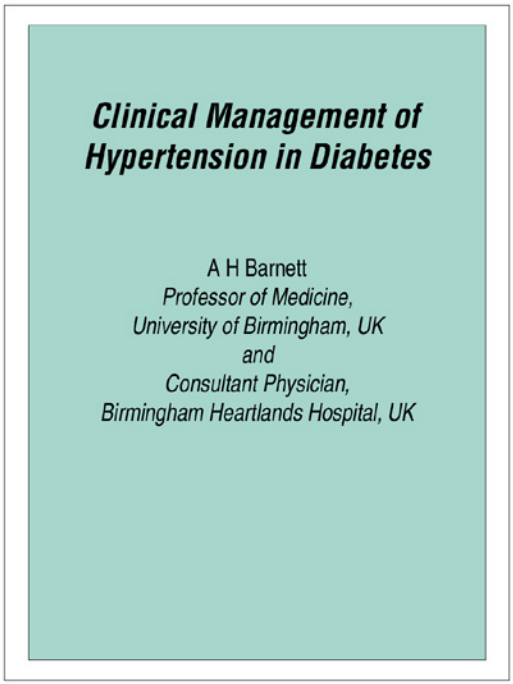

MARTIN DUNITZ

Clinical Management of Hypertension in Diabetes

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A H Barnett
Professor of Medicine,
University of Birmingham, UK
and
Consultant Physician,
Birmingham Heartlands Hospital, UK

MARTIN DUNITZ

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The Livery House, 7–9 Pratt Street, London NW1 0AE

Tel.: +44 (0) 20 74822202
Fax.: +44 (0) 20 72670159
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Contents

Foreword

Within the next 20 years, cardiovascular disease will overtake infectious diseases as the biggest killer not only in Western society, but also in the developing world. This trend coincides with a worldwide exponential increase in prevalence of type 2 diabetes. It is perhaps no coincidence, therefore, that similar risk factors apply to both disorders and clearly we are looking increasingly at the development of a syndrome of chronic cardiovascular risk. Risk may relate to inherited factors, but the most important appear to be environmental, including obesity and lack of exercise. Whatever the underlying reasons, there is no doubt that the major cardiovascular risk factors commonly co-exist in the same person at a frequency greater than that expected by chance.

These risk factors include type 2 diabetes, hypertension, dyslipidaemia, (central) obesity and cigarette smoking. It is now clear that we need to focus on cardiovascular disease, which kills 80% of diabetic patients (many prematurely) if we are to make an impact on type 2 diabetes. The purpose of this book is to draw attention to these issues, with particular emphasis on management of diabetes and hypertension, but it includes an appraisal of other risk factors. Hypertension is much more common in diabetic patients than in the general population. It is only

recently, however, that we have had an excellent evidence base for treatment of hypertension in diabetes, which at last gives us a means of significantly reducing the tremendous rate of attrition from vascular disease.

This small book is directed at the multidisciplinary team, particularly general practitioners and practice nurses. I hope it provides a readable, interesting and highly practical account of this important subject area.

Tony Barnett

Diabetes and vascular disease – the scale of the problem

Diabetes affects about 200 million people worldwide. These numbers have increased exponentially over the past few decades and will continue to do so for the foreseeable future.[1] In the UK alone, about two million people have the disorder, and again numbers are expected to increase by a further million over the next decade. Although there has been a rise in numbers of people with type 1 diabetes, the greatest number, probably 95% of all cases worldwide, has type 2 diabetes.

Reasons for increasing prevalence of type 2 diabetes

- An ageing population.
- Increasing obesity (Figure 1).[2]
- Sedentary lifestyle.
- As a racial characteristic in some ethnic groups, particularly those of Asian and Afro-Caribbean extraction.[3]

The prevalence of type 2 diabetes is under 1% in rural South Asia, for example, but on migration to cities and to

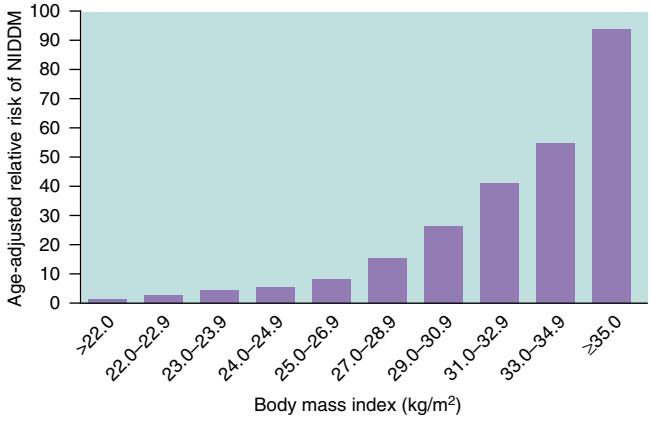


Figure 1
Dramatic increase in prevalence of type 2 diabetes with increasing obesity. (Adapted with permission from Colditz et al, Ann Intern Med 1995;122:481–6.[2])

Westernized countries, prevalence rates in the adult population can exceed 20%. These increases occur so rapidly that they must be due to environmental influences associated with urbanization, changes in diet, and a more sedentary lifestyle, although genetic predisposition in these populations is also a factor.

Morbidity and mortality of diabetes

- Diabetes is associated with major morbidity and mortality from long-term vascular complications.[3–6]
- Cardiovascular disease causes around 80% of deaths, and also causes much premature morbidity and mortality.
- In addition, microvascular complications include diseases of the eye (retinopathy), kidney (nephropathy) and nerve damage (peripheral neuropathy).

Type 2 diabetes commonly occurs together with other major cardiovascular risk factors, particularly hypertension and dyslipidaemia.[7] Hypertension, in particular, is at least twice as common in type 2 diabetic patients than in the general population.[6] This co-occurrence of cardiovascular risk factors in the same patient explains, at least in part, the accelerated atherosclerosis and its sequelae so common in people with diabetes.

Cardiovascular disease

Type 2 diabetes is a condition of premature (accelerated) cardiovascular disease.

Pathogenesis

The underlying pathology is similar or identical to that in the non-diabetic but the atherosclerotic process is accelerated. The arteries of a diabetic are about ten years "older" than their chronological age would suggest.

Accelerated atherosclerosis[8] (Figure 2) is associated with:

- alterations in endothelial cell function and platelet interactions
- lipid and lipoprotein abnormalities.

Raised glucose and dyslipidaemia per se adversely affect vascular endothelium and hypertension increases the risk of vascular endothelial injury with subsequent:

- macrophage and platelet aggregation
- release of growth factors that stimulate proliferation of smooth muscle cells and deposition of lipid-laden foam cells.

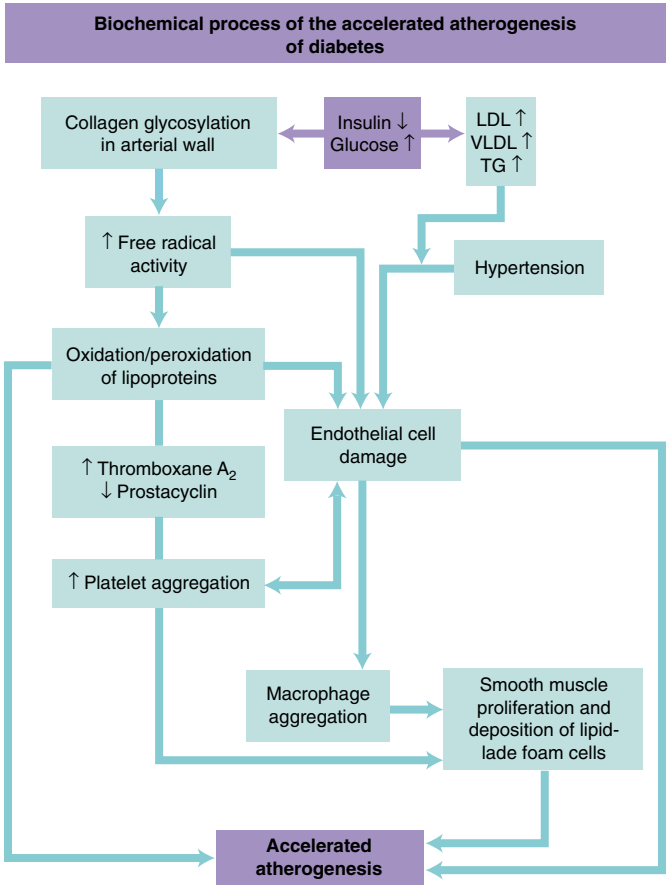


Figure 2

Possible processes involved in accelerated atherosclerosis associated with diabetes. LDL, VLDL: low, very low density lipoproteins; TG: triglyceride. (Adapted with permission: Barnett AH. Dyslipidaemia and vascular disease. In: Dodson PM, Barnett AH (eds). Lipids, diabetes and vascular disease 2nd edn. London; Science Press Ltd, 1998:27.)

Coronary heart disease

Coronary heart disease leading to angina, myocardial infarction (Figure 3) and premature mortality is between

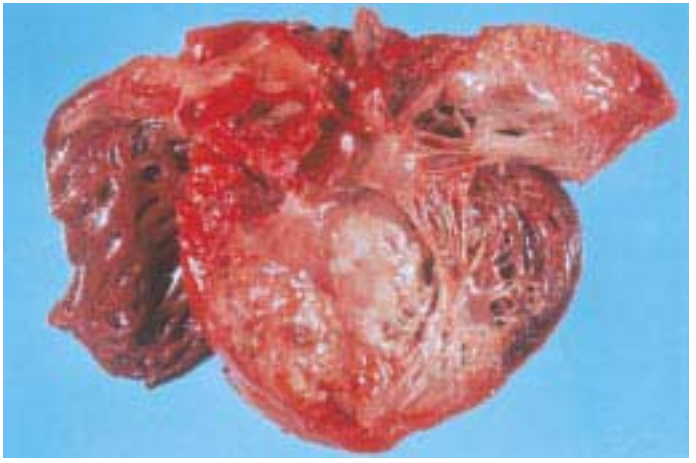


Figure 3
Post-mortem specimen of heart showing left ventricular hypertrophy secondary to hypertension. This diabetic patient died of a myocardial infarction (photos courtesy of Dr J Newman).

two and four times more common in diabetic patients than in the non-diabetic population.[4–6] This relates to accelerated atherosclerosis and the common presence of other cardiovascular risk factors. Not only is the incidence of coronary artery disease increased, but also the long-term outlook, particularly after myocardial infarction, is much worse for diabetic patients than for their non-diabetic counterparts.

Cerebrovascular disease

This is between two and six times more common in diabetic patients than in non-diabetic people and may particularly relate to the much higher prevalence of hypertension in the diabetic population.[9,10] The other major risk factors also apply, and the consequences include increased risk of arteriosclerotic dementia, transient ischaemic episodes and stroke (Figures 4a, b).

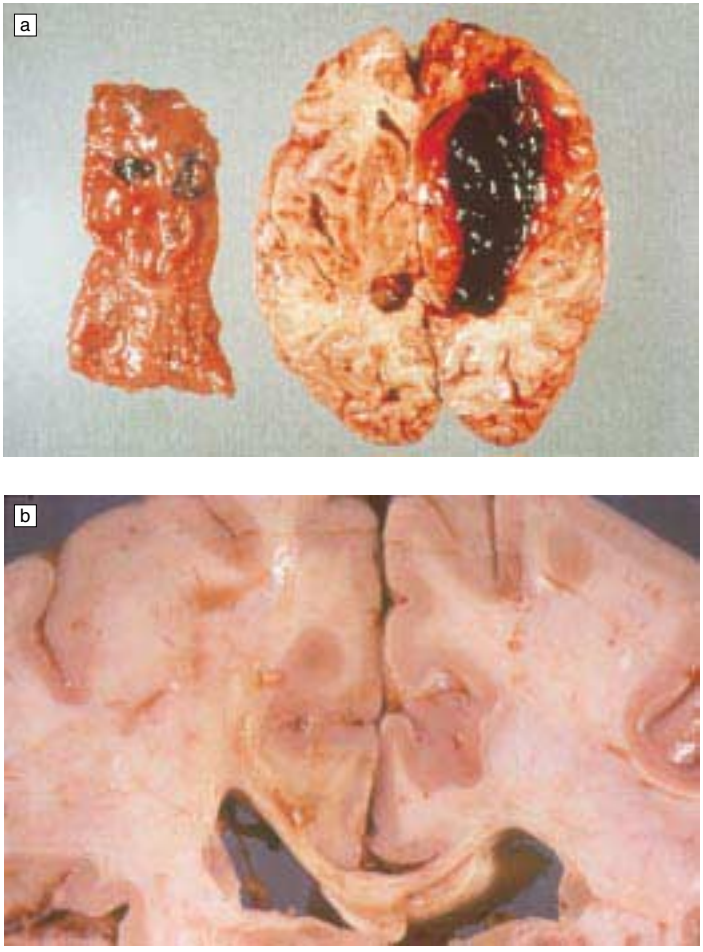


Figure 4
a, b) Post-mortem specimen of brain of a patient who has died from a stroke associated with hypertension.

Peripheral vascular disease

A diabetic over the age of 70 years is seventy times more likely to develop digital gangrene (Figure 5) than a non-dia-

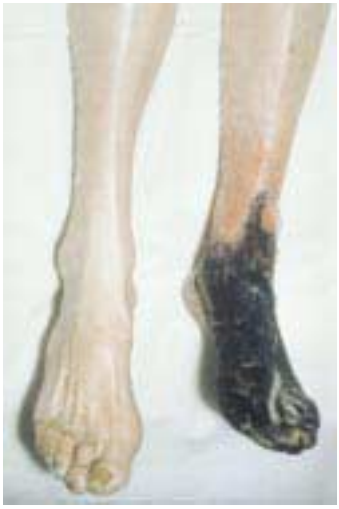


Figure 5
Severe gangrene in the leg of a long-term diabetic secondary to peripheral vascular disease.

betic of the same age! The basic pathology is accelerated atherosclerosis, which tends to be a generalized process that may affect much of the arterial supply to the legs and feet.[11] In the context of diabetes, cigarette smoking and hypertension are both major risk factors for development and progression of the disorder. For these reasons, it is vital that all diabetic patients, and particularly those with peripheral vascular disease, have excellent foot-care advice.

Microvascular disease (microangiopathy)

This is a generalized disease of the small blood vessels, clinically apparent in the eyes (retinopathy), kidneys (nephropathy) and vasa nervorum of peripheral nerves (peripheral neuropathy). Major susceptibility factors include duration of disease and degree of metabolic control. There is also increasing evidence that **hypertension is important in progression (and perhaps initiation) of microvascular disease.**

Pathogenesis of microangiopathy

The mechanism of development is not entirely understood[12,13] but appears to involve

- abnormalities of capillary basement membrane
- haemostatic abnormalities
- redox status
- several other metabolic pathways
- growth factors
- hypertension, and
- genetic susceptibility.

The process includes glycation of long-lived tissue proteins, such as collagen, in capillary basement membrane. This involves non-enzymatic chemical attachment of glucose to tissue protein, culminating in formation of advanced glycation end products (AGE: Figure 6). These lead to capillary basement membrane thickening and leakage through capillary walls (Figure 7).

In the presence of intracellular hyperglycaemia, alternative pathways of glucose metabolism are also activated, including the sorbitol/polyol pathway (Figure 8). This pathway consumes a vital co-enzyme, NADPH, which if in short supply results in increased free radical activity, these being highly reactive chemicals produced by normal metabolism. Excess free radicals result in lipid peroxidation, and protein denaturation and aggregation. This process leads to capillary endothelial cell damage, platelet aggregation and vasoconstriction.

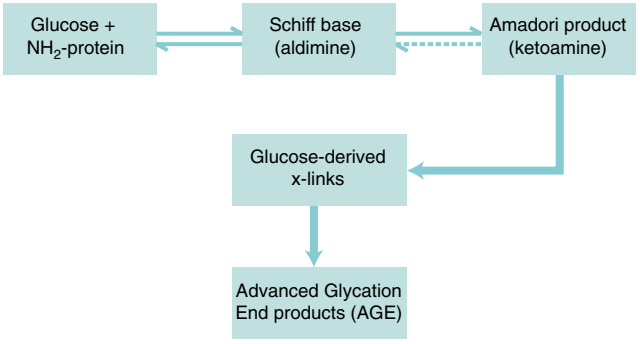


Figure 6
The process of development of advanced glycation end products (AGE) fundamental to the development of diabetic microvascular disease.

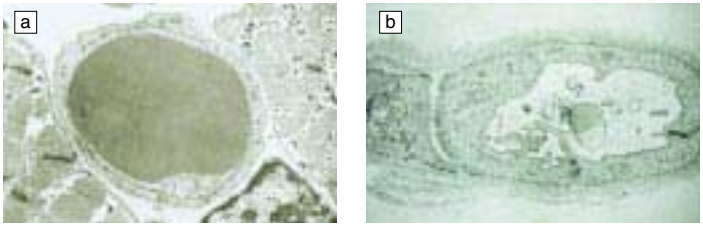


Figure 7
Electron micrographs of cross section of a capillary from a) normal person b) longstanding diabetic with microvascular disease. In the latter there is basement membrane thickening, the basement membrane is leaky and leaks plasma protein.

The results of the above processes include capillary basement membrane abnormalities, protein leakage, microthrombus formation and ischaemia (Figure 9).

Evidence for genetic susceptibility to microvascular disease has also accrued, together with a role for various growth factors, which include vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-beta) and angiotensin II (AII).

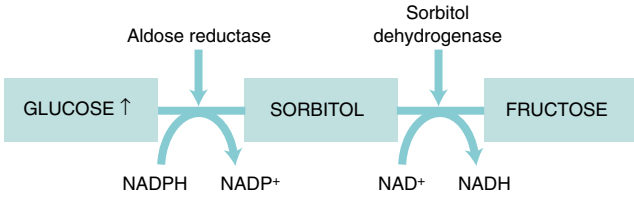


Figure 8

The sorbitol/polyol pathway activated in the presence of intracellular hyperglycaemia, which may contribute to the development of microangiopathy.

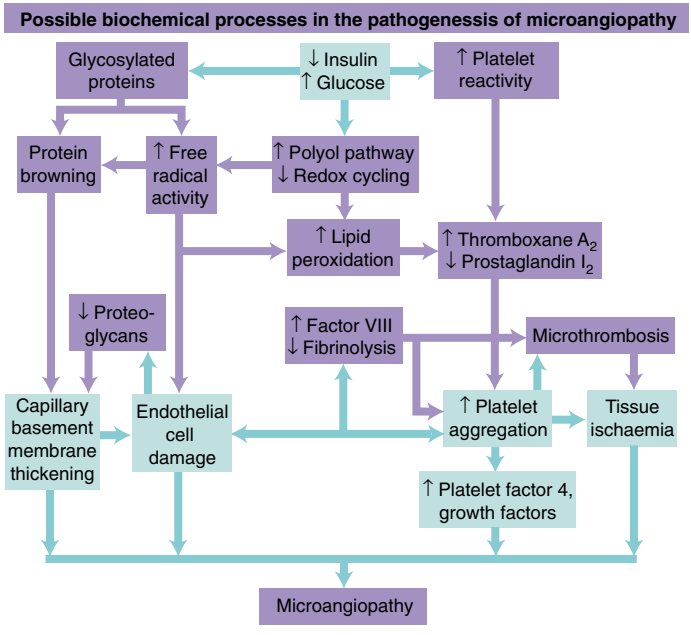


Figure 9

Current understanding of the mechanism of development of diabetic microangiopathy. (Adapted with permission from ref 12 and reproduced with permission from Barnett AH. Hypertension as a risk factor for diabetic vascular disease. In: Barnett AH, Dodson PM (eds). Hypertension and Diabetes. London; Science Press, 2000:11–20).

Recent data have also suggested a role for increased protein kinase C (PKC) activation in microangiopathy.[14] Hyperglycaemia leads to increased glucose flux across membranes and increased synthesis of diacyl glycerol which activates PKC. Increased PKC activity may be associated with a range of processes (Figure 10), which link in with the pathways described above.

Hypertension has a role in progression of microangiopathy, particularly retinopathy and nephropathy. Progression of diabetic nephropathy, and perhaps also retinopathy, is largely determined by increased blood pressure. Control of blood pressure, particularly using inhibitors of the renin angiotensin system (RAS), will slow down and may even prevent progression.

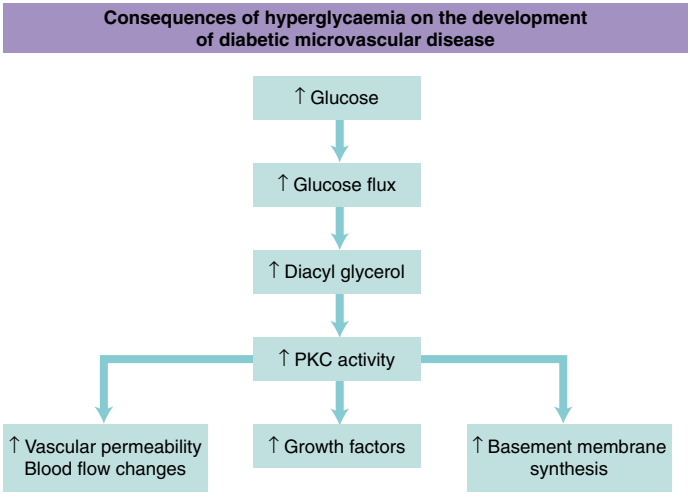


Figure 10

The process of protein kinase C (PKC) activation and its possible role in development of microvascular disease. (Adapted with permission from Giardino and Brownlee, in Textbook of Diabetes, 2nd ed. Oxford: Blackwell Science Ltd, 1996;16.[13])

Diabetic retinopathy

This is the commonest cause of blindness and visual deterioration in the working population of the UK, USA and western Europe. The majority of diabetic patients will show evidence of retinopathy with time.

Background retinal changes (Figure 11) may progress to sight-threatening maculopathy (Figure 12) or pre-proliferative (Figure 13) and proliferative (Figure 14) retinopathy with new vessel formation, which can lead to catastrophic haemorrhage, fibrosis and retinal detachment (Figure 15). Retinal screening through dilated pupils is a mandatory part of the annual review that every diabetic should have as an absolute minimum of care, since laser treatment can be sight saving.

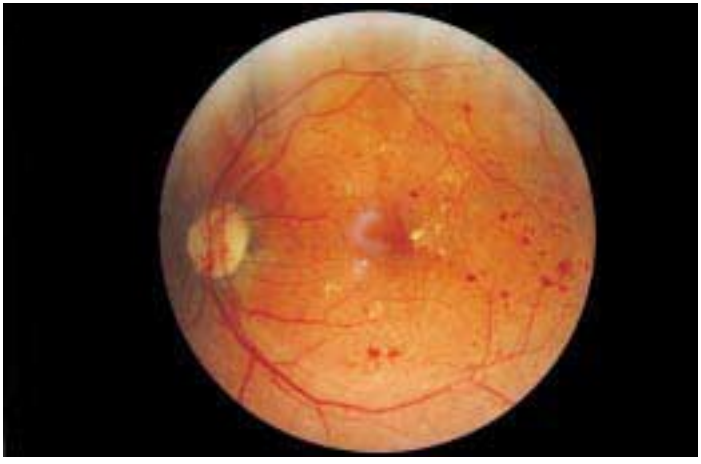


Figure 11
Diabetic background retinopathy showing microaneurysms, hard exudates (lipid deposits) and blot haemorrhages.

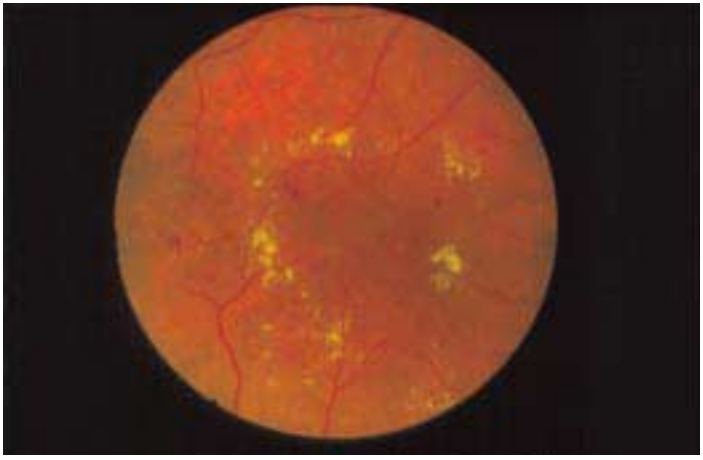


Figure 12
Progressing retinopathy showing hard exudates coalescing in circles around the macula indicative of macular oedema (maculopathy), which can cause visual deterioration and blindness.

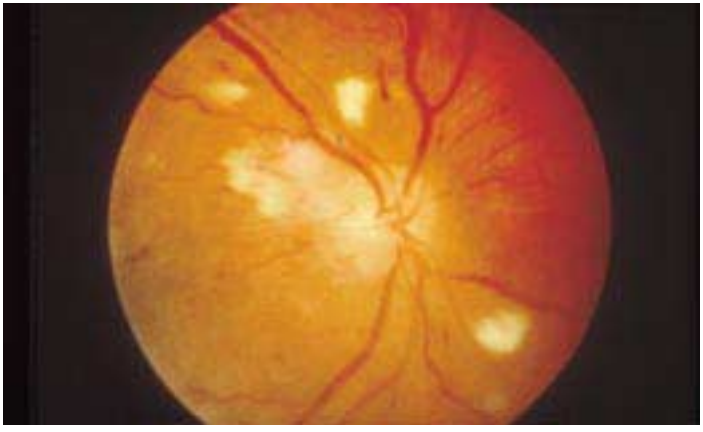


Figure 13
Retinal photograph of pre-proliferative retinopathy with cotton wool spots and venous dilatation.

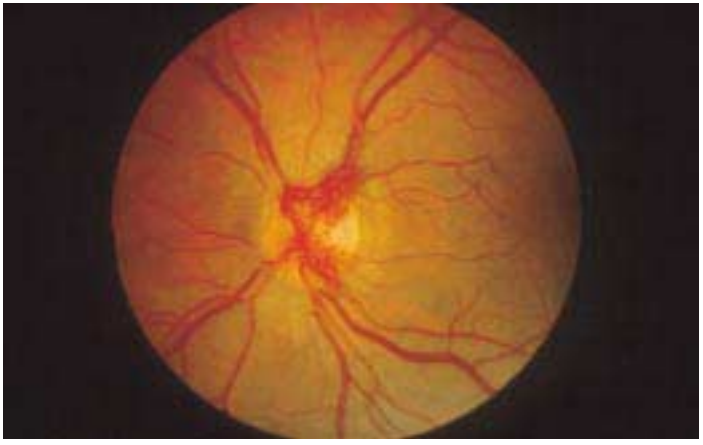


Figure 14
Retinal photograph of new vessels growing over the disk of the eye. These grow forwards into the vitreous, are brittle, and are likely to bleed with catastrophic haemorrhage.

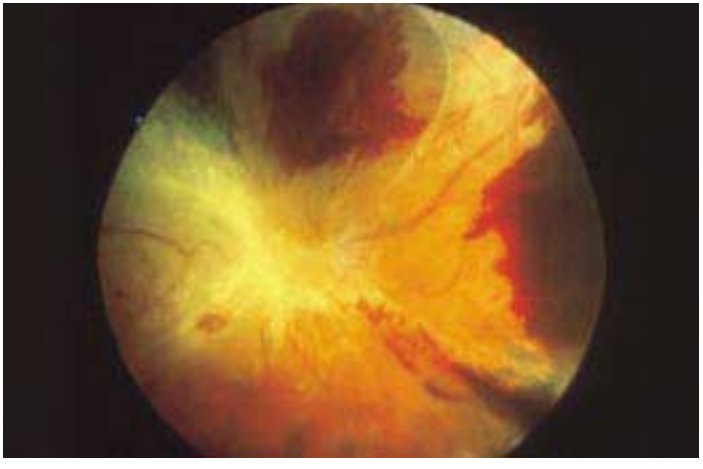


Figure 15
End-stage diabetic retinopathy. The eye is now blind with massive vitreous haemorrhage, retinal detachment and fibrosis.

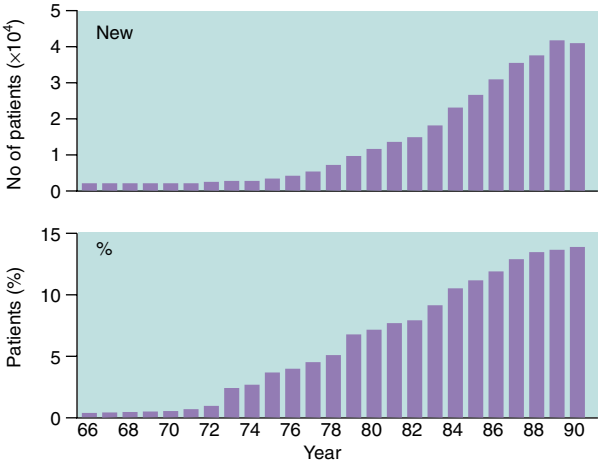


Figure 16

The greatly increased uptake of dialysis because of chronic renal failure in both type 1 and type 2 diabetic patients in recent decades. Patients (%) = percentage of patients, who require dialysis, who have diabetes. (Reproduced from Raine et al, Nephrol Dial Transp 1992;2:7–35 with permission from Oxford University Press.)

Diabetic nephropathy

This will affect about 25% of all type 1 and type 2 diabetic patients and is now the most common single reason for chronic renal failure and requirement for dialysis in the UK, western Europe and the USA[15] (Figure 16). The various stages in the development of diabetic nephropathy are shown in Figure 17.

Incipient nephropathy	Renal blood flow ↑ GFR ↑ Microalbuminuria
Overt nephropathy	Macroalbuminuria GFR ↓ Renal failure

GFR: glomerular filtration rate.

Figure 17

The development stages of diabetic nephropathy.

Microalbuminuria is defined as an albumin excretion rate (AER) above the normal range but below the level of dipstick detection. In type 1 and type 2 diabetic patients it is associated with greatly increased cardiovascular risk.[16,17] In type 1 diabetes it is also a good predictor of later chronic renal failure, but less so in those with type 2 disease since so many die from cardiovascular disease long before they die from uraemia (Figures18a, b).

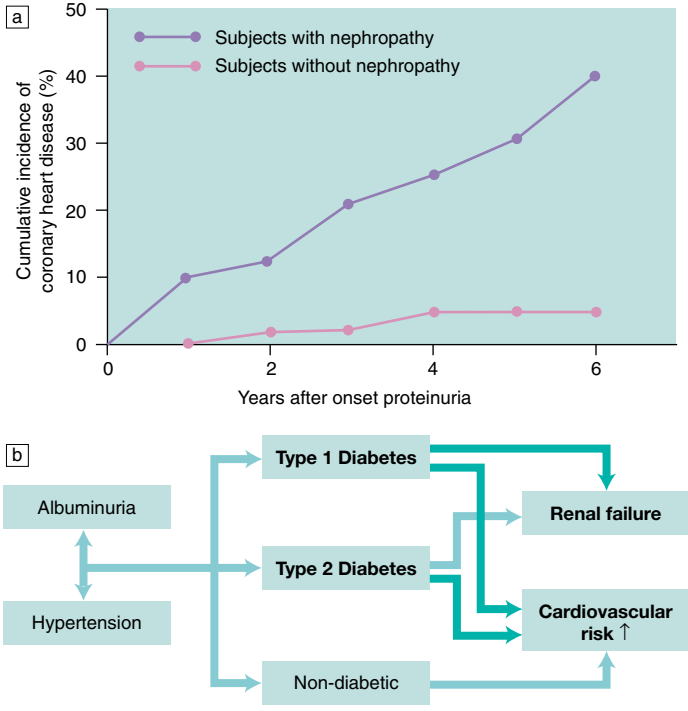


Figure 18

Shows a) the massively increased rate of cardiovascular disease and mortality in diabetic patients in association with diabetic nephropathy. (Adapted with permission from Jensen T et al, Diabetologia 1987; 30: 144–8.) b) Association between proteinuria and hypertension and risk of nephropathy and cardiovascular disease in type 1 diabetes, type 2 diabetes and non-diabetics.

Diabetic vascular disease – hypertension and other risk factors

Recent years have seen changes in diabetes management from a predominant focus on glycaemia to a much greater consideration of a whole range of risk factors involved in development of vascular disease.

The syndrome of chronic cardiovascular risk

The greatly increased prevalence of hypertension in association with type 2 diabetes is both remarkable and not entirely explained. It has been known for many years that the major cardiovascular risk factors, which include type 2 diabetes, hypertension and dyslipidaemia, commonly co-exist in the same patient and in 1988 the American physician, Gerry Reaven, suggested that this might relate to insulin resistance, a primary underlying abnormality[7] (Figure 19).

Insulin resistance defines resistance of the body to the biological actions of insulin. It may have an inherited component but the most important factors are environmental, particularly (central or visceral) obesity and sedentary lifestyle.[18] Obesity has reached epidemic proportions in many parts of the world with adult rates in the USA and UK (Figure 20) being around 30% and 20% respectively, and it is now becoming a problem even in childhood.[19] The increase is thought to relate to sedentary lifestyle and to

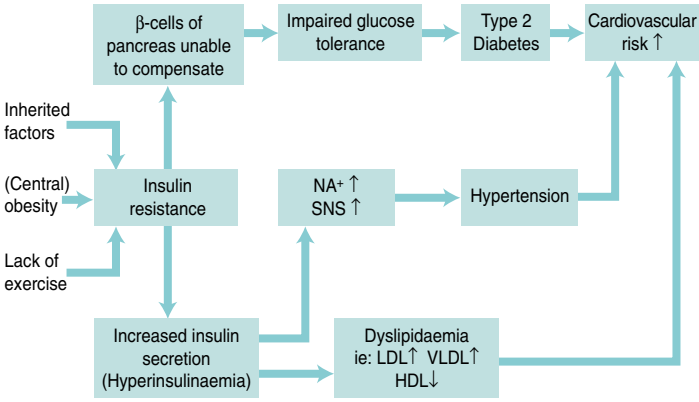


Figure 19

Reaven's original hypothesis linking insulin resistance with the development of a metabolic syndrome involving increased risks of dyslipidaemia, hypertension and type 2 diabetes, all of which are major risk factors for cardiovascular disease. NA+: sodium reabsorption by kidney; SNS: sympathetic nervous system stimulation; LDL, VLDL, HDL: low, very low, and high density lipoproteins.

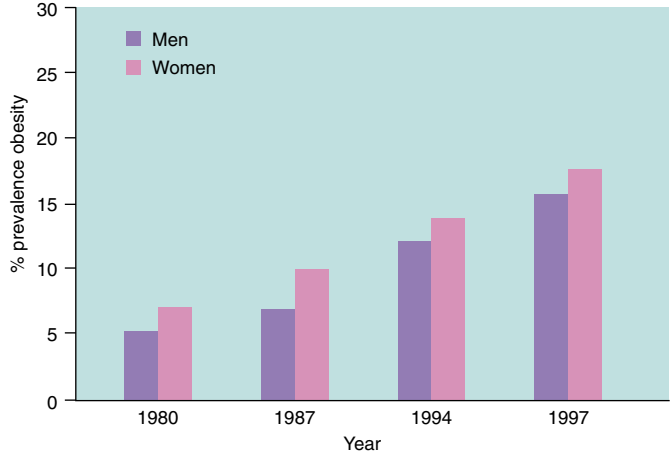


Figure 20

Increasing prevalence of obesity in men and women in England since 1980. (Adapted from ref 19 and Prentice AM. Obesity in Practice.1999;1:2.)

the increasingly high percentage of fat in our diets. Obesity rates in the UK alone have trebled in the past 20 years.

Reaven hypothesized that insulin resistance leading to hyperinsulinaemia would predispose to a dyslipidaemic, and consequently atherogenic, profile (see Figure 19), associated with significantly increased cardiovascular risk.

Reaven suggested that insulin resistance and hyperinsulinaemia might also cause, at least in part, an increased prevalence of hypertension in this syndrome. Hyperinsulinaemia is associated with increased sodium reabsorption from the kidney tubule and increased sympathetic nervous system stimulation.[20] Activation of the renin angiotensin system (RAS) may also be influential through angiotensin II mediated pathways and aldosterone-induced sodium retention.

Reaven also suggested that, in those with a predisposition, there would eventually be an inability of the pancreatic beta cells to secrete sufficient insulin to overcome the insulin resistance. Development of impaired glucose tolerance would be followed by type 2 diabetes. Indeed, insulin resistance may be found many years, sometimes decades, before the development of overt type 2 diabetes. Again, type 2 diabetes is itself an independent risk factor for cardiovascular disease.

This co-existence of cardiovascular risk factors in the same patient may explain, at least in part, the greatly increased risks of cardiovascular disease in diabetes.

Hypertension and diabetic microvascular disease

Diabetic retinopathy

Retinopathy and hypertension

There are now several reports of an association between risks of retinopathy and raised blood pressure. A prospec-

tive study of Pima Indians in Arizona, who have a very high incidence of type 2 diabetes, showed that over five years patients with diabetes and systolic pressure above 145 mm Hg had a doubled risk of development of retinal exudates compared with those with systolic pressure below 125 mm Hg.[21] Several studies have found associations between hypertension and different types of retinopathy, including proliferative retinopathy.[22–27]

Mechanism

The exact mechanism is not fully understood. One study showed impairment of retinal vascular autoregulation in response to raised systemic blood pressure in patients with diabetes, particularly in the presence of raised blood glucose.[28] There is also evidence that various growth factors[29] including VEGF, TGFβ and angiotension II may be involved, particularly in the development of proliferative retinopathy. There are also preliminary reports that inhibitors of the RAS may have a beneficial effect on progression of retinopathy, possibly through inhibition of this mechanism.[30]

Diabetic nephropathy

Nephropathy and hypertension

There is now overwhelming evidence that good blood-pressure control will slow (or even halt) progression of diabetic nephropathy.[31] Virtually all patients with type 2 diabetes who develop nephropathy are hypertensive. In the earlier phases of diabetic nephropathy in type 1 diabetes some are still normotensive by established criteria, although even in these cases blood pressures tend to be higher than in non-nephropathic peers.

Pathophysiology of hypertension in association with diabetic nephropathy

It is likely that correlates of the metabolic syndrome account for much of the excess cardiovascular disease/

hypertension found in association with type 2 diabetes. In type 1 diabetes, however, there is little evidence for an excess of hypertension in the absence of diabetic nephropathy. Indeed, the presence of hypertension and proteinuria is an extremely bad prognostic sign in both type 1 and type 2 diabetic patients, most of whom die of cardiovascular disease many years prematurely. The aetiology of hypertension in association with diabetic nephropathy is incompletely understood, but appears to have genetic, haemodynamic and metabolic correlates.

The stages of development of diabetic nephropathy are particularly well characterized in type 1 diabetes, and are initially recognized by glomerular hyperfunction and hypertrophy.[32,33] This is in turn associated with basement membrane abnormalities and urinary protein loss. Filtration is also affected by renal perfusion and increased intracapillary pressure, which is why lowering of intraglomerular pressure using inhibitors of the RAS prevents nephropathy in animal models of disease.

Other factors which may be involved include increased sodium reabsorption from the proximal renal tubule leading to increased plasma volume and fluid retention. Again, the RAS plays a pivotal role in the regulation of vascular tone and in sodium/water homeostasis.[34,35]

Given the very profound association between hypertension and progression of diabetic nephropathy, it is not too surprising that there is now overwhelming evidence to suggest that treatment of hypertension in type 1 and type 2 diabetic patients can delay or prevent the onset of diabetic nephropathy, and will also delay the progress of overt nephropathy.[31,36]

It is of particular interest that long-term follow-up studies have shown dramatic declines in cumulative death rates

ten years after onset of proteinuria compared with earlier reports (50–77% versus 18%).[16,37]

Other susceptibility factors for diabetic nephropathy

These include both genetic and metabolic factors:

Genetic

The evidence for genetic factors[38] is best in type 1 diabetes and includes familial clustering of nephropathy. Offspring with diabetes have a much greater risk of nephropathy if their parents have hypertension or cardiovascular disease than if their parents have neither of these. 70% of diabetic patients will never get nephropathy despite commonly having poor long-term diabetic control.

Several studies have reported possible susceptibility genes, particularly those involving the RAS, including the angiotensin converting enzyme (ACE) gene. No definitive associations have been established so far.[38]

Metabolic

The Diabetes Control and Complications Trial (DCCT) comparing intensive versus conventional treatment in type 1 diabetes showed a reduction in incidence of microalbuminuria of about 60% in favour of intensive treatment.[39] Those who had established microalbuminuria, however, did not achieve reduced progression despite improvement in glycaemia. This suggests that microalbuminuria may present at a fairly late stage in the progression of nephropathy.

The United Kingdom Prospective Diabetes Study (UKPDS) randomized over 5000 newly diagnosed type 2 diabetic patients to a regime of tight or conventional diabetic con-

trol. Tight control was associated with a significant reduction in incidence of micro or macro albuminuria compared with the conventionally treated group.[40]

Evidence base for treatment of hypertension in diabetes

Cardiovascular disease

Until recently, the evidence of benefit in treating hypertension in diabetes was based on extrapolation from clinical trials in the general hypertensive population. We now know for certain, from several clinical trials, that aggressive management of hypertension in diabetes has profound benefits.

United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS was the largest and longest prospective study ever conducted in type 2 diabetes.[40] Initially, over 5000 newly diagnosed type 2 diabetic patients were randomly assigned a regime of tight or conventional glycaemic control. A significant number were also hypertensive and were randomly assigned either conventional or tight blood-pressure control.[41]

Over the nine years of the study there was a difference of 10 mm Hg systolic and 5 mm Hg diastolic in favour of the tightly controlled group. This was associated with risk reductions of:

- 37% for progression of microangiopathy, particularly retinopathy
- 32% for diabetes-related death
- 44% for stroke, and
- 34% for combined macrovascular endpoints.

The study also proved the cost-effectiveness of such treatment and suggested a target blood pressure for therapy of 140/85 mm Hg or less. For most patients, two or more antihypertensive therapies from different classes were required to get down to target blood pressure in the intensively treated group.

The Hypertension Optimal Treatment (HOT) study

The HOT study[42] of more than 18 000 hypertensive patients (diastolic pressure 100–115 mm Hg) asked two questions

- "What is the optimal blood pressure for treatment?"
- "Are there any benefits of aspirin?"

The study included 1500 diabetic patients who were randomly assigned treatment to try and achieve diastolic blood pressures of less than 90, 85, and 80 mm Hg respectively. In addition, half of the patients in each group were randomly allocated aspirin.

The group assigned to tightest blood pressure control showed a 50% reduction in cardiovascular endpoints and mortality compared with the group with the least tight control (Figure 21). There was also evidence for benefit of aspirin in primary prevention in diabetic patients with hypertension, reducing cardiovascular events by a further

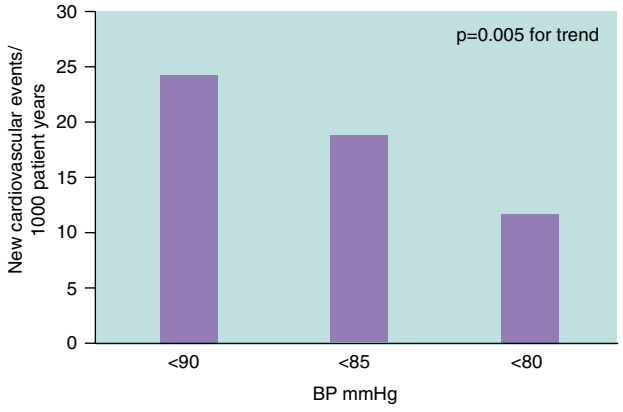


Figure 21
Data from the HOT study show 50% reduction in cardiovascular endpoints and mortality in favour of the most tightly controlled blood pressure group compared with the least tightly controlled.

15%, although this was associated with more non-fatal bleeding events.

Other studies

These data are supported by four other large, randomized prospective trials confirming the benefit of antihypertensive treatment on cardiovascular outcomes in diabetic patients.

Systolic Hypertension in the Elderly Programme (SHEP)

Almost 600 elderly diabetic patients were randomly assigned a thiazide diuretic, with a beta-blocker or reserpine, or placebo.[43] Over five years the active treatment group achieved a reduction in systolic blood pressure of about 10 mm Hg compared with the control group, and a reduction in relative risk of myocardial infarction of 45%.

The Systolic Hypertension in Europe (SYST-Eur) trial
The SYST-Eur trial contained almost 500 diabetic patients and again confirmed impressive reductions in cardiovascular events (41–70%) and mortality in favour of active treatment versus placebo.[44]

The various trials reported above used a range of antihypertensive agents. Two studies have now reported particular benefit from ACE inhibition.

CAPtopril Prevention Project (CAPPP)
This six-year randomized trial compared ACE inhibition with conventional therapy (beta-blocker or thiazide) in terms of cardiovascular morbidity and mortality in patients with hypertension.[45] Almost 600 diabetic patients showed no significant difference in blood pressure achieved between the two treatments. The group who received captopril, however, showed significant reductions in myocardial infarction (34%) and all cardiac events (67%).

Heart Outcomes Prevention Evaluation (HOPE) study
Perhaps the most impressive data for the benefit of ACE inhibition comes from the 4½ year HOPE study of patients at high cardiovascular risk.[46] Over 9000 patients aged 55 years or more with definite evidence of ischaemic heart disease, or diabetic patients with a previous cardiovascular event or at least one other cardiovascular risk factor, were randomly assigned ramipril 10 mg od or placebo. Patients in both groups could be on any other treatment. In the group of 3500 people with diabetes, ACE inhibition was associated with risk reduction of cardiovascular death (37%), myocardial infarction (22%), stroke (33%) and total mortality (24%) compared with placebo (Figure 22).

Unanswered questions

There is now a large amount of evidence to confirm the benefit of blood-pressure lowering on cardiovascular end-

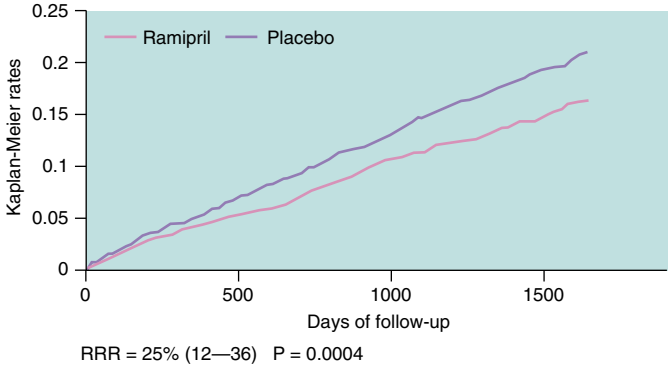


Figure 22

Relative risk reduction (RRR) in primary endpoints of myocardial infarction, stroke and death in favour of ACE inhibition in the HOPE study. (Reproduced from Heart Outcomes Prevention Evaluation Study Investigators, Lancet 2000;355:253–9 with permission from Elsevier Science.[46])

points and mortality in type 2 diabetic patients, although there is still a dearth of information about type 1 diabetes.

In addition, although we now have trials which have included beta-blockers, thiazide diuretics, calcium channel blockers and ACE inhibitors, there is still little hard endpoint information for newer agents such as the angiotensin II receptor blocking agents (AII antagonists) and the specific alpha blockers. Both are, however, included in the ongoing Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT).[47] Interim analysis, however, has resulted in the alpha-blocker group being stopped prematurely because of a 1.25-fold increase in the relative risk of combined cardiovascular disease endpoints (principally heart failure and stroke) compared with thiazide treatment.

It seems reasonable to expect that AII antagonists will show similar cardioprotective benefits to ACE inhibitors, since both classes of agents block the RAS. Hard endpoint data will be very useful in this area, particularly since these

agents have such good side-effect profiles and are metabolically neutral.

Microvascular disease

The UKPDS hypertension trial confirmed the benefits of tight blood-pressure control in reducing the risk of microvascular endpoints (by 37%), particularly retinopathy.[41]

Many studies have now been done in diabetic nephropathy, and in the UKPDS there was a significant reduction in urinary albumin excretion in the group randomized to tight control.[41] Early studies of overt diabetic nephropathy showed that antihypertensive therapy will slow the progression of, but will not stop, decline in renal function using a range of antihypertensive agents.[31] A more recent study using an ACE inhibitor in patients with type 1 diabetes showed protection against deterioration in renal function compared with blood-pressure control alone.[48]

There is also evidence for management of hypertension in incipient diabetic nephropathy with reduction/amelioration of disease progression, particularly with ACE inhibition. The EUCLID study compared the ACE inhibitor therapy (lisinopril) with placebo over two years in 490 type 1 diabetic patients who were normotensive and had either micro or normoalbuminuria.[49] In patients who were microalbuminuric, ACE inhibition was associated with a reduction in albumin excretion rate (AER) of almost 50% (Figure 23). These data are supported by smaller trials of captopril[50] or enalapril[51] in normotensive microalbuminuric type 1 diabetic subjects. The EUCLID study also showed a significant reduction in progression of retinopathy in favour of ACE inhibitor treatment.[30]

Similar data have also been reported for incipient nephropathy in hypertensive type 2 diabetic patients.[52] The benefit of ACE inhibition on reduction in AER was signifi-

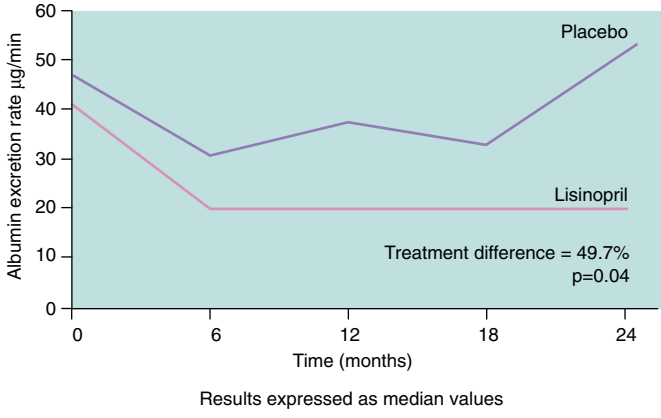


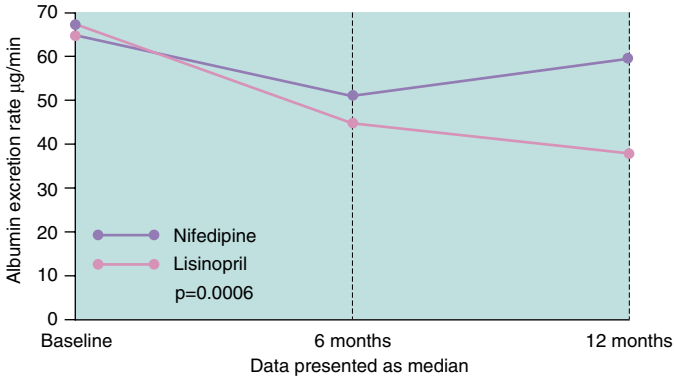
Figure 23

The almost 50% reduction in albumin excretion rate in favour of ACE inhibition in microalbuminuric, normotensive type 1 diabetic patients. (Adapted from The EUCLID Study Group, Lancet, 1997;349:1787–92 with permission from Elsevier Science.[49])

cantly greater with the ACE inhibitor lisinopril compared with the calcium channel blocker nifedipine, without any differences in blood pressure or glycaemic control over one year (Figure 24).

It is likely that ACE inhibitors have beneficial effects on the renal microcirculation over and above their systemic effects on lowering of blood pressure (Figure 25).[31] They reduce decline in GFR, mortality and endstage renal failure compared with placebo.[31] In addition, the subgroup of diabetic patients in the HOPE study[46] not only had profound cardiovascular protection, but also showed significant reduction in combined microvascular endpoints of overt nephropathy, dialysis or laser therapy for retinopathy in favour of ACE inhibition.

It is likely that the newer inhibitors of the RAS, the AII antagonists, will have similar benefits.



At 12 m between treatent difference 20 µg/min in favour of ACE inhibition

Figure 24

The significantly greater reduction in albumin excretion rate using an ACE inhibitor compared with a calcium channel blocker over 1 year in hypertensive type 2 diabetic patients with incipient nephropathy. (Adapted from Agardh, J Hum Hypertens, 1996;10:185–92.[52])

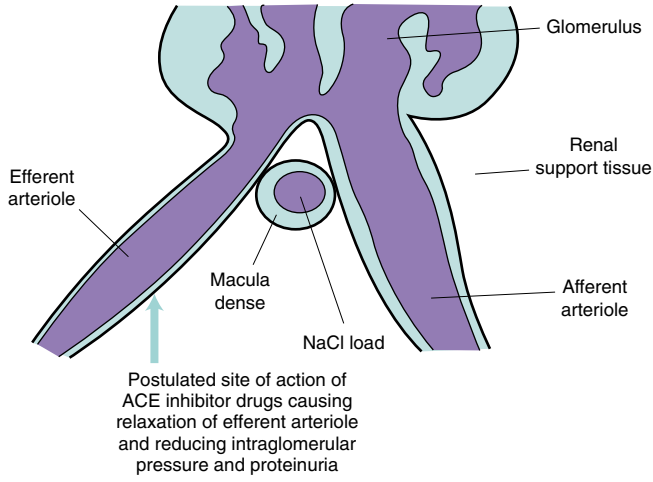


Figure 25

ACE inhibitors appear to exert their reno-protective effects by reduction of intraglomerular pressure and hence protein leakage, perhaps through relaxation of the glomerular efferent arteriole as well as through effects on reduction of systemic blood pressure.

Threshold for intervention and treatment targets

The old WHO criteria defined hypertension at blood pressure of 160/95 mm Hg or more. Impressive clinical trials now provide evidence that this is much too high a figure, particularly in diabetic patients. Evidence of benefit for macrovascular disease is shown down to blood pressures of less than 140/80 mm Hg and for microvascular disease, particularly nephropathy, additional benefits have been shown at even lower levels.

Various professional societies and international bodies have produced new guidelines for both intervention and treatment[53] (Table 1).

	BP (mm Hg)	
Threshold for intervention	≥140/90	
Target for treatment		
Non-nephropathy	≤140/80	
Nephropathy:		
Proteinuria <1 g/24 h	<130/80 (type 1 diabetes)	<130/85 (type 2 diabetes)
Proteinuria >1 g/24 h	≤125/75	

- If untreated BP consistently above these levels assess 10 year coronary heart disease risk. If it exceeds 15% then add statin and aspirin as well as antihypertensives.
- ACE inhibitor therapy first line in type 1 diabetes and ACE inhibitors in combination with calcium antagonists, thiazide diuretics or β-blockers in type 2 diabetes.
- Note: the great majority of patients, particularly those with type 2 diabetes, will require two or more agents to reach target blood pressures.

Table 1
BHS guidelines (diabetes)[53]

Diagnosis and assessment of hypertension in the diabetic patient

Hypertension is a major risk factor for both micro and macrovascular disease, and the results of both can be devastating. In addition, the combination of hypertension and diabetes should activate a search for other major cardiovascular risk factors in these patients, eg: dyslipidaemia, obesity (particularly central obesity) and cigarette smoking.

Making the diagnosis

Every person with diabetes should have their blood pressure measured on a regular basis and at the very least as part of the Diabetes Annual Review (Table 2). Many patients are overweight and care needs to be taken with cuff size. Ambulatory blood pressure monitoring may also be useful in borderline cases and those in whom "white coat" effect may be important. Where blood pressure is 140/90 mm Hg or more several more blood pressure readings need to be made over several weeks to confirm the diagnosis.

Further assessment

This is detailed in Tables 3–5.

- Assessment of diabetic control
- Cardiovascular risk assessment
  - Blood pressure
  - Lipids (Total and HDL cholesterol; possibly fasting triglycerides)
  - Cigarette smoking
- Complication screening
  - Eyes: visual acuity; pupillary dilatation; ophthalmoscopy; retinal photography
  - Kidneys: proteinuria; microalbuminuria (see text)
  - Feet: neuropathy; peripheral vascular disease
- Dietetic and educational review

Table 2
Components of a typical diabetes annual review (HDL: high density lipids)

- Age
- Duration of diabetes
- Glycaemic control
- History of previous cardiovascular and renal disease
- Family history of hypertension and premature cardiovascular disease
- Cigarette smoking, obesity, alcohol intake
- Drug history

Table 3
History

Screening for microalbuminuria

Microalbuminuria is defined as an albumin excretion rate (AER) above the normal range but below the level of dipstick detection (20–200 μg/min,[31] see earlier). It can be estimated on a timed overnight urine sample or on a full

Includes weight, height, body mass index and fat distribution plus evidence of end organ damage:

- Cardiac hypertrophy
- Carotid, renal and peripheral artery bruits
- Retinopathy/nephropathy
- Signs of dyslipidaemia
  eg: xanthelasma
  xanthomata
  corneal arcus

Table 4
Examination

- Urine for protein; if present, renal ultrasound
- ECG
- Total and HDL cholesterol; fasting triglycerides
- Electrolytes and full blood count
- Glycated haemoglobin
- Occasionally if clinical suspicion of secondary causes:
  24 h urinary catecholamines × 3 (phaeochromocytoma)
  24 h urinary free cortisol (Cushing's Syndrome)
  growth hormone (acromegaly)
  thyroid function (thyrotoxicosis)

Table 5
Investigations (ECG: electrocardiogram; HDL: high density lipids)

24-hour urine collection. An alternative, and much easier, screening procedure is to do a spot urinary protein/creatinine ratio on an early morning urine sample. Increased values suggest a need for a more comprehensive estimation. A diagnosis of incipient nephropathy/microalbuminuria should not be made on fewer than three separate urine collections at least several days apart.

Routine screening is controversial. It is worthwhile in people with type 1 diabetes of more than 5 years duration as, although they may remain normotensive for a time, they may still benefit from ACE inhibition.[49] The evidence base for renal protection using ACE inhibition in normotensive type 2 diabetic patients with proteinuria is significantly inferior, and indeed the finding of persistent proteinuria in the absence of hypertension in a type 2 diabetic patient usually indicates some other pathology.

For type 2 diabetic patients the finding of microalbuminuria is indicative of increased cardiovascular risk and risk of overt nephropathy, so aggressive treatment of hypertension (using inhibitors of the renin angiotensin system [RAS]) and dyslipidaemia, and avoidance of cigarette smoking is mandatory. This is the form of management that we should be advising for all type 2 diabetic patients, not just those with albuminuria.

Renal artery stenosis

There have been concerns about atherosclerotic renal artery stenosis, particularly since one might expect this to be more common in type 2 diabetic patients. There may be clinical implications for treatment with inhibitors of the RAS, since this may be associated with marked deterioration in renal function. Such an occurrence is, however, quite rare in diabetic patients and the dangers may have been overstated. It is wise, however, to check creatinine before and then 7 to 10 days after starting an inhibitor of the RAS. If there is significant deterioration in creatinine, then the drug should be discontinued, with further assessment and treatment.

Cardiovascular risk assessment

Recognition that a multiplicity of factors are involved in cardiovascular risk has led to the concept of assessment of

total risk either of coronary heart disease (CHD) or overall cardiovascular disease (which also includes stroke). This can be calculated based on the Framingham equation,[54] which takes into account age of the patient, sex, presence of diabetes, systolic or diastolic blood pressure, cigarette smoking, evidence of left ventricular hypertrophy, total and HDL cholesterol. The Chief Medical Officer in the UK suggests that for primary prevention a CHD risk of more than 30% over 10 years is an indication for intervention with lipid lowering agents.[55] Risks are considered so high from the point of view of secondary prevention that statin treatment is advised in all such patients with total cholesterol 5.0 mmol/l or more.

Many authorities feel that 30% is too high and indeed equates to an overall cardiovascular risk of about 40%! The recent BHS guidelines have suggested intervention at coronary heart disease risk of 15% over 10 years.[53] Indeed, various professional bodies are presently discussing whether all diabetic patients should be on a statin as their cardiovascular risk is so high.

Unfortunately, the Framingham equation is largely based on a white population and does not take into account the excess risks of cardiovascular disease seen in people of Asian extraction. In the UK these risks are about 1.5 times higher than in the white population and in the context of diabetes cardiovascular risk may be even more magnified. It is the author's practice, therefore, to advise intervention in Asian diabetic patients at CHD risk of more than 20%.

In addition, Framingham does not take into account the presence or absence of micro or macroalbuminuria, which again is associated with greatly increased cardiovascular risk. In the author's opinion, treatment of such patients should be based on secondary prevention recommendations.

Implications of the National Service Framework for diabetes

This is due to be published after publication of this book, but will almost certainly place emphasis on:

- A primary care led service but with strong collaborative links with secondary care
- Organization of care through multidisciplinary working
- Emphasis on cardiovascular risk reduction through:
  — lifestyle changes (weight loss, increased activity, cessation of cigarette smoking, etc)
  — aggressive screening for and management of hypertension, dyslipidaemia and glycaemia
- Reduction in:
  — amputation rates
  — blindness
  — renal failure
- Pregnancy outcomes close to those expected in the non-diabetic population
- Patient empowerment and a more holistic approach to diabetes management

These will be all great challenges to health professionals, and none will be greater than cardiovascular risk assessment and treatment.

Therapy for hypertension in the diabetic patient

Non-pharmacological

For those patients with mild to moderate hypertension (systolic 140–160 mm Hg and/or diastolic 90–100 mm Hg) a trial of non-pharmacological therapy, particularly for overweight type 2 diabetic patients, is worthwhile.

Weight loss, increased physical activity, and reduction of excessive alcohol intake will improve:

- insulin resistance
- hyperinsulinaemia
- glycaemia
- the lipid profile, and
- blood pressure.

Additional advice includes:

- not adding salt to food
- increasing fibre intake

- increasing the proportion of calories consumed as unrefined carbohydrate, and

- reduction in saturated fat intake.

Such measures can result in significant reductions in blood pressure. In most cases, however, lifestyle changes in combination with antihypertensives will be necessary to get down to the newly recommended, much tighter targets.

Pointers which suggest a need for early intervention with pharmacotherapy include:

- evidence of target organ damage, eg: left ventricular hypertrophy, hypertensive retinopathy, nephropathy, renal impairment, or

- past history of cardiovascular disease and those at high cardiovascular risk (>15% over 10 years).

For patients with type 1 diabetes, early antihypertensive intervention may be especially relevant, particularly with ACE inhibitor treatment (see below).

Pharmacological agents in the management of hypertension

Hypertension is a major risk factor for micro and macrovascular disease in diabetic patients, so aggressive and effective treatment is mandatory. There are, however, special difficulties in diabetic patients, which include:

- Concerns about adverse metabolic effects, which may in turn have adverse effects on other aspects of metabolic syndrome including increasing insulin resistance and provoking dyslipidaemia, together with electrolyte imbalance.

- Patients with autonomic neuropathy, peripheral vascular disease or renal disease may be intolerant of some antihypertensives.

- It is difficult to get down to target levels of blood pressure using single agents in most patients, necessitating use of several drugs from different antihypertensive classes, which provoke concerns regarding drug interactions, patient compliance and cost.

The ideal drug for patients with diabetes should:

- be efficacious in lowering blood pressure.

- have no adverse metabolic effects, or interact with oral hypoglycaemic agents or insulin, and should not impair ability to recognize hypoglycaemia.

- not cause postural hypotension, impair limb blood flow, increase risk of impotence or decrease renal function.

- reduce susceptibility to cardiovascular disease.

The major classes of antihypertensive drugs are outlined below.

Thiazide diuretics

These agents are effective in lowering blood pressure, can be used in once-daily dosing, are cheap, and there is evidence that the incidence of stroke, heart failure and cardiovascular risk is reduced.[56–58]

Concerns have been expressed, however, about adverse metabolic side-effects:

- deterioration in glycaemia[59–61]

- precipitation of diabetes in those with impaired glucose tolerance or those predisposed to the disease[59–61]
- electrolyte imbalance leading to hypokalaemia, and
- adverse effects on the lipid profile[62–67] with increases in total, LDL and VLDL cholesterol, increased triglyceride and insulin resistance
- erectile dysfunction.[68]

On a positive note, many of the studies were done with high-dose diuretics, and it is known that these agents show a dose plateau above which enhanced blood-pressure reduction is rare but adverse metabolic effects increase. These drugs are generally recommended for use in low dose and usually as part of combination therapy, rather than as first-line treatment of hypertension in diabetes.

Beta-blockers

These are efficacious in lowering blood pressure, are relatively cheap, and some can be used once daily. They reduce cardiac output, heart rate and renal blood flow and increase peripheral resistance. They have antianginal effects and, given the frequent co-occurrence of angina in diabetic patients, may be a useful first-line treatment.[69]

Potential side-effects[69] include worsening of:

- glycaemia
- lipid profile
- symptoms of peripheral vascular disease, together with
- masking of warning symptoms of hypoglycaemia and increased insulin resistance.

It is likely, however, that the metabolic and hypoglycaemic problems have been overstated.[69,70]

On the positive side, beta-blockers are cardioprotective and are particularly useful after myocardial infarction.[71–73] In addition, data from the UKPDS hypertension trial, one group of which used a beta-blocker, showed clear benefit in reducing cardiovascular risk and mortality in patients with type 2 diabetes.[41]

Generally, because of the potential for adverse metabolic effects, these agents are advised in combination with more modern agents, rather than as first-line treatment, except where there is co-incident angina or after myocardial infarction. If a beta-blocker is to be used, a beta-selective drug is preferable.

Calcium channel blockers

Calcium channel blockers have peripheral vasodilating properties, directly decreasing total peripheral resistance and therefore blood pressure. There are two main classes, the dihydropyridines and the non-dihydropyridines. The latter have a longer elimination half-life and can be used as a single daily dose, with probably fewer side-effects.

They have been shown to have anti-anginal, cardioprotective, and antiarrhythmic properties[74] and in human beings they have a neutral metabolic profile with no adverse effects on lipids or glycaemia.[75,76]

Other potential advantages include their vasodilatory properties with some improvement of blood flow to the limb, possible lowering of the risk of impotence, and providing benefit in peripheral vascular disease. Postural hypotension is not a problem, and there may also be beneficial effects on the kidney with some reduction in protein leakage in those with overt nephropathy.[77]

Calcium channel blockers may improve coronary blood flow by dilatation and possibly by reducing platelet stickiness.[78] They also reduce afterload and may therefore reduce the work the heart is doing. There is evidence for regression of the structural changes of left ventricular hypertrophy in animals and human beings.[79]

Overall, calcium antagonists can be regarded as a first-line treatment in patients with diabetes and hypertension with a good safety profile, a high incidence of minor side-effects (such as ankle oedema and facial flushing), evidence for cardio and renal protection, and with particular benefit in the elderly.

Specific alpha-blockers

Older alpha-blockers, such as prazosin, sometimes caused severe first-dose hypotension and postural hypotension. The newer alpha-blockers are better tolerated and may be particularly useful in diabetic patients because of their neutral metabolic effects and reduction in insulin resistance.[80]

They work by decreasing peripheral vascular resistance and causing venous dilatation, thus decreasing venous return to the right side of the heart. This may be an advantage over direct vasodilatation in those with ischaemic heart disease, as cardiac output is not significantly increased.

These agents look very attractive in theory but there are no long-term hard endpoint data. Their role is being studied by the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). A recent interim analysis of the study[47] has resulted in the alpha-blocker group being discontinued prematurely because this treatment was associated with a 1¼ fold increase in relative risk of combined cardiovascular disease endpoints com-

pared with thiazide diuretics. This increased risk mainly related to heart failure and stroke. There was, however, no evidence of increased mortality and further work needs to be done.

At present these agents are not normally recommended as first-line treatment for hypertension in diabetes, but may be useful in combination with other classes of antihypertensive agents helping to reduce blood pressure and with a neutral metabolic profile.

Angiotensin converting enzyme (ACE) inhibitors

The RAS is important from the point of view of blood-pressure control and fluid and electrolyte balance.[81] A central component is angiotensin II, a powerful vasoconstrictor and mediator of adrenal aldosterone secretion (Figure 26). It also has an effect on the sympathetic nervous system, particularly on catecholamine release.

ACE inhibitors inhibit the conversion of inactive angiotensin I to the active component, angiotensin II. This results in:

- reduction of sympathetic tone
- decrease in elevated systemic vascular resistance
- enhanced perfusion of the heart and kidneys.

They are effective in lowering blood pressure, with evidence of reversal of cardiac hypertrophy, and have beneficial effects in patients with congestive heart failure, reducing both morbidity and mortality.

Metabolic profile

ACE inhibitors are at least neutral from the point of view of glycaemia, with some evidence that they may improve insulin resistance. There is the tantalizing possibility that in

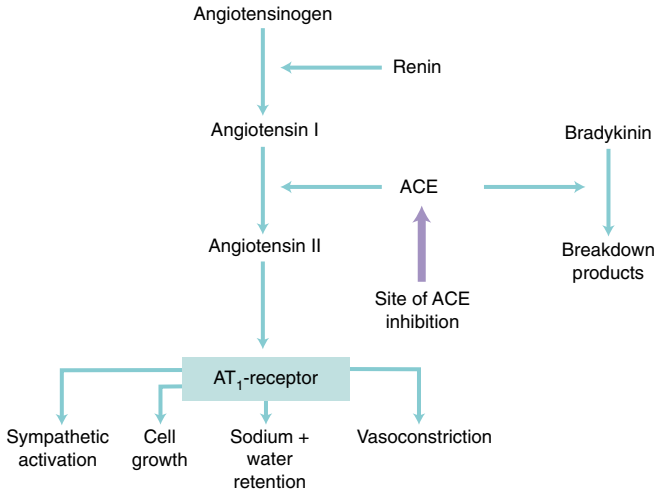


Figure 26

The renin angiotensin system and the central role of AII in blood pressure control. Shows site of action of ACE inhibitor drugs which inhibit AII production but also allow a build up of bradykinin (the latter may cause chronic cough and very rarely angio-oedema seen with these drugs). AII: angiotension II; ACE: angiotensin converting enzyme.

the non-diabetic population, ACE inhibitors may reduce the risk of later development of type 2 diabetes.[82–84]

At the very least these agents are lipid-neutral, although some studies suggest an improvement in lipid profile with increase in HDL cholesterol and an overall reduction in the total cholesterol to HDL ratio normally associated with reduced risk of cardiovascular disease.[84–86]

Effects on the vascular complications of diabetes

Microvascular

There is now a large literature on the benefits of blood-pressure lowering in the context of both incipient and overt diabetic nephropathy. The bottom line is “get the blood

pressure down, and the lower the better". Indeed, the recent BHS guidelines suggest that for those patients with albuminuria above 1 g/24 hr, blood pressure should be lowered to less than 125/75 mm Hg. In addition, there is evidence that ACE inhibitors or angiotensin II antagonists should normally be the first-line treatment. As well as reducing systemic blood pressure, ACE inhibitors also benefit the renal microcirculation by causing relaxation of the glomerular efferent arteriole, thereby reducing raised intraglomerular pressure and protein leakage and protecting the kidney[31] (Figure 25).

ACE inhibitors may slow/prevent deterioration from the microalbuminuric phase of incipient nephropathy to the macroalbuminuric phase of overt nephropathy in both type 1 and type 2 diabetic patients.[50,51] Indeed, even in normotensive type 1 diabetic patients, ACE inhibition has a renoprotective effect.[49]

In those with established nephropathy, there is increasing evidence that ACE inhibition is associated with slowing of the decline in renal function, with significant slowing of progression to end-stage renal failure and evidence of reduced mortality.[34,38]

Macrovascular

There is increasing evidence that ACE inhibitors are particularly useful in cardioprotection in those at high cardiovascular risk, including diabetic patients. The Heart Outcomes Prevention Evaluation (HOPE) study[46] looked at the incidence of myocardial infarction, stroke or cardiovascular death/total mortality in people at high risk of cardiovascular disease. Roughly 3500 of the 9500 patients were diabetic, with either a previous history of cardiovascular disease or one other cardiovascular risk factor. There was a clear split in survival curves in favour of treatment with ACE inhibitors, which gave highly significant reduction in mortality, myocardial infarction, stroke, transient ischaemic

attack and cardiovascular death (Figure 22). The benefit was noted between 6–8 months after treatment was assigned and occurred despite the fact that both control and active groups could have any other therapies prescribed.

There is also now a lot of evidence that testifies to the usefulness of ACE inhibitors, in combination with diuretics, in the management of heart failure. There is also evidence after myocardial infarction, including positive effects on mortality.[87] In hypertensive diabetic patients, ACE inhibition is associated with regression of structural changes in hypertrophied myocardium.[88]

Side-effects and contraindications

These agents generally have a very good side-effect profile, although chronic cough characteristically occurs in a proportion of patients and may require discontinuation. The problem may relate to an inhibition of enzymes that breakdown bradykinin.

First-dose hypotension may be a concern, particularly for those on diuretics, although generally this is rare. Despite this, the author normally advises patients to commence ACE inhibitors at the lowest dose, and to take the first dose just before bedtime to further diminish its likelihood. Discontinuation of diuretics for a few days before and just after starting an ACE inhibitor will also reduce risks.

ACE inhibitors should not be used in the context of renal artery stenosis since this may be associated with a rapid and potentially devastating deterioration in renal function.[89] In theory one might expect more problems in diabetic patients, particularly the elderly, because of an increased risk of atherosclerotic-related renal artery stenosis. In practice, such deterioration is rare, although it is wise to check creatinine 7–10 days after starting an ACE inhibitor, particularly in diabetic patients.

Summary and conclusions

ACE inhibitors have become an important first-line treatment for the management of hypertension in diabetes. The reasons for this include:

- good side-effect profile
- efficacy in lowering blood pressure
- suitability for a wide range of patients
- can be used in combination with any drug from another antihypertensive class
- evidence for reversal of cardiac hypertrophy
- evidence for both renal and cardiac protection. The latter is particularly the case in people at high cardiovascular risk who have had a previous event, or suffer from ischaemic heart disease, and also in diabetic patients with other cardiovascular risk factors.

Angiotensin II antagonists (angiotensin type 1 receptor blockers)

These agents are relatively new and also act as inhibitors of the renin angiotensin system (RAS), but by specifically blocking the effect of angiotensin II at the (type 1) receptor site[90] (Figure 27).

They are as effective in lowering blood pressure as ACE inhibitors, do not cause the chronic cough so often associated with the latter, and are at the very least metabolically neutral and may even improve the metabolic profile. There is also evidence that they are as effective as ACE inhibitors in delaying progression of renal injury in animal models of disease.[91] Small clinical studies have also shown improve-

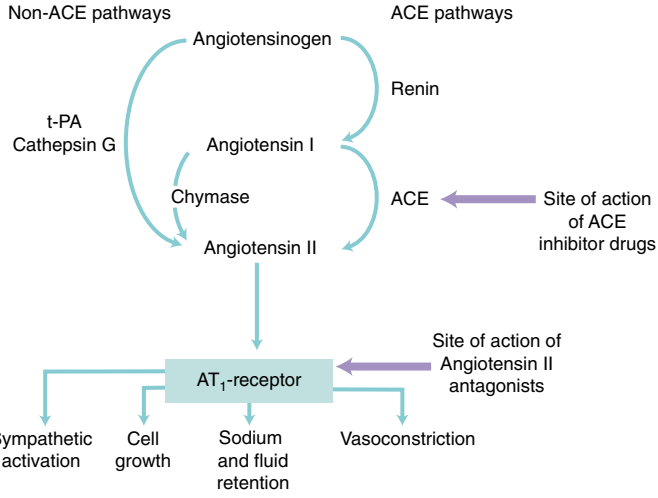


Figure 27
The renin angiotensin system and the site of action of ACE inhibitors and angiotensin II receptor antagonists.

ment in markers of renal protection, better than that seen with calcium channel blockers but with equal lowering of blood pressure.[92] There are also several large clinical trials at present of angiotensin II antagonists in patients with diabetes, to determine whether or not they are as effective as ACE inhibitors in renal protection and retinopathy. Other trials concentrate more on cardiovascular protection, including mortality and morbidity studies of several thousand patients with hypertension, heart failure, diabetes with renal impairment and after myocardial infarction.

It is possible that a combination of ACE inhibitor and angiotensin II receptor blocker may be used for the management of hypertension and with the possibility of additional cardio and renal protection,[92] although this needs to be tested. The rationale for this approach is that ACE inhibitors do not fully block the RAS and the combination should give a more complete blockade. It could be

argued, however, that using higher doses of AII antagonists might be as useful as such a combination.

Studies of angiotensin II receptor antagonists

Effects on cardiovascular structure

Since the RAS is involved in the development of cardiac and vascular hypertrophy associated with hypertension it is expected that inhibition of the system might have beneficial effects. ACE inhibitors have reduced cardiac mass and structural alterations in small arteries in animal and human studies. Data for AII antagonists is less extensive, but animal studies of the spontaneously hypertensive rat suggest regression of cardiac and vascular structure similar to that with ACE inhibitors.[93] There are also some human studies that have suggested reduction/normalization of structural alterations in small resistance arteries after long term use of ACE inhibitors and similar results with AII antagonists.[94] Studies on left ventricular mass have been more difficult to interpret, with some showing no change and others regression of left ventricular hypertrophy.[95]

Hypertension trials

These include the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, which is a comparison of this agent versus a beta-blocker (atenolol) on cardiovascular events and left ventricular mass in over 9000 patients over at least 4 years.[96] Other similar studies of AII antagonists (including candesartan, irbesartan and valsartan) are planned or are in progress, eg: the Study of Irbesartan in Left VEntricular hypertrophy Regression — SILVER study (unpublished); the Valsartan Antihypertensive Long term Use Evaluation study (VALUE).[97]

Heart failure trials

Several large trials are also trying to determine whether AII antagonists are as effective as ACE inhibitors for treatment of congestive heart failure. Five studies have compared

the effects of AII antagonists with those of ACE inhibitors on exercise capacity and symptoms in patients with heart failure.[98–102] None has reported a significant difference in these outcomes. Head-to-head comparisons between ACE inhibitors and AII antagonists remain controversial and await the outcome of further studies. It is reasonable, however, to recommend these agents for patients with heart failure who cannot tolerate ACE inhibitors. The possibility that dual therapy with these agents and an ACE inhibitor might provide further benefits is interesting, but not yet proven.

Current trials in diabetic patients

Several AII receptor antagonist trials are now underway, and three have just been reported, which are of particular relevance to the diabetic population. Two of these studies involve irbesartan and the third losartan. The irbesartan trials reported the effect of this drug in diabetic patients with both early and more advanced renal disease. The three year Irbesartan Diabetic Nephropathy Trial (IDNT) included more than 1700 hypertensive type 2 diabetic patients (blood pressure > 135/85 mm Hg).[103] This double blind randomised multicentre trial compared irbesartan versus the calcium channel blocker amlodipine versus placebo. Patients were randomised to once daily irbesartan (titrated up to 300 mg od) or amlodipine (titrated up to 10 mg od) or placebo. Other antihypertensives except for ACE inhibitors, AII receptor antagonists or calcium channel blockers were added to all three arms to get down to target blood pressure. At randomisation the patients had normal or raised creatinine (88–265 µmol/l in females and 106–265 µmol/l in males) and proteinuria above 900 mg per 24 hr. The primary outcome was time to a composite endpoint consisting of a doubling of the baseline creatinine level, end stage renal disease and death. The secondary outcomes included time to a composite endpoint of fatal or non-fatal cardiovascular events (including myocardial infarction, heart failure resulting in hospitalization, perma-

nent neurological deficit caused by a cerebrovascular event or lower limb amputation above the ankle).

The mean achieved blood pressures were, respectively, 144/80 (placebo), 141/77 (amlodipine) 140/77 (irbesartan). For the primary endpoint the irbesartan group had a relative risk reduction of 20% compared with placebo group ($p = 0.02$) and 23% compared with the amlodipine group ($p = 0.006$).

For each component of the primary endpoint, irbesartan was associated with 37% risk reduction versus amlodipine ($p < 0.001$) and 33% versus placebo ($p = 0.003$) for doubling of serum creatinine. For end stage renal disease, irbesartan showed a relative risk reduction of 23% compared with both groups ($p = 0.07$). The all cause mortality was 15–16% in all groups. For the secondary endpoints, irbesartan reduced proteinuria by 33% compared with 6% for amlodipine and 10% for placebo but none of the comparisons were significantly different between the groups. The study was not powered, however, to detect treatment differences between groups for secondary endpoints.

The second study looked at the effect of irbesartan on microalbuminuria in hypertensive patients with type 2 diabetes (IRMA II).[104] It included 590 patients with type 2 diabetes, hypertension (BP > 135/85) and microalbuminuria (albumin excretion rate 20–200 µg/min) and normal renal function. Patients were randomly assigned to irbesartan 150 mg od, irbesartan 300 mg od or placebo to assess whether this agent could slow progression of renal disease. The primary outcome was time to onset of diabetic nephropathy defined by persistent albuminuria in overnight specimens with AER > 200 µg/min and at least 30% higher than baseline. Secondary outcomes were changes in the level of albuminuria, changes in creatinine clearance and the restoration of normoalbuminuria (AER < 20 µg/min) by the time of last visit.

The irbesartan 300 mg group showed a significant risk reduction of 70% compared with the placebo group for the primary outcome ($p < 0.001$). The number needed to treat with microalbuminuria to prevent one person progressing to overt nephropathy was 10. For the 150 mg irbesartan group the relative risk reduction was 39% compared with control ($p = 0.08$). For secondary endpoints there was a significant reduction in overnight AER in both irbesartan groups compared with control. The percentage of patients who normalised AER was significantly higher in the 300 µg irbesartan group versus control (34% versus 21%, $p = 0.006$). There was also a non-significant reduction in non-fatal cardiovascular events compared with controls (8.7% control versus 4.5% irbesartan).

Since blood pressure reductions were similar in the three arms, one can conclude that the benefits compared with placebo were independent of blood pressure lowering. The results were also clearly better at the higher dose of irbesartan. Side effect profile was excellent with adverse events actually less than placebo.

A similar trial in diabetic nephropathy using losartan has also been reported.[105] The Reduction of Endpoints in NIDDM with Angiotensin II Antagonists Losartan (RENAAL) study compared losartan 50–100 mg versus placebo in hypertensive type 2 diabetic patients with proteinuria above 500 mg/day, with a target blood pressure of <140/90 mm Hg. The relative risk reduction for the primary composite endpoint (which was the same as in IDNT) was significant at 16% compared with control ($p = 0.02$). There was also a reduction in incidence of doubling of serum creatinine concentration (risk reduction 25%, $p = 0.006$) and end-stage renal disease (risk reduction 28%, $p = 0.002$). Proteinuria declined by 35% with losartan ($p < 0.001$). There was no significant difference in cardiovascular events or death.

Also underway but not yet completed is the Diabetes Exposed to Telmisartan And enalaprIL (DETAIL) Study, which is a comparison of the ACE inhibitor enalapril with the AII antagonist telmisartan over five years.[106] Patients have type 2 diabetes and mild to moderate hypertension with proteinuria ranging from 10 to 1000 µg/min. The primary endpoint is change in glomerular filtration rate (GFR) at 5 years, and secondary endpoints include annual change in GFR, cardiovascular events and mortality. A host of other trials, all of which are relevant to the diabetic patient, are also underway using these new agents both in hypertension and in heart failure.

Angiotensin II receptor blockers therefore appear to slow progression of renal disease both from the point of view of moving from microalbuminuria to overt nephropathy and also for overt nephropathy itself. These agents are therefore eminently suitable as first line drugs in these situations. This is in addition to their being suitable first line agents generally for the management of hypertension in diabetic patients.

Conclusions

Angiotensin II receptor antagonists are an important advance in the management of hypertension, and are particularly useful in diabetic patients because of their excellent metabolic and side effect profiles. The evidence to date is that they are as good at lowering blood pressure as ACE inhibitors, with a better side effect profile, and there is now good evidence from both animal studies and now longer term human studies of significant renal protection. There is also preliminary evidence of improvement in cardiovascular function although more studies are awaited.

These drugs may also be particularly useful in the elderly because of their excellent side effect profile, once daily

dosing and beneficial effects on systolic hypertension which is very common in the elderly.

The evidence for renal protection is now excellent and these drugs should now really be first line in this area. Several other trials are also underway, which will further decide their exact place in the management of hypertension and heart failure as well as their role in cardiac protection in both diabetic and non-diabetic individuals.

Combination therapy

Despite the wide choice of antihypertensive agents, many patients with hypertension remain untreated, and most of those who are treated are not getting down below recommended targets. Indeed, the situation is so bad in the UK that it is likely that fewer than 10% of hypertensive patients have their blood pressure controlled to levels below 140/90 mm Hg.[107]

Clearly, all antihypertensive agents will lower blood pressure, and combination therapy using drugs from different classes have an additive and perhaps a synergistic effect. The other benefit is that combination therapy may allow lower doses of each individual agent to be used, therefore reducing the incidence of side-effects. It should be noted, however, that the best evidence for cardiac and renal protection with inhibitors of the RAS is at the higher doses, and it is therefore recommended that such doses should be used in diabetic patients.[46,83,103,104]

Both ACE inhibitors and angiotensin II receptor antagonists look to be particularly useful in diabetic patients and are effective in combination with other antihypertensive agents from different classes.

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