**:601–6.
100. Schulman S, Granqvist S, Holmstrom M *et al.* The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;**336**:393–8.
101. Beyth RJ, Quinn LM, Landefeld S. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;**105**:91–9.
102. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. *Am J Med* 1998;**104**:332–8.
103. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A Allele in the coagulation factor V gene and the G20210A Allele in the prothrombin gene. *Thromb Haemost* 1999;**81**:684–9.
104. Hirsh J, Lensing A. Thrombolytic therapy for deep vein thrombosis. *Int Angiol* 1996;**5**:S22–S25.
105. Schweizer J, Kirch W, Koch R *et al.* Short- and long-term results after thrombolytic treatment of deep vein thrombosis. *J Am Coll Cardiol* 2000;**36**:1336–43.
106. Blackmon JR, Sautter RD, Wagner HN. Uokinase pulmonary embolism trial: phase I results. *JAMA* 1970;**214**:2163–72.
107. Dalen JE, Alpert JS, Hirsh J. Thrombolytic therapy for pulmonary embolism. Is it effective? Is it safe? When is it indicated? *Arch Intern Med* 1997;**157**:2550–6.
108. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M *et al.* Streprokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolys* 1995;**2**:227–9.
109. Decousus H, Leizorovicz A, Parent F *et al.* A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med* 1998;**338**:409–15.
110. Ginsberg JS, Hirsh J, Levine MN, Burrows R. Risks to the fetus of anticoagulant therapy during pregnancy. *Thromb Haemost* 1989;**61**:197–203.
111. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest* 2001;**119**:122S–31S.
112. Cogo A, Lensing AWA, Prandoni P, Hirsh J. Distribution of thrombosis in patients with symptomatic deep-vein thrombosis: Implications for simplifying the diagnostic process with compression ultrasound. *Arch Intern Med* 1993;**153**:2777–80.
113. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet* 1985;**ii**:515–18.
114. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981;**94**: 439–44.
115. Moser KM, Fedullo PF, LittleJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *JAMA* 1994;**27**:223–5.
116. Kruit WHJ, de Boer AC, Sing AK, van Roon F. The significance of venography in the management of patients with clinically

suspected pulmonary embolism. *J Intern Med* 1991;**230**: 333–9.
117. Hull RD, Raskob GE, Coates G, Panju AA, Gill GJ. A new non-invasive management strategy for patients with suspected pulmonary embolism. *Arch Intern Med* 1989;**149**:2549–55.
118. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest* 1995;**108**:978–81.
119. Bell WR, Simon TL. Current status of pulmonary embolic disease: pathophysiology, diagnosis, prevention, and treatment. *Am Heart J* 1982;**103**:239–61.
120. Ginsberg J, Kearon C, Douketis J *et al.* The use of D-dimer testing and impedance plethysmographic examination in patients with clinical indications of deep vein thrombosis. *Arch Intern Med* 1997;**157**:1077–81.
121. Hull RD, Carter CJ, Jay RM *et al.* The diagnosis of acute recurrent deep vein thrombosis: a diagnostic challenge. *Circulation* 1983;**67**:901–6.
122. Huisman MV, Buller HR, ten Cate JW. Utility of impedance plethysmography in the diagnosis of recurrent deep-vein thrombosis. *Arch Intern Med* 1988;**148**:681–3.
123. Wells PS, Anderson DR, Rodger M *et al.* Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;**83**:416–20.
124. Turkstra F, Kiujer PMM, van Beek E Jr, Brandjes DPM, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997;**126**:775–81.

62 Peripheral vascular disease

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Epidemiology

The prevalence of lower extremity arterial occlusive disease as judged by history has been examined in several studies. Large cohorts of patients have been questioned about symptoms of intermittent claudication. This has mostly been done using a questionnaire initially designed by Rose.[1] The method has an acceptable specificity but lacks sensitivity and, for obvious reasons, it does not detect asymptomatic arterial occlusive disease.[2] The prevalence of peripheral arterial occlusive disease varies between studies, with high figures reported from Russia and Finland.[3,4] With large and reliable studies, it is likely that the prevalence at the age of 60 is 3–6%.[5] Most studies report a prevalence of less than 5% at 50 years.

In order to detect lower extremity arterial occlusive disease more specifically, studies have been performed measuring ankle pressure with non-invasive techniques. In general it can be said that the prevalence of disease increases by a factor of 3 compared with studies based on questionnaires. There is a significant correlation between the ankle brachial pressure index (ABI) and the symptom of intermittent claudication, although the correlation is modest with *r* values between 0·1 and 0·2.[6] Based on such objective methods, 11·7% of the population in the Framingham study had peripheral arterial disease. Thus assessment of peripheral arterial disease by the symptom of intermittent claudication underestimates the true prevalence,[7] but the cut off points determining what is considered to be a pathologic ABI is of great importance for the estimation of the prevalence using objective methods.[8]

The prevalence is greatly influenced by age as pointed out in one of the major studies, the Framingham study.[9] Other important factors are cigarette smoking and sex. Thus non-smoking women in the age group 55–64 years showed a prevalence by history of 3·9% compared with smoking men in the age group 75–84 years where the prevalence was 14·5%. Additional factors increasing the risk are diabetes and fibrinogen levels.[10]

Few studies have examined the incidence of peripheral arterial occlusive disease by following normal subjects and determining when claudication appears. In the Framingham study, the yearly incidence increases from 0·2% in 45–55 year old men to 0·5% in 55–65 year old men.[9] In the last follow up after 38 years, the yearly rates were found to increase until the age 75 and then declined. The statistical analyses revealed that those with intermittent claudication were significantly older, had higher cholesterol levels, higher blood pressure, higher frequency of diabetes, and smoked more cigarettes.[11] The Edinburgh artery study provides similar figures with an annual incidence of 1·8 per 1000 randomly selected patients from general practitioners.[12]

Long-term outcome

The natural history of patients with lower extremity arterial disease has been studied regarding both the fate of the limb and mortality. Among patients with peripheral arterial occlusive disease, at most one in five will require surgical correction for their vascular disease[13] and 2–5% will undergo amputation.[5,9] The risk for amputation decreases if the patients can stop smoking.[14] Patients with peripheral arterial occlusive disease have a decreased life expectancy compared with the normal population. This is almost solely explained by cardiovascular disease in general and coronary artery disease in particular. After 10 years, only 52% of claudicants are still alive.[15] The relative risk of dying from cardiovascular disease and coronary heart disease (CHD) is reported to be 5–6 times that of the normal population over 10 years.[16] The severity of the peripheral arterial occlusive disease is associated with the risk of dying, since the lower extremity arterial disease is a surrogate variable reflecting the severity of atherosclerosis affecting the coronary arteries.[17] Smoking is also an important predictor of the risk of dying in these patient groups.[18] The greatest threat to the patient with peripheral arterial disease is thus death from cardiac causes. Patients with peripheral arterial disease and concomitant three vessel coronary artery disease (CAD) have an improved survival after coronary artery bypass grafting (CABG).[19] The natural course of intermittent claudication on the other hand is relatively benign in terms of limb survival as reflected by the low risk of amputation. This may, however, partly be explained by the fact that the mortality among patients with severe disease and high risk of amputation is considerably higher than for patients with mild disease.

Key points

- The prevalence of lower extremity arterial occlusive disease is high: 3–5% in individuals over 50 years of age.
- Patients with peripheral arterial occlusive disease have approximately fivefold increased risk of dying from cardiovascular causes over 10 years.
- Mortality and morbidity are increased by smoking, hypertension, and the severity of the disease.
- Intermittent claudication itself has a relatively benign course as reflected by a low risk of amputation.

Investigation of the patient with peripheral vascular disease

An adequate history and physical examination provide the basis for proper management of patients with peripheral vascular disease. The history should include a survey of relevant risk factors and possible symptoms of concomitant cardiovascular disease (for example, angina pectoris). Palpation of pulses and auscultation in the groin and over the femoral arteries may reveal signs of occlusion or stenoses in the vessels from the iliac artery down to the lower leg. The popliteal artery is best evaluated with the knee slightly elevated from the support and the tissue in the distal popliteal fossa pressed against the tibia. Palpation at this location is particularly important when a popliteal aneurysm is suspected. In cases with more severe ischemia, inspection may reveal a diminished growth of hair and nails, and distal ischemic ulcers often located on toes and heels. Elevation of the legs will cause a whitening of the most affected foot, which in the dependent position typically is more red than the contralateral one, owing to an increase of blood in the superficial venous plexa.

Measurement of the ankle pressure is of value as a quantitative estimate of the degree of arterial insufficiency. This is easily done with a continous wave pen-doppler detecting the pulse either in the posterior tibial or the dorsal pedal artery when a blood pressure cuff around the ankle is slowly deflated from a suprasystolic pressure. By dividing the measured value with the brachial pressure the ABI is determined. An index below 0·9 is considered pathologic. In patients with diabetes mellitus, the ABI may be falsely elevated owing to sclerosis of the media of the arteries, which resists compression by the cuff.

Further anatomic evaluation of the arterial system is needed only when invasive procedures are indicated. Duplex sonography is the method of choice, but in most cases has to be followed by angiography, when surgery is planned.

All patients with peripheral vascular disease should have blood tests to detect other treatable risk factors such as blood lipids, blood or plasma glucose, and serum creatinine. Systemic blood pressure is also a treatable risk factor that should be measured.

Key points

- History (symptoms, smoking, other cardiovascular diseases) and physical examination (peripheral pulses, blood pressure) are essential.
- Screen for cardiovascular risk factors (cholesterol, glucose).
- Measurement of ABI is valuable in all patients.
- Duplex sonography and angiography are required only when invasive procedures are considered.

Intermittent claudication

Pathophysiology

Intermittent claudication is caused almost exclusively by atherosclerotic lesions in the arteries to the legs. The lesion causing the symptoms may be located above the inguinal ligament (the aorta, iliac artery, or the common femoral artery) or below, in such cases often in the distal part of the superficial femoral artery. Combinations of series of stenosis or occlusions also involving the popliteal and lower leg vessels are not uncommon.

The evolution of the disease may be slow with gradual onset of symptoms but in many cases the occurrence of a thrombus in a severely stenosed area or overlying a ruptured atherosclerotic plaque may cause an acute onset of symptoms.

The most common location of pain is in the calf, since the majority of vascular occlusions occur in the superficial femoral artery. When the main lesion is in the iliac region, pain and muscular dysfunction may also be located in the gluteal muscles and the thigh. The symptoms are caused by an inappropriate blood supply in relation to the metabolic needs of the muscles during exercise. When occlusion of the artery occurs gradually, collaterals, often from the deep femoral artery, may compensate for the limited arterial supply through the natural artery.

Therapy

General measures

The aim of therapy for intermittent claudication is twofold:

- to reduce risk factors associated with the disease and thereby improving the long-term prognosis of the patient;
- to improve walking distance and thus the quality of life for the patient.

In the general management of the patient it is mandatory to screen for risk factors associated with atherosclerosis. Smoking should be stopped immediately as the risk for the patient with claudication for having an amputation in the

future is reduced to virtually zero.[14] **Grade B** Hyperlipidemia and hypertension should be treated according to guidelines outlined in other sections of this book. A meta-analysis of lipid lowering therapy in 698 patients with peripheral arterial disease indicated that active therapy reduced disease progression and the severity of claudication.[20] Recently the Heart Protection Study including 20 000 patients with coronary or non-coronary artery disease or diabetes was reported, showing that simvastatin 40 mg/day reduced cardiovascular mortality and morbidity. The 24% decrease of vascular events was consistent in all subgroups including patients with peripheral vascular disease and regardless of cholesterol levels.[21] **Grade A** Thus, a statin should be given as first-line therapy, but niacin could also be valuable since it increases serum HDL (high density lipoproteins) concentrations and lowers serum triglyceride concentrations, which are the most common lipid disturbances in patients with intermittent claudication.

A fear of reducing distal perfusion pressures in patients with claudication by antihypertensive treatment has sometimes prevented doctors from instituting adequate treatment of hypertension. In particular, β blockers have been considered by some to be contraindicated in this situation. Controlled studies have, however, shown that treatment of claudicants with β blockers only reduces walking capacity marginally or not at all.[22] Therefore, if strong indications, such as heart failure, or a previous myocardial infarction exist, β blockers should also be used in claudicants. **Grade A**

The HOPE study investigated the effect of the ACE inhibitor ramipril 10 mg/day compared with placebo.[23] The study included 1715 patients with symptomatic peripheral vascular disease and 3099 patients with an ABI $< 0{\cdot}9$. These subgroups benefitted at least equally well as the entire study population from the treatment. The beneficial effect was seen even among patients who already had adequate blood pressure control. Treatment with an ACE inhibitor should thus be strongly considered in patients with peripheral arterial disease. **Grade A**

If symptoms of increased ischemia of the legs occur during treatment for hypertension, this strengthens the indication for an invasive procedure in order to relieve the symptoms of leg ischemia. If this is not possible, the antihypertensive therapy should be reduced with caution.

Since patients with intermittent claudication have an increased risk for major cardiovascular events because of their generalized atherosclerotic disease, antiplatelet therapy should be given prophylactically, preferably with aspirin, based on conclusions from meta-analysis.[24] **Grade A** Although major studies on the effect of aspirin in patients with claudication are lacking, the effect in subgroups with claudication ($n = 3295$; risk reduction from 11·8% to 9·7% over 27 months) seems to be equivalent to the reduction seen in the atherosclerotic population as a whole.[24] The combination with dipyridamole may provide an additional preventive effect,[25] but so far only one study has shown an effect on major end points by this combination in the case of the secondary prevention of stroke.[26] In 687 claudicants studied over a 7 year period, ticlopidine 250 mg $\times 2$/day reduced the need for vascular reconstructive surgery by 51% compared to placebo.[27] In the same trial, the mortality rate was 29.1% lower (64 *v* 89 cases) in the ticlopidine group compared with the placebo group.[28] The same dose of ticlopidine may also produce some increase in walking capacity in comparison with placebo.[29] The disadvantage of this compound is the risk of adverse effects and the need for laboratory control of white blood cell counts. A better and safer alternative to ticlopidine for patients who cannot tolerate aspirin is clopidogrel, which was studied in the CAPRIE trial.[30] In the 6452 patients with peripheral arterial disease, clopidogrel 75 mg/day showed a relative risk reduction of 23·8% in ischemic stroke, myocardial infarction, or death from other vascular causes compared to aspirin 325 mg/day.[30]

Exercise

Patients with claudication should be instructed to walk as much as possible and, when pain occurs, they should try to walk despite the pain.[31] Training by intensive walking on treadmill or outdoors has been shown to be as effective or even better than other programs of physical training and, in most cases, will improve walking capacity by 100–200%.[31] In some cases the symptoms of claudication may even disappear completely. The optimal exercise program includes walking to near maximal pain for more than 30 minutes per session at least three times weekly during at least a 6 month period.[32]

Pharmacologic treatment to increase walking capacity

Different pharmacologic agents have been evaluated for improvement of walking distance in addition to physical training. Most of these treatments have been inconsistent in their effect and of marginal benefit. Generally, vasodilators have not been shown to be effective. The agent so far most extensively studied has been pentoxifylline, which is available in most countries for the treatment of intermittent claudication. The patients most likely to respond are those with a history of claudication over 1 year and an ABI of $<0{\cdot}8$.[33] A meta-analysis of the pentoxifylline studies has shown an increase of 44 meters in maximal walking distance on the treadmill compared with placebo.[34] The phosphodiesterase inhibitor cilostazol was approved in 1999 by the FDA for treatment of claudication. Cilostazol is primarily a platelet inhibitor and a vasodilator that has been shown to increase the walking distance compared with placebo and also with pentoxifylline.[35] However, the use of the drug is hampered by the risk for worsening heart

failure.[36] A randomized but open study[37] indicates that prostaglandin E1 given intravenously may be more effective than pentoxifylline (60·4% compared with 10·5% increase in walking capacity), but further studies are needed to establish the role of prostaglandins in this context.

Key points

- Quit smoking!
- Regular exercise – walking until intolerable pain.
- Intervention against other cardiovascular risk factors; treat hypertension and institute a statin to all patients with a normal or high cholesterol level.
- Antiplatelet therapy and ACE inhibitor to be considered for all patients.
- Other pharmacologic therapy of very limited benefit.

Critical ischemia

Pathophysiology

When the distal pressure in the leg is too low to provide sufficient perfusion in order to meet the metabolic demands of the tissue, pain will also occur in the resting situation, particularly in the supine position when there is no contribution to distal pressures by hydrostatic forces. Subsequently ulcers in the apical parts of the extremity may develop owing to an insufficient nutritional blood flow in the skin.

According to the European Consensus Document on chronic lower limb ischemia, critical ischemia is defined as "persistently recurring rest pain requiring regular analgesia for more than 2 weeks and/or ulceration or gangrene of the foot and toes in combination with an ankle systolic pressure less than 50 mmHg". In the case of diabetes, where the measurements of ankle pressures are unreliable because of incompressible arteries, the absence of palpable pulses are sufficient.[38] The definition has been criticized because many patients with critical limb ischemia according to the above definition still have an intact lower extremity after 1 year. This is exemplified by the findings in control groups of randomized trials regarding non-surgical treatment of critical limb ischemia.[39] Furthermore, some patients who do not fit into this definition may lose their legs because of ischemia.[40] A recent consensus document was made more practical. A patient with critical limb ischemia is defined as "a patient with chronic ischemic rest pain, ulcers and gangrene attributable to objectively proven arterial disease".[41]

The crucial factor regarding tissue nutrition is the flow through the capillary bed, which is dependent not only on the pressure in the arteries but also on other factors, such as blood viscosity and distribution of flow between nutritional and non-nutritional vessels – that is, arteriovenous shunts. Intravital capillaroscopy and transcutaneous oxygen tension are methods that can assess tissue nutrition, thereby offering additional prognostic information in these patients.[38] Patients with critical ischemia should be evaluated for possible vascular reconstructive surgery or endovascular treatment (see below).

General measures

When invasive procedures to restore blood flow (see below) are not possible or have failed, several therapeutic measures should be considered. Optimization of the hemodynamic situation is one aim. Heart failure and edema should be treated vigorously. Lowering the foot end of the bed at night may improve distal perfusion pressure and relieve symptoms. Shoes should be well fitting to avoid the risk of pressure against the skin. Ulcers should be treated with care, and more often dry dressings are preferable in order not to moisturize intact skin around the ulcer area.

Though not scientifically proven in this situation, anticoagulation may be of benefit. Thus, oral anticoagulants or low molecular weight heparin should be considered as an alternative or an addition to aspirin, since both arterial and venous thrombi are common in the severely ischemic leg.[42] Warfarin has been shown to lower the risk of occlusion in femoropopliteal vein grafts.[43] Pain should be treated by pharmacologic measures. Spinal cord stimulation could be used since this method has been shown to decrease pain possibly by increasing microvascular blood flow.[44]

The only pharmacologic agent so far convincingly shown to have a positive influence on the prognosis of patients with critical limb ischemia is a synthetic prostacyclin (Iloprost), which is given intravenously daily for a period of 2–4 weeks. In a meta-analysis, rest pain and ulcer size were found to improve in comparison with placebo and, more importantly, the probability of being alive with both legs still intact after 6 months was 65% in the Iloprost-treated group compared to 45% in the placebo-treated patients.[39] **Grade A** Pentoxifylline has been shown to be of benefit in a short-term perspective as a pain reliever but no long-term trials have been performed.[45] Spinal cord stimulation has been used to avoid amputations, but so far it has not benefitted patients with critical limb ischemia as a preventive treatment.[46]

Key points

- Evaluate possibilities for revascularization.
- Optimize cardiac hemodynamics.
- Avoid hypotension – lower foot end of bed at night.
- Provide adequate pain relief.
- Optimize local skin and wound care.
- Consider anticoagulation or antiplatelet therapy.
- Consider Iloprost treatment when revascularization is not possible or has failed.

Surgical treatment of intermittent claudication and critical ischemia

In this chapter both open surgery and endovascular treatment are considered. In the latter group percutaneous transluminal angioplasty (PTA) in combination with both thrombolysis and stenting are included. The major indications for reconstructive procedures for lower extremity ischemia are critical ischemia and claudication.

Preoperative cardiac evaluation

Since patients with peripheral vascular disease have a high frequency of cardiac comorbidity, the perioperative mortality and morbidity is dominated by cardiac problems. Many attempts have been made to identify patients with a high risk of perioperative cardiac complications. The rationale for such a strategy is to identify patients in need of coronary artery revascularization before the vascular procedure, and also to provide a basis for more intensive cardiac monitoring during peripheral vascular surgery. Although not specifically designed for peripheral vascular surgery, clinical risk scores according to Goldman[47] or Detsky[48] have been used. Further tests include ambulatory ECG, dipyridamole thallium scintigraphy, ejection fraction estimation by radionuclide ventriculography, and stress echocardiography. All these tests are effective in predicting perioperative cardiac mortality and morbidity, but dobutamine stress echocardiography seems to be most promising in a meta-analysis.[49] Patients who have reversible defects on preoperative thallium scintigraphy are at a high risk of perioperative cardiac mortality and morbidity,[50] and successful coronary revascularization decreases this risk following vascular surgery.[51] Nevertheless, routine evaluation of all patients scheduled for peripheral vascular surgery with thallium scintigraphy is not warranted.[52] The reason for this is that both coronary angiography and coronary revascularization add to the risk.[53] Today it can therefore be concluded that patients with a low risk, as reflected by either absence of angina pectoris or only mild disease, do not benefit from further evaluation aiming at coronary angiography.[54] Patients with high risk according to clinical scoring systems or careful history should be evaluated with dipyridamole thallium scintigraphy or dobutamin stress echocardiography. **Grade B** The use of bisoprolol, a β1 selective inhibitor, reduced the 30 day combined cardiac morbidity and mortality from 34% to 3·4% in high-risk patients undergoing peripheral vascular surgery.[55] Whether other β blockers have the same effect remains to be shown. **Grade B**

Open surgical vascular reconstructions

The vascular reconstructions for lower limb ischemia are mainly divided into supra- and infrainguinal reconstructions.

Suprainguinal vascular reconstructions

In the aortoiliac segment, vascular reconstructive procedures were initially dominated by thromboendarterectomy (TEA); this, however, requires large dissections. After the introduction of bypass grafting with synthetic materials TEA was largely abandoned except for short localized lesions. The results of aortobifemoral bypass with Dacron grafts for arterial occlusive disease are usually good with 1 year patency rates in the range of 95%. The patency rates are influenced by the outflow bed, so that patients with a patent superficial femoral artery (SFA) have better patency rates than those with an occluded SFA. There are no prospective randomized trials comparing TEA and aortofemoral bypass. TEA is said to have lower long-term patency rates, and another disadvantage is that the surgical procedure is more extensive. Aortofemoral bypass with a synthetic graft, however, has the disadvantage of risk of infection. Although this is an infrequent complication, it is associated with major morbidity and mortality, since an infected graft has to be removed.

During recent years the number of aortobifemoral reconstructions have declined owing to the more frequent use of endovascular methods, particularly PTA with or without stenting. Thus the extensive procedure of aortobifemoral bypass can be converted into a lesser procedure if at least one iliac artery can be opened with PTA. In such cases the contralateral leg can be revascularized with the aid of an extra-anatomic procedure – that is, femorofemoral bypass. The latter procedure has good patency rates, approximately 90% at 1 year and 65% at 5 years.[56–58] In patients who are unfit for major surgery and where the iliac arteries cannot be opened up with endovascular procedures another extra-anatomic bypass can be employed. In such patients axillobifemoral bypass can be used, but this type of extra-anatomic bypass is a compromise, since it has lower patency rates than aortobifemoral bypass.[59]

Infrainguinal vascular reconstructions

The standard procedure for infrainguinal occlusive disease is femoropopliteal bypass or bypass to the crural arteries. Bypass to the crural arteries is often performed in people with diabetes since their occlusive disease is in many cases more peripherally located than in non-diabetic patients with atherosclerosis. The most commonly used graft material is the saphenous vein but, if this is unavailable, arm veins or synthetic grafts may be used. In general it has been stated that use of autologous material is superior in infrainguinal reconstructions.[60] Some randomized studies have failed to detect a difference in long-term patency between synthetic grafts and saphenous vein grafts. One study did not show a significantly different patency at 2 years follow up, but after 4 years there was a significant difference in favor of saphenous

vein grafts, 68% patency versus 47%.[61] **Grade A** For bypass grafts with the lower anastomosis below the knee, autologous material is clearly preferred. This is particularly true when bypass procedures are done to the crural arteries where the use of synthetic grafts produces dismal results.

When an autologous vein is used, the original procedure implies excision and reversal of the vein so that the blood can flow freely across the valves. The "*in situ*" technique, originally introduced by Hall, has, however, in recent years gained more popularity:[62] the saphenous vein is left in its bed and the valves are destroyed by special instruments; tributaries are identified and tied off. Some prospective randomized trials have been performed comparing the two methods but no definitive advantage with either method has been shown.[63] Therefore the personal preference of the surgeon often decides which method should be used. The advantage with the *in situ* method is that the larger end of the vein is anastomosed to the larger artery, and the smaller end of the vein to the small distal artery. With meticulous technique it is said that the vein is exposed to less trauma, but the valve destruction definitely induces some damage to the vein.

In order to improve long-term patency rates, two methods have been employed: graft surveillance and pharmacologic treatment. Postoperative surveillance of vein grafts is used by many surgeons in order to detect a failing graft, defined as a graft with a developing stenosis that threatens to reduce the blood flow below a critical level. Only few randomized studies have been done examining the effect on long-term patency rates in surveillance programs identifying and treating critical graft stenosis. Conflicting results regarding the effectiveness of such programs have been obtained. One study reported a patency rate of 78% in an intensive surveillance program including duplex scanning of the graft after 3 years versus 53% without such a program.[64] Other studies, however, have failed to demonstrate an advantage of duplex scanning over clinical surveillance with measurements of ankle pressure.[65] Whether a graft surveillance program has a beneficial effect upon amputation rate also remains to be shown.

The effect of antiplatelet therapy on total mortality has been studied in several trials and it seems to reduce cardiovascular mortality.[66] There is only one trial that has studied the similar effects of oral anticoagulants, and this trial suggested that they both prevent graft occlusion and diminish the risk of cardiovascular death.[43] Pharmacologic therapy seems to improve the patency rate for infrainguinal vascular reconstructions. Most centers use antiplatelet therapy with acetylsalicylic acid, and a meta-analysis of randomized trials has indicated that such treatment improves the patency rate.[67] **Grade A** Oral anticoagulants are not used as widely as antiplatelet therapy but many surgeons use it selectively in patients where the prognosis for graft patency for some reason is bad. Whether antiplatelet therapy or oral anticoagulants differ in their effectiveness against graft occlusion is not known. Only one study has addressed this question and no significant difference in graft patency was found between patients treated with warfarin or acetyl salicylic acid. Subgroup analysis, however, revealed that oral anticoagulants seemed to be more effective in patients receiving autologous grafts and antiplatelet therapy in those receiving synthetic grafts.[68] **Grade B**

Key points

- For bilateral suprainguinal occlusions aortofemoral bypass is the standard procedure, but endovascular methods are used at an increasing rate.
- For unilateral suprainguinal occlusions femorofemoral bypass can be used.
- For infrainguinal occlusions saphenous vein bypass is the standard procedure, but synthetic grafts can be used if suitable veins are lacking.
- Bypass to infragenicular arteries using synthetic grafts produces inferior results compared to saphenous vein bypass.

Endovascular procedures

Since the introduction of transluminal dilation by Dotter, this field has grown enormously.[69] The introduction of PTA has resulted in more indications for endovascular procedures to some extent at the expense of open surgical reconstructions.

Percutaneous transluminal angioplasty

In common with other vascular reconstructive procedures the success rate of PTA is highly dependent upon various factors. In general it can be said that proximal lesions – that is, iliac lesions – have a better success rate than distal ones – that is, femoropopliteal lesions. The chance of a successful outcome is higher for stenoses rather than occlusions, irrespective of the site of the lesion. In common with surgical vascular reconstructions, the outflow determines the outcome also for PTA. Thus, in cases of a good outflow, the results are better than if the outflow is poor.[70] In summary, the chance of success is much higher when a short iliac stenosis is dilated in a patient with patent superficial femoral and profunda femoris arteries than after dilation of a popliteal occlusion in a patient with occlusions of two out of three crural arteries.

The indications for this procedure need to be considered. PTA of an iliac stenosis in a patient with claudication has a low risk and a high chance of success and may, therefore, be perfectly appropriate, even if the severity of the disease state is relatively mild, as compared with a patient with critical limb ischemia and a threat of amputation. On the other hand, a patient with an occluded popliteal artery and poor leg run-off with ischemic ulceration has a strong indication

for the procedure and, in such a patient, it may also be perfectly appropriate to make an attempt at PTA, even though the success rate is relatively low. For patients with critical ischemia, PTA of infrapopliteal vessels has also been performed successfully and could even be used for short occlusions.[71,72]

Subintimal angioplasty has been advocated.[73] The method implies that a guidewire enters the subintimal space and then re-enters the vessel distal to the occlusion, and the subintimal space is then dilated with the balloon. In the femoropopliteal segment, occlusions longer than 20 cm can be treated, whereas intraluminal angioplasty is generally not advocated for occlusions longer than a few centimeters. Patency rates of approximately 60% at 3 years for femoropopliteal occlusions have been reported after subintimal angioplasty.[74] The reported figures are patency rates for technically successful procedures, but in 20% the procedure cannot be performed. The method has also been used for infrapopliteal arteries.[75] Subintimal angioplasty, if proven successful, could be a future alternative to femoropopliteal bypass.

Formal comparisons in prospective randomized trials between PTA and surgery are relatively scarce. Such trials are difficult because, in order for a patient to be included, the lesion has to be suitable for PTA – that is, it should be either a stenosis or a short occlusion. Knowing that the treatment of a stenosis with PTA is relatively successful with less risk and shorter hospital stay, it is sometimes considered ethically questionable to include patients in a trial between PTA and surgery. In a study including 263 patients with lesions in the iliac, femoral, or popliteal arteries comparing bypass surgery and PTA, primary success favored surgery, while limb salvage favored PTA, but the differences were not statistically significant. After 4 years there was no significant difference in outcome.[76]

Randomized trials comparing angioplasty with non-surgical treatment for intermittent claudication have, however, been performed, but they are relatively small and the results are to some extent contradictory. In one study the treadmill distances improved in both groups but were superior in those undergoing an exercise program, and after 6 years there was no benefit in treadmill walking distance after angioplasty.[77] In another study, an improvement in ABI was shown 6 months following angioplasty, which could not be found in patients undergoing exercise programs. Significantly more patients were asymptomatic after 6 months in the angioplasty group compared with those treated with exercise programs. This study, however, had a shorter follow up, and the conservative treatment was not as active as in the study where no difference could be seen between exercise program and PTA.[78] It can still be concluded that PTA is suitable for stenoses or short occlusions in claudicants, but few claudicants have discrete lesions suitable for PTA.

Stenting has been used at an increasing rate over the last few years. It is generally advised not to use stents in smaller arteries, and this implies that stents are used relatively seldom in the femoropopliteal region. Stents, however, are used in the iliac arteries after PTA, particularly when there is recoil or dissection. Several types of stents have been used, both self-expandable and balloon-expandable ones. Stenting below the inguinal ligament is not generally recommended.

Thrombolysis

Thrombolysis of peripheral arterial occlusive disease is recommended for acute arterial occlusions, but it also has a place in subacute occlusions. Thrombolysis should be intra-arterial and preferably the thrombolytic agent should be delivered into the clot, either with an end hole catheter or a catheter with multiple side holes. Today recombinant tissue plasminogen activator (rtPA) is used most commonly. Other thrombolytic agents are, however, being developed and have been tried for indications other than peripheral arterial occlusive disease. The dosage and rate of administration of thrombolytic agents varies in different reports and makes comparisons difficult. There are, however, some prospective randomized trials comparing surgery with intra-arterial thrombolytic therapy. In one representative study, the mean duration of ischemia was almost 2 months and patients were included if the duration was less than 6 months. Overall the study favored surgery. Patients randomized to catheter-directed thrombolysis had significantly greater ongoing or recurrent ischemia, life-threatening hemorrhage, and vascular complications compared with surgical patients. Stratification by duration of ischemia, however, showed that patients treated within 14 days of onset of symptoms had an amputation rate after thrombolysis of 6% compared to 18% for those undergoing surgery. Patients treated with thrombolysis in this group also had a shorter hospital stay. In patients with acute ischemia the amputation-free survival at 6 months follow up was also better in those treated with thrombolysis.[79] Further analysis of this material reveals that thrombolysis provides a reduction of the predetermined surgical procedure in 50–60% of the cases.[80] **Grade B**

Key points

- PTA is more successful for stenoses than for occlusions.
- PTA is more successful for short than for long occlusions.
- PTA may be combined with stent if recoil occurs or if PTA produces dissection with intimal flaps.
- Thrombolysis should be performed by local intrathrombal administration of the drug.
- PTA may be preceded by thrombolysis in cases with recent occlusions.

Inflammatory vascular diseases – thromboangitis obliterans (Buerger's disease)

Temporal arteritis, Takayashu's disease of the aortic arch, and several diseases affecting the arterioles and microcirculatory vessels have an inflammatory or immunogenic origin. In this chapter these diseases are not considered.

Thromboangitis obliterans, or Buerger's disease, also has an inflammatory component, although the pathophysiology is still not fully known. The major pathogenetic factor, tobacco smoke, has been clearly established, however, for a long time. The patient is usually a young or middle aged man with excessive smoking habits. The disease is segmental and affects both veins and arteries leading to recurrent thrombophlebitis and, in more severe cases, to multiple ulcerations of toes and fingers owing to occlusion of distal arteries. Larger arteries are often affected, which in part may be due to concomitant atherosclerotic disease.

The treatment is based on total avoidance of tobacco smoke. Treatment with prostaglandins, especially the synthetic prostacyclin analog Iloprost (see critical ischemia above), has been shown to have positive effects regarding pain alleviation and healing of ulcers.[81]

References

1. Rose G. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull WHO* 1962;**27**:645–58.
2. Fowkes F. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988;**17**:248–54.
3. Bothig S, Metelisa V, Barth W *et al.* Prevalence of ischaemic heart disease, arterial hypertension and intermittent claudication, and distribution of risk factors among middle-aged men in Moscow and Berlin. *Cor Vasa* 1976;**18**:104–18.
4. Heliovaara M, Karvonen W, Vilhunden R, Punsar S. Smoking, carbon monoxide and atherosclerotic diseases. *BMJ* 1978;**I**: 268–70.
5. Dormandy J, Heeck L, Vig S. The natural history of claudication: risk to life and limb. *Semin Vasc Surg* 1999;**12**: 123–37.
6. Feinglass J, McCarthy W, Slavensky R, Manheim L, Martin G. Effect of lower extremity blood pressure on physical functioning in patients who have intermittent claudication. *J Vasc Surg* 1996;**24**:503–12.
7. Criqui M, Fronek A, Barrett-Connor E, Klauber M, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;**71**:510–15.
8. Hiatt W. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995;**91**:1472–9.
9. Kannel W, McGee D. Update on some epidemiological features of intermittent claudication. *J Am Geriat Soc* 1985;**33**: 13–18.
10. Dormandy J, Heeck L, Vig S. Predictors of early disease in the lower limbs. *Semin Vasc Surg* 1999;**12**:109–17.
11. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation* 1997;**96**:44–9.
12. Leng GC, Lee AJ, Fowkes FG *et al.* Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996;**25**:1172–81.
13. McGrath M, Graham A, Hill D *et al.* The natural history of chronic leg ischaemia. *Wld J Surg* 1983;**7**:314–18.
14. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand* 1987;**221**:253–60.
15. Kallero K. Mortality and morbidity in patients with intermittent claudicationas defined by venous occlusion plethysmography: a ten year follow up. *J Chron Dis* 1981;**34**:445–62.
16. Criqui M, Langer R, Fronek A *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;**326**:381–5.
17. Leng G, Fowkes F, Lee A, Dunbar J, Housley E, Ruckley C. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ* 1996;**313**:1440–4.
18. Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. *Acta Med Scand* 1982;**211**:249–56.
19. Rihal S, Eagle K, Mickel C *et al.* Surgical therapy for coronary artery disease among patients with combined coronary artery and peripheral vascular disease. *Circulation* 1995;**91**:46–53.
20. Leng GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis. *Cochrane Database Syst Rev* 2000;**2**.
21. The Heart Protection Study Presentation at AHA, 2001. www.heart-protection.com
22. Hiatt W, Stoll S, Nies A. Effect of beta-adrenergic blockers on the peripheral circulation in patients with peripheral vascular disease. *Circulation* 1985;**72**:1226–31.
23. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
24. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**:81–106.
25. Hess H, Mietaschik A, Deichsel G. Drug induced inhibition of platelet function delays progression of peripheral occlusive arterial disease: a prospective double blind arteriographic controlled trial. *Lancet* 1985;**1**:416–19.
26. Diener F, Coccheri S, Libretti A *et al.* European stroke prevention study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurolog Sci* 1996;**143**: 1–13.
27. Bergqvist D, Almgren B, Dickinson J. Reduction of requirement for leg vascular surgery during long-term treatment of claudicants patients with Ticlopidine: Results from the Swedish Ticlopidine Multicenter Study (STIMS). *Eur J Vasc Endovasc Surg* 1995;**10**:69–76.

28.Janzon L, Bergqvist D, Boberg J *et al.* Prevention of myocardial infarction and stroke in patients with intermittent claudication: effects of ticlopidine, results from STIMS, the Swedish Ticlopidine Multicenter Study. *J Intern Med* 1990;**227**: 301–8.

29.Balsano F, Coccheri S, Libretti A *et al.* Ticlodipine in the treatment of intermittent claudication. A 21-month double-blind trial. *J Lab Clin Med* 1989;**114**:84–91.

30.CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.

31.Hiatt W, Wolfel E, Meire R, Regesteiner J. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation* 1994;**90**:1866–74.

32.Gardner A, Poehlman E. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA* 1995;**274**:975–80.

33.Lindgärde F, Jelnes R, Björkman H *et al.* Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. *Circulation* 1989;**80**:1549–56.

34.Girolami B, Bernardi E, Prins MH *et al.* Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med* 1999;**159**:337–45.

35.Dawson DL, Cutler BS, Hiatt WR *et al.* A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000;**109**:523–30.

36.Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;**344**:1608–21.

37.Scheffler P, de la Hamette D, Gross J, Müller H, Schieffer H. Intensive vascular training in stage IIb of peripheral arterial occlusive disease. The additive effects of intravenous prostaglandin E1 or intravenous pentoxiphylline during training. *Circulation* 1994;**90**:818–22.

38.The European Working Group on Critical Leg Ischaemia. Second European consensus document on chronic critical leg ischaemia. *Circulation* 1991;**84**(Suppl. 4):1–22.

39.Loosemore T, Chalmers T, Dormandy J. A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994;**13**: 133–42.

40.Thompson M, Sayers R, Varty K, Reid A, London M, Bell P. Chronic critical leg ischaemia must be redefined. *Eur J Vasc Surg* 1993;**7**:420–6.

41.Group TW. Management of peripheral Arterial Disease. *J Vasc Surg* 2000;**31**(1, part 2).

42.Conrad M. Abnormalities of the digital vasculature as related to ulceration and gangrene. *Circulation* 1968;**49**:1196–201.

43.Kretschmer G, Herbst F, Prager M *et al.* A decade of oral anticoagulant treatment to maintain autologous vein grafts for femoropopliteal atherosclerosis. *Arch Surg* 1992;**127**:1112–15.

44.Jivegård LE, Augustinson LE, Holm J *et al.* Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischemia: a prospective randomised controlled study. *Eur J Vasc Endovasc Surg* 1995;**9**:421–5.

45.The European Study Group. Intravenous pentoxiphylline for the treatment of chronic critical limb ischemia. *Eur J Vasc Endovasc Surg* 1995;**9**:426–36.

46.Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JD, van Urk H. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. *Lancet* 1999;**353**:1040–4.

47.Goldman L, Caldera D, Nussbaum S. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;**297**:845–50.

48.Detsky A, Abrams H, Forbath N, Scott J, Hilliard J. Cardiac assessment for patients undergoing noncardiac surgery: a multifactorial clinical risk index. *Arch Intern Med* 1986;**146**: 2131–4.

49.Mantha S, Roizen M, Barnard J, Thisted R, Ellis J, Foss J. Relative effectiveness of four preoperative tests for predicting adverse cardiac outcome after vascular surgery: a meta-analysis. *Anaesth Analg* 1994;**79**:422–33.

50.Eagle K, Singer D, Brewster D, Darling R, Mulley A, Boucher C. Dipyridamole-thallium scanning in patients undergoing vascular surgery. *JAMA* 1987;**257**:2185–9.

51.Hertzer N, Beven E, Young J *et al.* Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results or surgical management. *Ann Surg* 1984;**199**:222–3.

52.Mangano D, London M, Tubau J *et al.* Dipyridamole thallium-201 scintigraphy as a preoperative screening test. *Circulation* 1991;**84**:493–502.

53.Mason J, Owens D, Harris D, Ryan A, Cooke J, Hlatky M. The role of coronary angiography and coronary revascularization before noncardiac vascular surgery. *JAMA* 1995;**273**: 1919–25.

54.Wong T, Detsky A. Preoperative cardiac risk assesment for patients having peripheral surgery. *Ann Intern Med* 1992;**116**:743–53.

55.Poldermans D, Boersma E, Bax JJ *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;**341**:1789–94.

56.Mason R, Smirnov V, Newton G, Giron F. Alternative procedures to aortobifemoral bypass grafting. *J Cardiovasc Surg (Torino)* 1989;**30**:192–7.

57.Becker GJ, Katzen BT, Dake MD. Noncoronary angioplasty. *Radiology* 1989;**170**:921–40.

58.Johnston KW. Iliac arteries: reanalysis of results of balloon angioplasty. *Radiology* 1993;**186**:207–12.

59.Swedenborg J, Bergmark C. Is there a place for primary axillofemoral bypass? In: Greenhalgh R, Fowkes F, eds. *Trials and tribulations of vascular surgery*. London: WB Saunders Company Ltd, 1996.

60.Michaels J. Choice of material above-knee femoropopliteal bypass graft. *Br J Surg* 1989;**76**:7–14.

61.Veith F, Gupta S, Ascer E *et al.* Six-year prospective multicenter randomised comparison of autologous saphenous vein and expaneded polytetrafluoroethylene grafts in infrainguinal arterial reconstruction. *J Vasc Surg* 1986;**3**:104–14.

62.Hall K, Rostad H. *In situ* vein bypass in the treatment of femoropopliteal atherosclerotic disease. A ten year study. *Am J Surg* 1978;**136**:158–61.

63.Moody A, Edwards P, Harris P. *In situ* versus reversed femoropopliteal vein grafts long-term follow-up of a prospective, randomized trial. *Br J Surg* 1992;**79**:750–2.

64.Lundell A, Lindblad B, Bergqvist D, Hansen F. Femoropopliteal-crural graft patency is improved by an intensive surveillance program: a prospective randomized study. *J Vasc Surg* 1996; **21**:26–33.
65.Ihlberg L, Luther M, Alback A, Kantonen I, Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein-graft failure? *Eur J Vasc Endovasc Surg* 1999;**18**: 395–400.
66.Tangelder MJ, Lawson JA, Algra A, Eikelboom BC. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. *J Vasc Surg* 1999;**30**:701–9.
67.Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-II: maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994;**308**:159–68.
68.The Dutch Bypass Oral Anticoagulants or Aspirin Study. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery: a randomised trial. *Lancet* 2000;**355**:346–51.
69.Dotter C, Judkins M. Transluminal treatment of arteriosclerotic obstructions. *Circulation* 1964;**30**:654–70.
70.Johnston K, Rae M, Hogg-Johnston S *et al.* 5-year results of a prospective study of percutaneous transluminal angioplasty. *Ann Surg* 1987;**206**:403–12.
71.Dorros G, Lewin R, Jamnadas P *et al.* Below-the-knee angioplasty: Tibioperoneal vessels, the acute outcome. *Catheter Cardiovasc Diag* 1990;**19**:170–8.
72.Sivananthan U, Browne T, Thorley P *et al.* Percutaneous transluminal angioplasty of the tibial arteries. *Br J Surg* 1994;**81**:1282–5.
73.Bolia A, Miles K, Brennan J, Bell P. Percutaneous transluminal angioplasty of occlusions of the femoral and popliteal arteries by subintimal dissection. *Cardiovasc Interven Radiol* 1990; **13**:357–63.
74.London N, Srinivasan R, Naylor A *et al.* Subintimal angioplasty of femoropopliteal artery occlusions: the long-term results. *Eur J Vasc Surg* 1994;**8**:148–55.
75.Nydahl S, London N, Bolia A. Technical report: recanalisation of all three infrapopliteal arteries by subintimal angioplasty. *Clin Radiol* 1996;**51**:366–7.
76.Wolf G. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. *J Vasc Intervent Radiol* 1993;**4**:639–48.
77.Perkins J, Collin J, Creasy T, Fletcher E, Morris P. Exercise training versus angioplasty for stable claudication. Long and medium results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg* 1996;**12**:167–72.
78.Whyman M, Fowkes F, Kerracher E *et al.* Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. *Eur J Vasc Endovasc Surg* 1996;**12**: 167–72.
79.The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE Trial. *Ann Surg* 1994;**220**: 251–68.
80.Weaver F, Comerota A, Youngblood M *et al.* Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: Results of a prospective randomized trial. *J Vasc Surg* 1996;**24**:513–23.
81.Fiessinger J, Schäfer M. Trial of Iloprost versus aspirin treatment for critical limb ischemia of thromboangitis obliterans. *Lancet* 1990;**335**:556–7.

Part IV

Clinical applications

Ernest L Fallen, Editor

Grading of recommendations and levels of evidence used in *Evidence-based Cardiology*

GRADE A

Level 1a Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively has at least as much data as one single well-defined trial.

Level 1b Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections).

Level 1c Evidence from at least one moderate-sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d Evidence from at least one RCT.

GRADE B

Level 2 Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3 Evidence from at least one high quality case–control study.

Level 4 Evidence from at least one high quality case series.

GRADE C

Level 5 Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles).

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies, and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of β blockers, but there is overwhelming evidence that mortality is reduced following MI. In such cases, some may recommend use of β blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventive or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

63 Clinical applications of external evidence

Ernest L Fallen, Salim Yusuf

External evidence derived from randomized clinical trials (RCTs) provides the practicing physician with a sound, rigorous and secure basis for making management decisions on individual patients. However, even vociferous advocates of evidence-based medicine will caution against the use of external evidence as the sole criterion for treating all patients. It is well to bear in mind that evidence obtained from clinical trials is derived from large population databases. More often than not, the entry criteria tend to define the boundaries of specified interest (for example, acute myocardial infarction), whereas exclusion criteria, such as age, sex, comorbid disease states etc., may well have denied entry to one's individual patient now awaiting treatment. These exclusions may be based on concerns related to patient safety, lack of applicability, historical considerations or confounders (for example, significant non-cardiac illness) that can affect the evaluation of treatment. Nevertheless, the practicing physician is left inquiring, "Where can I find my patient within the trial's data set?" Here is where interpretation and the application of external evidence requires a logical integration of overall trial results with a knowledge of biologic mechanisms, patient risk and clinical circumstances.

Evidence-based *v* patient centered medicine? Not an either/or choice

Few would deny an approach to therapeutic decision making based on proven external evidence combined with clinical experience, knowledge of pathophysiology and sensitivity to individual patient needs. To marry the two effectively is to recognize, and hence to avoid, their respective limitations if either were to be applied alone.

Recognizing the limitations of external evidence

For most RCTs, proving therapeutic efficacy necessitates certain constraints in patient selection. It is not uncommon that many patients in a physician's practice would not have fulfilled the restrictive entrance criteria of most moderate-size RCTs. For example, some RCTs have an age cut off that actually excludes more than half of all patients with the disorder. This by no means implies that the reputed benefit of the test drug is not applicable (effective) to the patients excluded, but it does beg the question. Entry criteria alone should never be the sole basis for denying a patient the benefit of proven therapy. Interpatient variability is inevitable in all RCTs and contributes much to the "random errors" seen in small and moderate-sized trials. However, the larger the trial the smaller the random error, and the more likely that benefit can be reliably extrapolated to some patients who do not necessarily qualify for entry.[1,2] For example, one may observe that the benefits are consistent across different subgroups, suggesting that the results may be applicable beyond the boundaries of patient selection, whereas on the other hand there may emerge reliable evidence for a lack of benefit in certain subgroups.

Evidence-based medicine that depends solely on external evidence is disease oriented rather than patient oriented. In other words, the verifiability of RCT data is often dependent on having a given diagnosis, as opposed to a clinical spectrum of risk associated with the diagnosis. This is the so-called "labeling" dilemma. For example, patients labeled as having "acute coronary syndrome" simply because they present with chest pain associated with non-ST segment elevation are often treated alike in an RCT, whereas the clinical expression of this entity may encompass a wide range from very low- to very high-risk patients. Translating external evidence based solely on a unified diagnosis into practice guidelines or clinical pathways has the unfortunate consequence of making management decisions dependent on a label rather than the presenting clinical circumstances and risk of the underlying disorder.

Another nagging problem with the "bottom line" of clinical trials is the emphasis on primary end points that are measurable. Statistical dependency on hard data such as mortality rates, prespecified clinical outcome events, rehospitalizations etc. fails to acknowledge the significance of clinically relevant "soft" data, such as impact on symptoms, quality of life, psychosocial wellbeing, attitudes, economic realities and patient preferences.

Finally, clinical trials all have finite time limits and, not uncommonly, the duration may be inadequate to

assess long-term benefits and risks, especially for any new drug. In such cases the information from RCTs may have to be supplemented by other sources of non-randomized evidence.

Recognizing the limitations of patient centered medicine

Who would have guessed that aspirin could reduce the relative risk of death and adverse coronary events in postmyocardial infarction patients by 25%? Or that β blockers would be so effective in class II–III chronic heart failure? Or that inotropic agents, despite improving hemodynamics and clinical wellbeing in patients with advanced heart failure, do so at the expense of shortened survival? Or that some antiarrhythmic agents, although they achieve cosmetic cleansing of so-called malignant ventricular ectopy from the electrocardiogram, are potentially hazardous? Previously held concepts of disease mechanisms as the basis for initiating new therapies or persisting with old therapies have been challenged by clinical trials results. And so, what is apparent as a "logical" management approach to a given clinical problem may commit even the most experienced physician to inappropriate prescribing practices. Patient centered medicine is not a concept that is firmly rooted in empirical medicine.[3] It does not guarantee that a physician, feeling secure in his or her realm of expertise, will be kept abreast of therapeutic advances based on clinical trial results. Unfortunately, this can lead to a tendency to persist in outmoded approaches.

Surely a cogent argument can be made to blend the positive features of patient centered and evidence-based approaches through a constant awareness of their respective limitations.

Some principles of application

> Knowing the person who has the disease is as important as knowing the disease that the patient has.[4]

Clinical decision making ought to incorporate the three following ingredients: (a) intelligent use of external evidence based on well established clinical trial results and epidemiologic data whenever available; (b) clinical expertise, knowledge of fundamental mechanisms of disease, and willingness to listen to the testimony of one's patients; and (c) sensitivity to patients' preferences, values, needs and beliefs.

1. It is well to bear in mind that for any given diagnosis (label), patients at the greatest risk of a disease will usually derive the greatest benefit from an established treatment, as the absolute benefit usually increases with risk whereas harm due to the treatment remains comparatively fixed across the risk spectrum.[5] Therefore, to avoid the hazard of labeling it is critical to risk stratify one's patient. It is only after one has listened carefully to the testimony of the patient, performed a proper examination and conducted the relevant tests that one can formulate a degree of attributable risk. Remember, it is just as important to identify the patient at very low risk, thereby sparing him or her unnecessary aggressive investigation and/or therapy, as it is to identify the high-risk patient for whom aggressive treatment can be life saving.
2. The absence of external evidence should not lead to therapeutic nihilism. Not all consensus recommendations are supported by grade A evidence. In fact, many consensus panel recommendations and clinical practice pathways are based on evidence that ranges from the use of clinical judgment, albeit under a cloud of uncertainty, to grade B through grade A evidence.[6,7] When external evidence is lacking, one's own clinical experience, knowledge of pathophysiology, reasoned judgment and awareness of the patient's needs are indispensable substitutes.
3. One should avoid using the trial entry criteria to determine whether a particular patient would benefit from the active treatment.[2,5] Failure to qualify for entry is determined by many factors, few of which necessarily compromise the potential for therapeutic benefit. For example, if a trial's age cut off was 65 years then a reasonable risk/benefit assessment can be done for those older by assessing whether, within the trial, age modified the treatment effect.
4. One should always try to use the best available external evidence science has to offer, but never at the expense of ignoring the patient's psychosocial conditions, beliefs, values and preferences. As medical decisions become more codified one should not fail to recognize and honor the importance of patient preferences.[8] A patient's medical decision based on his or her particular needs, preferences and beliefs should always be respected, as the patient is given the opportunity to hear the nature of the external evidence. Consensus recommendations are guidelines only. They represent an active process subject to continual review as new and as yet untested information emerges. When following any recommendation based on external evidence the physician should always exercise clinical judgment based on a close working interaction with the patient.

Section preview

The following case reports stress the importance of knowing *how* and *when* to apply best external evidence, not just to know *what* that evidence is. They represent an attempt to put a clinical face on a statistical bottom line by illustrating

practical solutions in the application of evidence-based medicine to individual patient problems. These case studies are real life presentations in which therapeutic decisions are either clearly guided by external evidence or require extra clinical reasoning skills in concert with best available evidence. From the files of these distinguished consultant cardiologists two different cases are presented for each of the 11 clinical topics. The first case in each series represents a clinical scenario where the management decision is unequivocally substantiated by use of the external best evidence. The second case is more complex and represents a challenge to incorporate external evidence with reasoned judgment, an experienced examination, a sound knowledge of cardiovascular pathophysiology, and sensitivity to the patient's needs and preferences.

References

1. Yusuf S, Held P, Teo KK. Selection of patients for randomized controlled trials: Implications of wide or narrow eligibility criteria. *Stat Med* 1990;**9**:73–86.
2. Yusuf S, Wittes HJ, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**:93–8.
3. Bensing J. Bridging the gap. The separate worlds of evidence-based and patient-centered medicine. *Patient Educ Counseling* 2000;**39**:17–25.
4. McCormick J. Death of the personal doctor. *Lancet* 1996; **348**:667–8.
5. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *BMJ* 1995;**311**:1356–9.
6. Fallen EL, Cairns J, Dafoe W *et al*. Management of the postmyocardial infarction patient: a consensus report. *Can J Cardiol* 1995;**11**:477–86.
7. Hayward RS, Wilson MC, Tunis SR *et al*. User's guide to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? *JAMA* 1995;**274**:570–4.
8. Kassirer JP. Incorporating patients' preferences in medical decisions. *N Engl J Med* 1994;**330**:1895–6.

64 Stable angina: choice of PCI *v* CABG *v* drugs

Douglas A Holder

Case scenario 1

While vacationing in Puerto Rico, a 51 year old Canadian woman sustains an uncomplicated inferior myocardial infarction. Upon returning to Canada she experiences angina up to four to five times per day, relieved by one or two nitroglycerin sprays. Her risk factors include a history of smoking, a positive family history of coronary artery disease, and a total cholesterol of 5·4 mmol/l (LDL-C 4·1; HDL-C 1·2) and triglycerides 1·34 mmol/l. Her medications are diltiazem 240 mg CD daily; transdermal nitroglycerin 0·4 mg/h patch ON in am and OFF hs; enteric coated aspirin 325 mg daily; salbutamol and beclomethosone dipropionate puffs. She is unable to take β blockers because of increased airways resistance secondary to chronic smoking.

A decision is made to proceed with coronary angiography with the view to revascularization. Coronary angiography which reveals a 90% stenosis of the midthird of a dominant right coronary artery (RCA) (Figure 64.1). Angiographically, the dominant RCA stenosis, being severe, non-calcified, and discrete, is technically suitable for percutaneous coronary intervention (PCI). After the second inflation with a 2·5 mm balloon the procedure is complicated by acute closure due to a spiral dissection which extends down well below the original stenosis towards the crux (Figure 64.2). A 2·5/28 mm stent and a 2·5/24 stent are deployed to tack up the intima from the distal end of the dissection back to and including the original stenosis. This results in an angiographically excellent result (Figure 64.3). The patient makes an uneventful recovery and is discharged on clopidogrel 75 mg daily in addition to her previous medications.

She is well for 2 months but then develops recurrent angina. An exercise (treadmill) thallium study is positive at $5\frac{1}{2}$ minutes with angina; 1 mm ST depression and reversible inferior wall ischemia on scanning. A repeat coronary angiogram reveals a discrete restenosis at the juncture of the two stents (Figure 64.4). The patient and her husband decide to choose coronary artery bypass surgery (CABG) rather than repeat PTCA.

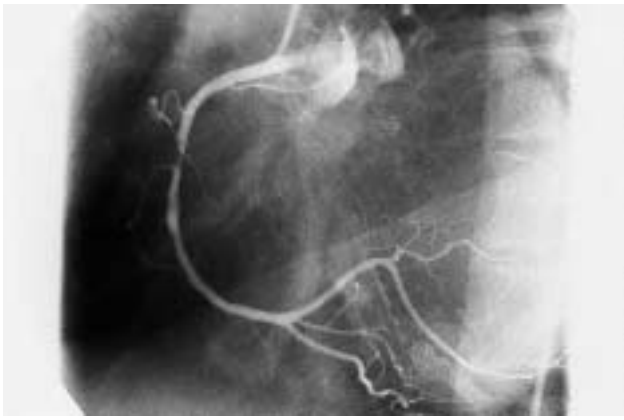

Figure 64.1 A 90% discrete stenosis in a dominant right coronary artery (RCA)

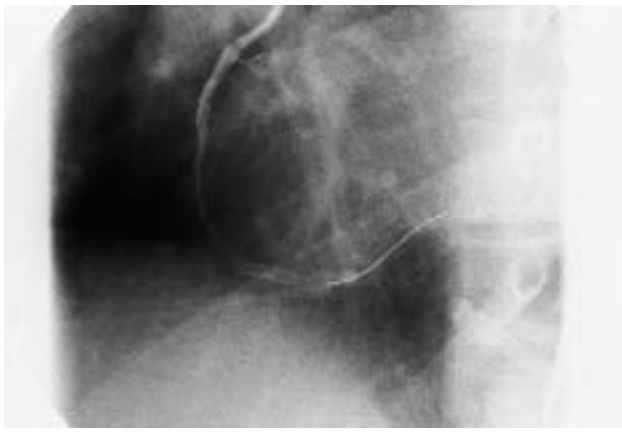

Figure 64.2 After the second balloon inflation, note the spiral dissection extending down toward the crux

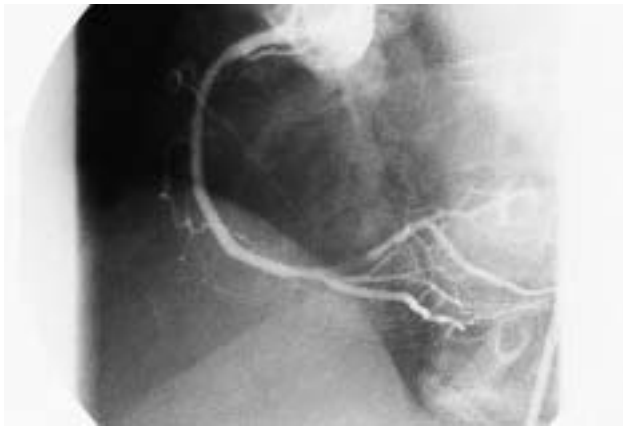

Figure 64.3 Post-stent deployment revealing adequate patency of the RCA

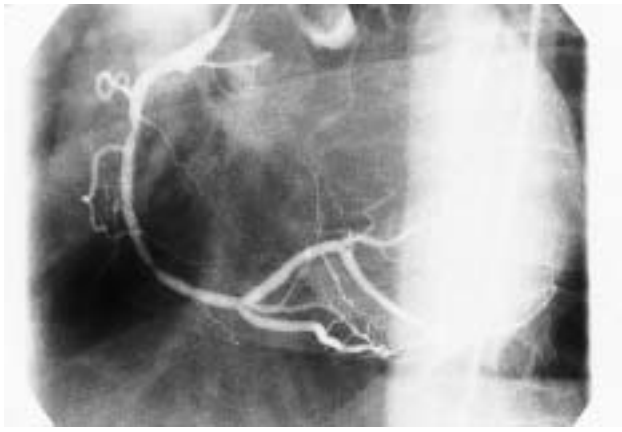

Figure 64.4 Restenosis at the juncture of the distal and middle stents 2 months after angioplasty

Question

Is there evidence to support these therapeutic steps?

Comment

There were three decision points where the patient was presented with options for therapeutic interventions.

1 Evidence to recommend initial PTCA

The patient presented with postmyocardial infarction angina due to single vessel RCA stenosis. To date, randomized controlled trials (RCT) comparing CABG to medical treatment have shown no survival benefit from surgery because of the low prognostic risk associated with single vessel right coronary disease.[1,2] There have been no direct comparisons of PTCA with CABG in this subset of single vessel disease, but the BARI study of multivessel disease showed no survival benefit for either treatment over a 5 year follow up period.[3] Thus, in making the therapeutic recommendation at this stage, prognosis was not the main issue. Symptom relief was.

The ACME trial compared medical treatment to PTCA for single vessel left anterior descending disease with the end point being anginal frequency and treadmill time at 6 months of follow up.[4] In this trial of 107 patients, 46% of medically treated patients were free of angina compared to 64% of PTCA patients ($P \leq 0{\cdot}01$) and there was an increase in treadmill time, 2·1 minutes over baseline in the PTCA group compared to 0·5 minutes in the medically treated group ($P = 0{\cdot}0001$). However, because of restenosis, those patients assigned to PTCA had a more frequent requirement for further procedures (16 patients required PTCA; 2 required CABG). In another trial comparing medical treatment to PTCA to left internal mammary artery (LIMA) grafting for proximal single vessel left anterior descending artery stenosis $\geq$80% there were no differences among the groups in mortality or infarction rates, but no patient needed further revascularization in the surgical group compared to 8/72 (11%) of those undergoing PTCA and 7/72 (10%) on medical treatment ($P = 0{\cdot}019$).[5]

Acknowledging that clinical trials that specifically apply to our patient are lacking, these studies nevertheless allow us to conclude that surgery would be an acceptable choice for achieving symptomatic relief, and that PTCA is intermediate between medical treatment and surgery in achieving symptomatic relief but at a cost of a higher likelihood of further revascularization in the future. The other considerations in comparing surgery to PTCA are higher initial mortality and morbidity with surgery, as well as the fact that the patency of a saphenous vein graft in the circulation is less than that of a mammary artery. The angiographic characteristics of the stenosis were consistent with a high likelihood of primary success with PTCA, and if restenosis did not occur then the time when CABG might have to be done could be delayed.

2 Evidence for the decision to employ a "bail-out" stent

Acute closure due to spiral dissection is a recognized complication, occurring in 1–2% of patients undergoing PTCA. The risk of surgical mortality in the setting of an emergency operation is approximately twice that of an elective procedure. Current stent design almost always allows prompt deployment of a stent which quickly tacks up the dissection and relieves the ischemia.[6] Thus, the need for immediate surgery is rare.

3 Evidence for the decision for coronary bypass surgery

Unfortunately, the patient developed restenosis within the stented segment of the RCA. This was discrete, distal to the

site of the original plaque, and very unlikely to dissect with repeat dilation because of the stent buttressing the vessel wall. Thus, this stenosis would have been amenable to either repeat PTCA or coronary bypass surgery (CABG). The clinical advice was to offer repeat PTCA. However, when the substance of the earlier discussion of PTCA versus medical therapy versus CABG was again reviewed, the patient and her husband opted for surgery as a more "definitive" method of dealing with her problem. She subsequently underwent single vessel bypass without incident and continues with secondary prevention therapy.

References

1. Alderman EL, Bourassa M, Cohen LSE. Ten year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation* 1990;**82**:1629.
2. European Coronary Surgery Study Group. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;**ii**:1173.
3. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;**335**:217–25.
4. Parisi AF, Folland ED, Hartigan P, for the Veterans Affairs ACME Investigators. A comparison of angioplasty with medical therapy in the treatment of single vessel coronary artery disease. *N Engl J Med* 1992;**326**:10.
5. Hueb WA, Bellotti G, deOliveira SA *et al.* A prospective randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending coronary stenosis. *J Am Coll Cardiol* 1995;**26**:1600.
6. Lincoff AM, Topol EJ, Chapekis AT *et al.* Intracoronary stenting compared with conventional therapy for abrupt closure complicating coronary angioplasty: a matched case control study. *J Am Coll Cardiol* 1993;**21**:866–75.

Case scenario 2

A 63 year old man tells the following story. Approximately $1\frac{1}{2}$ years previously he experienced a feeling of "indigestion" while walking. This led to a symptom limited exercise test that was considered positive by ECG criteria but was not accompanied by any symptoms. His symptom of "indigestion" did not recur and he continued to pursue outdoor activities such as canoe tripping, camping, and walking without limitation. Risk factors include type II diabetes mellitus and hypercholesterolemia. He is a non-smoker.

His current medications are humulin insulin 70/30; 20 units ac breakfast and 18 units ac supper, pravastatin 40 mg qhs (total cholesterol now is 4·47 mmol/l; LDL 2·87; HDL 1·12; TG 1·05), acebutolol 100 mg po bid, and enteric coated aspirin 325 mg po daily.

A stress MUGA scan reveals the following. Exercise duration 11 minutes and 31 seconds; maximum heart rate 144 per minute; maximum blood pressure 170/84 and no angina. The ECG shows 4·5 mm downsloping ST-segment at maximum stress. Ejection fraction: baseline 69%; 200 kpm 73%; 400 kpm 66%; 600 kpm 61%; 800 kpm 58%; post-exercise recovery 67% indicating a fall in EF at higher workloads. Left ventricular wall motion analysis demonstrated hypokinesis of the septum, posterolateral, and inferior walls.

Conclusion

Silent ischemia. Suggest referral for coronary angiography. Coronary angiography reveals a normal left main coronary artery trifurcating into left anterior descending, intermediate, and circumflex branches (Figure 64.5). There is a "left main equivalent" distribution of disease with stenoses involving the LAD 75%, intermediate 90%, and circumflex 90%. The RCA is diffusely diseased with a maximal narrowing of 60% in the midthird segment. LV systolic function is normal at rest.

Question

Is conservative medical management optimal at this point?

Comment

Here, the decision rests, in part, on whether clear evidence is available to offer sound advice to an asymptomatic patient with objective evidence of three vessel disease and exercise induced silent ischemia. If this patient had symptoms of classic angina pectoris the therapeutic decision for recommending coronary bypass surgery (CABG) with the expectation of symptom relief and improved prognosis could be substantiated. If the patient had a definite left main stenosis, or depressed LV function, the argument for CABG is strongly made because in this setting CABG improves prognosis even in the absence of symptoms.[1,2] This patient is somewhat unusual in that not only is he asymptomatic but he is capable of a good workload (800 kpm of supine bicycle exercise). However, there is convincing evidence of significant ischemia at this level of work with ST depression

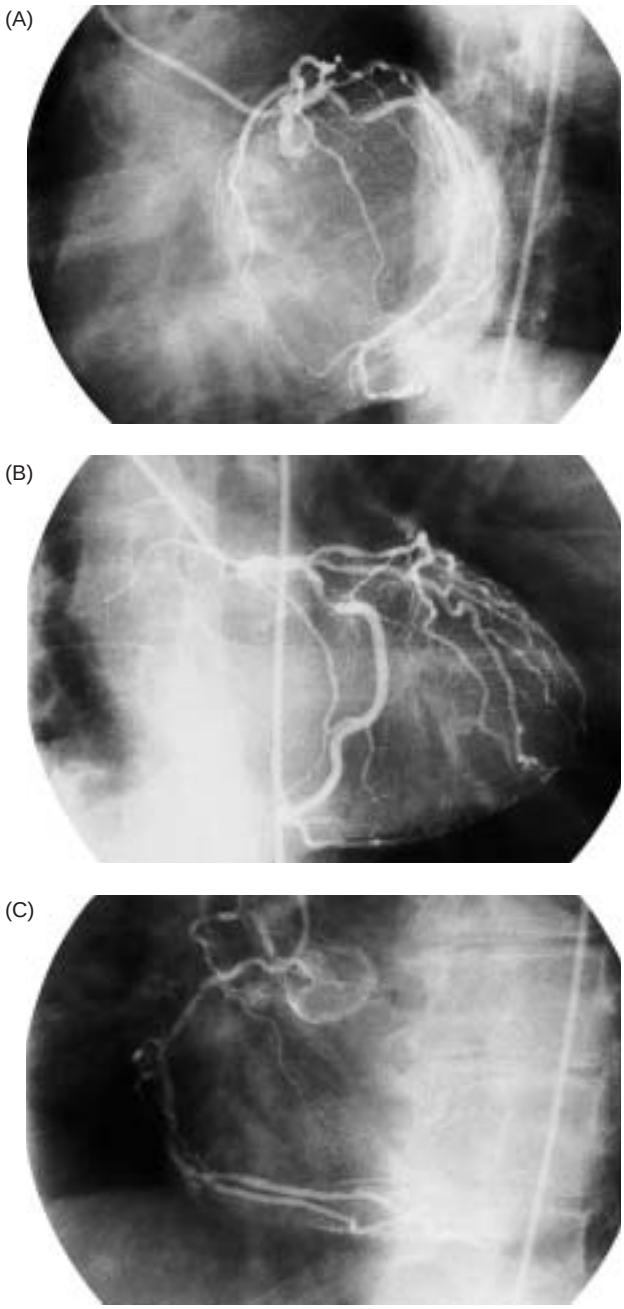

Figure 64.5 Multivessel coronary artery stenoses suggesting a "left main equivalent" with (A) LAD 75%, (B) intermediate 90%, and (C) circumflex 90%. The RCA is diffusely diseased

of 4.5 mm and a reduction in ejection fraction from 69% at rest to 58% with maximal effort. There is also evidence of LV wall motion abnormality in multiple sites consistent with the extent of coronary artery disease noted on the angiogram.

The question therefore is one of prognosis rather than symptom relief. Common sense alone argues that his myocardium would benefit from revascularization. There is evidence to suggest that the long-term prognosis of patients with documented silent ischemia is similar to those with symptomatic angina pectoris,[3,4] and thus our treatment should be aimed at the coronary disease substrate, rather than the clinical chest pain syndrome. Given the left main equivalent distribution as well as the diseased RCA, this patient was referred for consideration of coronary bypass surgery. The nature of the left coronary disease is also amenable to PCI although the procedure is somewhat riskier because of the proximal nature of the plaque in the LAD vessel. In addition, the likelihood of restenosis is significant because of the need for multivessel stenting in this diabetic patient. If the initial enthusiasm for coated stents is borne out with further observation then a PCI approach might well be a reasonable alternative in the future. Currently, the decision to undergo CABG is supported by evidence gleaned from a careful review of all major trials on bypass surgery for different severities of coronary artery disease.[5]

References

1. Alderman EL, Bourassa M, Cohen LSE. Ten year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study (CASS). *Circulation* 1990; **82**:1629.
2. European Coronary Surgery Study Group. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;**ii**:1173.
3. Lotan C, Lokovitsky L, Gilon D *et al.* Silent myocardial ischemia during exercise testing. Does it indicate a different angiographic and prognostic syndrome? *Cardiology* 1994;**85**:407.
4. Marwick TH. Is silent ischemia painless because it is mild? *J Am Coll Cardiol* 1995;**25**:1513–15.
5. Yusuf S, Zucker D, Peduzzi P *et al.* Effect of coronary artery bypass surgery on survival. *Lancet* 1994;**344**:563–70.

65 Acute coronary syndromes

George J Philippides

Case scenario 1

A 64 year old diabetic woman presents to the emergency ward with left arm discomfort, diaphoresis, nausea, and shortness of breath lasting 10 minutes. She has had similar episodes intermittently for the past 6 months, lasting up to 2 minutes. However, these episodes were usually brought on by heavy exertion and relieved by resting. The episodes have become more frequent over the past month and have been occurring with minimal exertion during the past 48 hours.

Physical examination is within normal limits except for a blood pressure of 150/90 mmHg and a heart rate of 110. The initial ECG and the one taken an hour later after resolution of symptoms show no ischemic ST or T wave changes. Serum troponin and creatine kinase-MB isoenzyme (CK-MB) levels are not elevated.

Question

What initial and further measures should be taken in this patient?

Comment

This case represents a good example of unstable angina without "classic" chest pain. The initial evaluation should aim to answer two important questions: First, do the presenting symptoms and signs represent ischemic heart disease? Second, is this patient at significant risk for an adverse clinical outcome?

While myocardial ischemia usually causes deep, poorly localized chest or arm discomfort, some patients may have no chest discomfort but present with epigastric, jaw, arm, or neck discomfort. Other "atypical" symptoms that may suggest angina even in the absence of chest pain include dyspnea, nausea, vomiting, and diaphoresis. If these symptoms are brought on by emotional stress or physical exertion and are relieved by rest or nitroglycerin, they should be considered equivalent to angina. Atypical angina is more common in women than men, and more prevalent in elderly people and in patients with diabetes. It is important to remember that new-onset or worsening dyspnea on exertion is the most common "anginal equivalent", especially in elderly patients. Although this patient does not complain of classic exertional chest pain, the diagnosis of an unstable coronary syndrome is likely given her history of diabetes and exertional dyspnea (Table 65.1).

The recent change in pattern culminating in ischemic symptoms with minimal exertion is of concern. However the patient's presentation lacks other "high risk" characteristics that are associated with an increased short-term risk of death or non-fatal myocardial infarction (MI) (Table 65.2). These include: rest pain for greater than 20 minutes, transient ST segment changes of greater than 0·5 mV, and elevated serum cardiac enzymes. Current published guidelines suggest that she should be admitted to the hospital in a unit that offers continuous rhythm monitoring and careful observation for recurrent ischemia.

Initial medical management should include an aspirin, nitrates, a β blocker, and antithrombotic therapy in the form of full dose, IV unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH).[1]

Aspirin remains the gold standard for antiplatelet therapy. In unstable angina trials, aspirin therapy significantly reduced the relative risk of fatal or non-fatal MI by 60%.[2] An oral loading dose of 160–325 mg/day non-enteric

Table 65.1 Likelihood that signs and symptoms represent an ACS secondary to CAD

Feature	High likelihood Any of the following:	Intermediate likelihood Absence of high-likelihood features and presence of any of the following:	Low likelihood Absence of high- or intermediate-likelihood features but may have:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age >70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥0·05 mV) or T wave inversion (≥0·2 mV) with symptoms	Fixed Q waves Abnormal ST segments or T-waves not documented to be new	T-wave flattening or inversion in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

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Abbreviations: CAD, coronary artery disease; CK-MB, creatine kinase-MB isoenzyme; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; TnI, troponin I; TnT, troponin T

formulation should be given initially followed by 75–160 mg/day maintenance therapy. In patients who are aspirin intolerant, the adenosine diphosphate receptor antagonist clopidogrel can be substituted. This oral antiplatelet agent was shown in the Clopidogrel versus Aspirin in Patient at Risk of Ischemic Events (CAPRIE) trial to reduce the risk of cardiovascular events in patients with established vascular disease by 8·7% compared with patients treated with aspirin.[3] Recently, the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial showed that treatment with clopidogrel in addition to aspirin reduced the risk of future ischemic events compared to aspirin therapy alone.[4] A loading dose of 300 mg clopidogrel should be given followed by 75 mg/day orally.

The widespread use of oral, topical, and IV nitrate preparations in unstable angina is based on their well-established physiologic and clinical effects, rather than on data from large-scale randomized trials. Nitroglycerin (NTG) reduces myocardial oxygen demand and improves regional myocardial blood flow by dilating epicardial coronary vessels. Patients with unstable symptoms can be given three 0·4 mg NTG tablets sublingually. Intravenous NTG should be initiated and titrated as needed in patients with refractory symptoms.[5]

β Receptor antagonists should be started early in all patients who do not have contraindications. Intravenous boluses of metoprolol 5 mg or propranolol 1 mg can be given slowly over 1 to 2 minutes and repeated every 5 minutes until the target heart rate of 50–60 is reached. Oral therapy can be initiated 30–60 minutes later. An overview of several small studies of β blocker therapy in unstable angina suggests a small, but significant, reduction in the risk of progression to myocardial infarction.[6]

Rate controlling, non-dihydropyridine calcium-channel blockers (verapamil or cardizem) can be used as initial therapy for patients with contraindications to β blockers, for patients who continue to have ischemic symptoms despite treatment with nitrates and β blockers, and for patients with variant angina.[7] In general short-acting dihydropyridine calcium-channel blockers such as nifedipine should be avoided, and special care must be taken when using any calcium-channel blocker in patients with depressed left ventricular function.

Antithrombotic therapy with unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) should be started immediately to reduce the risk of myocardial infarction, death, or recurrent ischemia. The most recent guidelines from the American College of Cardiology recommend

Table 65.2 Short-term risk of death or non-fatal MI in patients with unstable angina[a]

Feature	High risk At least one of the following must be present:	Intermediate risk No high-risk feature but must have one of the following:	Low risk No high- or intermediate-risk feature but may have any of the following features:
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 minutes) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min) relieved with rest or or sublingual NTG	New-onset or progressive CCS Class III or IV angina the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD (see Table 65.1)
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 years	Age >70 years	
ECG	Angina at rest with transient ST-segment changes >0·05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0·2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (e.g. TnT or TnI >0·1 ng/ml)	Slightly elevated (e.g. TnT >0·01 but <0·1 ng/ml)	Normal

[a] Estimation of the short-term risks of death and non-fatal cardiac ischemic events in unstable angina is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms.

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Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerine; TnI, troponin I; TnT, troponin T.

60 units of UFH followed by 12 units/kg/hour infusion. Alternatively, the low molecular weight heparin enoxaparin 1 mg/kg SQ ×2/day can be used. Two trials that studied over 7000 patients showed a roughly 20% reduction in the rate of death, MI, and need for urgent revascularization in those treated with enoxaparin rather than UFH.[8] The biggest advantage of LMWH over UFH is ease of administration as monitoring of activated partial thromboplastin time (APTT) is not required.

Subsequent management depends on the patient's clinical course. Repeat ECG and cardiac marker measurements should be performed 6–12 hours after the onset of symptoms. Elevated serum cardiac enzymes[9] or recurrent ischemic symptoms,[10] despite treatment with aggressive pharmacotherapy as described above, would necessitate early coronary angiography with an eye toward percutaneous or surgical revascularization. In the absence of these "high-risk features", the patient can safely undergo non-invasive testing after the doses of nitrates and β blocker agents have been titrated and the heparin has been stopped. Patients with inducible ischemia or severely depressed left ventricular function (LVEF < 35%) should also be considered for coronary angiography (Figure 65.1).

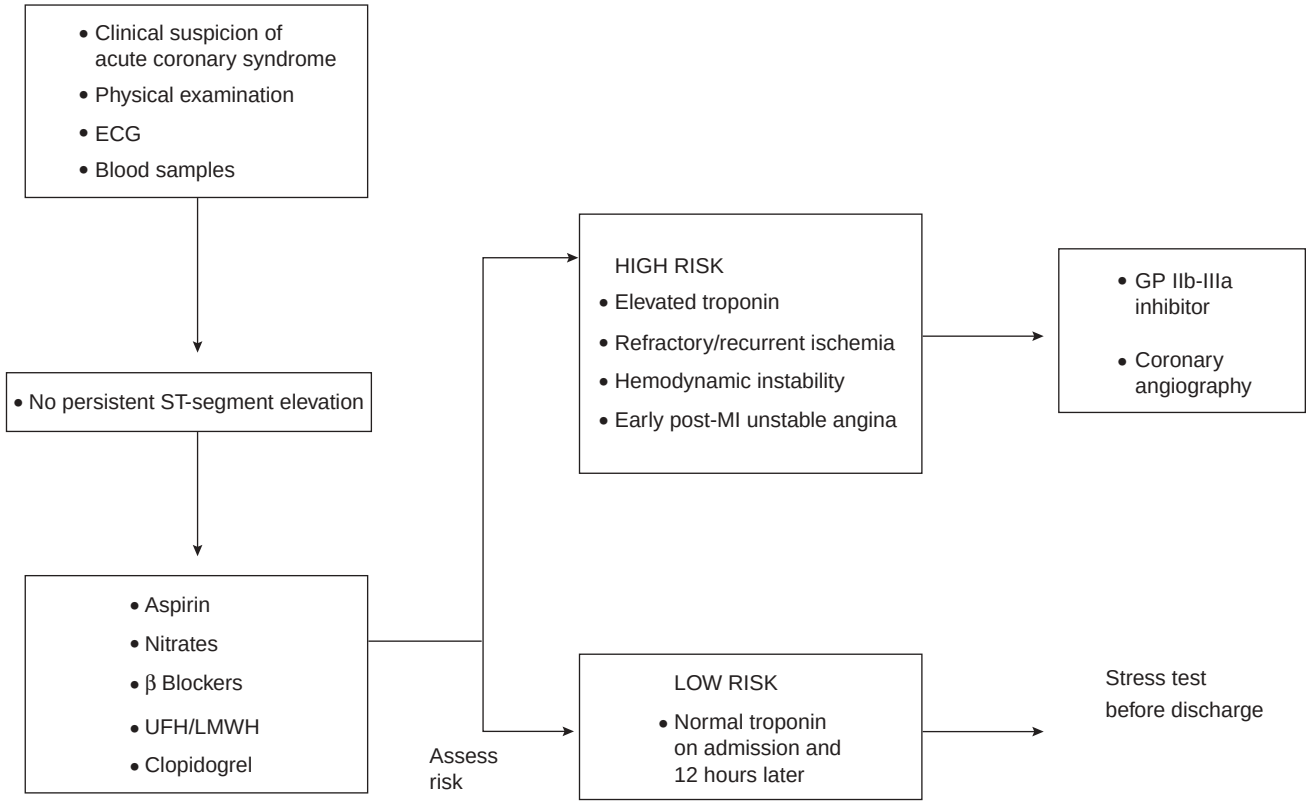

Figure 65.1 Recommended strategy in unstable angina/non-ST elevation MI
Abbreviations: UFH, unfractionated heparin; LMWH, low molecular weight heparin
Adapted with permission from Bertrand ME *et al.* Management of acute coronary syndromes without persistent ST segment elevations: Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;**21**:1424

References

1. Braunwald E, Antman EM, Beasly JW *et al.* ACC/AHA Guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2000;**36**:970–1062.
2. Theroux P, Ouimet H, McCans J *et al.* Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;**319**: 1105–11.
3. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events. *Lancet* 1996;**348**:1329–39.
4. The Clopidogrel in Unstable Angina to Prevent, Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation *N Engl J Med* 2001;**345**:494–502.
5. Conti CR. Use of nitrates in unstable angina pectoris. *Am J Cardiol* 1987;**60**:31H–34H.
6. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease, II: unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;**260**:2259–63.
7. Held PH, Yusuf S, Furberg CD. Calcium-channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;**299**:1187–92.
8. Antman EM, Cohen M, Radley D *et al.* Assessment of the treatment of effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;**100**:1602–8.
9. Cannon CP, Weintraub WS, Demopoulos LA *et al.* for the TACTICS-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–87.
10. Boden WE, O'Rourke RA, Crawford MH *et al.* Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH). Outcomes in patients with acute non-Q wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;**338**:1785–92.
11. Bertrand ME, Simoons ML, Fox KAA *et al.* Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation: Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;**21**:1406–32.

Case scenario 2 *A 77 year old male with a longstanding history of stable, class I angina is seen in the emergency ward with non-exertional precordial chest pain radiating to the left shoulder and dyspnea for 30 minutes. He has had similar episodes over the last year lasting up to 5 minutes but these were brought on by exertion and relieved with rest or sublingual nitroglycerin. On examination the blood pressure is 100/50, the heart rate is 120 bpm. The physical examination reveals rales to the mid lung fields bilaterally. The initial ECG is shown in Figure 65.2. The serum troponin level is 6·8.*

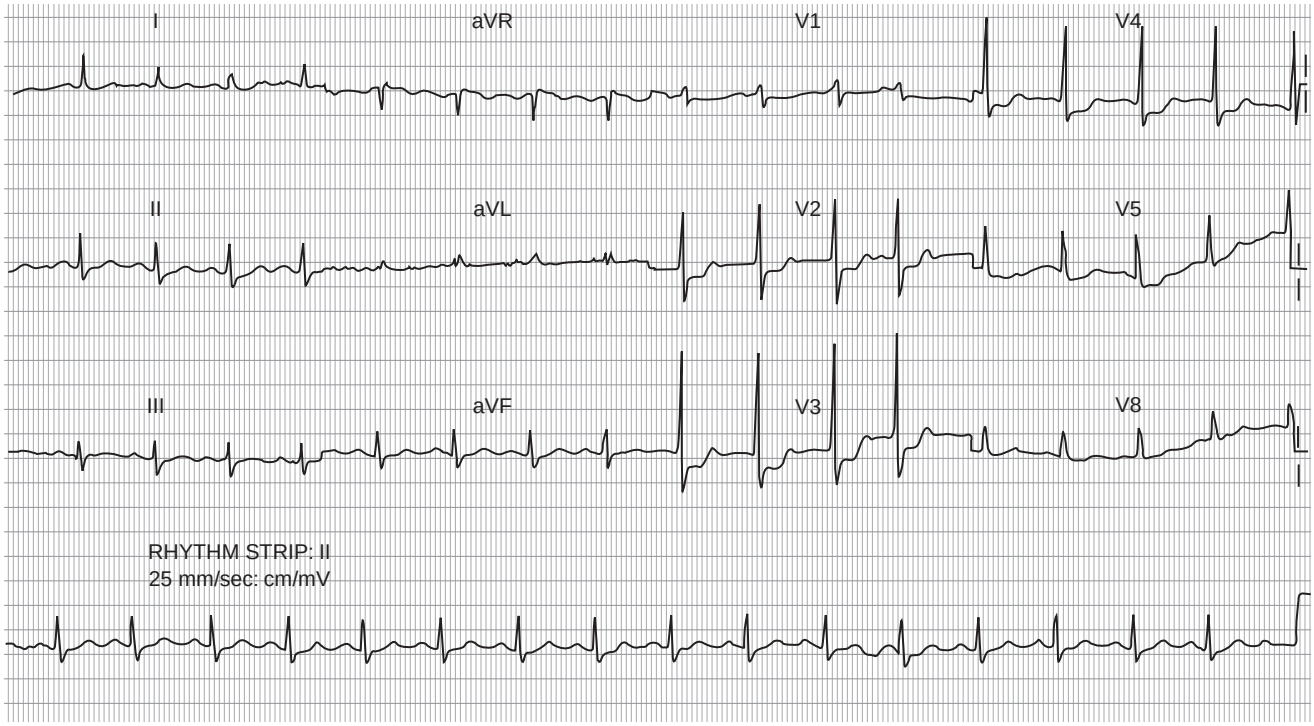

Figure 65.2 ECG of Case 2

Comment

This patient presents with a classic acute coronary syndrome, and a diagnosis of non-ST-elevation MI (NSTEMI) is confirmed by an elevated serum troponin level.

As usual, prompt treatment with a regimen of aspirin, heparin, nitrates, and β blockers is mandated in order to decrease the risk for recurrent ischemic events. However several aspects of this patient's clinical presentation suggest that he remains at high risk for death or myocardial infarction despite appropriate medical therapy. These "high-risk features" include advanced age, an accelerating tempo of ischemic symptoms over the preceding 48 hours, rest pain for greater than 20 minutes, evidence of pulmonary edema or hypoperfusion, new or worsening mitral regurgitation, dynamic ST changes >1 mm, and elevated serum cardiac markers.[1–3]

A review of the randomized clinical trials of GP IIb-IIIa receptor antagonists suggests that these agents should be administered, in addition to aspirin and heparin, in patients with many of these high-risk clinical features, in patients with continuing ischemia, and in patients who are scheduled for percutaneous coronary intervention (PCI).[4,5] Patients with elevated serum troponin levels appear to derive the greatest benefit from GP IIb-IIIa inhibitor therapy. While the benefits of GP IIb-IIIa inhibition appear to be greatest in patients undergoing PCI, several trials have shown that GP IIb-IIIa inhibitors are also effective in reducing the rate of ischemic events in the acute, "pre-cath" phase of medical management, and this benefit is maintained and heightened if a PCI is subsequently performed.[6] Furthermore, similar to data from clinical trials of thrombolytic therapy in acute ST elevation MI, patients with unstable angina and NSTEMI who are treated the earliest after symptom onset with a GP IIb-IIIa inhibitor appear to derive the most benefit.[7]

Early coronary angiography should also be strongly considered. The Thrombolysis in Myocardial Infarction (TACTICS-TIMI-18) Trial randomized 2220 patients with

unstable angina or NSTEMI to an early invasive strategy, which included cardiac catheterization within 48 hours, and revascularization if appropriate versus a conservative strategy, in which catheterization was performed only if spontaneous or inducible ischemia was observed. All patients were treated with aspirin, heparin, and the glycoprotein IIb-IIIa inhibitor tirofiban. Early invasive therapy was associated with a significantly reduced rate of death or MI at 6 months (7·3% *v* 9·5%; OR, 0·74; $P > 0·05$).[8]

Early coronary angiography in patients with acute coronary syndromes yielded similar reductions in ischemic events in the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II trial.[9] Both trials found that the benefit of an early invasive strategy was greatest in intermediate- and high-risk patients with elevated troponin levels and/or ischemic ST changes on the admission electrocardiogram.

Based on these recently published clinical trials and practice guidelines, this "high-risk" patient should be treated with an aggressive antithrombotic and antiplatelet regimen that includes an intravenous glycoprotein IIb-IIIa inhibitor in addition to aspirin and heparin. An early invasive strategy consisting of coronary angiography with an eye toward revascularization if necessary should also be pursued (Figure 65.1).

Competing interest: the author has received educational grants for Aventis, and has spoken on unstable angina at events sponsored by Aventis.

References

1. Braunwald E, Antman EM, Beasly JW *et al.* ACC/AHA guidelines for the management of patients with unstable angina and non ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2000;**36**:970–1062.
2. Antman EM, Corbalan R, Huber K, Jaffe AS. Issues in early risk stratification for UA/NSTEMI. *Eur Heart J Supplements* 2001;**3**(Suppl. J):J6–J14.
3. Antman EM, Cohen M, Bernick P *et al.* The TIMI risk score for unstable Angina/non-ST-elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000; **284**:835–42.
4. The PRISM-PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338**:1488–97.
5. The PURSUIT Trial Investigators. Inhibiton of platelet glycoprotein Ilb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;**339**:436–43.
6. Boersma E, Akkerhuis KM, Theroux P *et al.* Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;**100**:2045–8.
7. Bhatt DL, Marso SP, Houghtaling P *et al.* Does earlier administration of eptifbatide reduce death and MI in patients with acute coronary syndromes? *Circulation* 1998;**98**:1560–1.
8. Cannon CP, Weintraub WS, Demopoulos LA *et al.* for the TACTICS-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–87.
9. Fragmin and Fast Revascularization during Instability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;**354**:708–15.

66 Acute myocardial infarction

Bryan F Dias, Ernest L Fallen

Case 1

A 68 year old woman with an 18 month history of chronic stable effort angina presents to the emergency room of a community hospital with a 2 hour history of increasing retrosternal chest pain associated with weakness, diaphoresis and nausea. Three applications of nitroglycerin spray 5 minutes apart fail to offer relief. She is a well controlled type 2 diabetic on glyburide 5 mg od. She also has esophageal acid reflux disease but clearly distinguishes her reflux symptoms from angina. There is no history of gastrointestinal bleeding.

On examination she is pale, anxious and diaphoretic. Her blood pressure is 110/80 in both arms and her pulse is 70 and regular. Her neck veins are elevated 3 cm at 45 degrees, with a sustained hepatojugular reflux. She has a soft late crescendo apical systolic murmur. Her lungs are clear. An ECG is immediately ordered and reveals the following (Figure 66.1).

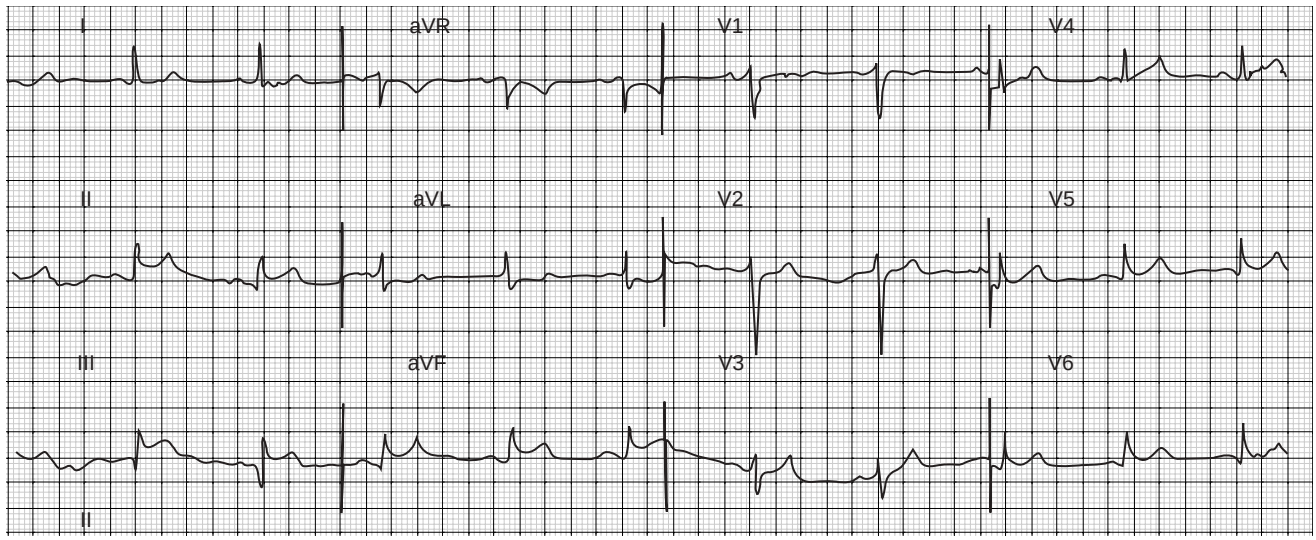

Figure 66.1 Twelve-lead ECG showing hyperacute ST segment elevation in leads II, III and AVF, signifying acute inferior wall ischemic injury/infarction

Question

What is the proper course of action at this juncture?

Comment

There is overwhelming evidence from major clinical trials that early intervention with thrombolytic therapy, combined with aspirin for acute myocardial infarction, substantially reduces mortality and the risk of recurrent ischemic events.[1–4] Does this case fit the entrance criteria? The symptoms of prolonged chest pain unresponsive to nitroglycerin, together with accompanying symptoms of nausea, weakness and diaphoresis, raise a strong suspicion of acute myocardial infarction. This is substantiated by the ECG findings of hyperacute ST segment elevation in leads II, III and AVF, signifying an acute inferior wall myocardial infarction.

With an evolving infarction less than 3 hours from pain onset there is Grade A evidence that the treatment of choice is prompt coronary thrombolysis plus aspirin.[1–4] The patient is therefore given aspirin 160 mg to chew while an intravenous line is inserted. After confirmation that the patient has no contraindication (recent bleed, stroke, trauma, surgery etc.) she is given streptokinase 1·5 million units intravenously over 1 hour. There is no evidence that rtPA (recombinant tissue plasminogen activator) alteplase or reteplase is superior to the less expensive streptokinase in patients with first-onset acute inferior myocardial infarction.[5,6]

The patient is monitored in the coronary care unit, where relief of anxiety and pain is achieved by administering oxygen, intravenous nitroglycerin and morphine as needed. She is prescribed an oral β blocker (metoprolol 50 mg bid), which will be continued indefinitely.[7–9] Because there is no major complication, such as congestive heart failure or intermittent chest pain, the patient will continue on aspirin and the β blocker without the need for full-dose or low molecular weight heparin.[5,6] There is also no echocardiographic evidence of significant left ventricular dysfunction (her estimated ejection fraction is >40%) to warrant an ACE inhibitor during the acute phase of the infarction.[10]

The community hospital where she is admitted does not have coronary angiographic facilities; the nearest hospital with such facilities is several hours away. If such facilities were immediately available this patient would be a candidate for primary coronary intervention (PCI), that is angioplasty with stent.[11]

References

1. GISSI trial. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**1**:397–401.
2. ISIS II trial. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988;**ii**:349–60.
3. FTT Collaborative group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
4. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infaction. *N Engl J Med* 1993;**329**:673–82.
5. Cairns J, Armstrong P, Belenkie I *et al.* Canadian Cardiovascular Society Consensus Conference on coronary thrombolytics – 1994 update. *Can J Cardiol* 1994;**10**:517–29.
6. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;**336**:847–60.
7. BHAT Study Group. A randomized trial of propanolol in patients with acute myocardial infarction. *JAMA* 1982;**247**:1707–14.
8. The Norwegian Multicenter Study Group. Six year follow up on Timolol after acute myocardial infarction. *N Engl J Med* 1985;**313**:1055–8.
9. Yusuf S, Peto R, Lewis JA *et al.* Beta blockade during and after myocardial infarction: a review of randomized trials. *Prog Cardiovasc Dis* 1985;**27**:335–71.
10. Syed M, Borzak S, Jafri SM *et al.* ACE Inhibition after myocardial infarction with special reference to the ISIS-4 Trial. *Prog Cardiovasc Dis* 1996;**39**:201–6.
11. Ryan TJ *et al.* ACC/AHA guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1999;**34**:890–909.

Case 2

A 66 year old man presents to the emergency room with severe chest pain. He has had two previous coronary artery bypass operations (2 and 12 years ago) and a history of two previous myocardial infarctions prior to his last bypass. For the past year his functional status has been stable, with Canadian Cardiovascular Society class I angina.

He is now 3 hours following the onset of retrosternal chest pain unrelieved by sublingual nitroglycerin (0·6 mg × 3). The pain is characterized as 10/10 severity, crushing in nature, with radiation to the jaw. Associated symptoms include dyspnea, diaphoresis and weakness. These symptoms are similar to those he had with the onset of his previous infarctions.

Physical examination reveals an acutely ill-looking man. He is in painful distress, pale and clammy. His blood pressure is 100/80, equal in both arms. His pulse is 90 bpm and regular. Lung fields are clear. His neck veins are not abnormally elevated. There are no murmurs or extra heart sounds. His ECG is shown in Figure 66.2.

Question

What action would you now take?

Comment

Here is an example where strict adherence to clinical pathway algorithms based on the results of clinical trials can be

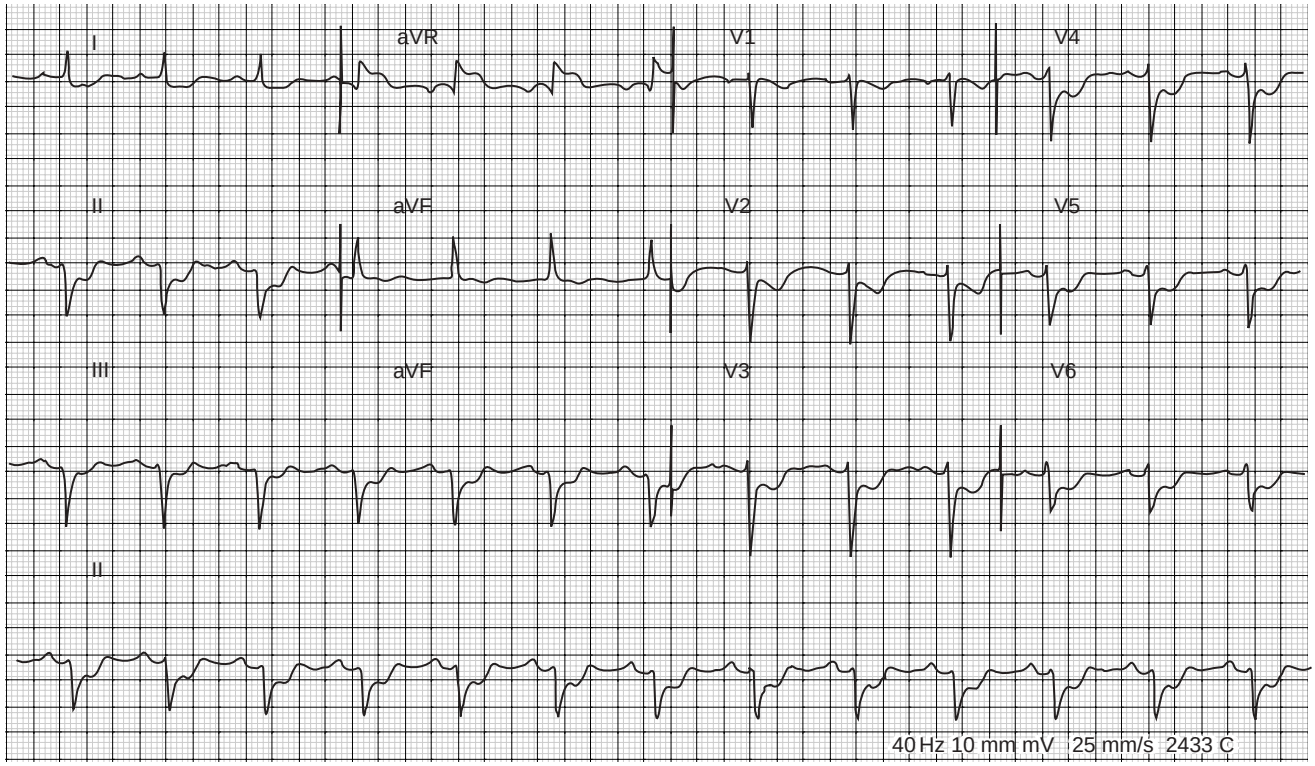

Figure 66.2 Twelve-lead ECG showing widespread ST segment depression with left axis deviation. There are no Q waves nor ST segment elevation, except in lead AVR.

misleading. In this case the widespread ST segment depression led to the initial diagnosis of subendocardial ischemia, manifested as either unstable angina or non-ST segment elevation (NSTEMI) infarction (so-called acute coronary syndrome, or ACS). The use of thrombolysis for unstable angina or NSTEMI infarction has been studied but results show a trend towards no benefit or possible harm.[1,2] The patient was therefore given aspirin 325 mg and full-dose intravenous heparin, starting with a 7 units/kg bolus followed by 1200 units/h IV. Within the next hour neither sublingual nor intravenous nitroglycerin had any effect on the pain, which persisted at 10/10 severity. Similarly, an intravenous β blocker (propanolol 5 mg IV × 3 every 10 min) and morphine (10 mg IV over 30 min) had little effect. The pain persisted unabated, and serial ECGs showed ongoing ischemic changes but no evidence of injury (ST elevation).

This patient initially received the standard treatment for the diagnosis of acute coronary syndrome (ACS), namely aspirin and an antithrombotic (unfractionated heparin in this case[3–5]), and yet these measures, plus intensification of the antianginal therapy, failed to relieve his symptoms. One could make a case for a different antithrombotic/antiplatelet approach. Studies examining low molecular weight heparin (LMWH) versus unfractionated heparin (UHF) in patients presenting with ACS have shown equivalency.[6,7] As for an additional antiplatelet agent, clopidogrel, an adenosine diphosphate receptor antagonist, when combined with aspirin in patients with ACS, showed a relative risk reduction of death, myocardial infarction or stroke by 18% compared to aspirin alone in the CURE Study.[8] The use of glycoprotein IIb/IIIa receptor antagonists (eptifibatide or tirofiban) has been shown to be effective in acute ischemic situations when added to aspirin and heparin.[9,10]

However, there is a strong suspicion that this patient is actually suffering an acute myocardial infarction with total coronary artery occlusion. He had experienced identical symptoms with his previous infarctions; he is acutely ill with diaphoresis, weakness and restlessness – symptoms that are characteristic of myocardial necrosis, as opposed to reduced perfusion. On reflection the ECG changes may be construed as misleading in view of his chronic history of multiple ischemic insults. A decision was therefore made to proceed immediately with thrombolytic therapy. Within 45 minutes following IV infusion of rtPA the patient's pain had completely abated and his ECG normalized, with only persistent T wave negativity in the anterior leads. Subsequent investigations revealed a peak creatinine kinase of 2969 with a strongly positive CKMB fraction. The patient went on to an uneventful recovery and was discharged from hospital on day 7.

Although the evidence from clinical trials would not necessarily support the routine use of thrombolytic agents based on the ECG changes seen in this case, here is an example

where exclusive reliance on a test (ECG) without appreciating clear clinical signs of myocardial necrosis, due probably to an occlusive thrombus, can result in misdirected therapy. A case could be made for primary angioplasty should facilities be available. However, in view of the probability of extensive three-vessel coronary disease and multiple blocked bypass grafts it would be more prudent to consider invasive investigation and intervention on an elective basis.

References

1. Freeman MR, Langer A, Wilson RF, Morgan CD, Armstrong PW. Thrombolysis in unstable angina: A randomized double blind trial of tPA and placebo. *Circulation* 1992;**85**:150–7.
2. The TIMI-IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q infarction. Results of the TIMI-IIIB Trial. *Circulation* 1994;**89**:1545–56.
3. Theroux P, Ouimet H, McCans *et al*. Aspirin, heparin or both to treat unstable angina. *N Engl J Med* 1988;**319**:1105–11.
4. Cairns JA, Gent M, Singer J *et al*. Aspirin, sulfinpyrozone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985;**313**:1369–75.
5. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA guidelines for the management of patients with unstable angina and non-ST elevation myocardial infarction. *J Am Coll Cardiol* 2000;**36**:970–1062.
6. Eikelboom JW, Anand SS, Malmberg K *et al*. Unfractionated heparin and low molecular weight heparin in acute coronary syndrome without ST elevation: a metaanalysis. *Lancet* 2000; **355**:1936–42.
7. Antman EM, McCabe CH, Gurfunkel EP *et al*. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q wave infarction. Results of the thrombolysis in myocardial infarction (TIMI IIB trial). *Circulation* 1999; **100**:1593–601.
8. The CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST elevation. *N Engl J Med* 2001;**345**:494–502.
9. The Pursuit trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;**339**:436–43.
10. PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**339**:1498–505.

67 Postmyocardial infarction: preventive measures

Ernest L Fallen

Case 1

A 53 year old sedentary, overweight male chartered accountant, previously symptom free, was admitted to hospital 6 days ago with an acute anteroseptal infarction. He received thrombolysis with rtPA (total dose 100 mg). The acute phase of his illness was complicated by frequent isolated ventricular ectopic beats (>10/h) and mild cardiac decompensation (Killip class IIa). His risk factors include a positive family history, a 30 pack year smoking history, mild hypertension and obesity (body mass index BMI = 29). His lipid status is unknown, except for a single LDL-C = 3·0 mmol/l at the time of hospital admission.

He is now ready for discharge and is free of heart failure and chest pain. His ECG shows a sinus rhythm at 65 bpm with qS waves and T inversion in leads V1–V3 without ST elevation. His echocardiogram reveals severe hypokinesis of the septum and apex, but no other regional wall abnormalities. There is no left ventricular dilatation and his estimated ejection fraction is 45%. There is no valvular abnormality and no endocardial thrombus.

On physical examination he is in sinus rhythm with a blood pressure of 122/80 and a supine respiratory rate of 16 breaths per minute. His lungs are clear. There is a soft S4 but no murmurs. He has good peripheral pulses, no neck vein distension and no arterial bruits.

Question

What advice would you now give him?

Comment

Here is a case where a physician's advice to an otherwise recalcitrant patient is strongly fortified by clear evidence that preventive strategies post acute myocardial infarction yield favorable outcomes. The patient is now chest pain and failure free. He has one non-modifiable risk factor (family history) and several modifiable ones (smoking, sedentary lifestyle, obesity, and a propensity for hypertension). His lipid status is unknown, although the LDL-C of 3·0 on the first day of his infarct raise suspicion of a hyperlipidemic state. Evidence from clinical trials ought to persuade the patient that a preventive strategy of pharmacologic prophylaxis, combined with risk factor modification and lifestyle changes, can reduce his likelihood of suffering a major event in the foreseeable future.

Secondary prophylaxis

To reduce his risk of recurrent ischemic events and death he should continue indefinitely on enteric coated aspirin 81–325 mg/day[1] and a β blocker.[2,3] In view of his reduced LV function a number of clinical trials support the use of an ACE inhibitor.[4–6]

Risk stratification

For risk stratification he should be scheduled for a symptom-limited exercise test in 2–4 weeks, with a view to (a) assessing his exercise capacity; (b) determining whether he is high, intermediate or low risk; and (c) ruling out severe underlying ischemia that might warrant early coronary angiography. For instance, a low-risk patient is one who can achieve more than 8 METS of exercise with no chest pain or ST segment changes. A high-risk patient would be one who either experiences angina or significant ST segment depression at a low workload, or whose blood pressure either fails to rise or decreases during exercise.

Risk factor modification/lifestyle changes

A proper rehabilitation program[7] should include (a) an exercise program; (b) nutrition counseling; (c) smoking cessation strategies; and (d) maintenance of ideal weight (BMI < 25). He should have his lipids checked (total cholesterol, LDL-C, HDL-C and triglycerides) in about 4–6 weeks. Efforts should be made to ensure that his LDL-C is less than 2·6 mmol/l and his total cholesterol to HDL-C ratio is less than 4·5 (see Chapters 12, 13 and 36).

In summary, using evidence-guided recommendations[8,9] the patient's chance of avoiding recurrent ischemic events and returning to a satisfactory quality of life is significantly enhanced by adherence to a program consisting of daily aspirin, β blocker, a statin and an ACE inhibitor, combined with regular exercise and cessation of smoking. Our patient has shown signs of depression, which is another significant risk factor, but it has not yet been confirmed with certainty that antidepressants reduce the risk of postinfarction ischemic events.

References

1. ISIS 2 Trial. Randomized trial of intravenous streptokinase and aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988;**ii**:349–60.
2. Pederson TR (for the Norwegian Multicenter Study Group). Six year follow up of the Norwegian Multicenter Study on Timolol after acute myocardial infarction. *N Engl J Med* 1985;**313**:1055–8.
3. Yusuf S, Peto R, Lewis JA *et al.* Beta blockade during and after myocardial infarction: a review of the randomized trials. *Prog Cardiovasc Dis* 1985;**27**:335–71.
4. ISIS-4 Study Group. A randomized factorial trial assessing early oral captopril, oral mononitrate, oral magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669–85.
5. The SOLVD Investigators. Effect of enalapril on survival inpatients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;**325**:293.
6. The Heart Outcomes Prevention Evaluation Study investigators (HOPE). Effects of an angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000;**342**:145–53.
7. Oldridge NB, Guyatt GH, Fischer ME *et al.* Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. *JAMA* 1988;**260**:945–50.
8. Fallen EL, Cairns JA, Dafoe W, Frasure-Smith N *et al.* Management of the post myocardial infarction patient: a consensus report – revision of 1991 CCS guidelines. *Can J Cardiol* 1995;**11**:477–86.
9. Ryan TJ *et al.* 1999 Update ACC/AHA guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1999;**34**:890–9.

Case 2

A 66 year old woman sustains an acute inferoposterior myocardial infarction for which she receives streptokinase (1·5 million units over 1 hour) and aspirin to chew. She makes a satisfactory recovery. The only complications are persistent but asymptomatic sinus bradycardia (45–50/min), papillary muscle dysfunction with moderate mitral regurgitation, and an estimated left ventricular ejection fraction of 0·35. There are no overt signs of heart failure or ventricular irritability. She is angina free post MI.

Her risk factors include heavy smoking (40 pack years); severe peripheral vascular disease with asymptomatic carotid bruits (80% stenosis of the right internal carotid artery), and intermittent claudication of the right leg. She has elevated triglycerides, at 6·5 mmol/l. Her previous total cholesterol (3 months ago) was 5·8 mmol/l and HDL-C was 0·98. She is 22 years post hysterectomy and bilateral oophorectomy. That operation was complicated by phlebitis and a pulmonary embolus. Her only medication at the time of hospital admission was an H_2 receptor antagonist because of a history of upper gastrointestinal bleeding 12 years ago and episodic epigastric burning. There is mild renal impairment, with a creatinine of 180. There is no family history of heart disease. However, her mother died of breast cancer at age 65.

Physical examination at the time of hospital discharge shows a resting heart rate of 48 bpm. Her blood pressure is 160/85. Her urea is 9·5 and creatinine 180. An ECG shows sinus rhythm but with a first-degree atrioventricular block of 0·24 seconds.

Question

What advice would you now give her?

Comment

This case raises several issues regarding the risk versus benefit of routine prophylactic strategies which, for most post-MI

patients, are supported by strong evidence from well designed clinical trials. For instance, one would wish to be cautious about reflexly prescribing a β blocker. Remember, she has persistent bradycardia with partial AV block, symptomatic peripheral vascular disease, hyperlipidemia and impaired LV function. On the other hand, β blockers have been shown to be especially effective in reducing mortality in post-MI patients with mild to moderate LV dysfunction.[1] Here the benefit of a β blocker probably outweighs the overall risk because it has the combined effect of protecting the ischemic myocardium, reducing the risk of sudden cardiac death and stabilizing blood pressure.

In view of her LV dysfunction, she would also be a candidate for an ACE inhibitor, but she is a non-diabetic with an elevated creatinine, peripheral vasculopathy and persistent hypertension, probably due to renovascular disease. Here an ACE inhibitor need not be denied if careful and frequent monitoring of renal function is carried out over the first month or so post discharge. As for hormone replacement therapy with estrogen, the alleged benefit on endothelial function has not so far been substantiated by carefully designed clinical trials.[2] Besides, the patient is asking some hard questions regarding the history of breast cancer in the family and her previous history of phlebitis and pulmonary embolus. Finally, the history of gastrointestinal bleeding raises caution with respect to aspirin prophylaxis. The clinical trials unfortunately have not provided satisfactory guidelines on how to weigh the risk versus the benefit of postinfarction prophylaxis for patients with certain potential hazards, such as this case. Although this case does not easily qualify for entrance criteria to most of the large post-MI clinical trials, it is not a reason to deny her useful protective measures as indicated above.

As for rehabilitative measures, although it would be difficult for her to achieve a high level of exercise training using leg exercise, there is evidence that a well supervised upper arm exercise program may be useful.[3] If she is intolerant of an ACE inhibitor perhaps a combination of hydralazine and nitroglycerin[4] might serve to improve circulatory function, control her hypertension and improve her heart rate. She should continue on aspirin as long as she also continues with an H_2 blocker or, better still, reduce the dose of aspirin to 81 mg a day and add clopidogrel.[5] As for her lipids, she probably would benefit from a fibrate rather than a statin, although there are no clinical trials that have compared the two, head to head, for this particular type of patient.

References

1. Beta Blocker Heart Attack Study Group. A randomised trial of propanolol in patients with acute myocardial infarction. *JAMA* 1982;**247**:1707–14.
2. Hulley S, Grady D, Bush T *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in post menopausal women. HERS Research group. *JAMA* 1998;**280**:605–13.
3. Ghilarducci LE, Holly RG, Amsterdam EA. Effects of high resistance training in coronary artery disease. *Am J Cardiol* 1989;**64**:866–70.
4. Cohn JN, Archibald DG, Ziesche S *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–52.
5. The CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001;**345**:494–502.

68 Metabolic risk and secondary prevention of coronary disease

Jacques Genest Jr

Case 1

The patient is a 55 year old man post acute myocardial infarction. His initial treatment consisted of thrombolytic therapy within 4 hours of presentation. He was in Killip class I and 4 days after his myocardial infarction a submaximal stress test did not reveal ischemia at 9·2 METS. He was initially treated with aspirin 325 mg od, metoprolol 50 mg po bid and simvastatin 40 mg po qhs. Six months after his infarction his metabolic profile revealed a total cholesterol of 4·20, plasma triglyceride of 1·2 mmol/l, HDL cholesterol of 1·2 mmol/l and an LDL cholesterol of 2·45 mmol/l. The patient had stopped smoking and his body mass index was 26·7·

Question

Is his metabolic risk profile adequate for the treatment he is on?

Comment

The results of the Heart Protection Study[1] have dramatically altered the way in which clinicians should be identifying and treating lipoprotein disorders in high-risk individuals. The currently accepted strategy supported by the National Cholesterol Education Program (Adult Treatment Panel III) in the USA[2] and the Canadian Guidelines for the Diagnosis and Treatment of Dyslipoproteinemias,[3] as well as the European Task Force for the Prevention of Cardiovascular Disease, is an evaluation of global cardiovascular risk based on the patient's gender, age, total (or LDL) cholesterol, HDL cholesterol, cigarette smoking, blood pressure and diabetes. In patients at high risk for cardiovascular disease or those with established atherosclerotic cardiovascular disease, some notable differences between European, Canadian and US guidelines have emerged. From a strategy of reaching target values (for example, LDL cholesterol less than 2·5 mmol/l in Canada) the Heart Protection Study shows that baseline levels of LDL or total cholesterol do not markedly influence the positive impact of treatment.

And so, for our patient the widespread use of the statin class of drugs post acute coronary event has now become standard therapy. Although some lipid specialists may disagree with initiating a statin drug without knowledge of prior basal measurements of serum lipids, this class of drugs has proved safe and highly efficacious in improving outcome. Obtaining a lipoprotein profile within 24 hours of hospital admission remains sound clinical practice, but the initiation of treatment as soon as possible after diagnosis, and verification 6 weeks to 6 months later, is useful. In this case, the LDL cholesterol is below the recommended target and it remains to be determined whether allowing the LDL to exceed 2·5 mmol/l should invite further intervention.

Case 2

A 55 year old woman, recently postmenopausal, presented to the emergency department with retrosternal squeezing chest pain of 30 minutes' duration. The ECG showed anterolateral ST segment depression and the troponins were slightly elevated. Urgent cardiac catheterization revealed an 85% proximal circumflex stenosis, which was successfully dilated and stented. A lipid profile done in hospital showed her total cholesterol to be 4·1 mmol/l, plasma triglyceride 2·6 mmol/l, HDL cholesterol 0·62 mmol/l and an LDL cholesterol 2·3 mmol/l. Her body mass index was 27·2, her blood pressure was 150/86 and her fasting glucose was 5·2 mmol/l.

Question

What would be optimum metabolic management for this patient?

Comment

This case represents a therapeutic challenge. The Veterans Affairs HDL intervention trial (VA-HIT) showed that patients with a low HDL cholesterol benefited from the drug gemfibrozil 600 mg po bid.[4] The recently released HATS trial showed that low-dose simvastatin with niacin greatly improved both HDL and the total cholesterol to HDL ratio, and was associated with a decrease in the progression of atherosclerosis.[5] The Health Protection Study (HPS), however, showed that in patients whose total cholesterol was higher than 3·5 mmol/l simvastatin 40 mg/day conferred a dramatic benefit.[1] The optimal treatment of high-risk patients with very low HDL cholesterol and mild to moderate triglycerides is still an issue of intense debate. Our patient has an HDL that is markedly below the fifth percentile for age- and gender-matched subjects.

The fibric acid group of medications has been shown in clinical trials to decrease cardiovascular mortality[4] and are an appropriate option. The combination of a low-dose statin with niacin is also an appropriate choice here, and yet the use of a statin as seen in the HPS[1] and 4S[6] studies appears to confer benefit. Each of these therapies has been shown to be superior to placebo alone. The use of postmenopausal estrogen (partly because of its effect on increasing HDL cholesterol levels) has been questioned in view of the negative findings in the HERS trial.[7]

Case 3

A 60 year old man with hyperglycemia (fasting blood sugar 7·6 mmol/l) treated with diet also has moderate hypertension (150/92) and an abnormal lipid profile. His total cholesterol is 6·4 mmol/l, plasma triglyceride 3·2 mmol/l, HDL cholesterol 0·8 mmol/l and LDL cholesterol 4·15 mmol/l. He has a positive exercise tolerance test at 8·2 METS using the Bruce protocol and his body mass index is 29·8 with a waist circumference of 104 cm. He has a sedentary lifestyle and his wife reports that he snores loudly at night.

Question

What is the approach to this patient with multiple metabolic risk factors?

Comment

Since the last edition of *Evidence Based Cardiology* a major rethink has taken place in preventive cardiology. Landmark clinical trials have shown unequivocally that patients with atherosclerotic disease who have multiple metabolic risk factors, such as diabetes and hyperlipidemia, have a risk of future cardiovascular events not dissimilar to those who have already suffered an acute coronary event. Therefore, the previously narrow definition of secondary prevention has been widened to include individuals with multiple risk factors where the rate of hard cardiovascular events exceeds 20% in 10 years. This "high-risk strategy" centers on the identification of global cardiovascular risk, as seen in this patient. This patient has the typical manifestations of the metabolic syndrome, consisting of abdominal obesity, increase in abdominal girth, low HDL cholesterol, elevated plasma triglycerides, hyperglycemia (insulin resistance) and hypertension. These patients tend to have small dense LDL particles and elevated apolipoprotein B levels. They may also have elevated procoagulant factors, as well as an altered tPA : PAI-1 ratio and endothelial dysfunction. Although these patients represent some of the highest cardiovascular risk, current algorithms, including the Framingham Heart Study, may not provide a true estimation of risk because obesity, plasma triglycerides and other factors are not included in the cardiovascular risk calculations.

Nevertheless, the treatment of these patients is multifactorial. Clearly, blood pressure control with appropriate medications is warranted. Although fibric acid derivatives will lower plasma triglyceride and raise the HDL cholesterol somewhat,[4] the preferred medication in this case would be a statin at a moderately high dose.[1] Although statins have a modest effect on HDL *per se* (unless, as in this case, there is hypertrigyceridemia) they significantly improve the total cholesterol to HDL ratio. In addition they do lower plasma triglyceride levels.

Overall, the patient is urged to engage in a concerted effort to reduce all the metabolic risk factors. This can be helped by making the patient aware of the clustering of his risk profile and the potential effect on his cardiovascular health. The patient needs to lose weight, change diet and exercise regularly. The loss of even a few kilograms of intra-abdominal fat will significantly decrease fasting blood glucose levels and insulin resistance. It will also reduce his triglyceride and help increase his HDL cholesterol levels, as well as lower his

blood pressure. This constitutes a great therapeutic challenge which can best be achieved by a multidisciplinary team approach, including a dietician and exercise rehabilitation specialists.

References

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering in 20536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;**340**:7–12.
2. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285**:2486–97.
3. Fodor JG, Frohlich JJ, Genest JJ Jr *et al.* Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *Can Med Assoc J* 2000;**162**:1441–7.
4. Rubins HB, Robins SJ, Collins D *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *N Engl J Med* 1999;**341**:410–18.
5. Brown BG, Zhao XQ, Chait A *et al.* Simvistatin and niacin, antioxidant vitamins or the combination for prevention of coronary disease. *N Engl J Med* 2001;**345**:1583–92.
6. Ballantyne CM, Olsson AJ, Cook TJ *et al.* Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvistatin therapy in 4S. *Circulation* 2001;**104**:3046–51.
7. Barrett-Connor E. Looking for the pony in the HERS data. Heart and estrogen/progestin replacement study. *Circulation* 2002;**105**:902–3.

69 Peripheral vascular disease with suspect coronary artery disease

Peter C Spittell

Case 1

Over the past several years a 74 year old man has noticed progressive left leg discomfort with walking. Standing still provides complete relief. His walking distance has gradually decreased to less than one block in the past year. He is a non-smoker, non-diabetic, and has no prior cardiac history. His medications include captopril and dyazide for hypertension.

On examination, his blood pressure is 140/80 mmHg (both arms) and his resting pulse is 65 bpm and regular. There is a right carotid bruit and reduced femoral pulses with bilateral bruits. Pulses are non-palpable below the femoral level on the left. On the right, the popliteal and posterior tibial pulses are mildly reduced and the dorsalis pedis pulse is absent. Elevation pallor is grade III (pallor is less than 30 seconds) on the left and grade 0 (no pallor in 60 seconds) on the right. The remainder of the physical examination is normal.

A resting ECG reveals normal sinus rhythm with a non-specific T wave abnormality. The chest radiograph is normal. Routine hematology and chemistry values are normal.

The resting ankle : brachial systolic pressure indexes (ABI, normal >0·9) are 1·0 on the right, 0·6 on the left. After walking 124 yards (113 m) on a treadmill (10% incline, 1·5 mph) and developing left hip, thigh and calf claudication, his postexercise ABIs are 0·3 on the right and 0·2 on the left, consistent with moderate (right) and moderately severe (left) peripheral arterial occlusive disease, respectively.

Carotid ultrasound demonstrates a large amount of atheromatous plaque in the right carotid bulb associated with a 70–99% stenosis.

Question

What would be the most appropriate management at this point?

Comment

Here, one seeks evidence to guide the management of an elderly patient with extensive peripheral vascular disease who may or may not have concomitant coronary artery disease. The finding of an asymptomatic high grade carotid stenosis (>60%) warrants consideration of prophylactic carotid endarterectomy if the patient's general health is good. A 60% diameter reducing stenosis (carotid ultrasound) is considered as an indication for surgical intervention in asymptomatic patients who are in a low-risk surgical category: using a ratio of 3·2 for the peak systolic velocity at the site of narrowing divided by that from the carotid artery, a sensitivity of 92% and a specificity of 86% can be achieved. This gives a positive predictive value of 85%, a negative predictive value of 93% and an overall accuracy of 89%.[1] The evidence shows that carotid endarterectomy in patients with an asymptomatic carotid stenosis >60% in severity significantly reduces the risk of ipsilateral stroke, perioperative stroke or death compared to medical therapy alone.[2]

In view of the patient's age and widespread peripheral vascular disease it is prudent to assess his perioperative cardiac risk. Dobutamine stress echocardiography was performed and was negative for ischemia. This test is associated with a high negative predictive value.[3]

The patient underwent right carotid endarterectomy without complications. Postoperatively, following a discussion with the patient regarding the natural history of intermittent claudication and indications for restoration of pulsatile flow,[4] he elected a conservative treatment program which included aspirin 325 mg/day, a walking program for intermittent claudication, and foot care and protection.

References

1·Edwards JM *et al.* Duplex ultrasound criteria for determining >50% and <60% internal carotid artery stenosis: implications for screening examinations. Noninvasive vascular laboratory and vascular imaging. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral vascular diseases*, 2nd edn. St Louis: Mosby, 1996.

2·Executive Committee for the Asymptomatic Carotid Atherosclerosis (ACAS) Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;**273**:1421–8.

3.Eichelberger JP, Schwarz KQ, Black ER, Green R, Ouriel K. Predictive value of dobutamine echocardiography before noncardiac vascular surgery. *Am J Cardiol* 1993;**72**:602–7.

4.McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 1989; **3**:273–7.

Case 2

A 52 year old man presents with progressive exertional right calf discomfort over the past year. Standing still provides complete relief but his walking distance has gradually shortened to one block. He notes similar but less severe discomfort in the left calf. His claudication is severely limiting his lifestyle.

He is taking amlodipine for systemic hypertension, has smoked tobacco for the past 34 years and has a history of hyperlipidemia treated by diet. Blood glucose is normal. He denies a history of angina pectoris or diabetes mellitus.

On examination his blood pressure is 140/90 mmHg (both arms), resting pulse is 85 bpm and regular. A grade 1/4 systolic murmur at the cardiac apex and a right carotid bruit are present. A small abdominal aortic aneurysm is also palpable. The popliteal, posterior tibial and dorsalis pedis pulses are absent on the right. On the left, the popliteal and posterior tibial pulses are moderately reduced. The dorsalis pedis pulse is absent. Elevation pallor is grade III (pallor in less than 30 seconds) and grade I (pallor in less than 60 seconds) on the right and left, respectively.

A resting ECG shows normal sinus rhythm without other abnormalities. Routine hematology and chemistry values are normal.

Resting ankle:brachial systolic pressure index (ABI) is 0·5 on the right and 0·6 on the left (ABI normal > 0·9). After walking 282 yards (258 m) on a treadmill (10% incline, 2 mph) and developing right calf claudication, his postexercise ABIs are 0·2 on the right, 0·7 on the left, consistent with severe peripheral arterial occlusive disease on the right and mild disease on the left. Carotid ultrasound reveals a right external carotid artery stenosis with mild atherosclerotic disease in the right carotid bulb, but is otherwise normal. Abdominal ultrasound confirms a small abdominal aortic aneurysm (2·5 cm).

After a discussion of peripheral arterial occlusive disease with the patient, including its natural history, prognosis, treatment and goals of treatment, he elects to pursue restoration of pulsatile flow.

Question

How would you proceed at this point?

Comment

This case is somewhat more complex insofar as there is more suspicion of concomitant coronary artery disease. Therefore, with the decision to pursue vascular surgery, an assessment of the patient's perioperative cardiac risk is warranted.[1] Although he has no history of angina pectoris he has a number of cardiovascular risk factors (male gender, tobacco, hypertension, hyperlipidemia). Furthermore, his intermittent claudication limits his activity and may prevent him from experiencing exertional angina. To further assess his perioperative cardiac risk, dobutamine stress echocardiography was performed and demonstrated normal left ventricular size and function, but was positive for ischemia (new regional wall motion abnormalities in the mid and apical anterior wall). A positive dobutamine stress echocardiogram has a positive predictive value of 35% for a perioperative cardiac event. When ischemia occurs at a significantly lower heart rate during dobutamine stress (<70% of the age-corrected maximal heart rate) the positive predictive value increases to 53%.[2]

Medical therapy was elected (suspect single vessel disease with normal left ventricular function), and it was felt safe to proceed with peripheral revascularization. Peripheral angiography demonstrated a high grade stenosis involving a short segment of the distal right superficial femoral artery. Percutaneous transluminal angioplasty of the stenosis was performed. Although no well designed large scale clinical trial has yet been done to determine the efficacy of percutaneous angioplasty for this type of patient, percutaneous angioplasty was none the less felt to be indicated because the prognosis for limb loss in patients with intermittent claudication is related mostly to the severity of disease, as assessed by ankle pressure measurements, at the time of study entry.[3] After the procedure, a normal dorsalis pedis pulse was restored on the right. The intermittent claudication completely resolved following the procedure. He was placed on aspirin (325 mg/day), advised to stop smoking and instructed in foot care and protection. Amlodipine was continued for treatment of his hypertension, and the importance of adequate control of hypertension was discussed. Ultrasound of the abdominal aorta in 1 year was recommended to re-evaluate his abdominal aortic aneurysm. Additional instruction on dietary therapy for hyperlipidemia was given and a follow-up lipid profile was arranged in 3 months.

References

1. Eagle KA, Brundage BH, Chaitman BR *et al.* Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. ACC/AHA Task Force report. *Circulation* 1996;**93**:1278–317.
2. Poldermans D, Arnese M, Fioretti PM *et al.* Improved cardiac risk stratification in major vascular surgery with dobutamine stress echocardiography. *J Am Coll Cardiol* 1995;**26**:648–53.
3. McDaniel MD, Cronenwelt JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 1989; **3**:271–7.

70 Heart failure

Michael M Givertz

Case 1

A 58 year old man with non-insulin dependent diabetes mellitus and coronary artery disease presents to your office with progressive dyspnea on exertion and lower extremity edema. He is status post anterior myocardial infarction 15 years ago. Following cardiac rehabilitation, he returned to work full-time as an electrical engineer and remained asymptomatic without angina or heart failure until 1 year ago, when he started to "slow down". Over the last several months he has noted increasing shortness of breath with usual daily activities, and more recently the onset of bilateral lower extremity edema. He can no longer play with his grandchildren because of fatigue. He denies chest pain, palpitations or lightheadedness. He sleeps comfortably on one pillow and has had no recent change in his weight or appetite. His current medications include captopril 12·5 mg tid, furosemide 20 mg qd, glyburide 5 mg qd and aspirin.

On physical examination he is a well-nourished older-appearing man who appears comfortable lying supine. Blood pressure is 130/70 mmHg and heart rate is 100 beats per minute and regular. Jugular venous pressure is 8 cmH_2O. Lungs are clear bilaterally. Cardiovascular examination reveals a displaced PMI, grade 2 over 6 holosystolic murmur at the apex, and soft S3 gallop. The liver edge is palpable 2 cm below the right costal margin, and there is 1+ pitting edema to the mid-calves bilaterally. His feet are warm with intact distal pulses. Laboratory tests are notable for a serum sodium of 136 mmol/l, creatinine of 1·8 mg/dl, and hemoglobin A1c of 6·2%. His electrocardiogram reveals normal sinus rhythm with a non-specific intraventricular conduction delay and old anterior myocardial infarction. A transthoracic echocardiogram demonstrates moderate left ventricular dilation with anteroapical akinesis, left ventricular ejection fraction of 25%, mild right ventricular dysfunction, and 2+ mitral regurgitation.

Question

How would you manage this patient?

Comment

To summarize, this is a middle-aged man with diabetes and an ischemic cardiomyopathy who presents with New York Heart Association functional class III heart failure. There is both clinical and laboratory evidence of left ventricular systolic dysfunction and volume overload, without clinical evidence of decreased cardiac output. In addition, his echocardiogram shows findings consistent with left ventricular remodeling without intracavitary thrombus formation. There is no clear precipitant to his recent clinical decompensation. He has been compliant with his medications and fluid and salt restriction, and does not drink alcohol. His blood sugars have been well controlled and he has had no recent infection. A complete blood count and thyroid function tests should be checked to rule out anemia and hyperthyroidism, respectively.

Although we have not identified a *precipitating factor* in this case, it is reasonable to consider treatment of the *underlying cause* of heart failure.[1] The patient is status post myocardial infarction many years ago, and may have developed recurrent ischemia, either silent or with dyspnea as an anginal equivalent. An exercise imaging study should be performed to rule out reversible ischemia. If this is negative, an assessment of myocardial viability with low-dose dobutamine stress echocardiography, resting thallium scintigraphy or positron emission tomography should be considered.[2] Several studies have shown that patients with ischemic cardiomyopathy and viable myocardium have significant improvement in left ventricular function following surgical revascularization.[3,4] However, in the absence of angina or inducible ischemia, the superiority of surgery over medical therapy in prolonging survival in patients with ischemic cardiomyopathy remains unproven. A National Institutes of Health-sponsored trial (STICH) is currently under way to test this hypothesis.

The overall goals in the management of heart failure are to eliminate symptoms, improve quality of life and prolong survival. Non-pharmacologic management of heart failure should be reviewed with the patient and his family. The importance of salt and fluid restriction and daily monitoring of home weights should be reinforced. Once euvolemia has been achieved (see below), a submaximal exercise program (for example, walking, stationary bicycle) should be encouraged. Recent studies suggest that exercise training may result in improvement in symptoms and functional capacity, improved blood flow and skeletal muscle metabolism, and reduced hospitalizations for heart failure.[5] The effect of exercise training on survival in heart failure remains unknown.

Pharmacologic therapy should be optimized according to recent consensus guidelines.[6] The patient is currently taking captopril, an angiotensin converting enzyme (ACE) inhibitor, at a relatively low dose. Several large prospective randomized controlled trials have demonstrated the beneficial effects of ACE inhibitors on exercise tolerance, salt and water balance, symptoms, neurohormonal activation, quality of life and survival in patients with chronic heart failure.[7] Furthermore, in this patient with mild diabetic nephropathy, ACE inhibitor therapy may slow the progression of renal dysfunction; also, as demonstrated in the SAVE study, captopril reduces the risk of recurrent myocardial infarction and stroke in patients with post-MI left ventricular dysfunction.[8] The optimal dosing of ACE inhibitors remains controversial. One prospective study (ATLAS) demonstrated the superiority of high-dose versus low-dose ACE inhibitor therapy in patients with chronic heart failure without increased toxicity.[9] Current guidelines recommend increasing the dose of captopril to 50 mg tid as blood pressure and renal function tolerate.

For the treatment of systemic and pulmonary venous congestion, more aggressive diuresis is warranted. The daily dose of furosemide should be increased until the required response is achieved (for example, the absence of jugular venous distention, hepatomegaly and edema). If this strategy is not effective, combination therapy with a thiazide diuretic should be tried. Adequate diuresis with careful attention to weight and renal function will generally result in improved symptoms and may slow the progression of chamber dilation by reducing ventricular filling pressures. However, diuretic therapy may also cause renal dysfunction, electrolyte depletion and neurohormonal activation. It should be emphasized that there have been no randomized controlled trials demonstrating the long-term efficacy and safety of diuretic therapy in patients with heart failure.

Follow up 1

The patient undergoes exercise echocardiography, which is negative for ischemia, and resting thallium scintigraphy demonstrates no significant viability of the anterior and apical walls. He diureses 8 lb on an increased dose of oral furosemide, and captopril is titrated to 37·5 mg tid. Jugular venous distention and lower extremity edema resolve, but blood pressure, heart rate and renal function are unchanged. Despite adjustment of vasodilator and diuretic therapy, there is no change in his exertional dyspnea.

Question

He remains moderately symptomatic despite treatment with an ACE inhibitor and diuretic. What is the next step?

The next step is to initiate therapy with a β adrenergic antagonist. Traditionally, β blockers were contraindicated in the treatment of heart failure because of concern about negative inotropic effects leading to clinical deterioration. In the late 1970s and early 1980s, small uncontrolled trials suggested a beneficial effect of β blockers in patients with dilated cardiomyopathy. Subsequent randomized controlled trials have demonstrated that β blockers improve symptoms and cardiac function, and reduce morbidity and morality in patients with chronic heart failure due to left ventricular systolic dysfunction.[10] Consensus guidelines recommend the use of β blockers, in addition to ACE inhibitors and diuretics, in the management of patients with mild to moderate heart failure,[6] and more recent data suggest their safety and efficacy in patients with severe heart failure.[11] Because euvolemia has been achieved, β blocker therapy can be initiated safely at a low dose and titrated gradually at regular intervals (for example, every 1–2 weeks). Renal insufficiency should not prevent the initiation of β blocker therapy, as the patient's renal function has remained stable on ACE inhibitor therapy. However, renal function should be followed during β blocker titration.

Follow up 2

Carvedilol, a non-selective β blocker with α_1 blocking properties, is initiated at a dose of 3·125 mg bid. One week later the patient returns to clinic with complaints of increased dyspnea on exertion and recurrent lower extremity edema. His clinical evaluation is consistent with worsening heart failure, a known adverse effect of β blocker therapy, and this responds to a doubling of the furosemide dose for 2 days. Over the next 2 months carvedilol is titrated to a target dose of 25 mg bid. During this period, symptoms of worsening heart failure occur on one additional occasion. Close monitoring of symptoms and weight, and adjustments in diuretic dosing, enable the patient to achieve a target dose of β blocker therapy. After 6 months, a follow-up echocardiogram reveals a decrease in the left ventricular end-diastolic dimension and an increase in the left ventricular ejection fraction to 35%. This time-dependent reverse remodeling of the left ventricle has been demonstrated with several different β blockers, including metoprolol[12] and carvedilol.[13]

Question

After remaining clinically stable for 1 year, he develops worsening heart failure. What is the next step in management?

For persistent or recurrent heart failure symptoms despite treatment with an ACE inhibitor, β blocker and diuretic, several adjunctive therapies may be considered. Digoxin is an oral positive inotropic agent with antiadrenergic effects that has been shown to be safe and effective in patients with symptomatic heart failure. Although the DIG trial showed no difference in survival in heart failure patients treated with digoxin versus placebo, there were fewer deaths attributable to progressive heart failure in the digoxin-treated group.[14] Another class of medications that may provide symptomatic benefit in heart failure are the organic nitrates.[15] These may be used to reduce both systemic and pulmonary venous congestion. As with diuretics, it should be remembered that nitrates alone have not been shown to reduce morbidity or mortality in patients with chronic heart failure. If, despite these therapies, the patient develops severe heart failure, other medical and surgical options may be considered. The aldosterone antagonist spironolactone has been shown to prolong survival in patients with severe heart failure,[16] and more recently biventricular pacing has been approved for patients with symptomatic LV dysfunction and intraventricular conduction delay.[17] For refractory heart failure, mechanical cardiac assist and cardiac transplantation may be considered in selected cases.[18]

Case 2

A 74 year old woman is referred to you by her primary care physician for evaluation of "new-onset heart failure". Her cardiac risk factors are positive for hypertension, diabetes and hypercholesterolemia. She was told that she had a myocardial infarction many years ago, but details are not available for review. Four years ago, an echocardiogram obtained as part of a preoperative evaluation for laparoscopic cholecystectomy revealed a left ventricular ejection fraction of 45% and moderate mitral regurgitation. She was treated briefly with an angiotensin converting enzyme inhibitor, but this was changed to an angiotensin receptor antagonist because of cough. She remained stable until 2 months ago, when she presented with progressive dyspnea on exertion, associated with dull chest pain and pedal edema. The addition of digoxin and furosemide resulted in a 5 lb weight loss and improvement in symptoms.

Her past medical history is significant for osteoarthritis, peptic ulcer disease and hypothyroidism. Her medications include losartan 50 mg qd, furosemide 40 mg qd, digoxin 0·25 mg qd, pravastatin 40 mg qhs, levothyroxine 100 micrograms qd, and ibuprofen 400 mg tid. She does not smoke cigarettes or drink alcohol. On physical examination she appears anxious but in no respiratory distress. Blood pressure is 140/80 mmHg, heart rate is 58 beats per minute and regular, and weight is 148 pounds. Jugular venous distention and hepatojugular reflux are absent. Lungs are clear to auscultation bilaterally. Cardiovascular examination reveals a non-palpable PMI, S3 and S4 gallops, and a soft systolic ejection murmur at the apex without radiation. Her abdomen is non-tender, without hepatosplenomegaly. Her extremities are warm and without edema.

Laboratory tests reveal a serum sodium of 141 mmol/l, potassium 4·4 mmol/l, BUN 25 mg/dl, creatinine 1·4 mg/dl, digoxin level 1·6 ng/ml, TSH 2·1 mU/l, and hematocrit 38%. Chest radiography shows cardiomegaly without congestion. Her 12-lead electrocardiogram reveals sinus bradycardia and left bundle branch block. An echocardiogram demonstrates mild left ventricular enlargement, left ventricular ejection fraction of 20% with inferior and apical akinesis, normal right ventricular size and function, and mild thickening of the mitral valve leaflets with 2–3+ central mitral regurgitation. Right heart catheterization reveals a right atrial pressure of 9 mmHg, pulmonary artery systolic and diastolic pressures of 58 and 24 mmHg, respectively, mean pulmonary capillary wedge pressure of 26 mmHg, and cardiac output of 4·8 l/min. Angiography reveals no significant coronary artery disease, and ventriculography confirms severe left ventricular dysfunction with 3+ mitral regurgitation.

Question

What is your assessment of this patient?

In summary, this is an elderly woman with hypertension, diabetes and a non-ischemic dilated cardiomyopathy who presents for further management. The cause of her left ventricular systolic dysfunction remains incompletely defined.

Although she has a high likelihood of having ischemic heart disease based on her cardiac risk factors, history of "myocardial infarction", left bundle branch block on electrocardiogram and regional wall motion abnormalities on echocardiogram, coronary angiography demonstrates no significant coronary artery disease. This case highlights the lack of specificity of the history, ECG and echocardiogram for diagnosing ischemic heart disease in the presence of severe left ventricular systolic dysfunction.[19] Not infrequently, patients are told by their physician that they may have had a "heart attack" based on the presence of a left bundle branch block. In the evaluation of heart failure, cardiac catheterization is indicated not only to define coronary anatomy, but also to assess hemodynamics and, in this case, to determine the severity of mitral regurgitation.

If ischemic heart disease does not explain this patient's LV dysfunction, what are the other possible causes? There is no history of myocarditis, anemia or significant alcohol use. She has a history of hypothyroidism, but is maintained on thyroid hormone replacement therapy and has no clinical or biochemical evidence of active thyroid disease. Chronic mitral regurgitation (MR) may result in heart failure and left ventricular remodeling, and it is often difficult to distinguish primary mitral valvular disease causing advanced heart failure from MR secondary to left ventricular dilation (for example, following myocardial infarction). In this case, moderate LV dysfunction was noted 4 years ago in association with moderate MR, suggesting that myocardial disease is the primary process. Other echocardiographic findings that make primary MR less likely are the lack of structural abnormalities of the mitral valve or subvalvular apparatus, normal left atrial size, and the absence of pulmonary hypertension or right ventricular dysfunction. Alternatively, the presence of a left bundle branch block and known LV dysfunction make the diagnosis of idiopathic dilated cardiomyopathy likely,[20] although recent studies have shown that up to 20% of these cases may be familial.[21] In general, idiopathic dilated cardiomyopathy is a diagnosis of exclusion.[22]

A "bedside" clinical assessment should be performed on all patients with chronic heart failure to assess the presence or absence of congestion and hypoperfusion.[23] In addition, functional status should be determined both for prognostic reasons and to assess the response to therapy. This patient presents with exertional dyspnea and chest pain; pedal edema has resolved with diuresis. Although her examination does not suggest the presence of pulmonary or systemic venous congestion, right heart catheterization is notable for elevated right and left heart filling pressures and moderate pulmonary hypertension with adequate systemic perfusion. Importantly, this case demonstrates the limited reliability of physical signs[24] and chest radiography[25] for estimating hemodynamics in patients with chronic heart failure. Some findings, such as an S3 gallop or cardiomegaly, are highly sensitive but lack the specificity to be of diagnostic value; other findings, such as pulmonary rales and jugular venous distention, are highly specific but insensitive. The clinical utility of other non-invasive tools to assess cardiac filling pressures, such as myocardial tissue Doppler imaging or plasma B-type natriuretic peptide (BNP) levels, remains unproven.

To better define her functional capacity, exercise treadmill testing with continuous gas exchange analysis (also termed cardiopulmonary exercise testing) should be considered. Numerous studies have demonstrated the independent prognostic value of peak oxygen consumption in patients with heart failure,[26] and cardiopulmonary exercise testing may be used to assess the response to therapy. If the patient is unable to undergo maximal exercise testing, a submaximal test such as the 6-minute walk test may provide an estimate of peak functional capacity, and is better tolerated.[27] Quality of life assessment, although commonly used in clinical research protocols and for quality improvement analyses, is not a standard of care in clinical practice.

Question

How would you manage this patient?

Despite the presence of significant mitral regurgitation, there is no proven role for mitral valve repair or replacement in the treatment of patients with dilated cardiomyopathy, although there are surgical proponents of this approach.[28] Appropriate initial medical therapy would be to increase diuresis, which can be accomplished with higher doses of furosemide. Without the assistance of a pulmonary artery catheter or a reliable non-invasive tool to measure cardiac filling pressures,[29] clinical end points such as decreased dyspnea with stable renal function should be targeted. As previously noted, the long-term efficacy and safety of diuretics in the treatment of heart failure remain unknown. Ibuprofen, a non-steroidal anti-inflammatory agent that may contribute to fluid retention in heart failure,[30] should be discontinued.

Neurohormonal antagonist therapy should be maximized. The patient is taking a moderate dose of losartan, an angiotensin receptor blocker (ARB), in place of an ACE inhibitor, which was discontinued because of cough. Based on available clinical trials data[31] and according to consensus guidelines,[6] ACE inhibitors *rather than* ARBs continue to be the agents of choice for blockade of the renin–angiotensin system (RAS) in heart failure. Cough, although not uncommon with ACE inhibitors, is not an absolute contraindication to ACE inhibitor therapy and requires discontinuation of medication in less than 5% of patients.[31] In addition, cough may be due to the heart failure itself, rather than the ACE inhibitor prescribed to treat heart failure. In the present case it would be reasonable to rechallenge the patient with an ACE inhibitor and titrate to a target dose (for example, lisinopril 40 mg qd).[9] Although there has been increasing interest in the combined use of an ACE inhibitor and

ARB for maximal RAS blockade, preliminary data from the Val-HeFT study raises concerns about this approach in patients who are also taking a β blocker.[32] In this case, β blocker therapy should be initiated and titrated to target doses (for example, carvedilol 25 mg bid, Toprol-XL 200 mg qd) to achieve important survival benefits.[10] Sinus bradycardia and left bundle branch block are not contraindications to β blocker therapy, but require close monitoring. If symptomatic bradycardia occurs, implantation of a permanent pacemaker should be considered rather than discontinuation of the β blocker.

Digoxin may be contributing to bradycardia in this case. Although the serum digoxin level of 1·6 ng/ml is within the normal range, the level may not correlate with symptoms or electrocardiographic evidence of digoxin toxicity.[33] During β blocker titration it would be reasonable to decrease the digoxin dose to 0·125 mg qd and maintain serum digoxin levels in the low normal (0·5–1·0 ng/ml) range. However, the role of monitoring digoxin levels in patients with chronic heart failure remains controversial.

Follow up

The patient responds well to an increase in her furosemide dose with improved exertional tolerance and resolution of chest pain. Arrangements are made to initiate β blocker therapy on an outpatient basis. On the evening prior to her scheduled visit, she has a witnessed syncopal event without prodromal symptoms while standing in the bathroom. An ambulance is called and the emergency medical technicians find her lying on the floor, awake but mildly confused, with spontaneous respirations and pulse. Her blood pressure is 100/70 mmHg. A rhythm strip obtained on route to the hospital reveals sinus tachycardia at a rate of 108 beats per minute with occasional premature ventricular complexes and a 3-beat run of non-sustained ventricular tachycardia. In the emergency room she is alert and oriented, without focal neurologic deficits, postural hypotension or evidence of gastrointestinal bleeding. She has no sustained arrhythmias on telemetry.

Question

What would you do next?

The evaluation and management of syncope has been well described[34] and is beyond the scope of this chapter. Syncope in patients with symptomatic LV dysfunction is particularly concerning, as it may be caused by ventricular arrhythmias and is associated with an increased risk of sudden death. Among survivors of *sustained* ventricular tachycardia associated with syncope and LV failure, the implantable cardioverter defibrillator (ICD) has been shown to improve survival compared with antiarrhythmic drug therapy.[35] Furthermore, in patients with coronary artery disease, reduced ejection fraction and asymptomatic *non-sustained* VT, the ability to induce ventricular tachycardia at the time of electrophysiologic study is an indication for ICD placement.[36] Finally, Moss *et al* recently demonstrated that in patients with a prior myocardial infarction and advanced LV dysfunction, prophylactic implantation of a defibrillator improves survival.[37] However, the role of ICD therapy in patients with syncope and heart failure due to non-ischemic cardiomyopathy is less clear. Some would advocate placement of an ICD in this patient based on observational data showing improved outcomes compared with medical therapy alone.[38] Alternatively, evidenced-based cardiologists will await the results of primary prevention trials of sudden cardiac death in the broad population of patients with LV dysfunction.[39]

References

1. Givertz MM, Colucci WS, Braunwald E. Clinical aspects of heart failure; high-output heart failure; pulmonary edema. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia: WB Saunders, 2001.
2. Bonow RO. The hibernating myocardium: implications for management of congestive heart failure. *Am J Cardiol* 1995; **75**:17A–25A.
3. Tamaki N, Kawamoto M, Tadamura E *et al*. Prediction of reversible ischemia after revascularisation. Perfusion and metabolic studies with positron emission tomography. *Circulation* 1995;**91**:1697–705.
4. Bax JJ, Comel JH, Visser FC *et al*. Prediction of recovery of myocardial dysfunction after revascularization. Comparison of fluorine-18 fluorodeoxyglucose/thallium-201, SPECT, thallium-201 stress-reinjection SPECT and dobutamine echocardiography. *J Am Coll Cardiol* 1996;**28**:558–64.
5. Coats AJ. Exercise training for heart failure: coming of age. *Circulation* 1999;**99**:1138–40.
6. Hunt SA, Baker DW, Chin MH *et al*. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1995 Guidelines for the Evaluation and Management of Heart failure). *J Am Coll Cardiol* 2001;**38**:2101–13.
7. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;**273**:1450–6.
8. Loh E, Sutton MS, Wun CC *et al*. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;**336**:251–7.
9. Packer M, Poole-Wilson PA, Armstrong PW *et al*. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 2000;**100**:2312–18.
10. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;**101**:558–69.

11.Packer M, Coats AJ, Fowler MB *et al.* Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344**:1651–8.
12.Hall SA, Cigarroa CG, Marcoux L *et al.* Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta- adrenergic blockade. *J Am Coll Cardiol* 1995;**25**:1154–61.
13.Doughty RN, Whalley GA, Gamble G *et al.* Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia–New Zealand Heart Failure Research Collaborative Group. *J Am Coll Cardiol* 1997;**29**:1060–6.
14.The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–33.
15.Elkayam U, Karaalp IS, Wani OR *et al.* The role of organic nitrates in the treatment of heart failure. *Prog Cardiovasc Dis* 1999;**41**:255–64.
16.Pitt B, Zannad F, Remme WJ *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–17.
17.Abraham WT, Fischer WG, Smith AL *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**: 1845–53.
18.Hunt SA, Frazier OH. Mechanical circulatory support and cardiac transplantation. *Circulation* 1998;**97**:2079–90.
19.Costanzo MR, Augustine S, Bourge R *et al.* Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 1995; **92**:3593–612.
20.Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;**331**:1564–75.
21.Michels VV, Moll PP, Miller FA *et al.* The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med* 1992;**326**:77–82.
22.Felker GM, Thompson RE, Hare JM *et al.* Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–84.
23.Givertz MM, Stevenson LW, Colucci WS. Hospital management of heart failure. In: Antman Em, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease, 2nd edn. Philadelphia: WB Saunders, 2002.
24.Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;**261**:884–8.
25.Chakko S, Woska D, Martinez H *et al.* Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med* 1991;**90**:353–9.
26.Mancini DM, Eisen H, Kussmaul W *et al.* Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:778–86.
27.Lipkin DP, Scriven AJ, Crake T *et al.* Six minute walking test for assessing exercise capacity in chronic heart failure. *BMJ* 1986;**292**:653–5.
28.Bolling SF, Pagani FD, Deeb GM *et al.* Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;**115**:381–6.
29.Sanders GP, Mendes LA, Colucci WS *et al.* Noninvasive methods for detecting elevated left-sided cardiac filling pressure. *J Card Fail* 2000;**6**:157–64.
30.Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med* 2000; **160**:777–84.
31.Pitt B, Poole-Wilson PA, Segal R *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;**355**:1582–7.
32.Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–75.
33.Hauptman PJ, Kelly RA. Digitalis. *Circulation* 1999;**99**: 1265–70.
34.Kapoor WN. Syncope. *N Engl J Med* 2000;**343**:1856–62.
35.The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**: 1576–83.
36.Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–40.
37.Moss AJ, Zaveha W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardiol infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
38.Fonarow GC, Feliciano Z, Boyle NG *et al.* Improved survival in patients with nonischemic advanced heart failure and syncope treated with an implantable cardioverter-defibrillator. *Am J Cardiol* 2000;**85**:981–5.
39.Klein H, Auricchio A, Reek S *et al.* New primary prevention trials of sudden cardiac death in patients with left ventricular dysfunction: SCD-HEFT and MADIT-II. *Am J Cardiol* 1999; **83**:91D–7D.

71 Atrial fibrillation

Michael Klein

Case 1

A 74 year old woman who had been followed with annual examinations requested an interim office visit because of exertional shortness of breath and palpitations. Review of her medical records confirmed the absence of asthma, diabetes or cardiovascular disease and the presence of easy bruising when using aspirin on a regular basis. Recent blood pressures have been 150–160/70–80 mmHg and the possibility of drug treatment for systolic hypertension had been discussed, but she opted for a healthy lifestyle, including recreational exercise three to four times a week. On this occasion her BP was 156/72. The lungs were clear and there was no ankle edema. Cardiac examination showed variable intensity S1, A2 > P2, No S3 and a 1/6 mitral systolic ejection murmur. Thyroid examination was normal and thyroid chemistries were TSH 4·0, total T_4 7·2 micrograms/dl, total T_3 1·2 ng/ml. ECG confirmed atrial fibrillation with a ventricular rate of 96/min, normal voltage and QRS interval, and a QRS axis of minus 45 degrees, signifying left anterior fascicular delay.

Question

What should be done now?

Comment

Three issues need to be reviewed with the patient: the most likely cause of the atrial fibrillation; the desirability of cardioversion, with restoration and maintenance of sinus rhythm; and the rationale for lifelong anticoagulation therapy.

In this case, lacking any clinical features of coronary, hypertensive, valvular or myopathic heart disease, the atrial fibrillation is most likely to be due to electrical and, perhaps, mechanical remodeling of the atria. Heterogeneous electrical properties throughout the atria have evoked the trigger to provoke atrial fibrillation and the substrate to sustain it.[1,2] Moreover, the persistence of atrial fibrillation undermines effective heart rate control, resulting in exertional dyspnea and palpitations, and is associated with thrombus formation, especially in the left atrial appendage.[3] Consequently, there is an increased risk of thromboembolic stroke, particularly when atrial fibrillation converts back to sinus rhythm.

Careful appraisal of the patient's story suggested that her symptoms had been present for several days. Three options for abrogating the atrial fibrillation were reviewed with her: (1) anticoagulation and antiarrhythmic drug usage with interim transthoracic echocardiography (TTE) to quantify left ventricular systolic function, left atrial size, and search for atrial thrombus; then, elective cardioversion in 3–4 weeks, if drug therapy did not remit the atrial fibrillation; (2) 3–4 weeks of warfarin anticoagulation and interim TTE, followed by elective cardioversion with an INR 2·0–3·0 to minimize the risk of thromboembolic stroke;[4] (3) anticoagulation with heparin, expedited hospitalization for transesophageal echocardiography (TTE), and facilitated cardioversion, if there were no evidence of atrial thrombi. The patient was assured that TEE would provide a clearer view of the left atrial appendage than TTE;[5] could quantify left atrial appendicular inflow and outflow blood velocity, enhancing clot identification and possibly improving stroke risk estimate;[6] and had been carefully documented in a randomized clinical trial to be an effective and safe alternative strategy for guiding cardioversion of atrial fibrillation, with an embolic event risk 0·8% compared to conventional 3–4-week anticoagulation with TTE of 0·5%.[7] Additionally, TEE-guided cardioversion could reduce the rate of recurrent atrial fibrillation during the year following restoration of sinus rhythm.[8] Because the electrical remodeling and reverse remodeling processes that accompany atrial fibrillation and its correction occur over several days,[9] other mechanisms, such as reverse mechanical or structural remodeling of the atria, would be beneficially involved in the prevention of atrial fibrillation by prompt cardioversion.[1] The patient understood that the longer atrial fibrillation persisted the more difficult it would be to restore sinus rhythm and prevent recurrence of this disorder, and opted for facilitated cardioversion.

Follow up

The TEE showed normal LV wall thickness, size and function (LVEF 60%); the LA was normal in size (38 mm) and contained no clot even in its appendage. That same morning cardioversion was successfully accomplished with a 100 J transthoracic countershock restoring sinus rhythm. The patient was discharged on low molecular weight heparin for several days, and anticoagulation with warfarin with an intended INR of 2·0–3·0 was continued. The absence of diabetes, heart failure or prior thrombotic stroke or transient ischemic attack suggested a low future risk for atrial fibrillation related stroke,[10] as did the normal LV and LA parameters on echocardiography.[11] Because population-based studies have showed the attributable risk of stroke for atrial fibrillation to increase substantially in the eighth and ninth decades,[12] plans were made for long-term anticoagulation and warfarin surveillance via an anticoagulation clinic. Low-dose β blocker and angiotensin converting enzyme inhibitor therapy was given to lower systolic pressure.[13] Agents of these two antihypertensive classes were also selected to blunt adrenergically mediated triggers for atrial fibrillation[1] and to suppress angiotensin II contributions to an arrhythmogenic electrical dispersion substrate via regional increases in L-type Ca currents (I Ca, L), regional decreases in transient outward potassium currents (It_0), and atrial fibrosis and atrial myocyte hypertrophy.[14,15]

References

1. Allessie MA, Boyden PA, Camm AJ *et al.* Pathophysiology and prevention of atrial fibrillation. *Circulation* 2001;**103**: 769–77.
2. Fareh S, Villemaire C, Nattel S. Importance of refactoriness heterogenity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. *Circulation* 1998;**98**:2202–9.
3. Aberg H. Atrial fibrillation. A study of atrial thrombosis and system embolism in a necropsy material. *Acta Med Scand* 1996;**195**:373–9.
4. Laupacis A, Albers G, Dalen J, Dunn MI, Jacobson AK, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest* 1998; **144**(Suppl.):579s–89s.
5. Manning WJ, Weintraub RM, Waksmonski CA *et al.* Accuracy of transesophageal echocardiography for identifying left atrial thrombi: A prospective intraoperative study. *Ann Intern Med* 1995;**123**:817–22.
6. Atrial fibrillation investigators. Atrial fibrillation risk factors for embolization and efficacy of antithrombotic therapy. *Arch Intern Med* 1994;**154**:1149–57.
7. Klein AL, Grimm RA, Murray RD *et al.* For the assessment of cardioversion using transesophageal echocardiography investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–20.
8. Silverman DI, Manning WJ. Strategies for cardioversion of atrial fibrillation: time for a change? *N Engl J Med* 2001;**344**:1468–9.
9. Yu WC, Lee SH, Tai CT *et al.* Reversal of atrial electrical remodeling following cardioversion of longstanding atrial fibrillation in man. *Cardiovasc Res* 1999;**42**:470–6.
10. Stroke Prevention in Atrial Fibrillation Investigators. Prevention of thomboembolism in atrial fibrillation: I. Clinical features of patients at risk. *Ann Intern Med* 1992; **116**:1–5.
11. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;**116**:6–12.
12. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991;**22**:983–8.
13. Kaplan NM. New issues in the treatment of isolated systolic hypertension. *Circulation* 2000;**102**:1079–81.
14. Sadoshima J, Isumo S. The cellular and molecular response of cardiac myocytes to mechanical stress. *Annu Rev Physiol* 1997;**59**:551–71.
15. Goette A, Arndt M, Röcken C *et al.* Regulation of angiotensin II receptor subtypes during atrial fibrillation in humans. *Circulation* 2000;**101**:2678–81.

Case 2

A 69 year old man had a history of chronic coronary heart disease. He had sustained two prior myocardial infarctions which cumulatively had resulted in congestive heart failure. Persistent exertional angina prompted cardiac catheterization, which identified three-vessel severe (>70% luminal diameter narrowing) obstructive coronary artery disease and severe LV systolic dysfunction (LVEF 30%). Three-vessel coronary bypass surgery was successfully completed, with perioperative use of amiodarone to suppress atrial fibrillation (AF). Medical therapy with angiotensin converting enzyme inhibitor, glycoside, diuretic, statin, aspirin and β blocker was continued for chronic heart failure. During outpatient cardiac rehabilitation monitoring sinus rhythm with rare atrial and ventricular premature beats was confirmed and no exertional angina was observed. Exercise capacity improved. One year later the patient complained of exertional fatigue. Repeat ECG showed AF with a ventricular rate of 90 at rest, left ventricular hypertrophy, and old anteroseptal and inferior myocardial infarction patterns. On examination there was no evidence of pulmonary congestion or peripheral edema and the BP was 116/70.

Question

What is the best course of action?

Comment

The principal hazard from atrial fibrillation would be enhanced thromboembolic stroke risk. Warfarin anticoagulation can reduce this risk by about two thirds;[1] although it has not been conclusively proved that restoration of sinus rhythm will significantly reduce cardiovascular mortality,[2] in this case resumption of coordinated atrial contraction (atrial transport and booster pump function) would enhance left ventricular filling by >25%, fortifying left ventricular stroke output via a Starling mechanism while tending to lower left atrial pressure. Symptoms of exertional fatigue and shortness of breath would thereby be improved. Warfarin was initiated, and 3 weeks after attaining an INR of between 2·0 and 3·0 transthoracic electrical cardioversion using a damped sign wave monophasic waveform was attempted. Countershocks of up to 400 J were unsuccessful in restoring sinus rhythm, however.

Question

What should be done now?

Further comment

The patient was informed that antiarrhythmic drug therapy with amiodarone could reduce the heterogeneity of regional atrial electrical properties seen in AF, and that it had been successfully used to suppress AF at the time of his coronary bypass surgery. He was also informed that clinical trial evidence had indicated a significantly lower frequency of AF in this setting (22·5% *v* 38·0%).[3] Additional clinical data had also showed the value of amiodarone in the conversion to and maintenance of sinus rhythm in chronic heart failure patients with AF.[4] In the event that AF still persisted after amiodarone therapy then transthoracic cardioversion could again be attempted, this time using a rectilinear *biphasic* waveform device. These devices have greater efficacy and require less countershock energy in restoring sinus rhythm.[5] They utilize impedance compensation, ensuring a constant current delivery to depolarize the heart, and are especially advantageous in patients with high impedance.[6] The patient concurred with these plans. Amiodarone therapy 400 mg tid for 1 week, followed by 400 mg daily, was established. Digoxin dosage was reduced from 0·125 mg daily to three times a week to accommodate the amiodarone reduction in digoxin excretion. Warfarin daily dosage was also modified downward to allow for its interaction with amiodarone. The INR was maintained between 2·0 and 3·0. With persisting AF after 1 month of amiodarone therapy, electrical cardioversion was successfully accomplished using a biphasic waveform device. Amiodarone was then reduced to 200 mg daily and aspirin reduced to 81 mg daily as INR-adjusted warfarin was continued.

Follow up

The patient was now taking seven drugs for his chronic heart failure. The quartet of agents (ACE inhibitor, glycoside, diuretic, β blocker) fortified the heart mechanically and mitigated excess adrenergic stimulation, thereby reducing triggering mechanisms for atrial fibrillation. They also provided a framework for interdicting the excess adrenergic stimulation that accompanies chronic heart failure and which is deleterious to the progressive LV dilatation and hypertrophy that accompanies this condition. The aspirin and warfarin were deployed to minimize the likelihood of recurrent heart attacks and both ischemic[7] and thromboembolic stroke,[8] associated with atrial fibrillation. The aspirin was also deployed to reduce mortality risk.[9] Amiodarone was utilized to maintain sinus rhythm. Post hoc analysis of clinical trial data provided an additional rational for combined β blocker/amiodarone usage: significant reductions in sudden and non-sudden cardiac deaths.[10] The complex drug regimen was justified in this case as atrial fibrillation did not recur, a crucial matter, as randomized clinical trial data have indicated that AF is associated with increased mortality in heart failure patients (CHF)[11] and is an independent predictor of mortality in CHF patients with implanted cardioverter defibrillators.[12] In the future more advanced dual channel implantable defibrillators may allow additional strategies for coping with AF in this seriously ill population.[13]

References

1. Hirsh J, Dalen JE, Anderson DR *et al.* Anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;**114**:445s–69s.
2. Wyse DG, Anderson JL, Antman EM *et al.* Atrial Fibrillation Follow-Up Investigation of Rhythm Management – the AFFIRM study design. *Am J Cardiol* 1997;**79**:1198–202.
3. Giri S, White CM, Dunn AB *et al.* Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomized placebo-controlled trial. *Lancet* 2001;**357**:830–6.
4. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher F, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: Observations from the Veterans Affairs Congestive Heart Failure Survival Trial Antiarrhythmic Therapy (CHF-STAT). *Circulation* 1998;**98**:2574–9.
5. Mittal S, Ayati S, Stein KM *et al.* Transthoracic cardioversion of atrial fibrillation. Comparison of rectilinear biphasic versus

damped sign wave monophasic shocks. *Circulation* 2000; **101**:1282–7.
6. Kerber RE, Martins JB, Kienzle MG *et al.* Energy, current, and success in defibrillation and cardioversion: clinical studies using an automated impedance-based method of energy adjustment. *Circulation* 1998;**77**:1038–46.
7. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW, Sutton GC. Antithrombotic agents in coronary artery disease. *Chest* 1998;**114**:611s–33s.
8. Albers GW, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 1998;**114**: 683s–98s.
9. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease. A propensity analysis. *JAMA* 2001;**286**:1187–94.
10. Boutitie F, Boissel J-P, Connolly SJ *et al.* and the EMIAT and CAMIAT investigators. Amiodarone interaction with β-blockers. Analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and the CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999;**99**:2268–75.
11. Dries DL, Exner DW, Gersh BJ *et al.* Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the Solvd trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998;**32**:695–703.
12. Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**: 1576–84.
13. Friedman PA, Dijkman B, Warman EN *et al.* for the Worldwide Jewel AF Investigators. Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. *Circulation* 2001;**104**:1023–8.

72 Ventricular dysrhythmias: pharmacologic *v* non-pharmacologic treatment

L Brent Mitchell

Case scenario 1

At the age of 60 years, Mr D presents a therapeutic choice in the management of a patient who has had ventricular tachycardia (VT). Two years previously he had experienced an acute anterolateral myocardial infarction but did not receive thrombolysis. When post-MI angina continued, he underwent cardiac catheterization which demonstrated three vessel coronary artery disease and compromised LV function. Accordingly, he underwent three vessel coronary artery bypass surgery. Thereafter, Mr D was free of any potential cardiovascular symptoms until now, when he presents to the Emergency Department after the sudden onset, while performing minor car maintenance, of presyncope followed by diaphoresis and dyspnea. He is found to have VT at a rate of 175 beats per minute with a right bundle branch "block" pattern, a left axis deviation QRS morphology and 2 : 1 retrograde VA block (Figure 72.1). His systolic BP is 85 mmHg. Under general anesthesia this rhythm is cardioverted with a 50 J QRS synchronous D/C shock to another VT with a right bundle branch "block" configuration and right axis deviation QRS morphology (Figure 72.2). A second 200 J QRS synchronous D/C shock restores normal sinus rhythm. His initial postconversion evaluation reveals no transient or reversible causes of VT (such as acute myocardial infarction, electrolyte disturbance or proarrhythmic drug effect).

On a treadmill exercise test Mr D exercises for 4 minutes, reaching stage II of the standard Bruce protocol. The end point was dyspnea at a maximum heart rate of 153 beats per minute (target heart rate = 136 beats per minute). The blood pressure response is flat. There is no evidence of reversible myocardial ischemia or exercise-related arrhythmia. A 24 hour ambulatory ECG shows sinus rhythm within the physiologic rate range and only rare isolated premature ventricular beats (two on the 24 hour recording). A cardiac catheterization demonstrates patent coronary bypass grafts and no new native coronary artery lesions. His left ventricular angiogram reveals an anteroapical LV aneurysm.

A catheter electrophysiologic study shows normal sinus nodal, atrial, and AV nodal electrophysiology. The HV interval is prolonged to 60 msec. Programmed ventricular stimulation induces sustained VT (Figure 72.3) that matches the initial presenting VT and could be pace terminated. The mechanism of the VT is not bundle branch re-entry. Intravenous procainamide is administered (total dose 1 g). Thereafter, VT is no longer inducible.

Question:

What treatment, if any, should now be applied?

Comment

For this case, current available "best" evidence does not define a single preferred therapeutic approach. This 60 year old male presents with hypotensive VT in the setting of stable atherosclerotic heart disease on the background of a previous anterolateral wall myocardial infarction and a left ventricular aneurysm. After ruling out a transient or reversible cause for his VT and optimizing the therapy of underlying structural heart disease, an electrophysiologic study demonstrated the persistence of a substrate for VT that was suppressed by intravenous procainamide.

Viable alternatives for the treatment of this man's high future risk of VT recurrence include (a) standard antiarrhythmic drug therapy individualized by the Holter monitoring

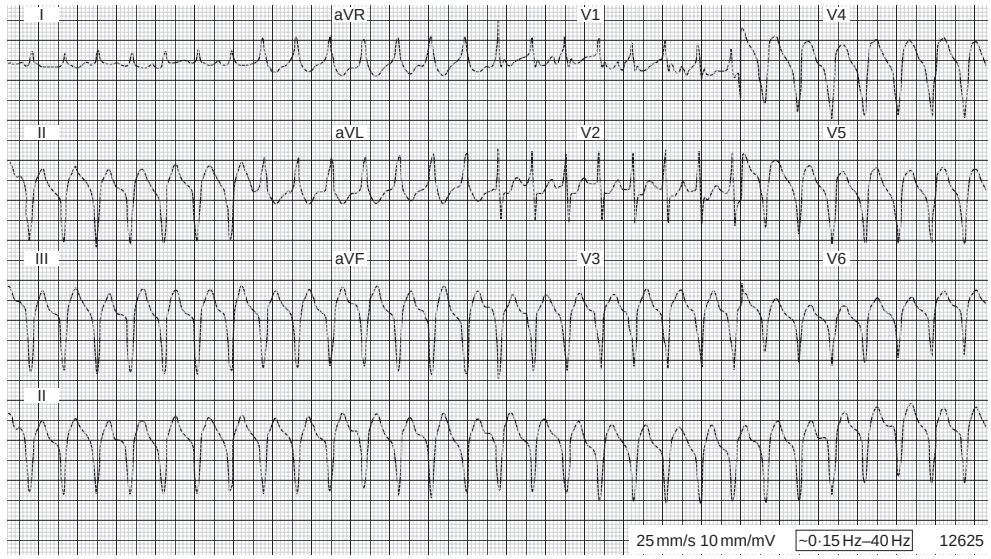

Figure 72.1 Presenting ventricular tachycardia of right bundle branch "block" pattern with left axis deviation QRS morphology and 2:1 retrograde VA block

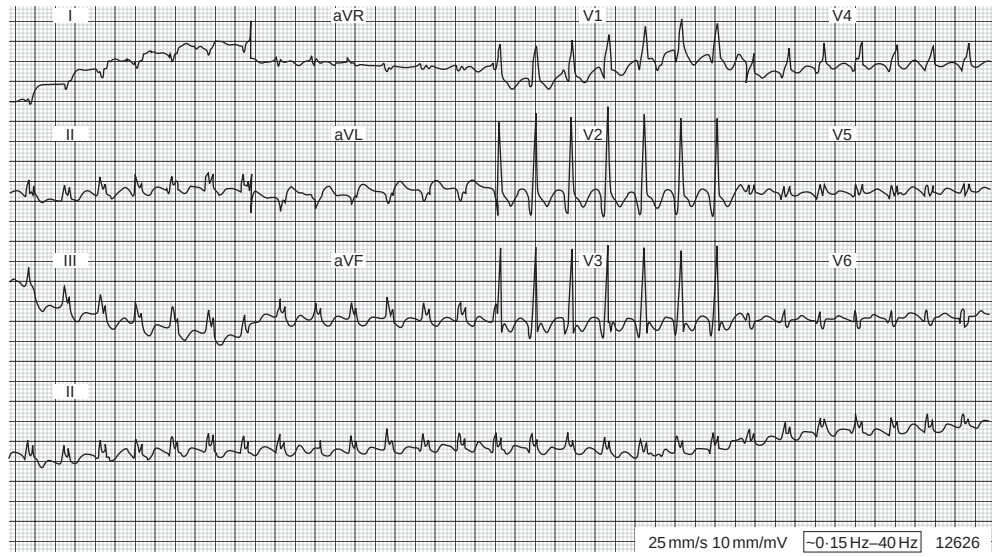

Figure 72.2 Ventricular tachycardia with right bundle branch "block" configuration and right axis deviation QRS morphology after low energy cardioversion

approach; or (b) the electrophysiologic study approach; or (c) empiric amiodarone therapy; or (d) implantation of a tiered therapy implantable cardioverter defibrillator (ICD); or (e) surgical/transcatheter ablative therapy. In addition, grade B evidence supports the concomitant use of ancillary β blocker therapy where possible.[1]

Mr D's clinical circumstance is a frequent clinical scenario, and such patients have been the most commonly recruited subjects of clinical trials evaluating treatment for life threatening VT. Nevertheless, there is still uncertainty as to the most appropriate initial form of therapy. Randomized clinical trials relative to the treatment of this patient population include the Calgary study;[2] ESVEM: Electrophysiologic Study versus Electrocardiographic Monitoring Study;[3] CASCADE: Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation;[4] the Antiarrhythmics versus Implantable Defibrillator (AVID) trial;[5] the Cardiac Arrest Study Hamburg (CASH);[6] and the Canadian Implantable Defibrillator Study (CIDS).[7] It should be noted that each of these trials compares one therapy to another therapy. To

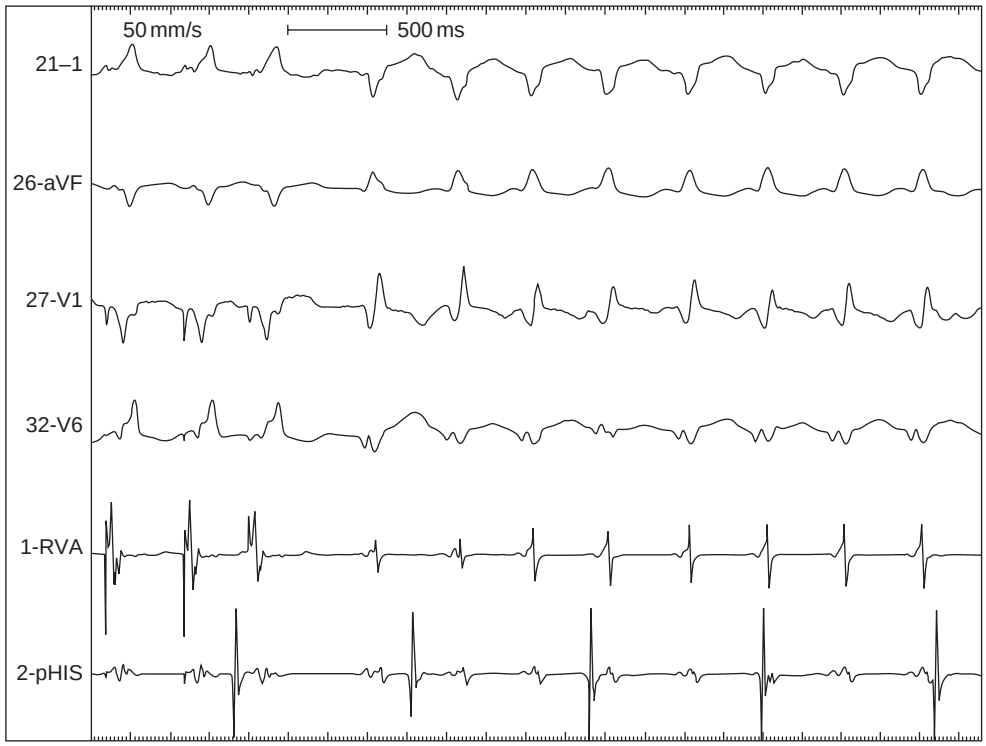

Figure 72.3 Ventricular tachycardia of right bundle branch "block" configuration and right axis deviation QRS morphology induced by program stimulation

date, ethical considerations have precluded comparisons of one form of therapy to no therapy.

Both the Calgary study and the ESVEM trial compared the long-term outcome of patients treated with standard antiarrhythmic drug therapy selected by the Holter monitoring approach to that selected by the electrophysiologic study approach. In a small population of drug naive patients with inducible VT, the Calgary study reported superiority of therapy selected by the electrophysiologic study approach. Furthermore, such therapy was associated with low VT recurrence and sudden death probabilities in the Calgary trial. In contrast, in a larger population of drug resistant patients with either inducible VT or VF, the ESVEM trial reported equivalence of therapy selected by either of the approaches. Furthermore, such therapy was associated with a high VT/VF recurrence rate in the ESVEM trial. Mr D's clinical situation was most comparable to the patients in the Calgary trial who had arrhythmia substrates for which the electrophysiologic study performs best (inducible VT in the setting of stable atherosclerotic heart disease). Furthermore, Mr D did not have sufficient spontaneous ventricular arrhythmia on his Holter monitor to provide an index to guide the Holter monitoring approach. Accordingly, Mr D had standard antiarrhythmic drug therapy – procainamide in this case – selected by the electrophysiologic study approach.

Empiric amiodarone therapy was considered. The most impressive data supporting the use of empiric amiodarone in a patient such as Mr D emerges not from randomized clinical trials but rather from descriptions of excellent long-term outcomes of patients who had failed other therapy and then received empiric amiodarone. Some would argue that CASCADE demonstrated the superiority of empiric amiodarone over standard antiarrhythmic drug therapy in this setting. However, we must recall that CASCADE included only patients with out-of-hospital VF cardiac arrests. Furthermore, in CASCADE, empiric amiodarone appeared superior to antiarrhythmic therapy selected by either the electrophysiologic study approach or the Holter monitoring approach (rather than the better of these two approaches). Finally, many of the patients in the standard antiarrhythmic therapy limb of CASCADE received therapy that was predicted to be (and presumably was) ineffective. Nevertheless, this report and the concerns regarding the inefficacy of standard antiarrhythmic therapy in the ESVEM trial have allowed empiric amiodarone to emerge as the "gold standard" pharmacologic therapy to which ICD therapy is being compared in ongoing trials. Accordingly, this therapeutic choice would also have been appropriate.

Electrosurgery/transcatheter ablation therapy was considered. Ablative therapies have had their greatest success in patients with atherosclerotic heart disease and previous myocardial infarction. This is particularly true if another indication exists for open heart surgery, such as a need for a coronary revascularization procedure. Nevertheless, this

approach exposes the patient to an important surgical mortality and may not be appropriate for patients with a single episode of VT who do not need coronary revascularization and have other therapeutic alternatives. Of course, had the electrophysiologic study demonstrated a VT that required the participation of the right bundle branch (bundle branch re-entry), then ablation of the right bundle branch would have been a preferred form of therapy.

The use of an implantable automatic cardioverter defibrillator (ICD) was considered. Once reserved for patients with VT/VF resistant to other therapy, the long-term results of ICD therapy have been impressive. Furthermore, the Data and Safety Monitoring Board of the AVID trial recently recommended that the study be terminated after slightly more than 1000 patients had been enrolled as a statistically significant advantage had emerged relative to all-cause mortality in favour of the ICD over antiarrhythmic drug therapy, consisting of empiric amiodarone for the vast majority of patients with a few having received sotalol, that was predicted to be effective by either the electrophysiologic study approach or the Holter monitoring approach. However, preliminary costing analysis has suggested that the ICD may not be an economically competitive strategy, with a cost per year of life saved of approximately $130 000. Nevertheless, patients such as Mr D frequently receive an ICD. Of note, the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT),[8] which suggested the superiority of ICD therapy over "conventional" therapy, are not relevant to patients such as Mr D. All the patients enrolled in MADIT had demonstrated drug-resistant VT by virtue of continued VT induction after the administration of IV procainamide.

Outcome

Mr D had therapy initiated with oral procainamide. On Procan-SR 1000 mg q 6 hours, his procainamide level was 26 μmol/l (therapeutic range 17–43 μmol/l) and his NAPA level was 19 μmol/l. A drug assessment electrophysiologic study was performed and no VT/VF was inducible. In follow up, Mr D's procainamide dosage has been altered to maintain the procainamide/NAPA levels that were predicted to be effective, requiring dosages as high as 1250 mg q 6 hours and as low as 750 mg q 6 hours. He has now been receiving this therapy for 6 years without arrhythmia recurrence.

References

1. Szabo BM, Crijns HJGM, Wiesfeld ACP *et al*. Predictors of mortality in patients with sustained ventricular tachycardias or ventricular fibrillation and depressed left ventricular function: importance of beta blockade. *Am Heart J* 1995;**130**:281–6.
2. Mitchell LB, Duff HJ, Manyari DE, Wyse DG. A randomized clinical trial of the noninvasive and invasive approaches to drug therapy of ventricular tachycardia. *N Engl J Med* 1987; **317**:1681–7.
3. Mason JW, Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias. *N Engl J Med* 1993;**329**: 445–51.
4. The CASADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASADE study). *Am J Cardiol* 1993;**72**:280–7.
5. AVID Investigators. Antiarrhythmics versus Implantable Defibrillator (AVID): rationale, design and methods. *Am J Cardiol* 1995;**75**:470–5.
6. Siebels J, Cappato R, Ruppel R *et al*, CASH Investigators. ICD versus drugs in cardiac arrest survivors: preliminary results of the cardiac arrest study Hamburg. *PACE* 1993;**16**:552–8.
7. Connolly SJ, Gent M, Roberts RS *et al*, CIDS Investigators. Canadian Implantable Defibrillator Study (CIDS): study design and organization. *Am J Cardiol* 1993;**72**:103F–108F.
8. Moss AJ, Hall J, Cannom DS, Doubert JP *et al*, Multicenter Automatic Defibrillator Implantation Trial Investigators (MADIT). Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.

Case scenario 2

Miss M presents a therapeutic choice in the management of a propensity to ventricular tachycardia (VT) at the age of 17 years. When Miss M was 3 years old her father died suddenly during sleep at the age of 28 years. The father's autopsy documented the presence of a right ventricular cardiomyopathy. When Miss M was 13 years of age her sister died suddenly during sleep at the age of 18 years. The sister's autopsy documented the presence of a right ventricular cardiomyopathy. Understandably, Miss M's mother became alarmed and Miss M was referred for her initial evaluation. That evaluation included clinical examination, a 2D echocardiographic examination, a biventricular radionuclide angiogram, a Holter monitoring examination, and a treadmill exercise test. All were entirely normal. Over the next three years, annual clinical examinations, Holter monitoring examinations, and echocardiographic examinations remained normal. However, her annual evaluation at the age of 17 years included a Holter examination showing frequent ventricular premature beats (14 VPB/hour) that were complex to the level of four beat salvos of consecutive ventricular beats. Accordingly, a search for evidence of right ventricular structural heart disease and for a propensity to ventricular tachyarrhythmia was undertaken.

An echocardiographic examination shows questionable right ventricular enlargement. A biventricular radionuclide angiogram shows normal right and left ventricular size and function at rest but the right ventricle becomes mildly and diffusely hypokinetic with supine bicycle exercise. Cardiac catheterization is performed and the right ventricular angiogram demonstrates two dyskinetic right ventricular segments. A treadmill exercise test precipitates a ventricular triplet. Finally, a transvenous catheter electrophysiologic study is performed. Triple ventricular extra stimuli applied during right ventricular pacing at a rate of 150 bpm initiates a polymorphic VT that then stabilizes into sustained monomorphic VT at a rate of 230 bpm. The monomorphic VT has a left bundle branch "block" configuration and normal frontal plane QRS axis morphology.

Question:

What treatment, if any, should now be applied?

Comment

Although this high-risk state is rare, there is persuasive evidence in the literature that should help guide therapy. The studies performed in this 17 year old female indicate both structural right ventricular disease and a propensity to VT with a QRS morphology consistent with a right ventricular "origin". One must conclude that Miss M has developed the same arrhythmogenic right ventricular dysplasia (ARVD) that had affected her father and her sister. The natural history of this disorder as defined by her father and her sister strongly suggests that Miss M is at high risk of sudden death. In this setting, Miss M's viable therapeutic alternatives include individualized antiarrhythmic drug therapy selected by (a) the Holter monitoring approach or (b) the electrophysiologic study approach; or (c) empiric amiodarone; or (d) electrosurgery/transcatheter ablation; or (e) placement of an implantable automatic cardioverter defibrillator (ICD).

Miss M's clinical circumstance is unusual and has not been the subject of specific randomized clinical trials. The closest patient population studied to date is that of the Multicenter Automatic Defibrillator Implantation Trial (MADIT),[1] which suggested that early use of an ICD was superior to "conventional" therapy. However, the study population of MADIT (patients with remote myocardial infarction, compromised left ventricular function, and inducible sustained VT/VF that could not be suppressed by intravenous procainamide) was unrelated to that of Miss M. Accordingly, a therapeutic decision was made without definitive clinical trial data.

Individualized antiarrhythmic drug therapy was considered. Both approaches to individualized antiarrhythmic drug therapy have been validated in patient populations dominated by atherosclerotic heart disease. Furthermore, such therapy is more prone to failure when the underlying structural heart disease is cardiomyopathic rather than atherosclerotic. Nevertheless, the factor that most recommended an alternative approach was that if a spontaneous episode of VT/VF subsequently occurred, it would be impossible to distinguish between a failure of drug therapy to prevent an episode of VT/VF that was inevitable and a proarrhythmic drug response that precipitated an episode of VT/VF that was not otherwise going to occur.

Empiric β blocker therapy was considered. Steinbeck *et al*[2] have published evidence suggesting that empiric β blocking therapy is as effective as antiarrhythmic drug therapy selected by the electrophysiologic approach for the prevention of VT/VF. Careful scrutiny of their results shows that empiric β blocking therapy is actually more effective than is standard drug therapy predicted to be ineffective by the electrophysiologic study approach, but is less effective than is a standard drug therapy predicted to be effective by the electrophysiologic study approach. Nevertheless grade B evidence supports the concomitant use of ancillary β blocking therapy where possible.[3]

Empiric amiodarone was considered. Empiric amiodarone has prophylactic efficacy in patient populations at high risk of VT/VF who have not yet experienced a spontaneous VT/VF episode. Such trials include that of Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA),[4] CHF-STAT,[5] the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT),[6] and the European Myocardial Infarct Amiodarone Trial (EMIAT).[7] Furthermore, GESICA and CHF-STAT suggested that empiric amiodarone is particularly effective when the underlying structural heart disease is cardiomyopathic rather than atherosclerotic. Finally, the proarrhythmic potential of amiodarone is very low (approximately 1%), rendering the probability of a future need to distinguish drug failure from proarrhythmia vanishingly small. Nevertheless, the factor that most recommended an alternative approach was the expected adverse effect profile of amiodarone in one so young who might require therapy for more than 50 years.

Electrosurgery/transcatheter ablation therapy was considered. Ablative therapies have had their greatest success in patients with atherosclerotic heart disease and previous myocardial infarction.[8] The probability of long-term success

is compromised in patients with a cardiomyopathy, especially when the natural history of that cardiomyopathy is progression with new lesion formation. Although a right ventricular disconnection electrosurgical procedure has been developed for the treatment of patients with arrhythmogenic right ventricular dysplasia, the long-term consequences of right ventricular failure are frequently devastating. Nevertheless, the factor that most recommended an alternative approach was consideration of the surgical risk in a person who has not yet had a spontaneous episode of VT/VF.

These considerations favored the implantation of an ICD. ICD therapy provides excellent protection from sudden death in patients whose structural heart disease is atherosclerotic or cardiomyopathic.[9] Furthermore, the proarrhythmia potential of an ICD is low, thereby reducing concern as to a future need to distinguish between therapeutic failure and therapy-related proarrhythmia. Finally, the availability of single lead transvenous ICD conformations allows the therapy to be instituted with a low-risk surgical procedure.

Outcome

Miss M had her ICD implanted when she was 17 years of age. The procedure was uncomplicated and her convalescence was unremarkable. Three years later, her ICD reached end of battery life indicators. During these years she did not have a spontaneous episode of VT/VF and had received no therapies from her device. A new ICD impulse generator was implanted when Miss M was 20 years of age. One year later, 4 years after her initial presentation, Miss M was playing baseball (at bat) when she suddenly felt marked presyncope followed by a shock from her ICD. She then felt well and completed her turn at bat. Subsequent interrogation of her ICD showed that the pre-event rhythm was sinus tachycardia at 162 beats per minute that gave way to a ventricular tachycardia at 300 beats per minute. These rhythm assessments were augmented by the availability of ICD stored intracardiac electrograms. She is presently undergoing genetic counseling relative to her desire to conceive a child – evidence of a satisfactory quality of life.

References

1. Moss AJ, Hall J, Cannom DS *et al.* Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.
2. Steinbeck G, Anderson D, Bach P *et al.* A comparison of electrophysiologically guided antiarrythmic drug therapy with beta blocker therapy in patients with symptomatic sustained ventricular arrythmias. *N Engl J Med* 1992;**327**:987–92.
3. Szabo BM, Crijns HJGM, Weisfeld ACP *et al.* Predictors of mortality in patients with sustained ventricular tachycardias or ventricular fibrillation and depressed left ventricular function: importance of beta blockade. *Am Heart J* 1995;**130**:281–6.
4. Doval HC, Nul DR, Grancelli HO *et al*, GESICA Investigators. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;**344**:493–8.
5. Singh SN, Fletcher RD, Fisher SG *et al*, CHF-STAT Investigators. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;**333**:77–82.
6. Cairns JA, Connolly SJ, Roberts R, Gent M, CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) Investigators. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations: CAMIAT. *Lancet* 1997;**349**:675–82.
7. Julian DG, Camm AJ, Frangin G *et al*, EMIAT Investigators. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;**349**:667–74.
8. Levy S. Non-medical therapy of ventricular tachyarrhythmias. *Eur Heart J* 1989;**10**(Suppl. E):48–52.
9. Gillis AM. The current status of the implantable cardioverter defibrillator. *Annu Rev Med* 1996;**47**:85–93.

73 Bradyarrhythmias: choice of pacemaker

John A Boone

Case scenario 1

A 66 year old man had a VVIR pacemaker implanted because of syncope owing to complete heart block. He was previously well except for one documented and, possibly, a second undocumented episode of atrial fibrillation. An ECG taken prior to pacemaker insertion showed sinus bradycardia. When he presented with transient complete heart block it was believed he would do well with VVIR pacing. However, he now presents with a form of "pacemaker syndrome" characterized by a combination of fatigue and the presence of cannon A waves from intermittent VA conduction (Figure 73.1). Furthermore, episodes of paroxysmal atrial fibrillation became more frequent and, interestingly, he was less symptomatic when in atrial fibrillation, presumably due to the absence of cannon waves. He was anticoagulated with warfarin. As he was in sinus rhythm more often than in atrial fibrillation, and as he was symptomatic with asynchronous pacing, the VVIR pacemaker was removed and his pacing was "upgraded" to DDDR pacing (Figure 73.2).

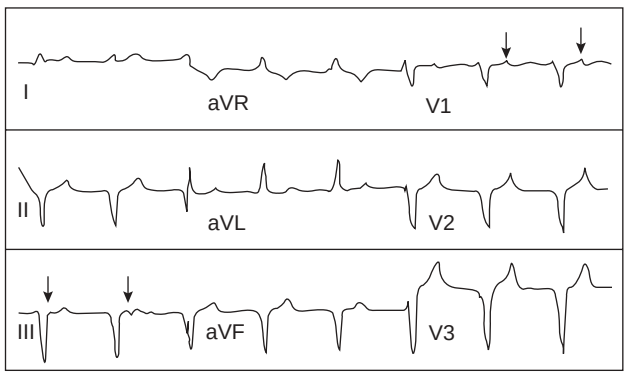

Figure 73.1 VVI pacing with ventricular dissociation (arrows)

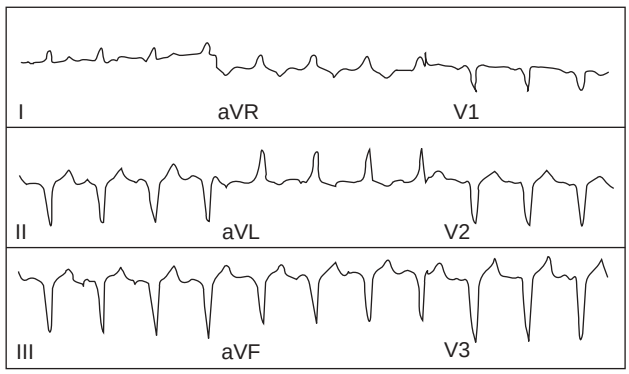

Figure 73.2 Pacing following implantation of DDDR pacemaker

Question

Should this patient have had a DDD type pacemaker inserted from the start?

Comment

With established symptoms of syncope in the presence of documented complete heart block there is little doubt about the need for pacemaker implant for this patient. Rather, one seeks evidence to support the choice of the optimum pacemaker mode. The treatment of symptomatic acquired complete heart block by cardiac pacing became established practice in the 1960s. Following the introduction of permanent cardiac pacing – initially VOO followed by VVI (see Chapter 42 for description of pacemakers) – published experience clearly documented that patients with complete heart block and syncope had an improved survival.[1–3]

Although one might have felt intuitively that "physiologic" pacing was indicated from the start in this patient, a recent trial that randomized patients to receive either VVI (R) or physiologic pacing failed to show the benefit expected from dual chamber pacing, this despite the observations from several older studies that demonstrated a benefit of atrial synchrony over VVI pacing[4–7] in evaluating cardiac output, exercise capacity, and feeling of wellbeing. However, the increase in cardiac output with exercise is mostly achieved by an increase in heart rate rather than by

AV synchrony.[8–10] It was on this basis, namely, to enable adequate tracking of the patient's physical activity, that VVIR pacing was originally chosen in this patient.

However, factors other than exercise capacity may determine suitability of a particular pacing mode, as exemplified by this patient, wherein VVI pacing caused a form of pacemaker syndrome – that is, a clinical state wherein stroke volume is reduced by virtue of asynchrony between atrial transport function and ventricular systole. The incidence of pacemaker syndrome in VVI pacing is not known but estimates vary from 0·1% to 5%.[11,12]

Other benefits attributed to DDD pacing include prevention of atrial fibrillation, prevention of embolic stroke and other systemic emboli as well as protection from congestive heart failure and early mortality. The data suggesting these benefits are mostly from studies that are retrospective and non-randomized.[13,14] However, when these data are used to calculate annual event rates, there is a two thirds risk reduction for atrial fibrillation and a one third reduction for death in patients who have received DDD pacing. One prospective randomized trial that compared atrial to ventricular pacing found significantly less atrial fibrillation and thromboemboli in the atrial-paced patients compared with those receiving ventricular pacing, but there was no significant difference in congestive heart failure or mortality. Future prospective randomized trials may or may not confirm these findings.

References

1. Friedberg CK, Donoso E, Stein WB. Nonsurgical acquired heartblock. *Ann NY Acad Sci* 1964;**111**:833–47.
2. Donmoyer TL, DeSanctis RW, Austen WG. Experience with implantable pacemakers using myocardial electrodes in the management of heartblock. *Ann Thorac Surg* 1967;**3**:213–27.
3. Edhag O, Swahn A. Prognosis of patients with complete heartblock or arrhythmic syncope who are not treated with artificial pacemakers: a long-term follow-up study of 101 patients. *Acta Med Scand* 1976;**200**:457–63.
4. Connolly SJ, Kerr CR, Gent *et al.* Effect of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators (CTOPP). *N Engl J Med* 2000;**342**:1385–91.
5. Perrins EJ, Morley CA, Chan SL, Sutton R. Randomized control trial of physiological and ventricular pacing. *Br Heart J* 1983;**50**:112–17.
6. Yee R, Benditt DG, Kostuk WJ *et al.* Comparative functional effects of chronic ventricular demand and atrial synchronous ventricular inhibited pacing. *PACE* 1984;**7**:23–8.
7. Rediker DE, Eagle KA, Homma S *et al.* Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. *Am J Cardiol* 1988;**61**:323–9.
8. Fananapazir L, Bennett DH, Monks P. Atrial synchronized ventricular pacing: contribution of the chronotropic response to improved exercise performance. *PACE* 1983;**6**:601–8.
9. Ehrsson SK. Influence of heart rate and atrioventricular synchronization on maximal work tolerance in patients treated with artificial pacemakers. *Acta Med Scand* 1983;**214**: 311–15.
10. McMeekin JD, Lautner D, Hanson S, Gulamhusein SS. Importance of heart rate response during exercise in patients using atrial ventricular synchronous and ventricular pacemakers. *PACE* 1990;**13**:59–68.
11. Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: the effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;**1126**:16–22.
12. Santini M, Alexidou G, Ansalone G *et al.* Relation of prognosis of sick-sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. *Am J Cardiol* 1990;**65**: 729–35.
13. Hesselson AB, Parsonnet V, Bernstein AD, Bonavita GJ. Deleterious effects of long-term single chamber ventricular pacing in patients with sick-sinus syndrome: the hidden benefits of dual chamber pacing. *J Am Coll Cardiol* 1992;**19**: 1542–9.
14. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PEB. Prospective randomized trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet* 1994;**344**:1524–8.

Case scenario 2

A 30 year old woman complains of sudden shortness of breath and exhaustion occurring during moderate to severe exertion. She is fine at the beginning of exercise, but if she continues she feels as if she had "hit a brick wall". She is a member of a womens softball team and the example she gives is when she hits what she believes to be a home-run she would run past first base without difficulty, but beyond that she would suddenly be incapable of running and would barely make it to second base. On one occasion she lost consciousness during exertion. Her history otherwise is unremarkable and clinical examination is completely normal. The ECG shows sinus rhythm with a first degree AV block and a PR interval of 0·38 seconds. An echocardiogram is normal. An exercise stress test is performed according to the Bruce protocol. Upon completion of Stage III her heart rate reaches 166 beats per minute with a PR interval of 0·34 seconds (Figure 73.3). The P waves are superimposed on the terminal portion of the QRS. At this point she experiences sudden exhaustion and the test is terminated.

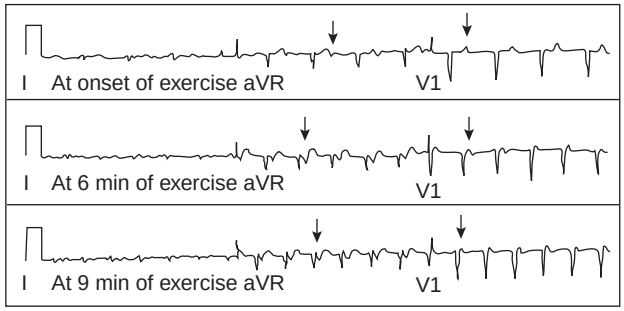

Figure 73.3 Exercise ECG prior to pacemaker implant. Arrows indicate P waves. Note the almost fixed first degree block such that, at the peak of exercise, atria and ventricles depolarize spontaneously

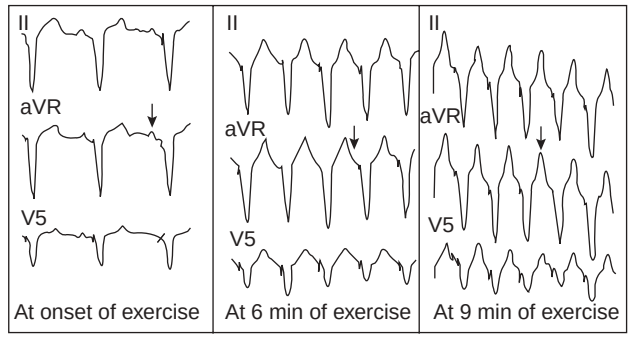

Figure 73.4 Exercise ECG after DDD pacemaker implant. Arrows indicate P waves. Note the DDD pacemaker mode maintains a physiologic AV interval

Question

What advice would you now give her?

Comment

In this rather unusual circumstance, a search for evidence from clinical trials to guide therapy would be better served by reliance on clinical judgment and a sound knowledge of electromechanical physiology. This woman's symptoms were the result of an almost fixed first degree AV block, such that with exercise atrial contraction would frequently occur against closed AV valves during the period of ventricular contraction. The consequence of this is that the atria "empty" in a retrograde fashion during atrial systole (producing the equivalent of "cannon waves") resulting in severely reduced filling volumes. The result is a reduced stroke volume and a fall in cardiac output during heart rate acceleration.

This patient received implantation of a DDD pacemaker with a good clinical result. The device was programmed to a nominal AV delay of 200 msec, thus permitting normal ventricular filling. A repeat exercise test demonstrated ventricular pacing "tracking" sinus rhythm with a more physiologic PR interval (Figure 73.4).

The original published ACC/AHA Task Force guidelines for the implantation of cardiac pacemakers in 1991 state that there is no evidence to support pacemaker implantation in patients with isolated first degree AV block, and thus assign this condition to a class III recommendation – that is, there is general agreement that pacemakers are not necessary. The revised guidelines, however,[1] acknowledge the usefulness of pacemaker implantation for patients with symptomatic first degree AV block. This wise decision is largely based on physiologic need substantiated by the comparison of atrioventricular versus ventricular pacemaker activity on cardiac function as well as the relative low prevalence of these types of cases in the population. This physically active patient clearly benefitted from the pacemaker.

References

1. Barold SS. ACC/AHA guidelines for implantation of cardiac pacemakers. *PACE* 1993;**16**:1221.

74 Valvular heart disease: timing of surgery

Adrian P Banning, Brian B Gribbin

Case 1

A 74 year old man is referred to the cardiology clinic with a 3 month history of worsening breathlessness. Three years earlier he was referred for cardiology review after a systolic murmur had been detected at a routine medical examination. At that time he was asymptomatic, despite an active lifestyle and a Doppler echocardiogram that had shown evidence of a calcified aortic valve with a peak Doppler instantaneous gradient of 70 mmHg (mean gradient 40 mmHg), left ventricular hypertrophy and dynamic left ventricular systolic function. In the absence of symptoms he was advised to avoid sudden or strenuous exercise and of the need for endocarditis prophylaxis. A 6 month follow-up appointment was arranged for clinical assessment and repeat Doppler echocardiography. Subsequently he defaulted from all medical follow up. He now presents with severe exertional dyspnea, orthopnea and paroxysmal nocturnal dyspnea. He has no risk factors for coronary artery disease and there is no history of exertional chest pain or presyncope. Examination reveals a slow upstroke carotid pulse, blood pressure of 115/75, elevated venous pressure, sustained left ventricular impulse, soft aortic closure sound and an ejection systolic murmur. Examination of the lungs reveals a right-sided pleural effusion and bibasal crepitations.

An ECG shows sinus rhythm with voltage criteria of severe left ventricular hypertrophy and a left ventricular strain pattern (Figure 74.1). Doppler echocardiography demonstrates a hypertrophied, dilated left ventricle with severe global impairment of systolic function, and an ejection fraction estimated at 0·20. There is evidence of moderate mitral regurgitation. The aortic valve is heavily calcified with restricted opening and a Doppler peak gradient of 40 mmHg (mean gradient 32 mmHg). The continuity equation measures the aortic valve area at 0·5 cm^2.

Question

Was the initial management of this man appropriate, and what is the appropriate management now?

Comment

This case presents two major issues calling for evidence to support the correct timing of surgical intervention for aortic stenosis: (a) the asymptomatic patient with severe aortic stenosis; and (b) the symptomatic patient with severe aortic stenosis but with a reduced transvalvular gradient, presumably due to impaired left ventricular function.

The incidence of sudden death is increased in patients with severe aortic stenosis. Fortunately, this rarely occurs without premonitory symptoms, and in the elderly in particular the risk of sudden death in an asymptomatic patient is less than the risk of valve replacement. Thus, following careful clinical and echocardiographic assessment, asymptomatic elderly patients with severe aortic stenosis can be managed conservatively with regular but close outpatient review at least every 6 months.[1] However, any genuine deterioration in exercise capacity must be declared and followed by early surgical assessment.[2]

Aortic valve replacement should always be considered in symptomatic patients, as their mortality rates with medical management are 50% at 3 years and 90% at 10 years.[3,4] Survival curves have shown that the interval from onset of symptoms to death is approximately 2 years in patients with heart failure, 3 years in patients with syncope, and 5 years in patients with angina.[5,6] Despite the increased incidence of sudden death, the principal cause of death is progressive heart failure.

In the absence of a myocardial infarct or atrial fibrillation, the concomitant development of severe heart failure with

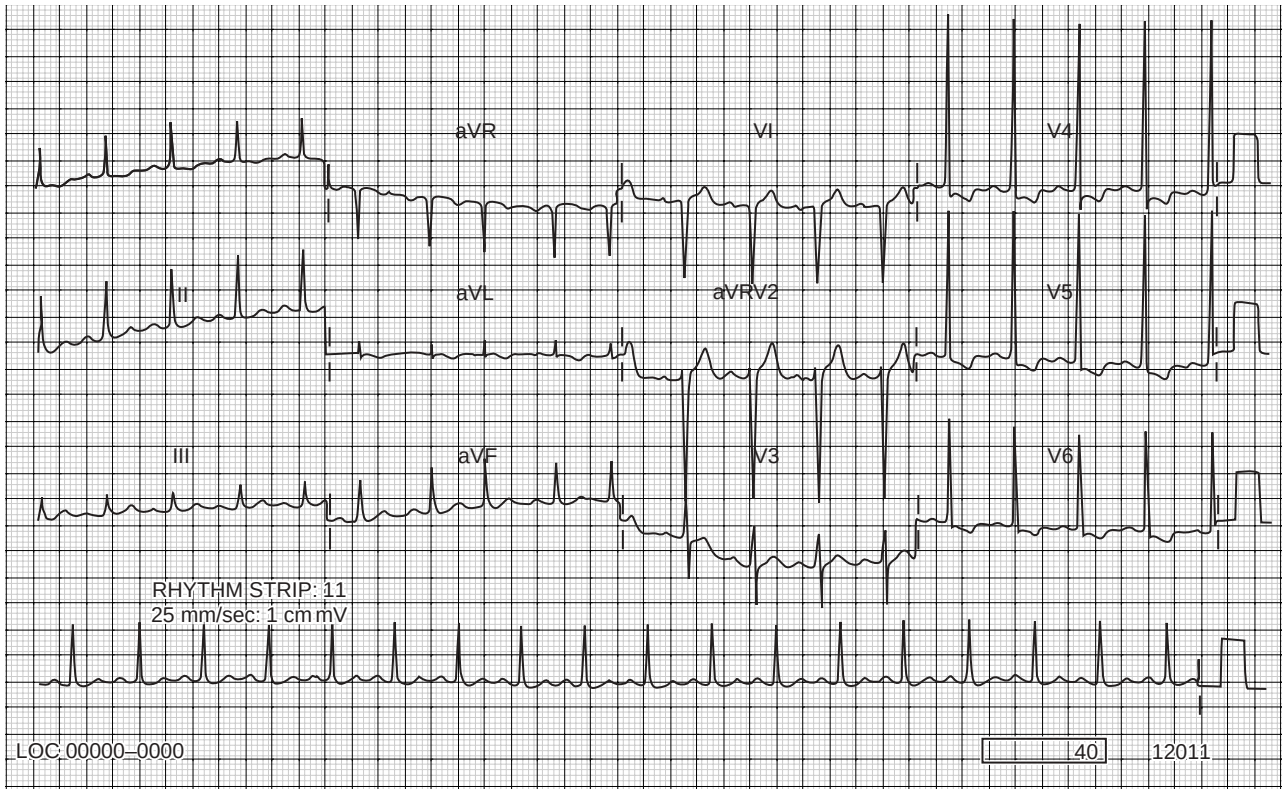

Figure 74.1 **Case 1**. A 12-lead ECG showing sinus rhythm with voltage criteria of severe left ventricular hypertrophy and a left ventricular strain pattern

a fall in the Doppler peak instantaneous gradient (from 70 mmHg to 40 mmHg) indicates critical aortic stenosis in this patient. Although left ventricular function is poor, valve replacement surgery is the treatment of choice, the alternative of balloon valvoplasty being only a temporary remedy.[7] Poor preoperative left ventricular function should never be a contraindication to valve replacement surgery, although those in congestive cardiac failure face an increased perioperative risk,[8] as do those with coronary artery disease.[9] However, the majority of surviving patients will experience functional improvement and a reduction in their NYHA classification.[9] Mitral insufficiency secondary to dilation of the left ventricle is common in patients with "end-stage" aortic stenosis. Following successful valve replacement, the degree of mitral regurgitation can be expected to improve and mitral valve surgery is rarely necessary unless the mitral valve is structurally abnormal or the mitral regurgitation is severe.

When 2D echocardiography shows a heavily calcified aortic valve with restricted opening and impaired left ventricular function, peak instantaneous gradients of less than 50 mmHg should be regarded as indicating significant stenosis until proved otherwise. Applying the continuity equation to measure the aortic valve area is recommended,[10,11] and cardiac catheterization need only be performed when coronary arteriography is necessary[12] and in those few patients in whom doubt remains despite careful echocardiographic assessment.

References

1. Selzer A. Changing aspect of the natural history of valvular aortic stenosis. *N Engl J Med* 1987;**317**:91–8.
2. Otto CM, Burwash IG, Legget ME *et al.* Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70.
3. Frank S, Johnson A, Ross J. Natural history of valvular aortic stenosis. *Br Heart J* 1973;**35**:41–6.
4. Rapaport E. Natural history of aortic and mitral valve disease. *Am J Cardiol* 1975;**35**:221–7.
5. Ross J, Braunwald E. Aortic stenosis. *Circulation* 1968; **38**(Suppl 5):V61–V67.
6. Olesen KH, Warburg E. Isolated aortic stenosis – the late prognosis. *Acta Med Scand* 1958;**160**:437–46.
7. Bernard Y, Etievent J, Mourand JL *et al.* Long-term results of percutaneous aortic valvuloplasty compared with aortic valve replacement in patients more than 75 years old. *J Am Coll Cardiol* 1992;**20**:796–801.

8. Obadia JF, Eker A, Rescigno G *et al.* Valvular replacement for aortic stenosis in NYHA class III and IV. Early and long term results. *J Cardiovasc Surg* 1995;**36**:251–6.
9. Connoly HM, Oh JK, Orszniak TA *et al.* Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction: prognostic indicators. *Circulation* 1997;**95**:2395–400.
10. Richards KL, Cannon RS, Miller JF, Crawford MH. Calculation of aortic valve area by Doppler echocardiography: a direct application of the continuity equation. *Circulation* 1986;**73**:964–9.
11. Zoghbi WA, Farmer KL, Soto JG, Nelson JG, Quinones MA. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation* 1986;**73**:452–9.
12. Hall RJC, Kadushi OA, Evemy K. Need for cardiac catheterization in assessment of patients for valve surgery. *Br Heart J* 1983;**49**:268–75.

Case 2

A 32 year old man with no previous medical history presents with severe exertional breathlessness and some orthopnea. Examination reveals a collapsing pulse, a blood pressure in the right arm of 120/45 mmHg, a volume overloaded and laterally displaced apex, an early diastolic murmur and a third heart sound. Femoral pulses and distal lower limb pulses are barely palpable.

Transthoracic echocardiography demonstrates a dilated left ventricle (LVEDD 7·9 cm, LVESD 5·9 cm) with severe global impairment of systolic function and an ejection fraction estimated at less than 0·2. The aortic valve is lightly calcified, bicuspid, and there is a broad jet of severe aortic reflux. Doppler interrogation of the descending aorta confirms coarctation with an estimated gradient of 30 mmHg. Magnetic resonance imaging (Figure 74.2) confirms a normal ascending aorta, coarctation in the upper descending aorta distal to the left subclavian artery, and some enlargement of the left internal mammary artery.

Question

What are the pharmacological and surgical management options for this man?

Comment

Here is a therapeutic challenge where one must strengthen what little external evidence exists with a combination of clinical judgment, experience, and a sound knowledge of cardiovascular pathophysiology. There are two issues to address: the aortic valve disease and the coarctation of the aorta.

A bicuspid aortic valve is commonly associated with coarctation of the aorta. When the valvular disease is significant, aortic stenosis is more common than aortic insufficiency, although a combination may occur. Coarctation results in a high vascular resistance and, when present, the combination of coarctation and dominant aortic regurgitation results in both a large volume and pressure load on the left ventricle.

The insidious onset of severe aortic insufficiency may be well tolerated for many years. In asymptomatic patients with isolated aortic insufficiency, vasodilation using nifedipine has been shown to lengthen the period before valve replacement is necessary.[1] In a patient with coarctation of the aorta, the elevated fixed afterload is unlikely to respond to vasodilator treatment and distal perfusion could be compromised. Treatment with nifedipine is also best avoided in patients with impaired left ventricular function.

When patients with aortic insufficiency do develop symptoms this is usually a reflection of left ventricular dysfunction and valve replacement is advised.[2] When left ventricular dysfunction is mild and prompt surgery is performed, the benefits are maximal. However, if surgery is delayed until symptoms or left ventricular dysfunction are established, the prognostic and symptomatic benefits of surgery can be limited.[2] Therefore, evidence of significant left ventricular dilation (end-systolic dimension $>5{\cdot}5$ cm)[3,4] or a reduction in the resting left ventricular ejection fraction[5] is usually considered sufficient reason to recommend valve replacement, even in the absence of symptoms.

In this patient, recovery of left ventricular function following valve surgery is likely to be limited if the coarctation is significantly obstructive. Doppler assessment of the severity of the coarctation is complicated by the valvar and myocardial dysfunction, but a gradient of 30 mmHg suggests significant but not critical obstruction. In adults, severe aortic coarctation is usually accompanied by increased collateral flow through enlarged branches of subclavian arteries. The presence of an enlarged internal mammary artery in this patient also suggests that the coarctation is likely to be hemodynamically significant. The risk of paraplegia during surgical repair of aortic coarctation is low, but this is enhanced when clamping of the left subclavian artery is necessary. As the coarctation does not involve the left subclavian artery in this

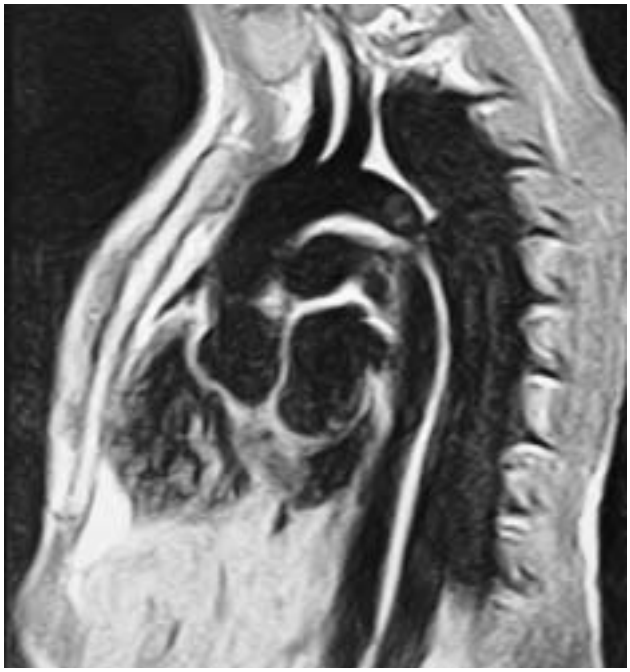

Figure 74.2 Case 2. Sagittal T_1-weighted magnetic resonance image of the descending aorta. There is a concentric narrowing of the upper descending aorta which does not involve the left subclavian artery.

patient, the risk of coarctation surgery is determined mainly by his left ventricular impairment.

Combined surgery attempting to replace the aortic valve and repair the coarctation could be considered as a single procedure. In practice, surgery could not be performed easily through the same incision (left thoracotomy for the upper descending aorta and median sternotomy for the aortic valve) and a protracted procedure could have a detrimental effect on the already compromised left ventricle.

If expertise is available, balloon dilation of the coarctation is an alternative, but in the absence of this expertise initial surgical repair of the coarctation is probably the initial management of choice,[6] although no well conducted comparative studies are available. Reducing afterload in this way, together with the introduction of an ACE inhibitor, is likely to reduce the degree of aortic regurgitation and improve left ventricular function. Subsequent aortic valve replacement could then be performed at a reduced risk. If, after successful coarctation surgery, the left ventricle remains severely compromised, cardiac transplantation could be considered.

References

1. Scognamigilo R, Rahimitoola SH, Fasoli G, Nistri S, Dalla Volta S. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994;**331**:689–94.
2. Bonow RO, Rosing DR, Kent KM, Epstein SE. Timing of operation for aortic regurgitation. *Am J Cardiol* 1982;**50**:325–36.
3. Stone PH, Clark RD, Goldschlager N, Selzer A, Cohn K. Determinants of prognosis of patients with aortic regurgitation who undergo aortic valve replacement. *J Am Coll Cardiol* 1984;**3**:1118–26.
4. Henry WL, Bonow RO, Borer JS *et al.* Observations on the optimum time for operative intervention for aortic regurgitation: 1. Evaluation of the results of aortic valve replacement in symptomatic patients. *Circulation* 1980;**61**:471–83.
5. Bonow RO. Radionuclide angiography in the management of asymptomatic aortic regurgitation. *Circulation* 1991; **84**(Suppl I):296–302.
6. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. *Circulation* 1989; **80**:840–5.

Index

For abbreviations used in subentries, please refer to the glossary page xxi
v denotes differential diagnosis or comparisons.