Evidence-based Therapy in Vascular Surgery

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Preface

The topic of this book is evidence-based vascular and endovascular surgery and vascular medicine. Thereby, all prevalent arterial vascular diseases are discussed, from extracranial carotid stenosis to thoracic and abdominal aortic aneurysms, peripheral arterial occlusive disease and the diabetic foot. Furthermore, especially significant for the outpatient field, therapy of varicose veins is included. The objective of this book is to assess surgical procedures and to aid the reader in resolving whether open or endovascular intervention should be preferred in a given situation. This initiates with recommendations from guidelines, which are not necessarily the same in all countries and sometimes may not be of the highest quality. The authors scrutinized which of the most frequently utilized guidelines were identical and which of them differed.

This leads us to the second focus of this book, the treatment results, which serve as a rudiment for an evidence-based therapy decision. Clinical studies are discussed and classified according to their significance; all important meta-analyses and Cochrane-Reviews are presented, and the recent results of randomized and large retrospective cohort studies are explained. Due to their inclusion and exclusion criteria, randomized controlled trials do not always simulate real-life conditions. The results of large registries like the National Surgical Quality Improvement Program (NSQIP) or the Swedvasc and Vascunet, therefore, are indispensable for decision making and are presented and discussed here, as well.

In the end, the reader determines which treatment (e.g., open or endovascular intervention) currently is the best founded. This addresses a wide readership; not only younger doctors in their training but also experienced practitioners can learn the latest developments in our field. The preparation of consultant recommendations is facilitated, which is useful not only for vascular surgeons.

The benefit of such a book depends on its stringent structure and up-to-the-minute data. The authors, therefore, systematically requested all study results from the last 5 years in a Medline (PubMed) search. Previous publications were consulted when only a paucity of new data was accessible. This enables the reader to be certain of encountering the latest study outcomes and guidelines. In view of the rapid developments in our field and the propagation of many cutting-edge endovascular

techniques, we furnish the readers with a compendium, with the help of which they can implement, in their daily practice, vascular and endovascular procedures, based on state-of-the-art techniques and technologies.

In conclusion, we thank all employees of the Springer publishing house, who participated in this project for their kind assistance, and especially Mr. Andre Tournois, who, from the inception, was convinced of our concepts and buttressed us energetically.

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Chapter 1
Extracranial Carotid Stenosis

1.1 Guidelines

1.1.1 European Society of Cardiology (ESC)

Recommendations for management of asymptomatic carotid artery disease (European Stroke Organisation et al. 2011):

- All patients with asymptomatic carotid artery stenosis should be treated with long-term antiplatelet therapy. (Class-I-recommendation/Level of evidence B)
- All patients with asymptomatic carotid artery stenosis should be treated with long-term statin therapy. (Class-I-recommendation/Level of evidence C)
- In asymptomatic patients with carotid artery stenosis ≥60%, CEA should be considered as long as the perioperative stroke and death rate for procedures performed by the surgical team is <3% and the patient's life expectancy exceeds 5 years. (Class-IIa-recommendation/Level of evidence A)
- In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centres with documented death or stroke rate <3%. (Class-IIb-recommendation/Level of evidence B)

Recommendations for management of symptomatic carotid artery disease:

- All patients with symptomatic carotid stenosis should receive long-term antiplatelet therapy. (Class-I-recommendation/Level of evidence A)
- All patients with symptomatic carotid stenosis should receive long-term statin therapy. (Class-I-recommendation/Level of evidence B)
- In patients with symptomatic 70–99% stenosis of the internal carotid artery, CEA is recommended for the prevention of recurrent stroke. (Class-I-recommendation/Level of evidence A)

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- In patients with symptomatic 50–69% stenosis of the internal carotid artery, CEA should be considered for recurrent stroke prevention, depending on patient-specific factors. (Class-IIa-recommendation/Level of evidence A)
- In symptomatic patients with indications for revascularization, the procedure should be performed as soon as possible, optimally within 2 weeks of the onset of symptoms. (Class-I-recommendation/Level of evidence B)
- In symptomatic patients at high surgical risk requiring revascularization, CAS should be considered as an alternative to CEA. (Class-IIa-recommendation/Level of evidence B)
- In symptomatic patients requiring carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centres with documented death or stroke rate <6%. (Class-IIb-recommendation/Level of evidence B)

1.1.2 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/VM/SVS

Recommendations for selection of patients for carotid revascularization (Brott et al. 2011):

Class I

- Patients at average or low surgical risk who experience non disabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging (Level of Evidence: A) or more than 50% as documented by catheter angiography (Level of Evidence: B) and the anticipated rate of perioperative stroke or mortality is less than 6%.
- CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6% (Level of Evidence: B)
- Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. (Level of Evidence: C)

Class IIa

- It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (Level of Evidence: A)

- It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention. (Level of Evidence: B)
- It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery. (Level of Evidence: B)
- When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery. (Level of Evidence: B)

Class IIb

- Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. (Level of Evidence: B)
- In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established. (Level of Evidence: B)

Recommendations for periprocedural management of patients undergoing carotid endarterectomy:

Class I

- Aspirin (81–325 mg daily) is recommended before CEA and may be continued indefinitely postoperatively. (Level of Evidence: A)

Class IIa

- Patch angioplasty can be beneficial for closure of the arteriotomy after CEA. (Level of Evidence: B)
- Administration of statin lipid-lowering medication for prevention of ischemic events is reasonable for patients who have undergone CEA irrespective of serum lipid levels, although the optimum agent and dose and the efficacy for prevention of restenosis have not been established. (Level of Evidence: B)

Recommendations for management of patients undergoing carotid artery stenting:

Class I

- Before and for a minimum of 30 days after CAS, dual-antiplatelet therapy with aspirin (81–325 mg daily) plus clopidogrel (75 mg daily) is recommended. For patients intolerant of clopidogrel, ticlopidine (250 mg twice daily) may be substituted. (Level of Evidence: C)

Class IIa

- Embolic protection device (EPD) deployment during CAS can be beneficial to reduce the risk of stroke when the risk of vascular injury is low. (Level of Evidence: C)

1.1.3 American Heart Association/American Stroke Association

Recommendations for selection of patients for carotid revascularization (Kernan et al. 2014):

1. For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, carotid endarterectomy (CEA) is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence A)
2. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (e.g., magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence B)
3. When the degree of stenosis is <50%, CEA and carotid angioplasty and stenting (CAS) are not recommended (Class III; Level of Evidence A).
4. When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery if there are no contraindications to early revascularization (Class IIa; Level of Evidence B).
5. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% (Class IIa; Level of Evidence B). (Revised recommendation)
6. It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (i.e., older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (i.e., stroke, MI, or death) and long-term risk for ipsilateral stroke (Class IIa; Level of Evidence B). (New recommendation)
7. Among patients with symptomatic severe stenosis (>70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable (Class IIa; Level of Evidence B). (Revised recommendation)
8. CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies (Class I; Level of Evidence B). (Revised recommendation)

1.1.4 Screening for Asymptomatic Carotid Artery Stenosis: U.S. Preventive Services Task Force Recommendation Statement

- The USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population. (D recommendation) (LeFevre 2014)

1.1.5 Systematic Review of Guidelines for the Management of Asymptomatic and Symptomatic Carotid Stenosis

Abbott et al. (2015) systematically compared and appraised contemporary guidelines on management of asymptomatic and symptomatic carotid artery stenosis. They identified 34 guidelines meeting the inclusion criteria. These were sets of recommendations on CEA or CAS, or both for asymptomatic carotid stenosis (ACS) or symptomatic carotid stenosis (SCS), or both published between January 1, 2008, and January 28, 2015, in 41 separate documents from 23 different regions/countries (including 2 representing Europe and 5 the United States).

1.1.5.1 Management of Moderate or Severe Carotid Stenosis

ACS: *Average-CEA-Risk/CEA Recommendations*

Of 25 guidelines with CEA recommendations for patients with moderate or severe ACS (≈50%–99% by NASCET criteria), 24 (96%) endorsed CEA for average-CEA-risk patients by either recommending that it should be provided (7 guidelines) or that it may be provided (17 guidelines).

ACS: Average-CEA-Risk/CAS Recommendations

Of 27 guidelines with CAS recommendations for moderate or severe ACS, CAS was endorsed for average-CEA risk patients in 17 (63%) by recommending that it should be provided (2 guidelines) or it may be provided (15 guidelines).

ACS: High-CEA-Risk/CAS Recommendations

Of 27 guidelines with CAS recommendations for moderate or severe ACS, 2 (7%) gave CAS recommendations specifically for patients considered high-CEA-risk because of vascular anatomy, and both recommended it may be provided. Nine guidelines (30%) gave CAS recommendations for patients with ACS considered high-CEA-risk because of vascular anatomy or medical comorbidities. Seven of these (26%) endorsed CAS by stating that it should be provided (2 guidelines) or that it may be provided (5 guidelines).

SCS: Average-CEA-Risk/CEA Recommendations

All 31 guidelines with CEA recommendations for SCS endorsed CEA for patients with severe (≈70%–99% by NASCET) average-CEA-risk SCS by recommending that it should be provided (28 guidelines) or may be provided (3 guidelines).

Thirty-one guidelines also endorsed CEA for patients with moderate (≈50%–69% by NASCET) average-CEA-risk SCS by recommending that it should be provided (14 guidelines) or it may be provided (17 guidelines).

SCS: Average-CEA-Risk/CAS Recommendations

Nineteen of thirty-three guidelines (58%) with CAS recommendations for SCS endorsed CAS for severe (≈70%–99% by NASCET) average-CEA-risk SCS by recommending that it should be provided (6 guidelines) or that it may be provided (13 guidelines). One guideline endorsed CAS in such patients only if aged <70 years and if revascularization was appropriate. CAS was specifically not recommended (advising it should not be provided) for patients with average-CEA-risk severe SCS in 9 guidelines (27%). Eighteen of thirty-three guidelines (55%) with CAS recommendations for SCS endorsed CAS for moderate (≈50%–69% by NASCET) average-CEA-risk SCS by recommending that it should be provided (3 guidelines) or that it may be provided (15 guidelines).

SCS: High-CEA-Risk/CAS Recommendations

Of 33 guidelines with CAS recommendations for SCS, 10 (30%) provided specific CAS recommendations for patients with moderate or severe (≈50%–99% NASCET) SCS considered high-CEA-risk according to vascular anatomy. CAS was endorsed in all 10 by stating that it should be provided (4 guidelines) or it may be provided (6 guidelines). Seven guidelines (21%) provided CAS recommendations for patients with moderate or severe SCS considered high-CEA risk because of vascular anatomy or medical comorbidities. All 7 endorsed CAS by stating that it should be provided (3 guidelines) or it may be provided (4 guidelines).

The authors concluded (Abbott et al. 2015): All current guideline procedural endorsements of CEA and CAS are still based only on trials of CEA versus medical treatment alone in which patients were randomized 12–34 years ago. Furthermore, there was underutilization of evidence on medical treatment, advances in medical treatment, stroke risk stratification for ACS, and evidence from nonrandomized trials (including routine practice). There was often under-representation of the hazards of CAS. These weaknesses encourage the use of costly carotid procedures, which, for many patients, are currently more likely to harm than help. There is a need for new guidelines that address these problems in the interests of patients and health professionals.

1.2 Results

1.2.1 Randomized Studies for CEA Versus CAS

Mas et al. (2014) reported long-term follow-up results of patients included in the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. This randomized, controlled trial of carotid stenting versus

endarterectomy in 527 patients with recently symptomatic severe carotid stenosis was conducted in 30 centers in France. At the 5-year follow-up, the main end point (ipsilateral stroke after randomization or procedural stroke or death) had occurred in 29 of the 265 patients who were assigned to stenting and in 16 of the 262 patients who were assigned to endarterectomy (cumulative probability 11.0% versus 6.3%). At the 10-year follow-up, this end point had occurred in 30 patients in the stenting group and 18 in the endarterectomy group (cumulative probability 11.5% versus 7.6%). The long-term benefit-risk balance of carotid stenting versus endarterectomy for symptomatic carotid stenosis favored endarterectomy, a difference driven by a lower risk of procedural stroke after endarterectomy. (The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stenting (Mas et al. 2006)). Both techniques were associated with low and similar long-term risks of recurrent ipsilateral stroke beyond the procedural period.

The International Carotid Stenting Study (ICSS) enrolled 1713 patients (stenting group, n = 855; endarterectomy group, n = 858) (International Carotid Stenting Study Investigators et al. 2010). Patients with recently symptomatic carotid artery stenosis were randomly assigned in a 1:1 ratio to receive carotid artery stenting or carotid endarterectomy. In the intention to treat analysis, the risk of stroke, death, or procedural myocardial infarction 120 days after randomization was significantly higher in patients in the stenting group than in patients in the endarterectomy group (8.5% vs 5.2%). These early results suggested that carotid endarterectomy should remain the treatment of choice for symptomatic patients with severe carotid stenosis suitable for surgery. The ICSS trial was terminated in 2011. Patients were followed up for a median of 4.2 years after randomization (Bonati et al. 2015). In the ITT population, the primary endpoint of fatal or disabling stroke between randomization and end of follow-up was seen in 52 of 853 patients in the stenting group (cumulative 5-year risk 6.4%), and in 49 of 857 patients in the endarterectomy group (cumulative 5-year risk 6.5%). In the per-protocol population, no difference was seen between treatment groups in the rates of fatal or disabling stroke. The analysis showed that the risk of stroke of any severity occurring in any territory during follow-up was increased in the stenting group (excess risk 1.1% compared with endarterectomy at 1 year, and 3.1% at 5 years), but strokes were mainly non-disabling events. Thus, long-term functional outcome was similar for stenting and endarterectomy for symptomatic carotid stenosis. The authors concluded that endarterectomy remains the treatment of choice for older patients and those with extensive white-matter disease, but stenting is an appropriate treatment alternative for patients with symptomatic carotid stenosis if the risk of periprocedural stroke is low, for example in younger patients and those with lower levels of pre-existing white-matter disease. Moreover, there were no differences in costs or QALYs between the treatments (Featherstone et al. 2016).

Mechanisms of procedural stroke following carotid endarterectomy or carotid artery stenting within the ICSS trial were analyzed by Huibers et al. (2015). Procedural stroke occurred within 30 days of revascularization in 85 patients (CAS 58 out of 791 and CEA 27 out of 819). Nearly all (97%) of the strokes associated with CAS were the result of infarction. In contrast, in the surgery arm a much

larger proportion of patients (18%) suffered from a haemorrhagic stroke. All haemorrhagic strokes in ICSS occurred several days after the procedure and most were preceded by severe hypertension. Nearly all strokes occurred in the ipsilateral hemisphere; however, a few (6) developed in a cerebral territory not directly related to the treated carotid artery. Non-ipsilateral strokes can be addressed to catheter-related disruption of the plaque in the aortic arch in patients undergoing CAS. In the CAS arm, stroke was most often caused by a haemodynamic mechanism.

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) compared the outcomes of carotid-artery stenting with those of carotid endarterectomy among patients with symptomatic or asymptomatic extracranial carotid stenosis (Brott et al. 2010). Patients were randomly assigned to one of the two treatments, resulting in a cohort of 2502 patients for all analyses. The primary end point was the composite of any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization. There was no significant difference in the estimated 4-year rates of the primary end point between carotid-artery stenting and carotid endarterectomy (7.2% and 6.8%, respectively). Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group: for death (0.7% vs 0.3%), for stroke (4.1% vs 2.3%), and for myocardial infarction (1.1% vs 2.3%). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively). Timaran et al. (2013) examined differences in outcomes between CAS and CEA performed by vascular surgeons in CREST. Vascular surgeons performed 237 of the 1136 CAS procedures (21%) and 765 of the 1184 CEAs (65%). Among randomized patients who underwent the assigned intervention performed by vascular surgeons, the periprocedural stroke and death rates were higher after CAS than CEA among symptomatic patients (6.1% vs 1.3%) and among asymptomatic patients (2.6% vs 1.1%). Conversely, MI rates were lower for CAS compared with CEA (1.3% vs 2.6%). Cranial nerve injuries (0.0% vs 5.0%) were less frequent after CAS than CEA. When vascular surgeons were compared with all other specialists performing CAS, they had comparable outcomes for the periprocedural primary end point (HR, 0.99) after adjusting for age, sex, and symptomatic status. Vascular surgeons also had similar results after CEA for the periprocedural primary end point compared with other specialists performing CEA (HR, 0.73).

Brott et al. (2016) now reported the outcomes after stenting and endarterectomy over 10 years of follow-up in the CREST trial. From 2000 through 2008, a total of 2502 patients underwent randomization. The median follow-up was 7.4 years. Consent for the long-term follow-up was obtained from 1607 patients. The 10-year risk of the primary composite endpoint (any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke thereafter) did not differ significantly between the stenting group and the endarterectomy group (hazard ratio in the stenting group, 1.10). At 10 years, the event rates were 11.8% in the stenting group and 9.9% in the endarterectomy group. There were no significant differences in the rate of the primary long-term end point – postprocedural ipsilateral stroke

over the 10-year follow-up – between the stenting group and the endarterectomy group (6.9% and 5.6%, respectively; hazard ratio, 0.99). In the stenting group, the rate of stroke at 5 years was 2.5% among symptomatic patients and 2.5% among asymptomatic patients; the rates in the endarterectomy group were 2.7% among symptomatic patients and 2.7% among asymptomatic patients. In conclusion, over 10 years of follow-up no significant differences were seen between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke.

1.2.2 Meta-analysis/Systematic Reviews for CEA Versus CAS

A Cochrane review assessed the benefits and risks of endovascular treatment compared with carotid endarterectomy or medical therapy in patients with symptomatic or asymptomatic carotid stenosis (Bonati et al. 2012). Sixteen trials involving 7572 patients were included. In patients with symptomatic carotid stenosis at standard surgical risk, endovascular treatment was associated with a higher risk of the following outcome measures occurring between randomisation and 30 days after treatment than endarterectomy: death or any stroke (odds ratio, OR 1.72), death or any stroke or myocardial infarction (OR 1.44), and any stroke (OR 1.81). The OR for the primary safety outcome was 1.16 in patients <70 years old and 2.20 in patients ≥70 years old. The rate of death or major or disabling stroke did not differ significantly between treatments (OR 1.28). Endovascular treatment was associated with lower risks of myocardial infarction (OR 0.44), cranial nerve palsy (OR 0.08) and access site haematomas (OR 0.37). The combination of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up (the primary combined safety and efficacy outcome) favoured endarterectomy (OR 1.39), but the rate of ipsilateral stroke after the peri-procedural period did not differ between treatments (OR 0.93). Restenosis during follow-up was more common in patients receiving endovascular treatment than in patients assigned for surgery (OR 2.41). According to this review, endovascular treatment is associated with an increased risk of periprocedural stroke or death compared with endarterectomy. However, this excess risk appears to be limited to older patients.

Paraskevas et al. (2016) performed a systematic review using outcome data in large, administrative dataset registries. The main aims were to (i) compare stroke/death rates after CAS/CEA in contemporary dataset registries, (ii) examine whether procedural stroke/death rates had fallen within AHA/ASA thresholds, 1, 2 and 3 and (iii) determine whether there had been a decline (over time) in procedural risk after CEA/CAS. Stroke/death after CAS was significantly higher than after CEA in 11/21 registries (52%) involving “average risk for CEA” asymptomatic patients and in 11/18 registries (61%) involving “average risk for CEA” symptomatic patients. CAS was associated with stroke/death rates that exceeded risk thresholds recommended by the AHA in 9/21 registries (43%) involving “average risk for CEA”

asymptomatic patients and in 13/18 registries (72%) involving "average risk for CEA" symptomatic patients. In conclusion, data from contemporary administrative dataset registries suggest that stroke/death rates following CAS remain significantly higher than after CEA and often exceed accepted AHA thresholds. There was no evidence of a sustained decline in procedural risk after CAS.

Tu et al. (2015) compared the outcomes of repeated CEA (redo CEA) and carotid artery stenting (CAS) for carotid restenosis (CRS) after CEA. Four thousand three-hundred and ninety-nine patients were included in this systematic review. No differences were observed in the 30-day perioperative mortality, stroke and transient ischemic attack rates in the comparative studies and the noncomparative studies. Patients undergoing redo CEA suffered more cranial nerve injuries (CNIs) than those undergoing CAS, but most of these cases recovered within 3 months. Patients treated with redo CEA exhibited similar myocardial infarction (MI) rates to those treated with CAS in the comparative studies, but the rate was higher in the noncomparative studies. Patients treated with CAS were more likely to develop restenosis than those treated with redo CEA in the long-term follow-up. In conclusion, both redo CEA and CAS were safe and feasible interventions for postendarterectomy restenosis. The main limitation of this systematic review was the lack of randomized, controlled trials. Another problem was the different follow-up period between the two groups. Furthermore, the influence of patients' symptoms (symptomatic or asymptomatic) could not be analyzed.

1.2.3 Registry Data CEA and CAS

Schermerhorn et al. (2013) analyzed 10,107 patients undergoing CEA (6370) and CAS (3737), stratified by Centers for Medicare and Medicaid Services (CMS) high-risk (HR) criteria (age ≥ 80 years/New York Heart Association (NYHA) congestive heart failure (CHF) class III/IV/left ventricular ejection fraction (LVEF) < 30%/recent myocardial infarction (within 30 days)/restenosis/radical neck dissection/contralateral occlusion/prior radiation to neck/contralateral laryngeal nerve injury/high anatomic lesion). The primary endpoint was composite death, stroke, and myocardial infarction (MI) (major adverse cardiovascular event [MACE]) at 30 days. CAS patients were more likely to have preoperative stroke (26% vs 21%) or transient ischemic attack (23% vs 19%) than CEA. Although age ≥80 years was similar, CAS patients were more likely to have all other HR criteria. CEA appeared safer for the majority of patients with carotid disease. For CEA, HR patients had higher MACEs than normal risk in both symptomatic (7.3% vs 4.6%) and asymptomatic patients (5% vs 2.2%). For CAS, HR status was not associated with a significant increase in MACE for symptomatic (9.1% vs 6.2%) or asymptomatic patients (5.4% vs 4.2%) (Table 1.1).

McDonald et al. (2014) determined whether adverse outcomes after CEA or CAS were similar using propensity score-matched analysis of retrospective data

Table 1.1 Thirty-day event rates for symptomatic and asymptomatic patients undergoing CEA and CAS stratified by risk group

	Asymptomatic patients				Symptomatic patients			
	CAS		CEA		CAS		CEA	
	HR	Non-HR	HR	Non-HR	HR	Non-HR	HR	Non-HR
Patients (N)	1844	193	1418	2546	1538	162	936	1470
MACE	5.4%	4.2%	5.0%	2.2%	9.1%	6.2%	7.3%	4.6%
Stroke/death	4.8%	3.6%	3.7%	1.4%	7.9%	4.9%	6.4%	3.9%
Mortality	1.7%	1.6%	1.3%	0.5%	2.4%	1.9%	1.8%	0.6%
Stroke	3.4%	2.6%	2.7%	1.1%	6.7%	3.7%	4.9%	3.5%
Myocardial infarction	1.1%	1.0%	1.6%	1.1%	1.4%	1.2%	1.4%	1.1%

According to Schermerhorn et al. (2013)
MACE Major Adverse Cardiovascular Event (= composite death/stroke/myocardial infarction), *HR* high preoperative risk

from a large hospital discharge database (Premier Perspective Database). After 1:1 propensity score matching, 24,004 (12,002 CEA and CAS) asymptomatic and 3506 (1753 CEA and CAS) symptomatic procedures were included. The risk of the modified primary composite end point (in-hospital mortality or stroke) was significantly higher for CAS recipients when compared with CEA recipients for both asymptomatic (2.5% versus 1.7%; hazard ratio for CAS, 1.49) and symptomatic (10.0% versus 3.5%, respectively; hazard ratio for CAS, 3.02) presentations. Acute myocardial infarction risk was not significantly different between revascularization therapies, regardless of clinical presentation.

Al-Damluji et al. (2015) examined frequency, timing, and diagnoses of 30-day readmission between patients undergoing CEA and CAS. Medicare fee-for-service administrative claims data were used. Of 180,059 revascularizations from 2287 hospitals, CEA and CAS were performed in 81.5% and 18.5% of cases, respectively. Crude 30-day readmission rates following CEA and CAS were 9.0% (13,222 of 146,831) and 12.0% (3980 of 33,228), respectively. Yet hospitals performing a greater proportion of revascularization via CAS did not have greater hospital 30-day risk-standardized readmission rates. Almost one-third of readmission diagnoses were potentially due to procedural complications, including cerebral events (10.7%), complications of care (8.6%), acute coronary syndrome (5.0%), and arrhythmias (4.0%).

Data from the Society for Vascular Surgery Vascular Registry were used by Jim et al. (2014) to determine the effect of gender on outcomes after CEA and CAS. There were 9865 patients (40.6% women) who underwent CEA (n = 6492) and CAS (n = 3373). The primary end point was a composite of death, stroke, and myocardial infarction at 30 days. For disease etiology in CAS, restenosis was more common in women (28.7% vs 19.7%), and radiation was higher in men (6.2% vs 2.6%). Comparing by gender, there were no statistically significant differences in the primary end point for CEA (women, 4.07%; men, 4.06%) or CAS (women, 6.69%;

men, 6.80%). In this report, women did not have a higher risk of adverse events after carotid revascularization.

Datasets from 2005 to 2011 of the Nationwide Inpatient Sample (NIS) were queried for patients undergoing carotid revascularization by Eslami et al. (2015). The majority (95%) of the carotid revascularizations were performed on asymptomatic patients. Overall, CAS utilization constituted 12.5% of carotid revascularization procedures. In all three periods of the study, and compared to carotid endarterectomy, the odds of mortality and postoperative stroke were significantly higher among patients who underwent CAS. Wallaert et al. (2016a) used Medicare claims (2002–2010) to calculate annual rates of CAS and CEA and examined changes by procedure type over time. In total, data from 456,267 Medicare beneficiaries who underwent carotid revascularization between 2002 and 2010 were analyzed. The majority of these were CEA (88%). Overall, annual rates of carotid revascularization decreased by 30% over time (3.2 procedures per 1000 Medicare patients in 2002 vs 2.3 per 1000 in 2010). This decrease was largely attributable to a decline in the number of CEAs being performed. However, since its approval by the FDA in 2004, the rate of CAS has increased by 5% (0.30 vs 0.32 per 1000). In 2002, the majority of stents (54%) were placed by radiologists and the remaining 31% and 15% by cardiologists and surgeons, respectively. However, by 2010, this distribution shifted dramatically, with carotid stenting by radiologists declining to only 15% and both cardiologists and surgeons increasing their use of stenting to account for 49% and 36% of all stents placed. Carotid revascularization increased as the density of cardiologists increased.

Jonsson et al. (2016) assessed long-term outcomes after CAS, compared with CEA, in a nationwide Swedish cohort study (Swedvasc). A total of 1157 patients were included, 409 CAS and 748 CEA. Median follow-up time was 4.1 years. In this study, CAS was associated with an increased long-term risk of ipsilateral stroke and death during after the perioperative phase when compared with CEA. Ipsilateral stroke or death of >30 days postoperatively occurred in 95 of 394 in the CAS group versus 120 of 724 in the CEA group (adjusted hazard ratio, 1.5).

Administrative data have been used to compare carotid endarterectomy and carotid artery stenting. However, there are limitations in defining symptom status, Centers for Medicare and Medicaid Services high-risk status, as well as complications. Therefore, Bensley et al. (2013) did a direct comparison between administrative data (1342 patients who underwent carotid revascularization, 1055 CEA and 287 CAS) collected for the National Surgical Quality Improvement Program (NSQIP) and physician chart review for CEA and CAS. When comparing NSQIP to chart review, NSQIP identified more symptomatic patients (44.1% vs. 30.3%), fewer physiologic high-risk patients (13.0% vs. 18.6%), fewer anatomic high-risk patients (0% vs. 6.6%), and a similar proportion of perioperative strokes (1.5% vs. 1.8%). Administrative data were poor at determining symptom status, high-risk status, and accurately detecting perioperative strokes after CEA and CAS. This was in large part due to the lack of specificity with ICD-9 diagnosis codes as they fail to provide information on the severity, laterality, and temporal onset of disease.

1.2.4 Registry Data CEA

Bekelis et al. (2013) retrospectively analyzed patients who underwent CEAs from 2005 to 2010 and were registered in the American College of Surgeons National Quality Improvement Project database for the years 2005–2010. 20,015 (56.1%) patients were asymptomatic and 15,683 (43.9%) patients were symptomatic. Symptomatic patients demonstrated a significantly higher incidence of stroke and death but not MI after CEA. The 30-day incidences of stroke, MI, death, or their combined after CEA were 2.33%, 0.78%, 1.04% and 3.70% for symptomatic patients, and 1.1%, 0.63%, 0.52% and 2.06% for asymptomatic patients.

Gupta et al. (2013) also used the NSQIP database. From 2005 to 2010, asymptomatic patients who underwent an elective CEA (n = 17,692) were identified. Thirty-day incidences of stroke, MI, and death were 0.9%, 0.6%, and 0.4%, respectively. The combined 30-day stroke, MI, or death incidence was 1.8%. On multivariable analysis, six independent predictors for combined 30-day stroke, MI, or death were identified. The predictors included age in years (<60: 0 point; 60–69: −1 point; 70–79: −1 point; ≥80: 2 points), dyspnea (2 points), chronic obstructive pulmonary disease (3 points), previous peripheral revascularization or amputation (3 points), recent angina within 1 month (4 points), and dependent functional status (5 points).

The Society for Vascular Surgery (SVS) Vascular Registry was examined by Brothers et al. (2015) to determine in-hospital and 30-day event rates for "normal-risk" (NR) patients, symptomatic (SX) and asymptomatic (ASX) patients undergoing CEA. NR was defined as patients without anatomic or physiologic risk factors as defined by SVS Carotid Practice Guidelines. There were 3977 patients (1456 SX, 2521 ASX) available for comparison. Perioperative stroke rates were higher for SX patients in the hospital (2.8% vs 0.8%) and at 30 days (3.4% vs 1.0%), which contributed to the higher composite death, stroke, and MI rates in the hospital (3.6% vs 1.8) and at 30 days (4.5% vs 2.2%) observed in SX patients. In conclusion, the SVS Vascular Registry results for CEA in NR patients were similar by symptom status to those reported for CREST.

Most studies based on state and nationwide registries evaluating perioperative outcome after CEA rely on hospital discharge data only. Therefore, the true 30-day complication risk after carotid revascularization may be underestimated. Fokkema et al. (2013) used the NSQIP database 2005–2010 to assess the in-hospital and post-discharge rate of any stroke, death, cardiac event, and combined stroke/death and combined adverse outcome (S/D/CE) at 30 days following CEA. A total of 35,916 patients who underwent CEA were identified. Thirty-day stroke rate was 1.6%, death rate was 0.8%, cardiac event rate was 1.0%, stroke or death rate was 2.2%, and combined S/D/CE rate was 2.9%; 33% of strokes, 53% of deaths, 32% of cardiac events, 40% of combined stroke/death, and 38% of combined S/D/CE took place after hospital discharge. With 38% of perioperative adverse events after CEA happening post-hospitalization, this emphasizes the need for reporting and comparing 30-day adverse event rates when evaluating outcomes for CEA, or comparing carotid stenting to CEA (Table 1.2).

Table 1.2 In-hospital, postdischarge, and 30-day events of 35,916 patients undergoing CEA

	In-hospital event rate, No. (%)	Postdischarge event rate No. (%)	30-day event rate No. (%)
Stroke	396 (1.1)	195 (0.5)	591 (1.6)
Death	128 (0.4)	144 (0.4)	272 (0.8)
Cardiac event	238 (0.7)	112 (0.3)	350 (1.0)
Stroke/Death	480 (1.3)	320 (0.9)	794 (2.2)
MACE	656 (1.8)	399 (1.1)	1043 (2.9)

According to Fokkema et al. (2013)

Because CEA in asymptomatic patients is a prophylactic intervention, it must be ensured that the long-term benefit of the intervention exceeds its risk. Wallaert et al. (2013) examined factors associated with 5-year survival following CEA in patients with asymptomatic internal carotid artery (ICA) stenosis. Prospectively collected data from 4114 isolated CEAs performed for asymptomatic stenosis across 24 centers in the Vascular Study Group of New England between 2003 and 2011 were used for this analysis. Overall 3- and 5-year survival rates after CEA in asymptomatic patients were 90% and 82%, respectively. However, there were patients selected for surgery with high risk profiles, such as those with multiple major risk factors including age ≥80, insulin-dependent diabetes, dialysis dependence, and severe contralateral ICA stenosis, who were unlikely to survive long enough to realize a benefit of prophylactic CEA for asymptomatic stenosis. Predicting survival is important for decision making in these patients (Table 1.3).

In addition, Wallaert et al. (2016b) examined relationships between survival, outcomes and costs within 2 years following CEA among 3097 asymptomatic patients. Greater than 90% of patients undergoing CEA lived long enough to realize the benefits of their procedure. Overall 2-year mortality was 6.7%. Age, diabetes, smoking, CHF, COPD, renal insufficiency, absence of statin use and contralateral internal carotid artery stenosis were independently associated with a higher risk of death following CEA. In-hospital costs averaged $7500 among patients defined as low risk for death, and exceeded $10,800 among high risk patients. Predictors of high cost at 2-years were severe contralateral ICA stenosis, dialysis dependence, and ASA Class 4.

1.2.5 Registry Data CAS

Werner et al. (2015) reported for the registry of a German working group of cardiologists 6116 CAS procedures performed in 5976 patients at 36 hospitals from February 1996 to December 2010. Median age of patients was 71 years, 71.6% were men; a symptomatic stenosis was treated in 50.3% and an embolic protection device (EPD) was used in 82.5% of the patients. The overall hospital mortality or stroke rate was 3.1%. Stroke or in-hospital death occurred in 4.0% of symptomatic patients and in 2.2% of asymptomatic patients. The use of an EPD

Table 1.3 Hazard ratio for reduced 5-year survival following CEA for asymptomatic carotid stenosis

Covariate	Hazard ratio
Age (years)	
<70	Referent
70–79	1.8
≥80	3.94
Diabetes	
Nondiabetic	Referent
Diet or oral medication	1.34
Insulin dependence	1.98
Past or current smoking history	1.68
Congestive heart failure	1.78
Chronic obstructive pulmonary disease	1.66
Not on statin	1.27
Renal function	
GFR ≥ 60 mL/min	Referent
GFR < 60 mL/min	1.30
Dialysis dependent	3.41
Degree of contralateral internal carotid artery stenosis	
<50%	Referent
50%–80%	1.25
≥80%–99%	1.95
Closed	1.69

According to Wallaert et al. (2013)

was significantly associated with a lower rate of death or stroke in the registry (OR 0.45). During the study period, the proportion of symptomatic stenoses decreased (from 84.6% to 24.7%), and the use of EPDs increased from 1.4% to 97.2%.

The Nationwide Inpatient Sample was analyzed by Modrall et al. (2014) to identify patients undergoing CAS. Between 2005 and 2009, 56,374 elective CAS procedures were performed nationwide, with a crude in-hospital stroke and death rate of 3.22%. A median of nine CAS procedures were performed annually per clinician. In this study, the stroke and death rate for CAS to treat carotid stenosis was inversely affected by the number of CAS and EVAR/TEVAR procedures performed by a clinician. Stroke and death rates for CAS decreased with increasing volume of CAS performed by a clinician (low-volume vs medium-volume vs high-volume: 4.43% vs 2.89% vs 2.27%). Similar patterns were noted between clinicians' volume of EVAR/TEVAR (low-volume vs medium-volume vs high-volume: 4.58% vs 3.18% vs 2.16%).

Jalbert et al. (2015) conducted an observational study with a mean follow-up time of approximately 2 years among 22,516 fee-for-service Medicare beneficiaries at least 66 years old undergoing CAS (2005–2009). The mean patient age was 76.3 years, 60.5% were male, 91.2% were at high surgical risk, 47.4% were symptomatic, and 97.4% had carotid stenosis of at least 70%. Crude 30-day mortality,

stroke or transient ischemic attack, and myocardial infarction risks were 1.7%, 3.3% and 2.5%, respectively. Mortality during follow-up was 32.0%, with rates of 37.3% among symptomatic patients and 27.7% among asymptomatic patients. Patients at higher risk of complications and mortality during and after the periprocedural period were older, had symptomatic stenosis, or underwent nonelective CAS. These findings demonstrate that the decision to perform CAS should be based on overall survival as well as on the risk of complications and their effect on quality of life. The study raises the question about whether performing CAS is justified if periprocedural risks are too high or if patients do not live long enough to benefit from the main advantage of CAS, which is stroke prevention. The generalizability of trials like the SAPPHIRE or CREST to the Medicare population may be limited, underscoring the need to evaluate real-world effectiveness of carotid stenosis treatments.

Villwock et al. (2015) extracted a population from the National Inpatient Sample (2012) and the Nationwide Inpatient Sample (2003–2011) composed of patients with carotid artery stenosis with infarction that were admitted non-electively and received endovascular revascularization. A total of 6333 admissions were identified. The majority was treated via CAS (89%, 5608); the remaining 725 treated with angioplasty alone. The incidence of mortality in the angioplasty-alone group was higher than in the carotid stenting group (9.0% vs. 3.8%). Similarly, the rate of iatrogenic stroke was greater in the angioplasty-alone group in comparison with carotid stenting (3.9% vs. 1.9%). The results of this study may represent selection bias, but it also may indicate that symptomatic patients with stroke suffer from severe stenosis and unstable plaques that would benefit from stent placement.

1.3 Special Questions

1.3.1 Volume Outcome Relationship

The effect of surgeon's specialty and volume on the perioperative outcome of CEA was analyzed retrospectively by AbuRahma et al. (2013). Nine-hundred and fifty-three CEAs were performed by 24 surgeons. Surgeons' annual volume was categorized into low volume (<10 CEAs), medium volume (10 to <30 CEAs), and high volume (≥30 CEAs). The perioperative stroke/death rates were significantly lower for high-volume surgeons: 1.3% vs 4.1% and 4.3% for medium- and low-volume surgeons. Surgical specialty appeared to play a smaller role in CEA outcomes. Although the study did show diminished perioperative stroke and death rates for the vascular surgeons (VS) (1.3%) compared with cardiothoracic surgeons (CT) (2.9%) and general surgeons (GS) (4.1%), the results were not statistically significant. However, a subgroup analysis, comparing a combined GS/CT surgery group against the VS group, demonstrated a statistically significant improvement in perioperative stroke rates in asymptomatic patients for the VS group (3.2% vs 0.72%). Kumamaru et al. (2015) used 2000–2008 Medicare claims data for all patients who underwent

inpatient CEA or CAS. They identified 454,717 patients and 8648 performing surgeons for CEA during the period of 2001–2008 and 27,943 patients undergoing CAS during 2005–2008. The observed 30-day mortality of CEA performed by surgeons with <10 past-year case-volume was consistently higher compared with those performed by higher case-volume surgeons (e.g., 1.79% in <10 case-volume versus 1.19% in ≥40 case-volume category in 2001–2002, and 1.42% versus 1.04% in 2007–2008).

Calvet et al. (2014) examined whether operator experience is associated with 30-day risk of stroke or death in the Carotid Stenting Trialists' Collaboration database. Interventionists who performed ≥6 CAS procedures every year had better outcomes than those performing fewer numbers. The authors concluded that carotid stenting should only be performed at centers where interventionists can achieve this rate of CAS procedures.

1.3.2 Restenosis After CEA

Patients undergoing CAS and CEA for restenosis between January 2003 and March 2012 were identified within the Vascular Study Group of New England (VSGNE) database by Fokkema et al. (2014). Out of 9305 CEA procedures, 212 patients (2.3%) underwent redo CEA (36% symptomatic). Of 663 CAS procedures, 220 patients (33%) underwent CAS after prior ipsilateral CEA (31% symptomatic). Stroke/death/MI rates were statistically similar between redo CEA vs CAS after prior CEA in both asymptomatic (4.4% vs 3.3%) and symptomatic patients (6.6% vs 5.8%). However, regardless of symptom status, the risk of reintervention was increased compared with patients undergoing primary CEA. No difference in cranial nerve injury was identified between redo CEA and primary CEA (5.2% vs 4.7%).

Radak et al. (2014) analyzed 319 patients (220 asymptomatic and 99 symptomatic) who underwent CAS from 2002 until 2012 for carotid restenosis after eversion endarterectomy. Technical success was 99.7%. In the early postoperative period, transient ischemic attack (TIA) occurred in 2.8% of the patients and stroke in 1.6% (one fatal stroke [0.3%]). Median follow-up was 49.8 ± 22.8 months. In the long-term follow-up, there were no TIAs or strokes, non-neurologic mortality was 3.13%, and the recurrent restenosis rate was 4.4%. Hynes et al. (2014) compared outcomes of patients undergoing CAS for ipsilateral restenosis, after either previous CAS or CEA (CAS-R group, n = 1996), with those of patients who had CAS performed for de novo carotid atherosclerotic stenosis (CAS-DN group, n = 10,122). In-hospital death or stroke or myocardial infarction (MI) occurred less often in the CAS-R compared with CAS-DN patients (1.9% vs. 3.2%). However, there was no significant difference in the composite of death, stroke, or MI at 30 days between both groups. This analysis indicated that CAS for patients with restenosis after previous ipsilateral carotid revascularization is comparable to CAS for de novo carotid artery disease.

1.3.3 Intraoperative Shunting During CEA

Bennett et al. (2015) determined the impact of intraoperative shunting during CEA on the incidence of postoperative stroke. The 2012 CEA-targeted American College of Surgeons National Surgical Quality Improvement Program database was used for this analysis. A total of 3153 patients were included for initial analysis (2023 "no-shunt" patients vs 1130 "shunt" patients). The overall combined 30-day incidence of postoperative stroke/TIA was 3.7% and did not differ between the two groups. From this overall sample, propensity score matching yielded a cohort of 1072 patients with or without intraoperative shunt placement who were well matched for all known patient- and procedure-related factors. There was no significant difference in the incidence of postoperative stroke/TIA between the two groups of this matched cohort (3.4% in the no-shunt group vs 3.7% in the shunt group). Analysis of a similarly well matched subgroup of patients with severe stenosis or occlusion of the contralateral carotid artery demonstrated a statistically nonsignificant increase in the incidence of postoperative stroke/TIA with the use of intraoperative shunting (4.9% in the no-shunt group vs 9.8% in the shunt group; P = .08). On the basis of these findings, the authors rejected the hypothesis that intraoperative carotid shunt placement will reduce the incidence of perioperative stroke during CEA, even among those patients who are at highest theoretical risk for clamp-induced cerebral hypoperfusion.

1.3.4 Patching During CEA

Malas et al. (2015) analyzed the outcomes in 1082 patients in the CREST trial, of whom 753 (70%) patients underwent CEA with patch angioplasty and 329 (30%) had CEA with primary closure. Fifty-two patients had restenosis, of whom 27 (52%) were symptomatic and 25 (48%) were asymptomatic at baseline; in follow-up, 5 of these patients had a stroke after identification of the restenosis. Two-year restenosis rates differed significantly between the patch versus no patch groups. Restenosis was less frequent in the patch cohort when analysis was adjusted for symptomatic status (HR, 0.26). This analysis of CREST data supports the use of patch angioplasty for closure of arteriotomy in CEA. More widespread use of patching should be considered because of the clear association of patch closure with reduction in the risk of restenosis, and thus with superior long-term durability.

1.3.5 Eversion (ECEA) or Conventional (CCEA) Technique

Data for CEA patients were obtained from the Society for Vascular Surgery Vascular Quality Initiative (SVS VQI) database for years 2003–2013 by Schneider et al. (2015). Two thousand, three-hundred and sixty-five ECEA and 17,155 CCEA were performed. CCEA was more often performed with general anesthesia (92% vs 80%;

P < .001) and with a shunt (59% vs 24%; P < .001). Immediate perioperative ipsilateral neurologic events (ECEA, 1.3% vs CCEA, 1.2%) and any ipsilateral stroke (ECEA, 0.8% vs CCEA, 0.9%) were uncommon in both groups. ECEA tended to take less time (median 99 vs 114 min). However, ECEA more often required a return to the operating room for bleeding (1.4% vs 0.8%). Estimated survival was similar comparing ECEA with CCEA at 1 year (96.7% vs 95.9%). In conclusion, ECEA and CCEA provided similar freedom from neurologic morbidity, death, and reintervention. Furthermore, ECEA obviated the expenses, including increased operative time, associated with use of a patch in CCEA, and a shunt, more often used in CCEA in this database.

1.3.6 Early Risk of Stroke After Cerebrovascular Event

In a systematic review and meta-analysis, the pooled early risk of stroke based on a random effects model was 3.5%, 8.0%, and 9.2% at 2, 30, and 90 days after TIA, respectively (Wu et al. 2007). In another review, the risk of recurrence of cerebrovascular events in patients with symptomatic carotid stenosis within the first days after a neurologic index event was as high as 6.4% (1.5–23.8), 19.5% (12.7–28.7) and 26.1% (20.6–32.5) after 2–3, 7 and 14 days, respectively (Tsantilas et al. 2015). However, data from Strömberg et al. (2015) suggest that the early risk of recurrent stroke in symptomatic significant carotid stenosis is not as high as some earlier studies have shown. Strömberg et al. identified 397 patients with symptomatic carotid stenosis. The risk of recurrent stroke in the total cohort was 2.0% by day 2, 4.0% by day 7, and 7.5% by day 30.

1.3.7 Early Intervention After Neurological Event

Sharpe et al. (2013) retrospectively examined in 475 recently symptomatic patients whether CEA in the hyperacute period (whether this was defined as <48 h, <7 days, or <14 days) was associated with a significant increase in procedural risk. Two-hundred and seventy-two patients (57%) presented with a TIA, 94 (20%) with amaurosis, and 109 (23%) presented with a stroke. Overall, 208 (44%) underwent surgery within 7 days of their most recent neurological event (30-day procedural risk = 1.9%), while 341 (72%) underwent CEA within 14 days (30-day risk = 1.5%). This audit found no evidence that the procedural risk was increased when CEA was performed in the hyperacute period whether this time period was defined as <48 h, <7 days, or <14 days. In a further retrospective study, a total of 761 symptomatic patients (40.1% with transient ischemic attack [TIA], 21.3% with amaurosis fugax, and 38.6% with ischemic stroke) were included, with an overall perioperative stroke and death rate of 3.3% after CEA (Rantner et al. 2015). The timing of CEA did not influence the perioperative outcome. A stroke and death rate of 4.4% for surgery

within 0 and 2 days, 1.8% between 3 and 7 days, 4.4% between 8 and 14 days, and 2.5% in the period thereafter was observed. These data showed that very urgent surgery in symptomatic patients can be performed without increased procedural risk. On the contrary, a study from Sweden demonstrated a very high incidence of perioperative complications for patients operated on by CEA within 48 h (Strömberg et al. 2012). They analyzed data for 2596 patients and found that the combined mortality and stroke rate for patients treated 0–2 days after qualifying event was 11.5% versus 3.6%, 4.0%, and 5.4% for the groups treated at 3–7 days, 8–14 days, and 15–180 days, respectively. In this study of patients treated for symptomatic carotid disease, it was safe to perform surgery as early as day 3 after a qualifying neurological event in contrast to patients treated within 0–2 days, which had a significantly increased perioperative risk. The national clinical guideline for stroke (Intercollegiate Stroke Working Party 2012) recommends that people with an acute non-disabling stroke with stable neurological symptoms or with a TIA who have symptomatic carotid stenosis of 50–99% according to the NASCET criteria should be assessed and referred for carotid endarterectomy to be performed within 1 week of onset of symptoms.

The peri-procedural risk with urgent CAS was analyzed by Jonsson et al. (2015) in a retrospective nationwide cohort study (Swedvasc). A symptomatic stenosis was defined as all ipsilateral carotid artery events within 180 days prior to the intervention. In total, 323 patients underwent CAS for symptomatic carotid stenosis. Major peri-operative complications (stroke/death/AMI) occurred in 21 of the 323 patients (6.5%). The 30-day combined stroke and death rate did not differ significantly between the groups; zero of 13 (0%) in the group treated 0–2 days versus 4 of 85 (4.7%) at 3–7 days, 5 of 80 (6.3%) at 8–14 days, and 6 of 145 (4.1%) for the patients treated at 15–180 days. In this national registry study, CAS performed within 1 week of the onset of a neurologic event was not associated with an additional risk of a perioperative complication compared with those treated subsequently. Villwock et al. (2014a) analyzed revascularization of carotid artery stenosis for patients admitted emergently using the Nationwide Inpatient Sample (2008–2011). Cases were classified as “ultra-early” if the revascularization was performed within 48 h of admission. Cases performed on a subsequent day, up to the 14th day of admission, were termed “deferred”. There were 72,797 non-elective admissions with a primary diagnosis of carotid artery stenosis that subsequently received carotid artery revascularization (81% CEA, 19% CAS; 79% without infarction, 21% with infarction; 52% within 48 h of admission, 48% within 2 weeks). No differences in iatrogenic stroke or mortality between CAS and CEA were observed for patients without infarction on admission (Table 1.4). Patients without infarction treated within 48 h, by CAS or CEA, had significantly lower mortality than those treated with deferred timing. However, ultra-early revascularization in patients with infarction on admission increased iatrogenic stroke and death; this increase in mortality was more dramatically seen in patients treated with CAS. In a further retrospective cohort study using the Nationwide Inpatient Sample from 2002 to 2011, patients

Table 1.4 Characteristics and outcomes of patients with carotid artery stenosis

	Carotid artery stenosis without infarction				Carotid artery stenosis with infarction			
	Early intervention	Deferred intervention	Early intervention	Deferred intervention	Early intervention	Deferred intervention	Early intervention	Deferred intervention
	CAS		CEA		CAS		CEA	
Patients (N)	8065	2478	26,936	19,729	1044	1883	1963	10,699
Age (years)	72	72	72	72	67	70	69	71
Male patients (%)	59.0	61.7	58.9	56.2	70.2	62.8	64.3	61.6
Mortality (%)[a]	0.2	1.0	0.4	0.8	7.8	2.4	1.3	0.9
Postoperative stroke (%)[a]	1.4	1.7	1.1	1.8	3.6	1.8	1.7	1.3

According to Villwock et al. (2014a)
Patients admitted with infarction are separated from those without infarction. Comparisons are performed between approaches for revascularization and within group comparisons between [ultra]-early (within 48 h of admission) and deferred (up to 2 weeks) revascularization
[a]In-hospital events, no 30-day evaluation

were included if they were admitted non-electively with a primary diagnosis of carotid artery stenosis with infarction and subsequently treated with revascularization (Villwock et al. 2014b). 27,839 cases met the inclusion criteria. In this study, the lowest odds of iatrogenic complications (OR = 0.643) and mortality (OR = 0.631) coincided with revascularization between days five and seven of hospitalization. The authors concluded that the optimum timing of revascularization may be near the end of the first week of hospitalization following acute stroke.

The relationship between outcomes and time from symptom to surgery was evaluated, too, by Loftus et al. (2016). They analyzed 23,235 patients undergoing CEA between January 2009 and December 2014 from 100 UK NHS hospitals. Intervals of time from symptoms to surgery, and 30-day postoperative outcomes were assessed. The proportion of patients treated within 14 days increased from 37% to 58% over time. Performing CEA within 48 h of symptom onset was associated with a small increase in the 30-day stroke and death rate: 3.1% (0–2 days) compared with 2.0% (3–7 days); but not with longer delays. The authors concluded that there may be a small increase in risk during the first 48 h after symptoms.

1.3.8 CEA After Intravenous Thrombolysis for Acute Ischemic Stroke?

The safety of CEA after intravenous thrombolysis (IVT) was analyzed by Rathenborg et al. (2014). The study group was a consecutive series of 5526 patients who had CEA for symptomatic carotid artery stenosis. Among these, 202 (4%) had IVT prior to surgery, including 117 having CEA within 14 days, and 59 within 7 days of thrombolysis. The 30-day combined stroke and death rate was 3.5% for those having IVT + CEA, 4.1% for those having CEA without previous IVT, 3.4% for those having IVT + CEA within 14 days, and 5.1% for those having IVT + CEA within

7 days. The study supports the indication that carotid endarterectomy can be performed within the recommended 2 weeks of onset of symptoms and thrombolysis without increasing the risk of perioperative stroke or death.

1.3.9 CEA and Coronary Bypass – Synchronous or Staged Approach?

A meta-analysis of studies comparing early outcomes of synchronous and staged approach of CEA and coronary artery bypass grafting has been performed by Sharma et al. (2014). Twelve studies were identified with a total of 17,469 and 7552 patients in the combined and staged group, respectively. The pooled analysis revealed no difference in the early mortality, postoperative stroke, combined early mortality or stroke, and combined endpoint of MI or stroke between the two surgical approaches. Hence, the two strategies can be used interchangeable in the clinical practice. Gopaldas et al. (2011), too, identified no significant difference in mortality or neurologic complications between staged and synchronous approaches in patients with concurrent carotid and coronary artery disease. They identified from Nationwide Inpatient Sample database 6153 (28.9%) patients who underwent CEA before or after CABG during the same hospital admission but not on the same day (staged) and 16,639 patients who underwent both procedures on the same day (synchronous). Mortality (4.2% vs 4.5%) or neurologic complications (3.5% vs 3.9%) were similar between the staged and synchronous groups. Staged procedures were associated with a greater risk of overall complications and higher hospital charges than synchronous. In synchronous patients, on-pump CABG increased stroke rates.

1.3.10 Local or General Anesthesia in CEA?

A Cochrane review (Vaniyapong et al. 2013) determined whether carotid endarterectomy under local anaesthetic: (1) reduces the risk of perioperative stroke and death compared with general anaesthetic; (2) reduces the complication rate (other than stroke) following carotid endarterectomy; and (3) is acceptable to patients and surgeons. Fourteen randomised trials involving 4596 operations, of which 3526 were from the single largest trial (GALA) were included in this analysis. There was no statistically significant difference in the proportion of patients who had a stroke or died within 30 days of surgery. In the local anaesthesia group 3.6% of patients had a stroke or died compared to 4.2% of patients in the general anaesthesia group. The incidence of strokes in the local anaesthesia group was 3.2% compared to 3.5% in the general anaesthesia group. This systematic review suggested that patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences.

1.3.11 Management of Asymptomatic Carotid Stenosis

A report on the effectiveness of three treatment strategies for asymptomatic carotid artery stenosis (medical therapy alone, CEA and medical therapy, and CAS and medical therapy) has been published by the Agency for Healthcare Research and Quality (Raman et al. 2012). This systematic review indicated that there has been a significant reduction in the incidence of ipsilateral stroke over time with medical therapy alone. The subgroup analysis showed that between the year 2000 and 2010, the current best medical therapy could reduce the risk of ipsilateral stroke to nearly 1% per year of follow-up. Thus, to reduce any future stroke-related events invasive procedures must carry an exceedingly low risk of peri-procedural adverse events, which may be difficult to achieve in routine clinical settings. In view of recent advances in medical therapy, the applicability or generalizability of the older CEA trial results to contemporary clinical practice requires careful interpretation.

1.4 Conclusions for Clinical Practice

1. CEA is the method of choice for the treatment of asymptomatic and symptomatic carotid stenosis. CAS may be considered as an alternative to CEA in high-volume centres with documented death or stroke rate <3% in asymptomatic patients, and <6% in symptomatic patients, respectively.
2. All current guideline procedural endorsements of CEA and CAS are still based only on trials of CEA versus medical treatment alone in which patients were randomized 12–34 years ago. Furthermore, there was underutilization of evidence on medical treatment, advances in medical treatment, stroke risk stratification for ACS, and evidence from nonrandomized trials (including routine practice). There is a need for new guidelines that address these problems.
3. In CEA and CAS, perioperative stroke/death rates are significantly lower for high-volume surgeons.
4. In symptomatic patients, the optimum timing of revascularization may be near the end of the first week of hospitalization following acute stroke.
5. In patients with symptomatic carotid stenosis and thrombolysis, CEA can be performed within the recommended 2 weeks of onset of symptoms and thrombolysis without increasing the risk of perioperative stroke or death.
6. Screening for asymptomatic carotid artery stenosis in the general adult population cannot be recommended according to current evidence.

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Chapter 2
Distal Aortic Dissection Type Stanford B

The Stanford classification system divides dissections into two categories. Type A dissections involve the ascending aorta regardless of the site of origin (surgery usually recommended). Type B dissections do not involve the ascending aorta (nonsurgical treatment usually recommended). Involvement of the aortic arch without involvement of the ascending aorta in the Stanford classification is labeled as Type B (Hiratzka et al. 2010). Note: in the following only dissections originating in the descending aorta distal to the left subclavian artery (distal aortic dissections Stanford type B), respectively type III dissections in the DeBakey classification system are discussed.

2.1 Guidelines

2.1.1 American Heart Association (AHA)

The guidelines of the American Heart Association (AHA) give the Class-I-recommendations (Hiratzka et al. 2010):

- Acute thoracic aortic dissection involving the descending aorta should be managed medically unless life-threatening complications develop (e.g., malperfusion syndrome, progression of dissection, enlarging aneurysm, inability to control blood pressure or symptoms). (Level of Evidence: B)
- For patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, open repair is recommended. (Level of Evidence: B)

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2.1.2 European Society of Cardiology (ESC)

The 2014 ESC guidelines on the diagnosis and treatment of aortic diseases recommend (Erbel et al. 2014):

- In all patients with aortic dissection medical therapy including pain relief and blood pressure control is recommended. (Class I/Level of Evidence: B)
- In uncomplicated Type B aortic dissection, medical therapy should always be recommended. (Class I/Level of Evidence: C)
- In uncomplicated Type B aortic dissection, TEVAR (thoracic endovascular aortic repair) should be considered. (Class IIa/Level of Evidence: B)
- In complicated Type B aortic dissection, TEVAR is recommended. (Class I/Level of Evidence: C). [The term 'complicated' means persistent or recurrent pain, uncontrolled hypertension despite full medication, early aortic expansion, malperfusion, and signs of rupture (haemothorax, increasing periaortic and mediastinal haematoma)].
- In complicated Type B aortic dissection, surgery may be considered. (Class IIb/Level of Evidence: B)

According to this guideline, surgery is rare in cases of complicated Type B aortic dissection. Open repair has been replaced largely by endovascular therapy.

2.1.3 Society of Thoracic Surgeons Expert Consensus Document

The Society of Thoracic Surgeons Expert Consensus Document on the treatment of descending thoracic aortic disease using endovascular stent-grafts (Svensson et al. 2008) notes:

- Acute descending (type B) aortic dissection is not as life-threatening as acute type A aortic dissection. Early survival is satisfactory using medical management alone, unless distal ischemic complications ("malperfusion") or aortic rupture occurs. In patients with uncomplicated acute type B aortic dissection, this constitutes a benchmark that will be difficult to surpass, or even to match, by endovascular stent-graft treatment.
- Patients with life-threatening complications of acute type B aortic dissection are at very high risk and require emergency treatment using thoracic aortic stent-grafting, open surgical aortic graft replacement, interventional or surgical flap fenestration, or catheter reperfusion or extra-anatomic surgical bypass, or both.
- Once a patient survives 14 days after initial onset of an acute aortic dissection, it is defined as chronic. This definition is based on autopsy studies demonstrating that 74% of patients who die from dissections die within the first 2 weeks. The group of chronic dissection patients comprises those surviving surgery for acute indications and those initially treated with medical therapy alone.

- Although primary medical therapy for uncomplicated type B dissection may improve hospital survival, it has not changed long-term survival. Most deaths are related to comorbid conditions, but late complications from distal aortic dissection are estimated to occur in 20–50% of patients. These sequelae include new dissection, with associated new complications, rupture of a weak false channel, and, most commonly, saccular or fusiform aneurysmal degeneration of the thinned walls of the false channel, which can lead to rupture and exsanguination.
- Regardless of the approach used, as long as patients have residual dissected aorta, they remain at risk for late aneurysmal degeneration and rupture of the false lumen and require indefinite serial imaging surveillance, close blood pressure monitoring, and negative inotropic medical therapy.

2.1.4 Interdisciplinary Expert Consensus Document

An interdisciplinary expert consensus document on management of type B aortic dissections has been developed by Fattori et al. (2013b). The consensus describes algorithms for treatment of type B dissections.

Acute aortic dissection type B (first 2 weeks after onset of symptoms)

- Patients with uncomplicated acute type B aortic dissection should be treated with medical therapy. At present, there is no evidence of advantage with TEVAR or open surgery.
- TEVAR, when feasible, should be considered the first-line treatment in complicated acute type B dissection. A survival benefit is achieved by TEVAR in comparison with open surgery.
- Aneurysmal evolution and eventual rupture may occur even in the absence of warning symptoms, and imaging follow-up must be performed at regular intervals. MDCT or MRI scan should be used to monitor uncomplicated dissections and should be performed at admission, 7 days, discharge, and 6 weeks, because the risk of instability is higher in the early phase.
- Despite reasonably low early operative morbidity and mortality, there is the likelihood of aortic adverse events after TEVAR, and all patients need to be followed with imaging after treatment.

Panelists' suggestions for definition of complicated type B acute aortic dissection

- Malperfusion is indicative of impending organ failure and must be recognized early. Diagnosis of static or dynamic organ malperfusion is corroborated by laboratory markers (bilirubin, amylases, enzymes, creatinine) and imaging data.
- Hypertension is indicative of complications in acute type B aortic dissection only when associated with malperfusion or persisting with uncontrolled high values despite full medical therapy.
- Increases in perioaortic hematoma and hemorrhagic pleural effusion in two subsequent CT examinations during medical expectant management of acute type B aortic dissection are findings suggestive of impending rupture

Subacute aortic dissection type B

- The subacute phase in aortic dissection (>2 to 6 weeks from onset) may sometimes reveal signs of instability, such as changes in aortic morphology (expanding diameter >4 mm, new onset of periaortic hematoma, and/or pleural hemorrhagic effusion), refractory hypertension, recurrent thoracic pain, and recurrent malperfusion. In these cases, TEVAR may be considered. However, data to support prognosis and complication rates in subacute type B aortic dissection are very limited.

Chronic aortic dissection type B

- Most chronic type B aortic dissections are managed medically until complications develop. A tight control of systemic pressure with best medical treatment is of utmost importance to limit false lumen aneurysmal dilation over time.
- Recurrence of symptoms, aneurysmal dilation (total aortic diameter >55 mm), or a yearly increase (> 4 mm) of aortic diameter should be considered signs of instability in the chronic phase and indication for TEVAR, or in unsuitable anatomy, indication for open surgery. Early mortality in complicated chronic type B aortic dissection is lower for TEVAR compared with open surgery. In uncomplicated chronic type B aortic dissection, yearly clinical and imaging follow-up is recommended, irrespective of diameter and treatment applied (TEVAR/medical/open surgery).

Panelists' suggestions for definition of complications in chronic type B aortic dissection

- In patients under medical management after the acute phase, recurrence of symptoms, aneurysmal dilation (>55 mm), or an aortic yearly increase of > 4 mm are indicative of higher worse prognosis without additional treatment (chronic complicated type B aortic dissections).

2.2 Results

2.2.1 Acute Uncomplicated Type B Aortic Dissection

2.2.1.1 Best Medical Treatment

In a systematic review and meta-analysis, outcome data of best medical therapy (BMT) were available for 2347 patients from 15 studies who underwent conservative medical management for acute type B aortic dissection (Moulakakis et al. 2014). The pooled 30-day/in-hospital mortality rate was 2.4%. The pooled rate for cerebrovascular events was 1%, for spinal cord ischemia 0.8% and for overall neurologic complications 2%. Survival rates ranged from 86.2% to 100% at 1-year and from 59.0% to 97.2% at 5-years, whereas freedom from aortic events ranged from 34% to 83.9%.

Although medical therapy is recommended for uncomplicated acute type B aortic dissection, the risk of aneurysm development with subsequent rupture in the

long-term run should not to be neglected. Van Bogerijen et al. (2014) systematically reviewed and summarized the current available literature on prognostic variables related to aortic enlargement during follow-up in uncomplicated type B aortic dissection. A total of 18 full-text articles were found. The following predictors of aortic growth in these patients were identified: age <60 years, white race, Marfan syndrome, high fibrinogen-fibrin degradation product level (≥20 μg/mL) at admission, aortic diameter ≥40 mm on initial imaging, proximal descending thoracic aorta false lumen (FL) diameter ≥22 mm, elliptic formation of the true lumen, patent FL, partially thrombosed FL, saccular formation of the FL, presence of one entry tear, large entry tear (≥10 mm) located in the proximal part of the dissection, FL located at the inner aortic curvature, fusiform dilated proximal descending aorta, and areas with ulcer-like projection. In conclusion, a significant group of patients develops aneurysmal degeneration along the dissected segments during follow-up and might benefit from closer follow-up or early endovascular intervention.

Risk factors for failure of conservative treatment in acute type B aortic dissection (TBAD) were identified by Grommes et al. (2014) in a retrospective analysis of 104 patients. During the follow-up period, the initial medical treatment was converted to surgical treatment in 21 patients (20.2%) after a median of 333 days. In 5 patients (4.8%), endovascular surgery was performed during the acute dissection phase (within 14 days) because of acute complications, despite best medical treatment. In 16 patients (15.4%), surgery was performed after a median of 189 days. Surgical treatment was indicated because of aortic enlargement (n = 14), rupture (n = 1), or lower-limb ischemia (n = 1). In total, 16 patients (15.4%) died after a median of 774 days. Two patients died of aortic rupture during the acute phase of dissection, and further 14 patients died during the chronic phase of dissection, 6 of them due to dissection-related causes. Patients aged more than 66 years with a maximum aortic diameter greater than 40 mm at admission had a 6.87-fold higher mortality risk than younger patients and patients with smaller aortic diameters. Whether particularly older patients and those with early aortic dilatation benefit from prophylactic TEVAR, has to be questioned.

Durham et al. (2015b) identified a total of 298 patients with initially medical managed acute type B aortic dissections. Failure of medical therapy was defined as any death or aorta-related intervention. Early failure occurred within 15 days of presentation. There were 37 (12.4%) early failures, of which were 15 deaths and 25 were operative interventions. Thus, early mortality was 5%. The indication for early operation in a majority of patients was either renal ischemia (36.0%) or mesenteric ischemia (28.0%). Early aneurysmal degeneration was the indication for intervention in 24.0% of early operations. During a mean follow-up of 4.3 ± 3.5 years, failure of medical therapy occurred in 174 patients (58.4%). There were 87 (29.2%) aorta-related interventions and 119 (38.3%) deaths. An open operative approach was taken in 63 cases (72.4%). In 57 patients (65.5%), the indication for operation was aneurysmal degeneration. The actuarial freedom from intervention was 77.3% ± 2.4% after 3 years and 74.2% ± 2.5% after 6 years. Moreover, the intervention-free survival of the entire cohort was only 41% at 6 years, with end-stage renal disease being the only predictor of medical failure. These authors in addition

presented 200 patients (61% men) with medically managed acute type B dissections receiving multiple imaging studies (Durham et al. 2015a). Mean follow-up was 5.3 years. At 5 years, only 51% of patients were free from aortic growth. Fifty-six patients (28%) required operative intervention (50 open, 6 endovascular repair) for aneurysmal degeneration, and the actuarial 5-year freedom from intervention was 76%. After excluding five patients (2.5%) with early rapid degeneration requiring intervention within the first 2 weeks, the mean rate of aortic growth was 12.3 mm/y for the total aortic diameter, 3.8 mm/y for the true lumen diameter, and 8.6 mm/y for the false lumen diameter. Complete thrombosis of the false lumen was protective against growth (odds ratio, 0.19). In conclusion, further study is needed to determine which patients presenting with acute type B dissection will benefit from early intervention (e. g., thoracic endovascular aortic repair) to prevent late aneurysm formation.

In contrast, Charilaou et al. (2016) reported nearly normal 6-year survival in patients with uncomplicated acute TBAD who underwent BMT. In this study, all 65 uncomplicated patients (100%) were treated medically and survived the initial hospitalization. Long-term survival in uncomplicated patients was 91%, 87%, 78%, and 55% at 1, 3, 5, and 8 years. That is, medically treated patients with uncomplicated acute TBAD achieved similar long-term survival as apparently healthy, age-matched and gender-matched controls. These good long-term results are contrary to the perspective of routine thoracic endovascular aortic repair for all TBAD patients.

2.2.1.2 Best Medical Treatment and Endovascular Aortic Repair

Luebke and Brunkwall (2014b) reviewed comparative studies of patients treated either with TEVAR or best medical treatment for uncomplicated type B aortic dissection (TBAD). Although the selected studies were not homogenous (with the risk of selection bias), the review strongly suggested that TEVAR may be beneficial compared to BMT in the treatment of uncomplicated Stanford Type B dissection, which is in agreement with the findings of the INSTEAD-XL trial. However, the early TEVAR-related deaths and complications, as well as trends toward higher paraplegia and stroke rates, raise concerns that moderate the better survival with TEVAR at 5 years.

The ADSORB ("acute dissection stent grafting or best medical treatment") – study (Brunkwall et al. 2012) is the first prospective randomized multi-center-trial on acute dissections (symptom onset to diagnosis ≤14 days) comparing BMT with BMT and stent grafting of the proximal tear in patients having an uncomplicated acute dissection of the descending aorta. The objective of the study was to assess whether stent grafting will produce thrombosis and remodelling of the false lumen with a reduction in aneurysm formation and re-intervention. The primary endpoint of the study was a combination of incomplete/no false lumen thrombosis, aortic dilatation, or aortic rupture at 1 year. Thirty-one patients were randomised to the BMT group and 30 to the BMT + stent graft group (Brunkwall et al. 2014). During the first 30 days, no deaths occurred in either group, but there were three crossovers

from the BMT to the BMT + stent graft group, all due to progression of disease within 1 week. At the 1-year follow up there had been another two failures in the BMT group: one malperfusion and one aneurysm formation. One death occurred in the BMT+ stent graft group. Incomplete false lumen thrombosis, was found in 13 (43%) of the BMT + stent graft group and 30 (97%) of the BMT group. The false lumen reduced in size in the BMT + stent graft group, whereas in the BMT group it increased. The true lumen increased in the BMT + stent graft group whereas in the BMT group it remained unchanged. The overall transverse diameter was the same at the beginning and after 1 year in the BMT group (42.1 mm), but in the BMT+ stent graft group it decreased (38.8 mm). In this trial remodelling with thrombosis of the false lumen and reduction of its diameter was induced by the stent graft. However, the question remains as to whether endovascular treatment with a stent graft in the acute phase of type B aortic dissection is associated with improved survival compared with medical treatment alone.

Shah et al. (2014) identified 4706 patients with uncomplicated TBAD from the National Inpatient Sample (NIS) for the years 2009 and 2010. Five-hundred and four patients were treated with TEVAR, 4202 were treated by medical management. The overall adjusted in-hospital mortality was similar for both groups (8.5% for TEVAR vs 10.3% for medical management). The TEVAR carried higher risk of stroke (odds ratio = 1.61). The TEVAR was associated with prolonged LOS (12 vs 5.6 days) and patients were less likely to be discharged home (odds ratio 0.73). Whether these findings support the more widespread use of TEVAR to treat patients with uncomplicated TBAD cannot be decided.

2.2.2 Acute Complicated Aortic Dissections Type B

2.2.2.1 Endovascular and Open Repair

A meta-analysis of the literature identified 2531 patients with acute complicated type B dissection that were treated with TEVAR (Moulakakis et al. 2014). The pooled rate for 30-day/in-hospital mortality was 7.3%. The pooled estimates for cerebrovascular events, spinal cord ischemia (SCI) and total neurologic events were 3.9%, 3.1% and 7.3%, respectively. Survival rates ranged from 62% to 100% at 1-year and from 61% to 87% at 5-years, whereas freedom from aortic events ranged from 45% to 77%. Comparative data for open treatment of acute complicated type B dissection in this meta-analysis were rather unfavorable. A total of 1276 patients from nine studies who underwent open surgical repair for acute complicated type B aortic dissection were analyzed. The pooled rate for 30-day/in-hospital mortality was 19.0%. The pooled rate for cerebrovascular events was 6.8%, for SCI 3.3% and for total neurologic complications 9.8%. Survival rates ranged from 74.1% to 86.0% at 1-year and from 44.0% to 82.6% at 5-years, whereas freedom from aortic events could not be estimated as there were no available data. The findings from Moulakakis et al. (2014) regarding in-hospital mortality with TEVAR were confirmed by a

further systematic review where overall mortality and morbidity rates for TEVAR were 8.07% and 30.8%, respectively, in 1574 patients with symptomatic Stanford-B-dissection (Ramdass 2015).

Hogendoorn et al. (2014) assessed the comparative effectiveness of TEVAR vs. open surgical repair (OR) of complicated acute type B aortic dissections (cTBAD) using decision analysis. Main outcomes were quality-adjusted life years (QALYs). In the reference case, a cohort of 55-year-old men, TEVAR was preferred over OR: 7.07 QALYs vs. 6.34 QALYs for OR. The difference of 0.73 QALYs is equal to 8.5 months in perfect health. TEVAR was more effective in all analyzed cases and age groups. Perioperative mortality was the most important variable affecting the difference between OR and TEVAR, followed by the relative risk and percentage of aortic-related complications. Total expected reinterventions were 0.43/patient (TEVAR) and 0.35/patient (OR). The results of this decision model for the treatment of complicated acute TBAD suggest that TEVAR is preferred over OR. Although a higher number of reinterventions is expected, the total effectiveness of TEVAR is higher for all age groups. OR should be reserved for patients whose aortic anatomy is unsuitable for endovascular repair. Luebke and Brunkwall (2014a) also weighed the cost and benefit of TEVAR vs open repair (OR) in the treatment of acute complicated TBAD. In this cost-utility analysis OR appeared in terms of QALYs to be more expensive (incremental cost of €17,252.60) and less effective (−0.19 QALYs) compared with TEVAR. TEVAR yielded more QALYs and was associated with lower 1-year costs compared with OR in patients with an acute complicated TBAD and is therefore the dominant therapy over OR for this disease.

2.2.2.2 Clinical Studies and Case Series

Results of a prospective, nonrandomized, multicenter clinical trial for TEVAR of acute, complicated type B aortic dissection were reported by Bavaria et al. (2015). The trial enrolled 50 patients who were a mean age of 57.2 ± 12.9 years. All 50 patients had dissection-related symptoms at enrollment, including malperfusion (80%), rupture (14%), and malperfusion and rupture (6%). Thirty-day mortality was 8%. All 4 early deaths were considered dissection related. The Kaplan-Meier estimate of freedom from all-cause mortality was 14.6% at 12 months. Three patients (6%) required stent graft-related secondary procedures up to 30 days after implant, and an additional 3 patients (6%) underwent four late secondary procedures between 30 days and 12 months.

Excellent long-term results with TEVAR in 50 patients with acute complicated type B dissection, and in another 10 patients with acute complications, including rupture, end-organ ischaemia and acute dilatation during the primary hospitalisation, but >14 days after onset of symptoms were reported by Steuer et al. (2011). Within 30 days, two (3%) deaths, one (2%) paraplegia and three (5%) strokes were observed. Five-year survival was 87% and freedom from re-intervention at 5 years was 65%. Long-term results were also presented by Hanna et al. (2014). Fifty consecutive patients underwent TEVAR for management of acute complicated

TBAD. Indications for intervention included rupture in 10 (20%), malperfusion in 24 (48%), and/or refractory pain/impending rupture in 17 (34%) patients. One patient (2%) had both rupture and malperfusion indications. In-hospital and 30-day rates of death were both 0%; 30-day/in-hospital rates of stroke, permanent paraplegia/paraparesis, and new-onset dialysis were 2%, 2%, and 4% respectively. Overall survival at 5 and 7 years was 84%, with no deaths attributable to aortic pathology. Thirteen (26%) patients required a total of 17 reinterventions over the study period. These data support the use of TEVAR for acute complicated type B aortic dissection but also highlight the importance of life-long aortic surveillance.

Midterm results of emergency endovascular stent grafting for patients with life-threatening complications of acute TBAD were reported by Wiedemann et al. (2014). One-hundred and ten patients with complications of acute TBAD were treated with TEVAR for malperfusion (55.5%) or aortic rupture (53.6%) in five major European referral centers and one U.S. referral center. Overall hospital mortality was 12% (n = 13), with 14 late deaths after hospital discharge. In-hospital complications occurred in 36%. Actuarial survival at 1 and 5 years was 85% and 73%, respectively. Freedom from treatment failure was 82%, 75%, and 59% at 1, 3, and 5 years.

A 13-year, single-center experience with the treatment of acute TBAD was given by Afifi et al. (2015). Of 442 patients, 60.6% had uncomplicated acute TBAD and were treated medically, and 39.4% had complicated acute TBAD, of whom 39.0% were treated medically, 30.0% with open repair, 21.3% with TEVAR, and 9.7% with other open peripheral procedures. Intervention-free survival at 1 and 5 years was 84.8% and 62.7% for uncomplicated acute TBAD, 61.8% and 44.0% for complicated acute TBAD-medical, 69.2% and 47.2% for complicated acute TBAD-open, and 68.0% and 42.5% for complicated acute TBAD-TEVAR. In this study, overall survival was significantly related primarily to complicated presentation. Although uncomplicated acute TBAD was associated with favorable early survival, late complications still occurred, mandating radiographic surveillance and open or endovascular interventions. Results of this study are shown in Table 1.

2.2.2.3 Aortic Fenestration

Because TEVAR in the meantime has become the first-line- treatment of complicated acute TBAD, reports on surgical aortic fenestrations are very rare. Trimarchi et al. (2010) presented the largest series with long-term follow-up outcomes of patients treated with surgical aortic fenestration for complicated acute TBAD. Eighteen patients were treated with either suprarenal (n = 10) or infrarenal surgical fenestration (n = 8). The in-hospital mortality was 22% (n = 4), which included two deaths after suprarenal and two deaths after infrarenal fenestration. Median follow-up of the surviving patients was 10.0 years. During follow-up, none of the patients developed renal or visceral ischemia, or ischemic complications to the lower extremities, and no significant dilatations of the treated aortic segments were noted. The authors concluded that this conservative surgical technique may be

Table 1 Outcomes of patients with acute type B (DeBakey III) aortic dissection (Afifi et al. 2015)

Variable	Uncomp, n (%)	C-Med, n (%)	C-Open, n (%)	C-TEVAR, n (%)
Overall (n = 442)	268 (60.6)	68 (15.4)	52 (11.8)	37 (8.4)
Paraplegia	0 (0.0)	11 (16.2)	2 (3.9)	4 (10.8)
Ruptured	0 (0.0)	4 (5.9)[a]	9 (17.3)	3 (8.1)
Postoperative outcomes				
Stroke	0 (0.0)	6 (8.8)	1 (1.9)	3 (8.1)
Paraplegia	0 (0.0)	0 (0.0)	1 (1.9)	2 (5.4)
Encephalopathy	6 (2.2)	15 (22.1)	2 (3.9)	6 (16.2)
Early mortality	6 (2.2)	13 (19.1)	6 (11.5)	5 (13.5)
Late follow-up				
1-year overall survival	91%	70.6%	76.9%	78.4%
5-year overall survival	76.6%	58%	62.7%	58.8%

Uncomp uncomplicated patients treated with medical therapy, *C-Med* complicated patients treated with medical therapy, *C-Open* complicated patients treated with open aortic repair, *C-TEVAR* complicated patients treated with thoracic endovascular aortic repair

[a]Three of these patients died during their medical stabilization

used as an alternative treatment in case of contraindications or failure of endovascular management of complicated acute TBAD.

Another approach to relieve end-organ ischemia in patients with acute TBAD, which is rarely used, is the percutaneous flap fenestration. In this technique, the dissection flap is fenestrated, and the aortic true lumen is then stented open to prevent dynamic collapse onto the origin of the branch vessel. Branch vessel stenting is then performed for associated continued static obstruction. Outcomes of 69 patients presenting with acute type B dissection with malperfusion were analyzed by Patel et al. (2009). Early mortality was seen in 12 patients (17.4%). Kaplan–Meier analysis of survival demonstrated 1-, 5-, and 8-year survivals of 76.2%, 63.5%, and 55.3%, respectively. Fourteen patients sustained aortic rupture (n = 5, all in-hospital) or need for aortic resection (n = 9) during follow-up. Kaplan–Meier analysis of freedom from aortic rupture or need for aortic repair demonstrated a mean time to rupture or need for repair of 79.2 months.

Results of a new aortic endovascular fenestration technique, the funnel technique, consisting of an uncovered aortic stent graft, inserted between the false and the true lumen, were reported by Vendrell et al. (2015). In this series 9 patients with acute TBAD and 19 patients with type A dissection presented acute malperfusion syndrome. Primary technical success was 86%, and secondary technical success was 96% (27 of 28), with no intraprocedural complications. Thirty-day mortality was 7%, major complications occurred in 3.6%. In this series, the funnel technique versus other techniques to treat malperfusion syndrome during aortic dissection had better efficacy and a lower rate of morbidity. As an alternative to covering the primary entry tear, when this is unfeasible, it protects against short-term ischemic recurrence. In the long run, it permits a decrease in pressure in the false lumen, protecting against potential thoracic aortic dilatation, which occurs in 20–50% of cases.

2.2.3 Chronic Aortic Dissections Type B

2.2.3.1 Systematic Reviews

Thrumurthy et al. (2011) presented the first focussed systematic review of mid-term outcomes of TEVAR for chronic type B aortic dissection. Seventeen articles were identified, which encompassed the endovascular management of 567 patients. The most common stated indication for intervention was a maximum descending aortic diameter exceeding 50 mm (10/17, 58.8%). Other indications included rapid aortic enlargement (>10 mm/year), proven or imminent aortic rupture, refractory chest pain, refractory hypertension and end-organ ischaemia. The technical success rate was 89.9%. The mean 30-day mortality after TEVAR for chronic TBAD was 3.2%. Mid-term mortality was 9.2% (46/499) and survival ranged from 59.1% to 100% in studies with a median follow-up of 24 months. Re-intervention rates ranged from 0% to 60% in studies with a median follow-up of 31 months. 7.8% of patients (26/332) developed aneurysms of the distal aorta or continued false lumen perfusion with aneurysmal dilatation. Rates of complete false-lumen (FL) thrombosis ranged from 38.5% to 100% (median 85.7%) in studies with a median follow-up of 17 months. The lack of natural history data for cases treated medically or by open repair, significant heterogeneity in case selection and absence of consensus reporting standards for intervention were significant obstructions to interpreting these data, and making robust comparisons of TEVAR against open repair or best medical treatment.

Tian et al. (2014) summarized the outcomes of open surgical repair for chronic TBAD, with particular focus on contemporary data in the current endovascular era. In 19 studies, 970 patients underwent open surgery for chronic TBAD. Pooled short-term mortality was 11.1% overall, and 7.5% in the nine contemporary studies. Stroke, spinal cord ischemia, renal dysfunction, and reoperation for bleeding were 5.9%, 4.9%, 8.1%, and 8.1%, respectively, for the contemporary series. Absolute late reintervention was identified in 13.3% of patients overall, and in 11.3% of patients in the contemporary series. Aggregated survival at 1-, 3-, 5-, and 10-years of all patients were 82.1%, 74.1%, 66.3%, and 50.8%, respectively. The authors found the short-term outcomes of modern open surgery acceptable, although they appear poorer compared to TEVAR.

2.2.3.2 Randomized Study

In the INSTEAD-XL-study (Nienaber et al. 2013) a total of 140 patients with uncomplicated stable TBAD between 2 and 52 weeks after onset (clustering at 10–12 weeks) were randomized to optimal medical treatment (BMT) and TEVAR (n = 72) versus BMT alone (n=68). TEVAR was successfully completed in 70 patients with no death or intraprocedural conversion. The risk of all-cause mortality (11.1% versus 19.3%), aorta-specific mortality (6.9% versus 19.3%), and progression (27.0% versus 46.1%) after 5 years was lower with TEVAR than with optimal

medical treatment alone. TEVAR in the subacute (stable) phase of distal aortic dissection induced aortic remodeling and reduced aorta-related mortality >5 years as compared with controlled medical management with optional crossover to TEVAR or open repair when complications emerged. Preemptive TEVAR seems useful for younger patients, although advanced age and severe comorbidities may still favor medical management.

2.2.3.3 Case Series

van Bogerijen et al. (2015) accounted a total of 122 patients undergoing descending aortic repair for chronic TBAD. Patients were selected for either open aortic repair (OR) (n = 90) or TEVAR (n = 32). Early mortality was seen in 5 patients (4.1%), all of whom underwent open repair. By Kaplan-Meier analysis, the estimated 15-year survival was 58.4% ± 6.7% for the entire cohort. Stratified by treatment algorithm, 5-year survival was similar between groups (OR 86.7% vs TEVAR 78.1%). Cox regression analysis revealed that important predictors of late mortality for the entire cohort included peripheral vascular disease (HR 2.5) and baseline creatinine (HR 1.7), but not treatment strategy, even with adjustment for propensity score. Stratified by therapeutic strategy, OR was associated with higher 3-year treatment efficacy (freedom from aortic rupture or need for reintervention) (96.7%) vs TEVAR (87.5%). Due to these results the authors advocated for open repair in chronic TBAD for appropriate surgical candidates and believed this to be the first line approach for extensive type IIIB chronic dissections.

Fujikawa et al. (2015) presented 234 patients who underwent open surgery for chronic TBAD using left heart bypass. A total of 216 patients were treated electively for false aortic lumen (FL) aneurysm, 18 patients underwent emergency or urgent operation. A total of 127 (54.3%) patients had descending thoracic aortic enlargement, and 107 (45.7%) had thoracoabdominal aortic enlargement. Overall in-hospital mortality rate was 8.5%, and for elective operations in-hospital mortality rate was 6.0%. Overall operative death was 3.9% after descending aortic repair (1.6% in elective cases), and 10.3% after thoracoabdominal repair (8.3% in elective cases). Major adverse outcomes occurred in 17.5% of patients. Of these, permanent paraplegia occurred in 2.1%, and paraparesis occurred in 3.8%. The 1- and 3-year post-operative survival rates were 87.6% and 86.5%, and the freedom from re-intervention rate was 97.0%.

Conway et al. (2014) treated 86 patients with chronic TBAD, eight of them for rupture. OR was performed in 25 (29%) and 61 (71%) patients for descending thoracic and thoracoabdominal chronic TBAD, respectively. The operation in most patients was completed with the aid of distal aortic perfusion, mild permissive hypothermia (32 °C–34 °C), and cerebrospinal fluid (CSF) drainage. Hospital mortality occurred in 5 patients (5.8). Two patients (2.3%) each developed paraplegia, stroke, and renal failure requiring permanent hemodialysis in the postoperative period. Overall survival at 1, 5, and 7, years was 92%, 83%, and 70%. Freedom from reoperation was 99%, 90%, and 86% at 1, 5, and 7 years, respectively.

Long-term outcomes in those patients who survive confirm that OR reverses the natural history of chronic TBAD and provides a durable outcome.

A cohort of patients who underwent TEVAR for complications of chronic TBAD was presented by Andacheh et al. (2012). Indications for intervention included aneurysmal enlargement (n = 62), failure of medical management (n = 7), and perforation (n = 4). TEVAR was successfully performed in 72 out of the 73 patients (99%). At 30 days, the procedure-related mortality rate was 14%. Mean patient follow-up was 18 months. During this follow-up period, a total of 11 out of the 72 patients (15%) required a secondary intervention. The two determinants for reintervention were endoleak (n = 7) and persistent distal perfusion (n = 4). Expansion of the true lumen, compared with preoperative measurements, was noted in the follow-up period following TEVAR, and concomitant regression of the thoracic false lumen was observed. Overall maximal thoracic aortic diameter was observed to regress during the follow-up period. The authors considered TEVAR an appropriate treatment option for individuals with complications of chronic aortic dissection. However, infrarenal involvement of type B dissection appeared to be a risk factor for progressive infrarenal aortic enlargement following thoracic intervention.

Endovascular repair was performed in 58 consecutive patients for chronic TBAD by Mani et al. (2012). Eighty-four percent were treated electively for asymptomatic dilatation of the aorta, and 16% urgently for symptomatic disease. Ten (17%) patients required supra-aortic vessel bypass prior to stentgraft implantation. Three patients died perioperatively (5%, 1 urgent, 2 elective). Overall actuarial survival estimate of the 58 patients was 64% and the estimated reintervention rate was 29% at 3-years. During follow-up, 51% of the patients had a decrease in the maximum diameter of the descending thoracic aorta, 32% had no significant change and 17% had increased in size. Only 2/37 (5%) patients with false lumen thrombosis throughout the length of the stentgraft experienced expansion of the aortic diameter, compared to 4/10 patients (40%) of those with a patent false lumen at the level of the stentgraft. Mid-term survival was higher in patients with aortic remodelling (3-year 89%) than without (54%). Remodelling occurred with extensive false lumen thrombosis.

Three-hundred and three consecutive patients with chronic TBAD from four centers in China were prospectively enrolled and treated by either best medical therapy (BMT) (n= 95) or TEVAR (n=208) (Jia et al. 2013). No deaths occurred during index hospitalization in the two groups. In the TEVAR group, two patients (0.9%) suffered from retrograde type A dissection, and two (0.9%) suffered from paraplegia or paraparesis. The Kaplan-Meier analysis of survival probability at 2 and 4 years was 87.5% and 82.7% with TEVAR, respectively, and 77.5% and 69.1% with BMT. The estimated cumulative freedom from aorta-related death at 2 and 4 years was 91.6% and 88.1% with TEVAR, respectively, and 82.8% and 73.8% with BMT. The thoracic aorta diameter decreased from 42.4 (23.1) mm to 37.3 (12.8) mm in the TEVAR group and increased from 40.7 (18.6) mm to 48.1 (17.3) mm in the BMT group. In this series, the TEVAR group had a significantly lower aorta-related mortality compared with the BMT group (P = .0392), but TEVAR failed to improve the survival rate (P = .0678) or lower the aorta-related adverse event rate (P = .0978).

2.2.3.4 Registry Data

The Inpatient Medicare data from 2000 to 2011 were used by Mody et al. (2014) to determine trends in hospitalization rates for aortic dissection. Thirty-two thousands fifty-seven hospitalizations for aortic dissection were found. The overall aortic dissection hospitalization rate remained stable at 10 per 100,000 person-years across the study period. For patients undergoing surgical repair for TBAD, the observed 30-day mortality decreased from 24.9% to 21.0% and the observed 1-year mortality decreased from 36.4% to 32.5%. In the thoracic endovascular subgroup, 30-day mortality was 13.9% for type A&B aortic dissections, and 1-year mortality was 25.8% for the year 2011.

Medicare patients undergoing TBAD repair (2000–2010) were identified by Jones et al. (2014). Total thoracic aortic dissection repairs increased by 21% between 2000 and 2010 (from 2.5 to 3.0 per 100,000 Medicare patients). A concomitant increase in TEVAR was seen during the same interval (from 0.03 to 0.8 per 100,000). By 2010, TEVAR represented 27% of all repairs. Significant decreases were seen when annual perioperative mortality rates were stratified by procedure type. For open surgical repair, perioperative mortality improved from 47% in 2000 to 25% in 2010; for TEVAR, perioperative mortality improved from 47% for the two combined years 2000 and 2001 (when only 58 procedures were performed) to 18% in 2010. Patients undergoing TEVAR had a 3-year survival rate of 61%, which was not significantly different from the open repair 3-year survival rate of 59.0%.

The International Registry of Acute Aortic Dissection (IRAD) includes 28 international referral centers throughout North America, Europe, and Asia. Data were collected on an unselected population of 1476 IRAD patients who presented with acute TBAD from January 1996 through February 2013 (Pape et al. 2015). The majority of patients with acute TBAD were treated medically (63% of the entire cohort). This percentage decreased (from 75 to 57%) as endovascular management increased from 7% to 31%. Traditional surgical management of TBAD also decreased (from 17 to 8%). In the total cohort, in-hospital mortality was 17.2% with open surgical repair (33 of 192 patients), 12.3% with TEVAR (42 of 341 patients), and 8.7% with BMT (80 of 923 patients). In addition, 21 hybrid procedures that used surgical debranching techniques (left subclavian artery bypass or transposition) to facilitate endovascular intervention were reported with an in-hospital mortality of 14.3%. Long-term survival data from 1129 consecutive patients with acute TBAD enrolled in IRAD were reported by Fattori et al. (2013a). Eight-hundred and fifty-three (74.8%) patients were initially treated medically, and 276 (25.2%) were managed using an endovascular approach. Both groups were not comparable, TEVAR patients were most likely to present with complicated acute aortic dissection, defined as shock, periaortic hematoma, signs of malperfusion, stroke, spinal cord ischemia, mesenteric ischemia, and/or renal failure (61.7% vs. 37.2%). In-hospital mortality was similar in patients managed with endovascular repair compared with medically managed patients (10.9% vs. 8.7%). One-year mortality was also similar in both groups (8.1% endovascular vs. 9.8% medical). Among adverse events during follow-up, aortic growth/new aneurysm was most common, occurring in 73.3% of patients with medical therapy and in 62.7% of patients after

TEVAR, based on 5-year Kaplan-Meier estimates. Survival estimates showed that patients undergoing TEVAR had a lower death rate (15.5% vs. 29.0%) at 5 years. This analysis seems to corroborate a long-term benefit of endovascular repair over medical management, so that uncomplicated acute TBAD could become an indication for early elective endovascular stent grafting.

Midterm survival after thoracic endovascular aortic repair in Medicare patients was reported by Schaffer et al. (2015a). After TEVAR, patients had a median survival of 57.6 months. Of 11,966 patients who underwent TEVAR, 1637 had chronic aortic dissection, and 1217 had acute aortic dissection. Kaplan-Meier survival estimates at 5 years for patients with TEVAR for chronic aortic dissection were 53%, and for patients with acute aortic dissection 55%, respectively. Survival among patients who survived the perioperative period, that is alive at 180 days, was at 5 years 63% (chronic aortic dissection) and 71% (acute aortic dissection), respectively. Schaffer et al. (2015b) also analyzed data from the Medicare database between 1999 and 2010 for patients with open descending thoracic aortic repair (DTA). Median survival after open DTA repair was only 4.3 years for the total cohort of 5578 patients. There were 805 patients with acute aortic dissection and 920 with chronic aortic dissection, respectively. With open surgery, survival among patients who survived the perioperative period, that is alive at 180 days, was at 5 years 38% (chronic aortic dissection) and 42% (acute aortic dissection), respectively.

2.3 Conclusions for Clinical Practice

1. Patients with uncomplicated acute type B aortic dissections should be managed medically unless life-threatening complications develop. Regardless of the approach used, as long as patients have residual dissected aorta, they remain at risk for late aneurysmal degeneration and rupture of the false lumen and require indefinite serial imaging surveillance, close blood pressure monitoring, and negative inotropic medical therapy.
2. In retrospective studies, survival estimates showed that patients with acute TBAD undergoing TEVAR had a lower death rate at 5 years compared with medically treated patients. This seems to corroborate the increasing use of TEVAR in these patients. However, as long as long-term results of prospective studies are not available the question remains unsolved as to whether endovascular treatment with a stent graft in the acute phase of type B aortic dissection is associated with improved survival compared with medical treatment alone.
3. TEVAR, when feasible, should be considered the first-line treatment in complicated acute type B aortic dissection.
4. Most chronic type B aortic dissections are managed medically until complications develop. Recurrence of symptoms, aneurysmal dilation (total aortic diameter >55 mm), or a yearly increase (> 4 mm) of aortic diameter should be considered signs of instability in the chronic phase and indication for TEVAR, or in unsuitable anatomy, indication for open surgery.

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Chapter 3
Descending Thoracic Aortic (DTAA) and Thoracoabdominal Aortic Aneurysms (TAAA)

3.1 Guidelines

3.1.1 Surgical Indications

A. The guidelines of the American College of Cardiology Foundation /American Heart Association (AHA) are the most extensive; they recommend for the treatment of descending thoracic aortic aneurysms (DTAA) and thoracoabdominal aortic aneurysms (TAAA) (Hiratzka et al. 2010):

   Class I – recommendation

   1. For patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, open repair (OR) is recommended. (Level of Evidence: B)
   2. For patients with degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent grafting should be strongly considered when feasible. (Level of Evidence: B)
   3. For patients with thoracoabdominal aneurysms, in whom endovascular stent graft options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or less if a connective tissue disorder such as Marfan or Loeys-Dietz syndrome is present. (Level of Evidence: C)
   4. For patients with thoracoabdominal aneurysms and with end-organ ischemia or significant stenosis from atherosclerotic visceral artery disease, an additional revascularization procedure is recommended. (Level of Evidence: B)

B. The position paper from the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC) gives following

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statements concerning indications and contraindications for TEVAR (Grabenwöger et al. 2012):

- In asymptomatic TAA patients TEVAR is indicated (by consensus) when the maximum diameter of the aneurysm exceeds 5.5 cm or if rapid expansion (>5 mm in 6 months) occurs. In certain morphologic situations which are considered prone to rupture, e.g. saccular aneurysms, TEVAR may be justified at a diameter of less the above referenced 5.5 cm. Comorbidities and age of the patient have to be considered, and it may be appropriate to set a larger aortic diameter threshold in patients with increased operative risk.

C. The 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases recommend for interventions on descending aortic aneurysms (Erbel et al. 2014):

- TEVAR should be considered, rather than surgery, when anatomy is suitable. (Class of recommendation IIa/Level of evidence C)
- TEVAR should be considered in patients who have descending aortic aneurysm with maximal diameter ≥55 mm. (Class of recommendation IIa/Level of evidence C)
- When TEVAR is not technically possible, surgery should be considered in patients who have descending aortic aneurysm with maximal diameter ≥60 mm. (Class of recommendation IIa/Level of evidence C)
- When intervention is indicated, in cases of Marfan syndrome or other elastopathies, surgery should be indicated rather than TEVAR. (Class of recommendation IIa/Level of evidence C)

Note:

Maximum aneurysm diameter is one of the key factors in determining rupture risk, and is routinely used in clinicians' decisions of whether to recommend treatment or not. However, natural history data and the evidence base for threshold diameters at which DTAA repair becomes beneficial remain limited to single-centre series and registries. Rudarakanchana et al. (2014) asked 50 specialists, mainly (86%) vascular surgeons, to indicate their treatment preference (TEVAR or surveillance) in 25 hypothetical cases of DTAA, with variable patient attributes. Uncertainty about the benefit of TEVAR for DTAA by age, diameter, and sex was assessed. Specialists varied in the threshold diameter at which they would offer TEVAR over surveillance: median 6.0 cm for men and 5.5 cm for women. Uncertainty in the threshold for offering TEVAR was greatest for patients aged 80–85 years (up to 47% of respondents were "unsure"), and this increased with increasing aneurysm diameter (e.g., for an 80-year-old man 7% were unsure at 5.5 cm, 16% were unsure at 6.0 cm, and 33% were unsure at 7.0 cm). The uncertainty was greater for smaller diameters for women (e.g., for an 80-year-old woman 10% were unsure at 5.5 cm and 20% were unsure at 6.0 cm).

The Yale Center for Thoracic Aortic Disease (Elefteriades 2010) recommends the following surgical intervention criteria for thoracic aortic aneurysms:

1. Rupture
2. Acute aortic dissection
   (a) Ascending requires urgent operation
   (b) Descending requires a "complication specific" approach
3. Symptomatic states
   (a) Pain consistent with rupture and unexplained by other causes
   (b) Compression of adjacent organs, especially trachea, esophagus, or left main stem bronchus
   (c) Significant aortic insufficiency in conjunction with ascending aortic aneurysm
4. Documented enlargement
   (a) Growth ≥ 1 cm/year or substantial growth and aneurysm is rapidly approaching absolute size criteria
5. Absolute size
   (a) Ascending aorta: Marfan 5.0 cm; Non-Marfan 5.5 cm
   (b) Descending aorta: Marfan 6.0 cm; Non-Marfan 6.5 cm

3.1.2 Endovascular Versus Open Surgical Approach

Guidelines of the American College of Cardiology Foundation/American Heart Association (AHA) (Hiratzka et al. 2010) comment:

- The potential advantages of endovascular grafting over open operation include the absence of a thoracotomy incision and the need for partial or total extracorporeal circulatory support and clamping of the aorta, as well as lower hospital morbidity rates and shorter length of hospital stay.
- Endovascular grafting may be of particular value in patients with significant comorbid conditions (older age, substantial cardiac, pulmonary and renal dysfunction) who would be considered poor or noncandidates for open surgery.
- However, there are no data that conclusively demonstrate that the prevalence of spinal cord ischemic injury (lower extremity paralysis or paresis) is less for endovascular approaches than for open surgical repair. Similarly, there are no firm data to indicate that overall costs of medical care are lower with endovascular procedures.
- Absence of suitable "landing zones" above and below the aneurysm (usually 2–3 cm of normal diameter aorta without circumferential thrombus) is a contraindication for TEVAR. A width of the aorta at the landing zones that exceeds the recommended width for the largest available endovascular grafts (generally 10–15% larger than the width of the aorta) is also a contraindication.

Table 3.1 Summary of Society of Thoracic Surgeons recommendations for thoracic stent graft insertion (Hiratzka et al. 2010)

Entity/subgroup	Classification	Level of evidence
Penetrating ulcer/intramural hematoma		
Asymptomatic	III	C
Symptomatic	IIa	C
Acute traumatic	I	B
Chronic traumatic	IIa	C
Acute Type B dissection		
Ischemia	I	A
No ischemia	IIb	C
Subacute dissection	IIb	B
Chronic dissection	IIb	B
Degenerative descending		
>5.5 cm, comorbidity	IIa	B
>5.5 cm, no comorbidity	IIb	C
<5.5 cm	III	C
Thoracoabdominal/severe comorbidity	IIb	C

These guidelines comprise a summary of Society of Thoracic Surgeons recommendations for thoracic stent graft insertion (Table 3.1).

However, a Cochrane review (Abraha et al. 2013) found that randomized controlled trials in which patients with TAA were randomly assigned to TEVAR or open surgical repair are lacking. Though stent grafting of the thoracic aorta is technically feasible and non-randomised studies suggest reduction of early outcomes such as paraplegia, mortality and hospital stay, high quality randomized controlled trials assessing all clinically relevant outcomes including open-conversion, aneurysm exclusion, endoleaks, and late mortality are needed.

3.1.3 Spinal Cord Protection During Thoracic and Thoracoabdominal Aortic Surgery and Endovascular Aortic Repair

A position paper of the vascular domain of the European Association for Cardio-Thoracic Surgery recommends (Etz et al. 2015):

Recommendations for prevention

- Cerebrospinal fluid (CSF) drainage should be considered in patients undergoing TEVAR at high risk for SCI. (Class of recommendation IIa/Level of evidence C) (this panel of experts)
- CSF drainage is recommended in patients undergoing open thoracic or thoracoabdominal repair. (Class of recommendation I/Level of evidence B)

- Primary subclavian artery revascularization should be considered in patients undergoing TEVAR. (Class of recommendation IIa/Level of evidence C)
- CSF drainage should be continued for at least 48 h after TEVAR or open thoracic/thoracoabdominal repair. (Class of recommendation IIa/Level of evidence C) (this panel of experts)
- In case of feasibility, staging of segmental artery occlusion may be considered (secondary distal extension after frozen elephant trunk repair, minimally invasive segmental artery coil embolization). (Class of recommendation IIb/Level of evidence C) (this panel of experts)

Recommendations for diagnosis

- Motor evoked potentials/Somatosensory evoked potentials (MEP/SSEP) may be considered as an intraoperative tool for detecting spinal cord ischaemia in patients undergoing open thoracic or thoracoabdominal repair. (Class of recommendation IIb/Level of evidence C)
- MEP/SSEP may be considered as an intraoperative diagnostic tool for detecting spinal cord ischaemia in patients undergoing TEVAR at high risk for SCI. (Class of recommendation IIb/Level of evidence C)

3.2 Results

3.2.1 Descending Thoracic Aortic Aneurysms (DTAA)

3.2.1.1 Meta-analyses

A comprehensive meta-analysis with metaregression of available comparative studies to determine whether TEVAR improves morbidity, mortality, and resource-related outcomes compared with open surgery for adults presenting with thoracic aortic disease (degenerative aneurysm, dissection, traumatic rupture, intramural hematoma, and penetrating aortic ulcer) was performed by Cheng et al. (2010). Data from 42 comparative studies with a total of 5888 patients were included in this meta-analysis. Cumulative 30-day all-cause mortality was reduced for TEVAR versus open surgery (odds ratio: 0.44), but cumulative all-cause mortality at 1 year and at 2–3 years did not differ significantly between TEVAR and open surgery groups. At minimum, the existing evidence showed that survival for TEVAR is not worse than for open surgery at midterm. The overall risk of stroke was similar for TEVAR versus open surgery, paraplegia or paraparesis (permanent or temporary), however, were significantly reduced for TEVAR versus open surgery. TEVAR may also reduce length of hospital stay and overall complications including neurologic, cardiac, respiratory, renal, and bleeding complications, without a significant increase in the need for reintervention during mid-term follow-up.

Biancari et al. (2016) determined the efficacy of TEVAR for degenerative DTAA. Eleven studies reporting on 673 patients were selected for the analysis.

Technical success was reported in 91.0% of patients, and pooled overall 30-day, 1-year, 2-year, and 3-year survival rates were 96.0%, 80.3%, 77.3%, and 74.0%, respectively. Paraplegia occurred in 3.2% of patients and was permanent in 1.4% of patients. The stroke rate was 2.7%. Early type I endoleak was observed in 7.3%, type II endoleak in 2.0%, and type III in 1.2% of patients. At 3 years, freedom from reintervention was 90.3%. Death secondary to aneurysm rupture and/or fistula was reported in 3.2% of patients.

Jonker et al. (2010) identified 28 articles describing 224 patients with ruptured DTAA (rDTAA) between 1995 and 2009, including 143 patients (63.8%) treated with TEVAR and 81 (36.2%) treated with open repair. Endovascular repair was associated with a significantly lower 30-day mortality rate compared with open surgical repair (19% vs. 33%). The 30-day occurrence rates of myocardial infarction (11.1% vs 3.5%), stroke (10.2% vs 4.1%), and paraplegia (5.5% vs 3.1%) were increased after open repair vs TEVAR, but this failed to reach statistical significance for stroke and paraplegia. However, endovascular repair was associated with a considerable number of aneurysm-related deaths during follow-up, mainly caused by late rupture after TEVAR. The estimated aneurysm-related survival at 3 years after TEVAR was 70.6%.

3.2.1.2 Registry Data

Gopaldas et al. (2010) evaluated short-term outcomes of TEVAR and open aortic repair using the US Nationwide Inpatient Sample (NIS) data from 2006 to 2007. Only patients with an isolated DTAA were analyzed, patients with aneurysm rupture, aortic dissection, vasculitis, connective tissue disorders, or concomitant aneurysms in other aortic segments were excluded. Nine thousand one-hundred and six patients had undergone conventional OR and 2563 had undergone TEVAR. The patients who had undergone TEVAR were older and had higher comorbidity scores. The unadjusted LOS was shorter for the TEVAR patients (7.7 ± 11 vs 8.8 ± 7.9 days), but the unadjusted mortality was similar (TEVAR 2.3% vs OR 2.3%). TEVAR patients had 60% fewer complications overall (odds ratio, 0.39), and were 4 times more likely to have a routine discharge to home. In addition, Gopaldas et al. (2011) identified from NIS 923 patients who underwent ruptured DTAA repair in 2006–2008 and who had no concomitant aortic disorders. Of these patients, 364 (39.4%) underwent TEVAR and 559 (60.6%) underwent OR. Unadjusted mortality was 23.4% for TEVAR and 28.6% for OR. After risk adjustment, the odds of mortality, complications, and failure to rescue were similar for TEVAR and OR, but patients undergoing TEVAR had a greater chance of routine discharge (odds ratio = 3.3). In smaller hospitals, TEVAR was associated with lower complication rates than OR. Regression analysis revealed that smaller hospital size predicted significantly higher rates of mortality, complications, and failure to rescue in those undergoing OR but not in those undergoing TEVAR. The authors concluded that TEVAR may be an ideal alternative to OR for ruptured DTAA, particularly in small hospitals where expertise in OR may be lacking and immediate transfer to a higher echelon of care may not be feasible.

Further analysis of the NIS data came from Kilic et al. (2014). Adults undergoing DTAA repair between 1998 and 2008 were identified and patients with connective tissue disorders, aortic dissection, or thoracoabdominal aneurysms were excluded. A total of 20,568 DTAA patients (intact, 17,780; ruptured, 2788) underwent repair (open, 15,265; endovascular, 5303). Patients undergoing repair in the more recent era had higher comorbidity burdens than those undergoing repair in the earlier era. Despite of this, annual rates of repair for both intact and ruptured DTAA increased significantly during the study period (intact, 2.2–10.6 per 1 million; ruptured, 0.8–1.3 per 1 million), primarily because of increases in rates of endovascular repair in recent years. Operative mortality decreased from 10.3% to 3.1% for repairs of intact DTAA and from 52.6% to 23.4% for ruptured DTAA.

Goodney et al. (2011) studied 12,573 Medicare patients for the years 1998–2007 who underwent open procedures and 2732 patients who underwent TEVAR for DTAA. By presentation status, 13,998 patients presented for surgery with intact DTAA (11,565 open repair, 2433 TEVAR), whereas 1307 patients underwent surgery for ruptured DTAA (1008 open repair, 299 TEVAR). The lowest perioperative mortality rate occurred in patients undergoing repair of intact DTAA with TEVAR (6.1%), perioperative mortality rate for open repair was slightly higher (7.1%). Among patients presenting with ruptured thoracic aneurysms, perioperative mortality was 28.4% for TEVAR and 45.6% for open repair. Even though patients with intact DTAA selected for TEVAR had lower perioperative mortality, patients selected for open repair reclaimed survival advantage within 5 years (survival: 72% open repair, 62% TEVAR). After 5 years, <30% of patients were alive after repair of their ruptured DTAA regardless of the type of repair (26% open repair, 23% TEVAR). In this study, the survival advantage gained in the perioperative period after endovascular repair of intact DTAA was lost in the follow up period and survival at 5 years was significantly worse for patients selected for TEVAR compared with open repair. Therefore, the widespread application of TEVAR might have resulted in a cohort of patients who previously may not have undergone surgery but now are undergoing TEVAR (selection of "sicker" patients for TEVAR). Alternatively, these differences in survival could be explained by device-related complications occurring within the first 5 years after surgery.

This analysis of the Medicare database was extended and published additionally by Goodney et al. (2013). In this study, in thoracic aortic aneurysm repair a clear inverse relationship between caseload of hospitals and hospital mortality was shown for OR, but not for TEVAR. There was a significant difference in perioperative mortality across volume strata for open surgical repair (13.5% in very low-volume hospitals (annual volume 1–4 cases), 7.3% in very high-volume hospitals (annual volume > 46 cases)). However, there was no difference in perioperative mortality across volume strata for TEVAR (9.0% in very low-volume hospitals (annual volume 0–1 cases), 7.3% in very high-volume hospitals (annual volume > 18 cases)).

The volume-outcome relationship was also reviewed by Patel et al. (2013) in the Medicare Provider Analysis and Review (MEDPAR) data set from 2004 to 2007. Seven-hundred and sixty-three hospitals performing 3554 OR and 3517 TEVAR for intact DTAA were identified. Overall DTAA repair increased from 1375 in 2004 to

1987 in 2007. The proportion of hospitals performing open repair significantly decreased from 95% in 2004 to 57% in 2007, whereas those performing TEVAR increased from 24% to 76%. Overall repair type shifted from open (74% in 2004) to TEVAR (39% open in 2007). Overall mortality during the study interval for open repair was 15% at LV (low volume) hospitals (<8 cases/year) vs 11% at HV (high volume) hospitals (≥8 cases/year), whereas TEVAR mortality was similar, at 3.9% in LV vs 5.5% in HV hospitals. In conclusion, operative mortality for TEVAR was independent of hospital volume and type, whereas mortality after open surgery was lower at HV hospitals, suggesting that TEVAR can be safely performed across a spectrum of hospitals, whereas open surgery should be performed only at HV hospitals.

The Centers for Medicare and Medicaid Services administrative database for the years 2005–2010 was used by Schaffer et al. (2015a). They analyzed post-TEVAR survival in 3751 patients with isolated TAA. Midterm patient survival was 84% at 1 year and 54% at 5 years. This group (Schaffer et al. 2015b) also studied a total of 1767 patients from the Medicare database who underwent open DTAA repair in the period from 1999 to 2010. In this cohort, patients' survival was 74% at 1 year and 29% at 10 years after surgery. The late incidence of death beyond 180 days paralleled that of an age-, sex-, and race-matched general US population cohort. Independent hospital and surgeon effects, hospital and surgeon volume, and a more recent date of surgery correlated with improved survival.

Not only in the US, but also in England and Wales an increase in descending aortic repairs since the introduction of TEVAR has been observed (von Allmen et al. 2013). In 2005, the overall rate of repairs of DTAA was 0.7 versus 1.9 per 100,000 population in the year 2010. The most marked increase has been in those aged 75+ years. Whilst the rate of open repairs has been fairly steady, the increases were entirely attributable to the increased rate of TEVAR. For DTAA, TEVAR procedures have risen since 2006 from 0.65 to 1.71 and from 0.24 to 0.83 per 100,000 population in men and women, respectively. The authors emphasized that TEVAR is still a practice without a solid evidence base and the survival benefit in consequence of the rising number of procedures remains in doubt. This was demonstrated by another study from von Allmen et al. (2014) where patients aged over 50 years, without a history of aortic dissection, undergoing repair of a thoracic aortic aneurysm between 2006 and 2011 were assessed using mortality-linked individual patient data from Hospital Episode Statistics (England). Overall, 759 patients underwent DTAA repair, mainly for intact aneurysms (618, 81.4%). For intact aneurysms, the operative mortality rate was similar for TEVAR and open repair (6.5 versus 7.6%), but the 5-year survival rate was significantly worse after TEVAR (54.2 versus 65.6%). Aortic-related mortality was similar in the two groups, but cardiopulmonary mortality was higher after TEVAR. TEVAR was associated with more aortic-related reinterventions (23.1 versus 14.3%). There were 141 procedures for ruptured thoracic aneurysm, with TEVAR showing no significant advantage in terms of operative mortality. In conclusion, no clear data could be given to prove the clinical effectiveness of TEVAR compared with open repair for intact DTAA.

The influence of gender on outcomes of TEVAR for nonruptured DTAA examined Arnaoutakis et al. (2014) in a retrospective review of prospectively collected data in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2005 to 2011. The cohort overall consisted of 649 patients, with 279 women (43%) and 370 men (57%). Women had longer overall operative times and were also more likely to require an iliac artery exposure for device delivery. Unadjusted overall 30-day mortality was 4.4% and was higher in women (6%) than in men (3%). In multivariable analysis female gender did not reach statistical significance for an independent association with 30-day mortality. In contrast, advanced age, emergency surgery, and need for iliac artery exposure were all characteristics independently associated with greater odds of 30-day mortality. The results suggest a need for decreased device delivery size and improvements in endovascular technology.

3.2.1.3 Cost Analysis

A cost analysis of endovascular versus open repair in the treatment of TAA with the help of a retrospective, single institution review of elective thoracic aortic aneurysm repairs between 2005 and 2012 and a literature review was presented by Gillen et al. (2015). The cohort consisted of 131 TEVAR and 27 open repairs. TEVAR patients were significantly older (67.2 vs. 58.7) and trended towards a more severe comorbidity profile. Operative mortality for TEVAR and open repair was 5.3% and 3.7%, respectively. There was a trend towards more complications in the TEVAR group. In-hospital costs were significantly greater in the TEVAR group ($52,008 vs. $37,172). However, cost modeling utilizing reported complication and reintervention rates from the literature overlaid with this cost data produced a higher cost for the open group in-hospital ($55,109 vs. $48,006) and at 3 years ($58,426 vs. $52,825). A cost modeling using Monte Carlo simulation demonstrated lower costs with TEVAR compared to open repair at all time points up to 3 years post-intervention. This cost model argues that despite the costs associated with more frequent surveillance imaging and reinterventions, TEVAR remains the more cost-effective option even years after TAA repair.

3.2.1.4 Multicenter Study

Illig et al. (2015) evaluated the safety and effectiveness of the Zenith Alpha Thoracic Endovascular Graft for the treatment of DTAA and large ulcers. The Zenith Alpha Thoracic Endovascular Graft is a device designed for endovascular repair of thoracic aortic pathology allowing insertion through 16F to 20F sheaths. One-hundred and ten patients at 23 institutions were enrolled in this multicenter study. Eighty-two percent (90 of 110) of patients were enrolled for aneurysm and 18% (20 of 110) for ulcer. Access was percutaneous in 36% of patients and technical success was achieved in 98% (108 of 110) of patients. Spinal cord protection was used in 44

patients (40%), among whom 32 patients underwent cerebrospinal fluid drainage. No deaths, aortic rupture, or conversion to open repair occurred ≤30 days of repair. The spinal cord complication rate was low (one transient paraparesis, fully resolved; no long-term paraplegia). Thirty-day freedom from major adverse events was 96.4%. Overall survival at 1 year was 95%. Five deaths occurred ≤1 year; only one death was related to the thoracic aneurysm by independent adjudication, resulting in a 99% freedom from thoracic aortic aneurysm-related mortality. Three of 108 patients (2.8%) underwent a secondary intervention within 1 year.

3.2.2 Thoracic Abdominal Aortic Aneurysm (TAAA)

3.2.2.1 Endovascular vs Open Surgical Approach

Liao et al. (2012) collected data from the 2005 to 2008 US Nationwide Inpatient Sample (NIS). They found 2911 patients with the diagnosis of TAAA who underwent open thoracic aortic repair (OR), and 1838 patients who underwent TEVAR alone with branched endografts or TEVAR with a hybrid visceral debranching procedure. The rate of OR remained relatively stable over the study period (7.5/100 TAAA patients in 2005 vs 10.1/100 TAAA patients in 2008). In contrast, the rate of TEVAR increased significantly, from 1.4/100 TAAA patients in 2005 to 6.3/100 TAAA patients in 2008. In 2008, 13% of all TEVAR procedures were performed in small bed size hospitals, whereas only 3% of all OR procedures were performed in small hospitals. These findings suggest that more patients who were otherwise not surgical candidates or did not have traditional surgical indications for OR were treated with TEVAR, most commonly in regions or hospitals where OR is less often performed. Scali et al. (2011) confirmed the significant increase of TEVAR interrogating the Medicare Provider Analysis and Review (MEDPAR) file from 1998 through 2007. During the study interval, the total repair rate of TAA and TAAA increased substantially. In 1998, 10.8 procedures were performed per 100,000 Medicare beneficiaries. By 2007, however, this rate increased by 60% to 17.8/100,000. This increase in the repair rate was due almost entirely to a rapid increase in the use of TEVAR. OR procedures for thoracic and TAAA modestly increased by 10.8%, from 10.7/100,000 beneficiaries in 1998 to 12/100,000 beneficiaries in 2007. By 2007, repairs were endovascular in 31% of the study group and open in 69%. Among patients undergoing TEVAR, 51% had DTAA, 22% had TAAA, 17% were performed for aortic dissection-related pathology, such as aneurysmal degeneration, 7% were performed for ruptured DTAA, and 2% were performed for ruptured TAAA. Among those patients undergoing open repair, 54% were performed for DTAA, 12% for TAAA, 28% for aortic dissection-related pathology, 3% for ruptured DTAA, and 2% for ruptured TAAA.

A comparative analysis of outcome after endovascular and open repair for patients with TAAA, referred to three tertiary Italian vascular centers from 2007 to 2014, was reported by Ferrer et al. (2016). Patients in the TEVAR group were

treated with thoracoabdominal branched or fenestrated stent grafts. Preoperative cerebrospinal fluid drainage was used in all patients except one because of a coagulation disorder. In the OR group, preoperative cerebrospinal fluid drainage to prevent spinal cord ischemia (SCI) was used in every case of type I, type II, and type III TAAA and selectively in type IV (58.3%). Left-sided heart bypass was used in 86.1% of cases. After propensity matching, there were 65 patients in the TEVAR group and 65 in the OR group with correction of all differences in baseline characteristics. Thirty-day mortality was 7.7% in TEVAR and 6.2% in OR. Permanent paraplegia was observed in six patients after TEVAR (9.2%) and seven patients after OR (10.8%). Thirty-day rate of respiratory insufficiency was significantly reduced in TEVAR (0% vs 12.3%). In addition, intensive care unit stay (1.6 days vs 2.8 days) and total hospitalization time (6.3 days vs 16.3 days) were significantly shorter in the TEVAR group. According to Kaplan-Meier estimates, all-cause survival at 42 months was 82.8% in TEVAR and 84.9% in OR. Freedom from reintervention rates were 80.0% in TEVAR vs 79.9% in OR at 42 months. The study suggested that in matched populations of patients with TAAA, endovascular and open repair may be associated with a similar 30-day and 2-year mortality. Permanent SCI may also be comparable with the two treatments. Nevertheless, the 30-day overall morbidity may be two times lower with use of TEVAR.

Michel et al. (2015) compared 30-day outcomes and costs of fenestrated and branched stent grafts (f/b EVAR) and open surgery (OR) for the treatment of complex abdominal aortic aneurysms (AAA) and TAAA. Data of a multicenter prospective registry for patients treated with f/b EVAR were compared with a control group of patients treated with OR extracted from the national hospital discharge database for the years 2010–2012. Two-hundred and sixty eight cases and 1678 controls were included. There was no difference in 30-day mortality between cases and controls (6.7% vs. 5.4%), but costs were higher with f/b EVAR (€38,212 vs. €16,497). After group stratification, mortality was similar with both treatments for para/juxtarenal AAA (cases vs. controls, 4.3% vs. 5.8%) and supradiaphragmatic TAAA (11.9% vs. 19.7%), and higher with f/b EVAR for infradiaphragmatic TAAA (11.9% vs. 4.0%). Costs were higher with f/b EVAR for para/juxtarenal AAA (€34,425 vs. €14,907) and infradiaphragmatic TAAA (€37,927 vs. €17,530), but not different for supradiaphragmatic TAAA (€54,710 vs. €44,163). In conclusion, f/b EVAR did not appear justified for patients with para/juxtarenal AAA and infradiaphragmatic TAAA fit for OR but may be an attractive option for patients with para/juxtarenal AAA not eligible for surgery and patients with supradiaphragmatic TAAA.

3.2.2.2 Endovascular Repair

Iafrancesco et al. (2014) reported endovascular repair for 62 non-ruptured TAAA, extent I–III (n = 26) and IV (n = 36), with fenestrated (n = 39) or branched (n = 23) stentgrafts. The 30-day mortality was 1.6% (n = 1) and one further patient died on postoperative day 62 from respiratory complications. SCI developed in 5 (8%) patients. Two (3.2%) patients required temporary renal replacement therapy.

Guillou et al. (2012) analyzed a cohort of 89 patients treated electively for TAAA with custom-designed fenestrated/branched endografts. The in-hospital mortality rate was 10%. Technical success rate was 96.6%, and spinal cord ischemia rate was 7.8%. Actuarial survival was 86.8% ± 3.7% at 1 year and 74.7% ± 6% at 2 years.

Thirty-one patients with a median age of 71 years underwent total endovascular repair of TAAA (12 Crawford type I, 13 type III, and 6 type IV) in a series from the UK (Clough et al. 2012). Three patients (9.7%) died within 30 days of operation. There were no other cases of organ failure, paraplegia or major in-hospital complications. Three further patients have died during the follow-up period (median 12 months).

Ten-year experience with endovascular TAAA repair using fenestrated and branched stent grafts was presented by Verhoeven et al. (2015). During the study period, 166 patients were treated. One hundred and eight (65%) patients had been refused for open surgery. Seventy-eight (47%) patients had previously undergone one or more open and/or endovascular aortic procedures. Fifteen (9%) patients had an acute TAAA (11 contained rupture, 4 symptomatic). Types of TAAA according to the modified Crawford classification were: type I: 7.2%, type II: 30.1%, type III: 31.9%, type IV: 24.8%, and type V: 6%. Cerebrospinal fluid drainage was applied in 72.3% of patients. Technical success was achieved in 157 (95%) patients. Thirty-day operative mortality was 7.8%, including one patient with a contained rupture. In hospital mortality was 9% (15/166). Early re-intervention (≤30 days) was required in 7.2% of patients. Peri-operative SCI developed in 9%, with permanent paraplegia in 1.2%. Estimated survival at 1, 2, and 5 years was 83% ± 3%, 78% ± 3.5%, and 66.6% ± 6.1%, respectively. In this series 17% of the patients required at least one re-intervention within 2–3 years of the index procedure. Nevertheless, the majority (>85%) of re-interventions involved minimally invasive endovascular procedures with a high technical success rate (94%).

Additionally, Verhoeven et al. (2016) reported the outcomes of fenestrated endovascular aneurysm repair (FEVAR) as first line treatment strategy for short neck, juxtarenal, or suprarenal aortic aneurysms in 281 patients. Patients with type IV TAAA treated with fenestrated and branched techniques had been reported before (Verhoeven et al. 2015) and were excluded from this study. Technical success was 96.8%. The 30-day mortality was 0.7%. Mean follow up was 21 ± 15.9 months. Estimated survival at 1 and 3 years was 94.7% ± 1.6% and 84.6% ± 3.0%, respectively. At 3 years, estimated freedom from re-intervention was 90% ± 2.7%, and estimated target vessel stent patency 98.1% ± 0.6%. In conclusion, FEVAR in a "standard vascular population" was associated with high technical success, low operative mortality and morbidity rates, and excellent mid-term outcomes. The need for re-intervention was low, and most re-interventions could be performed by endovascular techniques.

3.2.2.3 Hybrid Technique

Totally endovascular repair of TAAA is not applicable to all patients due to morphologic constraints. In this situation, hybrid operations offer an alternative approach to TAAA management. They combine extra-anatomic bypass of the visceral vessels

("debranching") with subsequent (staged or immediate) endovascular aortic relining using aortic stent grafts. Because hybrid approaches avoid the extensive two cavity exposure, aortic cross-clamping, and mechanical circulatory support that comprise open TAAA repair, they offer the theoretical advantage of being less invasive. Canaud et al. (2013) provided a systematic review of hybrid repair for TAAA, with particular reference to any difference in results between single and staged procedures. Included were 19 studies describing 660 patients. The 30-day mortality ranged from 0% to 44.4%, with an overall (across studies) rate of 12.6%. After a mean follow-up of 26 months the overall mortality was 20.8%. Procedures were single-stage in 288 of 660 (43.6%) procedures and staged in 372 (56.4%). The study suggested that lower perioperative mortality may be associated with a two-stage hybrid repair of TAAA than with a single-stage procedure, but conclusive evidence was lacking.

The results of 76 hybrid procedures performed in 19 French university hospital centers between November 2001 and October 2011 were described by Rosset et al. (2014). The procedures were performed over 10 years, with an average of four procedures per center. Aneurysms involved thoracic, abdominal, and thoracoabdominal aorta in five, 14, and 57 cases respectively. A one-stage hybrid procedure was performed in 69.7% and a two-stage procedure in 30.3% of patients. The overall postoperative mortality rate was 34.2%. The mortality rate was 30.9% in the high volume centers versus 38.2% in the low volume centers. Nine patients (12.8%) had paraplegia (totally resolved in one case) following the hybrid procedure. Twenty-two patients (28.9%) had postoperative acute renal failure and the overall bowel ischemia rate was 17.1%. The results of this multicenter study were not satisfactory and questioned the benefit of this type of approach, especially in patients at high risk for conventional surgery. In contrast, a single center demonstrated considerably better results. Hughes et al. (2012) reviewed all patients (n = 58) undergoing hybrid repair involving complete visceral debranching and endovascular aneurysm exclusion for Crawford extents I, II and III TAAA between March 2005 and June 2012 at a single referral institution. The procedure was performed as a single stage in the initial 33 patients and as a staged approach in the most recent 25 cases. Thirty-day/in-hospital rates of death, stroke, and permanent paraparesis/paraplegia were 9%, 0%, and 4%, respectively. A staged approach yielded better results than simultaneous repair (30-day/in-hospital deaths 4.0% vs 12.1%). Over a mean follow-up of 26±21 months, visceral graft patency was 95.3%; all occluded limbs were to renal vessels and none resulted in permanent dialysis. All graft occlusions were detected on the 1-month follow-up scan with no new graft occlusions developing thereafter. Five-year freedom from re-intervention was 94%. Kaplan-Meier overall survival was 78% at 1 year and 62% at 5 years, with a 5-year aorta-specific survival of 87%.

Fifty-two high-risk patients who underwent hybrid TAAA repair between 2001 and 2012 in a single center were presented by Tshomba et al. (2012). Perioperative mortality was 13.5% and included multiple organ failure in two, myocardial infarction in two, coagulopathy in one, pancreatitis in one and bowel infarction in one patient. Overall major perioperative morbidity was 28.8%, including one case (1.9%) of irreversible paraplegia. At mean follow-up of 23.9 ± 19 months, three

patients died of sudden death potentially related to aortic rupture. The rate of visceral graft occlusion was 7.3% (11/151) leading to bowel infarction and death in 2 patients and loss of a kidney in one patient. In addition, seven non procedure-related deaths were recorded.

Outcome of visceral hybrid procedures in 46 patients with TAAA was retrospectively analyzed by Shahverdyan et al. (2013). A total of 31 patients underwent simultaneous repair and 15 patients underwent staged repair. One patient died between the two stages due to an occlusion of the graft to the superior mesenteric artery and a consecutive bowel ischaemia. After 30 days, 14 of 46 patients (30.4%) had died. The all-cause patient survival rate was 45.5 ±7.4% at 1 year, and 34.9 ±7.4% at 5 years. Long-term patency of the grafts was excellent except for the right renal artery. The primary patency of all grafts was after 1 year 87.9 ± 2.7% and after 5 years 86.1 ± 3.2. The patency was 87.2 ± 6% for the left renal artery and 69.6 ± 8.8% for the right renal artery after 5 years.

Gkremoutis et al. (2014) reported experience with hybrid procedures in the emergency treatment of patients with TAAA. Nineteen patients (63.3%) required emergency surgery, in 11 cases (36.7%) surgery was urgently indicated for symptomatic aneurysms. Thirty-day mortality reached 26.7% (36.8% in emergency patients and 9.1% in the urgent group). The cumulative postoperative survival rate after 12 months was 57.8%.

Jain et al. (2016) described a staged hybrid repair of extensive TAAA with a proximal thoracic stent graft used to effectively convert an extent I or II TAAA to an extent III, IV, or V TAAA, followed by a staged distal open repair. This approach combines established endovascular techniques and technology with traditional open TAAA repair. The staged approach distributes ischemia to the spinal cord over time, which allows potential collateral vessel development. Furthermore, this approach simplifies the open TAAA repair by eliminating the need for a proximal aortic anastomosis near the aortic arch. Nineteen patients with Crawford extent I (n = 1) or extent II (n = 18) TAAAs secondary to chronic aortic dissection underwent a staged hybrid repair from 2007 to 2014. There were no deaths, strokes, or chronic renal failure in this cohort. After stage 1 TEVAR, three patients required repeat intervention for endoleak before open repair. After stage 2 open repair, there was a single delayed permanent paralysis 2 weeks after discharge. At a median 3-year follow-up, there were no deaths, neurologic events, endoleaks, or TAAA reinterventions.

3.2.2.4 Open Repair

Bensley et al. (2013) identified 450 patients who underwent open surgical repair of an intact TAAA in the NSQIP database from 2005 to 2010. The 30-day mortality rate for all patients was 10.0% (21.9% for emergent cases vs 9.1% for elective cases), and postoperative complications occurred in 51.6% (50.0% for emergent cases vs 51.7% for elective cases). Pulmonary complications were the most common: failure to wean from ventilator (39.1%), pneumonia (23.1%), and reintubation (13.8%). Acute renal failure requiring dialysis occurred in 10.7% of patients.

From October 1986 to December 2014, 3320 consecutive open TAAA repairs were performed at Baylor College of Medicine (Coselli et al. 2016). Three thousand three-hundred and nine repairs could be evaluated, including 914 Crawford extent I TAAA repairs, 1066 extent II repairs, 660 extent III repairs, and 669 extent IV repairs. There were 249 operative deaths (7.5%), which included 37 of 193 repairs performed in octogenarians (19.2% mortality), 37 of 170 repairs involving rupture (21.8%), 14 of 439 repairs in patients aged 50 years or less (3.2%), 9 of 288 repairs in patients with Marfan syndrome (3.1%), and 58 of 1020 repairs of chronic dissection (5.7%). In 2586 elective repairs, operative death occurred in 6.2%, in 723 urgent or emergency repairs, operative death occurred in 12.2%. The rate of operative death differed among the 4 groups, being higher in extents II and III (9.5% and 8.8%) than in extents I and IV (5.9% and 5.4%, respectively). Permanent paraplegia and paraparesis occurred in 2.9% and 2.4%, respectively. Of 189 patients (5.7%) with permanent renal failure, the majority (56.6%) did not survive to hospital discharge. Permanent stroke was relatively uncommon (2.2%). There were 1864 late deaths. Estimated survival was 83.5% ± 0.7% at 1 year, 63.6% ± 0.9% at 5 years, 36.8% ± 1.0% at 10 years, and 18.3% ± 0.9% at 15 years. The data demonstrate that repairing TAAA poses substantial risks, particularly when the entire thoracoabdominal aorta (extent II) is replaced, even when performed at an experienced center.

Midterm survival and quality of life (QoL) after Crawford extent II TAAA repair in patients with Marfan syndrome (MFS) were also reported from this high-volume center (Ghanta et al. 2016). From 2004 to 2010, 49 consecutive patients with MFS (mean age, 43.4 ± 12.0 years) underwent extent II TAAA repair (41 elective and 8 urgent/emergent procedures) with intercostal reimplantation. Operative adjuncts included cerebrospinal fluid drainage (96%), left heart bypass (94%), and cold renal perfusion (96%). Two patients (4%) had adverse events (permanent renal failure). There were no operative deaths, strokes, or spinal cord deficits. The most common complication was left vocal cord paralysis (43%). Pulmonary complications occurred in 18 patients (37%). Eight (16%) late deaths occurred. Estimated survival was 97.9% ± 2.1% at 2 years and 84.2% ± 6.2% at 6 years. As regards the QoL of the surveyed patients, 58% had physical component scores greater than the general population norm, and 68% had mental component scores greater than the general population norm.

Estrera et al. (2015) examined experience with open thoracic and thoracoabdominal aortic repairs over a 24-year period. One thousand eight hundred and ninety-six descending thoracic (DTAA) or TAAA in 1795 patients were treated, including 1273 patients with TAAA extent I-V and 646 patients with DTAA. The mainstay for treatment included the adjunct of distal aortic perfusion, cerebrospinal fluid drainage (CSFD), and moderate hypothermia. Over the past decade, the adoption of neuromonitoring, motor and somatosensory evoked potentials, during TAAA repair occurred. Early mortality was 302/1896 (15.9%). Renal failure requiring dialysis occurred in 16.6%, postoperative stroke in 5%, and respiratory dysfunction in 39%. 7.1% of patients suffered permanent neurologic deficit. Preoperative predictors of early mortality were age, GFR (ml/min/1.73m^2), TAAA extents II or III, coronary artery disease and emergency presentation. For nonemergent procedures among

patients with poor baseline renal function (lowest GFR quartile <48.3), early mortality was 27% versus 5.2% among those with good baseline renal function (highest GFR quartile >95.3). For emergent procedures among patients with poor baseline renal function, early mortality was 51.9% versus 16.7% among those with good baseline renal function. Moreover, for patients with normal renal function, nonemergent, and nonextent II or III TAAA, the early mortality was 3.7%. Overall survival for the entire cohort at 5, 10, 15, and 20 years was 57.7%, 42.9%, 34.8%, and 31.6%, respectively.

Lancaster et al. (2013) described a total of 485 patients with TAAA. Extent I and II aneurysms were found in over half of the patients (53.4%) while extent III aneurysms were found in only 46.6%. One hundred patients underwent repair of their aneurysm with the use of distal aortic perfusion via atriofemoral bypass (AFB) and motor-evoked potentials (MEVP) (20.6%), while the remaining 385 patients (79.4%) underwent repair with a clamp and sew (CS) technique. The routine use of AFB/MEVP was the only change over the study period. The incidence of early postoperative death was reduced by half in the AFB/MEVP group (9.9% vs 4.0%), and the risk of stroke was reduced from 10.4% to 3.0%. Long-term (4-year) survival was improved in the AFB/MEVP group as well (73 ± 6% vs 60 ± 3%). The authors concluded that distal aortic perfusion with continuous monitoring of MEVP in order to guide selective reimplantation of intercostal arteries is the preferred method for open repair of extent I-III TAA.

Five-hundred and forty-two consecutive patients with open TAAA repair were presented by Murana et al. (2016). Distal aortic perfusion was established by left heart bypass using a centrifugal pump in 473 patients (87.3%). Extracorporeal circulation with deep hypothermic circulatory arrest was used when proximal clamping distal to the left common carotid artery was not deemed feasible or when the aneurysm was so large that a safe entry in the thorax was judged unsafe (69 patients). CSFD and evoked potential monitoring were used in 471 (86.7%) and 502 (92.6%) patients, respectively. Aneurysmal extent was as follows: 23.6% type I, 52.6% type II, 11.4% type III, 8.9% type IV and 3.5% type V. Permanent paraplegia occurred in 4.2%. Paraparesis was noted in 1.7%. Furthermore, overall perioperative stroke occurred in 23 patients (4.2%). Fifty-nine patients (10.9%) died during their initial hospitalization (overall in-hospital mortality). The observed 30-day mortality for elective TAAA repair was 7.1% (34/478). Overall in-hospital mortality was 13% in type II and 6.3% in type IV aneurysms. Follow-up was 100% complete with a mean duration of 6.3 ± 5.7 years. 25.7% of patients died after 30 days of hospitalization during the subsequent long-term follow-up. Kaplan–Meier estimate of survival at 1-, 3-, 5- and 10 years was 85.9 ± 1.5, 79.2 ± 1.8, 74.2 ± 2.0 and 61.6 ± 2.5%, respectively. Overall freedom from aortic reintervention at 1-, 3-, 5- and 10 years was 96.1 ± 0.1, 89.6 ± 1.5, 86.3 ± 1.8 and 80.7 ± 2.3%, respectively. These results demonstrate that open surgical TAAA repair is an extremely effective option and is associated with a low need for aortic reinterventions in high specialized centers.

3.2.3 Special Questions

3.2.3.1 Risk of Rupture and Growth Rates in TAA

Of 3247 patients with thoracic aortic aneurysm registered in an institutional database, Kim et al. (2015) identified 257 nonsyndromic patients with DTAA or TAAA without a history of aortic dissection in whom surgical intervention was not undertaken. The primary end point was a composite of aortic dissection/rupture and sudden death. Baseline mean maximal aortic diameter was 52.4±10.8 mm, with 103 patients having diameters ≥55 mm. During a median follow-up of 25.1 months, definite and possible aortic events occurred in 19 (7.4%) and 31 (12.1%) patients, respectively. Estimated rates of definite aortic events within 1 year were 5.5%, 7.2%, and 9.3% for aortic diameters of 50, 55, and 60 mm, respectively. Aortic size was the principal factor related to aortic events in unrepaired DTAA or TAAA. Although the risk of aortic events started to increase with a diameter >5.0 to 5.5 cm, it is uncertain whether repair of thoracic aortic aneurysms in this range leads to overall benefit, and the threshold for repair requires further evaluation.

Patterson and Brownrigg (2016) analyzed a group of patients with primary degenerative thoracic aortic aneurysms who had been counselled against early surgery due to comorbid conditions, or those who had refused surgery. Two hundred and fifty-seven patients were included, and median follow-up was 25.1 months. The end-point of interest was composite and included aortic dissection, rupture or sudden death that was most likely aortic. Event rates at 1, 3 and 5 years were 4.3±1.3%, 6.9±1.9% and 9.7±2.6% for definite aortic events. Those with a starting aortic diameter of <50 mm experienced an event rate of <1%, but the rate of definite or possible event rates rose to 2.7% or 8.1% at aortic diameter between 50 and 60 mm, and increased exponentially to 37.5% or 62.5% at >70 mm. The authors concluded that the incidence of aortic events in patients with thoracic aortic aneurysms may be higher than currently appreciated, especially in those with aneurysms between 50 and 60 mm.

Oladokun et al. (2016) performed a systematic review to assess growth rates of thoracic aortic aneurysms. The review identified an overall mean growth rate of 0.2–4.2 mm/year. Ascending/arch TAA expanded at a rate of 0.2–2.8 mm/year, while descending/thoracoabdominal TAA expanded at 1.9–3.4 mm/year. The main factors affecting TAA growth were the presenting aneurysm diameter (aneurysm size), anatomical location of the aneurysm, and presence of Marfan's syndrome or BAV (bicuspid aortic valve). The review demonstrated a shortfall in the understanding of TAA expansion rates. Existing studies were heterogeneous in methodology and reported outcomes. High-quality studies with a standardised approach to TAA growth assessment are required.

3.3 Conclusions for Clinical Practice

1. In patients with asymptomatic DTAA, TEVAR is indicated when the maximum diameter of the aneurysm exceeds 5.5 cm or if rapid expansion (>5 mm in 6 months) occurs.
2. The indication for open surgery is focused mainly upon patients with TAAA, in whom endovascular stent graft options are limited. In case series, results could be achieved with fenestrated or branched stent grafts as well as with the hybrid technology, being equivalent to OR. However, long-term follow-up data are missing as well as randomized comparative studies.
3. The decisive factor concerning outcome, especially with open repair of TAAA, is the experience of the surgeon and the center, which makes the treatment of these patients in specialized high volume centers absolutely necessary.

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Chapter 4
Abdominal Aortic Aneurysm (AAA)

4.1 Guidelines

4.1.1 Monitoring and Indication for Surgery

The treatment of an asymptomatic abdominal aortic aneurysm (AAA) is determined by its size (diameter), shape and growth rate. The aim of the treatment is to avoid any rupture. In case of a prophylactic surgery, the potential risk of rupture must be calculated against the risk of operative mortality. The clinical practice guidelines of the European Society for Vascular Surgery (ESVS) (Moll et al. 2011) give the following recommendations:

- There is consensus that for very small aneurysms, 3.0–3.9 cm, the risk of rupture is negligible. Therefore, these aneurysms do not require surgical intervention and should be kept under ultrasound surveillance at regular intervals.
- A policy of ultrasonographic surveillance of small aneurysms (4.0–5.5 cm) is safe and advised for asymptomatic aneurysms (evidence level 1a, grade A recommendation).
- When the threshold diameter (5.5 cm, measured by ultrasonography, in males) is reached or symptoms develop or rapid aneurysm growth is observed (>1 cm/year), immediate referral to a vascular surgeon is recommended (evidence level 3a, recommendation grade B). To prevent interval rupture, it is recommended that a vascular surgeon review patient within 2 weeks of the aneurysm reaching 5.5 cm or more in diameter (evidence level 5, grade D recommendation). In some centres an earlier referral, at between 5.0 and 5.5 cm is an acceptable alternative practice.
- Females should be referred to vascular surgeons for assessment at a maximum aortic diameter of 5.0 cm as measured by ultrasonography. Aneurysm repair should be considered at a maximum aneurysm diameter of 5.2 cm in females (evidence level 3b, recommendation grade C).

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Coincident in opinion of the ESVS guidelines are the recommendations of the American College of Cardiology (ACC) und der American Heart Association (AHA) (Hirsch et al. 2006; Anderson et al. 2013):

Class I- recommendation:

- Patients with infrarenal or juxtarenal AAAs measuring 5.5 cm or larger should undergo repair to eliminate the risk of rupture (Level of Evidence: B).
- Patients with infrarenal or juxtarenal AAAs measuring 4.0–5.4 cm in diameter should be monitored by ultrasound or computed tomographic scans every 6–12 months to detect expansion (Level of Evidence: A).

Class II a-recommendation:

- Repair can be beneficial in patients with infrarenal or juxtarenal AAAs 5.0–5.4 cm in diameter (Level of Evidence: B).
- Repair is probably indicated in patients with suprarenal or type IV thoracoabdominal aortic aneurysms larger than 5.5–6.0 cm (Level of Evidence: B).
- In patients with AAAs smaller than 4.0 cm in diameter, monitoring by ultrasound examination every 2–3 years is reasonable (Level of Evidence: B).

Class III-recommendation:

- Intervention is not recommended for asymptomatic infrarenal or juxtarenal AAAs if they measure less than 5.0 cm in diameter in men or less than 4.5 cm in diameter in women (Level of Evidence: A).

The latest guidelines are those of the European Society of Cardiology (Erbel et al. 2014). They specify distinct intervals for monitoring and treatment of small AAA and recommend:

- In patients with abdominal aortic diameter of 25–29 mm, new ultrasound imaging should be considered 4 years later (class-IIa-recommendation/evidence level B)
- Surveillance is indicated and safe in patients with AAA with a maximum diameter of <55 mm and slow (<10 mm/year) growth (class I recommendation/evidence level A)
- In patients with small (30–55 mm) AAAs, the following time interval for imaging should be considered (class-IIa-recommendation/evidence level B):
  - Every 3 years for AAA of 30–39 mm diameter
  - Every 2 years for AAA of 40–44 mm diameter
  - Every year for AAA ≥ 45 mm diameter
- AAA repair is indicated if (class I recommendation/evidence level B):
  - AAA diameter exceeds 55 mm
  - Aneurysm growth exceeds 10 mm/year

4.1.2 Cochrane Review

Filardo et al. (2015) compared mortality, quality of life, and cost effectiveness of immediate surgical repair versus routine ultrasound surveillance in people with asymptomatic AAAs between 4.0 and 5.5 cm in diameter. The results from four trials to date demonstrate no advantage to immediate repair for small AAA (4.0–5.5 cm), regardless of whether open or endovascular repair is used and, at least for open repair, regardless of patient age and AAA diameter. Thus, neither immediate open nor immediate endovascular repair of small AAAs is supported by currently available evidence.

4.1.3 Screening

The screening recommendations from the Society for Vascular Surgery (Chaikof et al. 2009) cover surveillance intervals of small AAAs which are listed in Table 4.1.

The guidelines of the European Society of Cardiology (ESC) recommend (Erbel et al. 2014):

Population screening for AAA with ultrasound

- Is recommended in all men > 65 years of age (Class-I-recommendation/evidence level A)
- May be considered in women > 65 years of age with history of current/past smoking (Class-IIb-recommendation/evidence level C)
- Is not recommended in female non-smokers without familial history (Class-III-recommendation/evidence level C)
- Targeted screening for AAA with ultrasound should be considered in first-degree siblings of a patient with AAA (Class-IIa-recommendation/evidence level B)

Opportunistic screening for AAA during transthoracic echocardiography

- Should be considered in all men >65 years of age (Class-IIa-recommendation/evidence level B)
- May be considered in women > 65 years of age with a history of current/past smoking (Class-IIb-recommendation/evidence level C)

The recommendations of the U.S. Preventive Services Task Force (LeFevre et al. 2014) are shorter:

- Men aged 65–75 years who have ever smoked:

  Screen once for AAA by ultrasonography (grade B-recommendation)

Table 4.1 AAA screening and surveillance intervals/recommendations of the Society for Vascular Surgery (Chaikof et al. 2009)

Target Group	Surveillance imaging intervals
One-time ultrasound screening for AAA is recommended for all men at or older than 65 years. Screening men as early as 55 years is appropriate for those with a family history of AAA	At 6-month for those patients with an AAA between 4.5 and 5.4 cm in maximum diameter
	At 12-month intervals for patients with an AAA of 3.5–4.4 cm in maximum diameter
One-time ultrasound screening for AAA is recommended for all women at or older than 65 years with a family history of AAA or who have smoked.	Follow-up imaging at 3 years for those patients with an AAA between 3.0 and 3.4 cm in maximum diameter.
	Follow-up imaging at 5- year intervals for patients whose maximum aortic diameter is between 2.6 and 2.9 cm

- Men aged 65–75 years who have never smoked:

  Selectively screen for AAA (grade C-recommendation)
- Women aged 65–75 years who have ever smoked:

  No recommendation (statement)
- Women who have never smoked:

  Do not screen for AAA (grade D-recommendation)

4.1.4 Management

The guidelines of the American College of Cardiology/American Heart Association for the management of AAA have been revised in 2011 (Rooke et al. 2011). They note that open and endovascular repair techniques of AAA have demonstrated clinical equivalence over time, with similar rates of overall and aneurysm-related mortality and morbidity. For patients with an estimated life expectancy >2 years and who are good risk surgical candidates open (OR) or endovascular repair (EVAR) is indicated. Although EVAR has the lower procedural mortality, this advantage would not be sustained over time, so the decision for one of the two methods is an individual one. Endovascular treatment should not be used in patients who do not meet the established anatomical criteria or who cannot comply with the required follow-up imaging requirements.

It is recommended:
Class I:

- Open or endovascular repair of infrarenal AAAs and/or common iliac aneurysms is indicated in patients who are good surgical candidates (Level of Evidence: A).
- Periodic long-term surveillance imaging should be performed to monitor for endoleak, confirm graft position, document shrinkage or stability of the excluded aneurysm sac, and determine the need for further intervention in patients who have undergone endovascular repair of infrarenal aortic and/or iliac aneurysms (Level of Evidence: A).

Class II a:

- Open aneurysm repair is reasonable to perform in patients who are good surgical candidates but who cannot comply with the periodic long-term surveillance required after endovascular repair (Level of Evidence: C).

Class II b:

- Endovascular repair of infrarenal aortic aneurysms in patients who are at high surgical or anesthetic risk as determined by the presence of coexisting severe cardiac, pulmonary, and/or renal disease is of uncertain effectiveness (Level of Evidence: B).

These guidelines emphasize the importance of life-long imaging follow-up after EVAR. In reality, however, the compliance with imaging follow-up recommendations after EVAR at least in the United States is well below the recommended rate (Schanzer et al. 2015). Among 19,962 patients who underwent EVAR, the incidence of loss to annual imaging follow-up at 5 years after EVAR was 50%. Especially older individuals and those who presented with a ruptured AAA (rAAA) were significantly more likely to be lost to annual imaging follow-up. Quality improvement efforts to encourage improved compliance with imaging follow-up are necessary.

The guidelines of the ESVS do not determine the choice of the surgical procedure, but recommend (Moll et al. 2011) that patient's preference for type of aneurysm repair should be considered (level 2a evidence, recommendation grade B) when selecting the surgical procedure. In symptomatic AAA, however, where morphologically suitable, patients should be offered EVAR, which has a lower operative mortality for symptomatic cases than open repair (evidence level 2c, recommendation grade B).

In the guidelines of the ESC (Erbel et al. 2014) finally, if a large aneurysm is anatomically suitable for EVAR, either open or endovascular aortic repair is recommended in patients with acceptable surgical risk (Class I recommendation/evidence level A). If a large aneurysm is anatomically unsuitable for EVAR, open aortic repair is recommended (Class I recommendation/evidence level C). In patients with asymptomatic AAA who are unfit for open repair, EVAR, along with best medical treatment, may be considered (Class IIb recommendation/evidence level B).

4.2 Results

4.2.1 Screening

4.2.1.1 Systematic Reviews/Metaanalyses

Ferket et al. (2012) studied in a systematic review article seven English-language guidelines for AAA screening. The consensus was merely about the fact that older men should be subjected to a one-time screening and that AAA> 5.5 cm should be treated. Furthermore, the US Preventive Services Task Force has published a systematic evidence review on the effectiveness of AAA screening (Guirguis-Blake et al. 2014a, b). Review of four randomized trials with a total of 137,214 participants demonstrated that one-time invitation for AAA screening in men aged 65 years and older reduced AAA rupture and aneurysm-related mortality rates (both about 50%) for up to 10–15 years, but had no statistically significant effect on all-cause mortality rates up to 15 years. Screening was associated with more overall and elective surgeries but fewer emergency operations and lower 30-day operative mortality rates at up to 10- to 15-year follow-up. One RCT involving 9342 women showed that screening had no benefit on AAA-related or all-cause mortality rates. The authors pointed out that it would be very optimistic to expect a reduction in the overall mortality rate from a single AAA screening in view of the fact that at the age of 65 years, the AAA prevalence is about 4%. For large aneurysms (>5 cm), the prevalence amounts to as low as only 0.5%, and the rupture rate is low (after 5 years 0.1–0.6%). It should be noted, however, that the late results of the MASS study, considered in isolation, revealed with regard to the overall mortality an advantage for the AAA screening (Thompson et al. 2012). Likewise, the current final report of the German Institute for Quality and Efficiency in Health Care (IQWiG) on ultrasound screening for AAA revealed unlike Guirguis-Blake et al. evidence for an advantage of ultrasound screening with regard to overall mortality in men (IQWiG 2015).

The surveillance intervals of smaller aneurysms depend on their growth rate. For this, a systematic review and meta-analysis of the literature was published (Thompson et al. 2013). According to that, any increase of the aneurysm diameter by 0.5 cm leads to an increase of the aneurysm growth by 0.5 mm/year with a doubling of the rupture risk. The growth rate in smokers is about 0.35 mm/year higher than for former or non-smokers, while conversely diabetics have a slower growth rate by 0.51 mm/year than non-diabetics. The rupture rates are about four times higher in women than in men. In current smokers (men), they are doubled and also patients with hypertension have a higher rupture rate. Based on this analysis, the authors concluded that surveillance intervals of several years are clinically acceptable for men with AAAs in the range of 3.0–4.0 cm. For AAAs from 4.0 to 4.9 cm they recommended an interval of around 1 year, whereas intervals of 6 months would be acceptable for 5.0–5.4-cm AAAs.

A not well-defined risk group that should eventually be included in a screening program, represent women who currently smoke. Based on the Swedish Mammography Cohort (35,550 women) Stackelberg et al. (2014) calculated the

AAA incidence per 100,000 women who currently smoke with 136 women, compared with 76 among men who have never smoked. Following smoking cessation, women had a more rapid decline in excess risk. The AAA risk was halved after 11 years among women and after 23 years among men.

4.2.1.2 Results

Svensjö et al. (2014a) reported the 5-year results of an AAA screening program in the county of Uppsala. In this population-based cohort-study, all men were invited to ultrasound screening of the aorta at age 65, and were re-invited at age 70. From 3268 men, 2736 followed the invitation (83.7%). After 5 years, 23 had completed elective AAA repair, of whom five subsequently had died of non AAA-related causes, and one had undergone rAAA repair and died during surgery. In addition, 239 men were reported dead without a history of AAA repair. Thus, of all men invited at age 65 years, 245 had died resulting in a 5-year mortality of 7.5%. The AAA prevalence increased from 1.5% at 65 to 2.4% at age 70. This data seems to confirm the conclusions of the US Preventive Services Task Force that it is possible to reduce the mortality due to aneurysm rupture with AAA screening, but the impact on overall mortality is rather limited.

In this context, the fact must be mentioned that all four randomized trials on which the screening recommendations of today are based on, expect a AAA prevalence which is no longer up to date. The incidence of AAA is declining in the last decade, at least in some Western European countries; this is also true for the incidence of rAAA, and is explained – among other things – due to a reduction in cigarette consumption (Anjum and Powell 2012; Anjum et al. 2012; Sensi et al. 2013; Svensjö 2013). This makes the screening programs now less effective than on the basis of data such as MASS suspected (Darwood and Brooks 2012). Jacomelli et al. (2016) found in 65-year-old men invited by the NHS AAA Screening Programme the prevalence of AAA (aortic diameter larger than 2.9 cm) was 1.34%. During the period of April 2009 to October 2013, 32,119 men received invitations for AAA screening at the southwest London screening center and 24,891 men were screened (77% attendance) (Benson et al. 2016). Those at highest risk of AAA were white British (1.35%), followed by black and black British (0.65%), and Asian/Asian British (0.23%). Number needed to screen to identify one AAA was calculated as 78, 154, and 431, respectively. In the prospective population-based Oxfordshire-study (Howard et al. 2015) the incidence of acute (acute symptomatic and ruptured) AAA events per 100,000 population per year was 55 in men aged 65–74 years, but increased to 112 at age 75–84 years and to 298 at age 85 years or above. Two-thirds of acute AAA events occurred at age 75 years or above, and more than 25 per cent of events were in women. In this study, the incidence of rAAA in men aged 65–74 years was lower than that found in the MASS trial (55 per 100,000 per year versus 96 per 100,000 per year in the MASS control group). Consistent with this finding, Otterhag et al. (2016) demonstrated a reduction in the overall incidence of rAAA in men during the last decade. They evaluated the Malmö population

regarding the incidence of rAAA and elective AAA surgery 4 years before and after start of AAA-screening in 2010. The study demonstrated a reduction in the overall incidence of rAAA in men even before start of AAA screening in the autumn of 2010. Nevertheless, AAA screening in its present form shall be cost-effective (Svensjö et al. 2014b, c). However, Svensjö (2013) indicates 597 as the number of persons to be screened today, to avoid 1 aneurysm-related death, compared with 192 at MASS. This means that one has to screen now three times as many persons as 10 years ago to achieve the same effectiveness of a screening program. Accordingly, the absolute risk reduction for an aneurysm-related death per 10,000 for screening invitees declined from 41.6 to 13.4. The number of years of life gained by screening per 10,000 invitees has also parallely declined (from 131.5 to 46.7 years).

4.2.2 Intact AAA

4.2.2.1 Randomized Studies Comparing Open and Endovascular Repair

Major RCTs comparing endovascular (EVAR) and open repair (OR) for nonruptured AAA have been published under the titles EVAR 1 (in the UK), DREAM (Netherlands), OVER (USA) and ACE (France).

In EVAR 1, EVAR (n = 614) was compared with OR (n = 602) in patients over 60 years of age with an AAA of at least 5.5 cm in diameter. The mean patient age was 74 years, 90% of the patients were men. Four emergencies respectively were included in both groups (Brown et al. 2012). 30-day mortality was significantly lower in the EVAR group (1.8%) vs. OR (4.3%), which was also true for hospital mortality (2.3% EVAR vs. 6.0% OR). Taking only elective interventions into account, hospital mortality was 2% with EVAR and 5.5% with OR. In the long-term follow-up, the advantage of the lower mortality rate in EVAR could not be sustained, mainly because of fatal endograft ruptures. The overall mortality after >4 years was 8.4 per 100 person-years with EVAR and 7.9 with OR, respectively. The aneurysm-related mortality was calculated to be 0.8 and 0.2 per 100 person-years respectively. Secondary interventions were significantly less after OR (1.7 per 100 person-years compared with 5.1 after EVAR).

In the following DREAM Study (Dutch Randomized Endovascular Aneurysm Management) 178 patients were assigned to OR, and 173 to EVAR (de Bruin et al. 2010). Mean patient age was 70 years, 91.7% of the patients were men, AAA diameter was at least 5 cm. 4.6% of patients died in hospital after OR, and 1.2% after EVAR. The median follow-up was 6.4 years. Six years after randomization, the cumulative overall survival rates were 69.9% for OR and 68.9% for EVAR. The increased perioperative mortality in the open repair group was counterbalanced by a larger number of deaths after discharge in the endovascular-repair group, so that there were no differences in the long-term survival between these two procedures. However, reinterventions were significantly less after OR, 6 years after randomization, the cumulative rates of freedom from secondary interventions were 81.9% for OR and 70.4% for EVAR. De Bruin et al. (2013) also determined renal function of

patients of the DREAM study in the long term. Again, there was no difference between OR and EVAR, neither surgical procedure accelerated the loss of renal function. (On a poorer renal function after EVAR compared to OR has been speculated owing to the administration of nephrotoxic contrast agents during intervention). In addition, National Surgical Improvement Program (NSQIP) database demonstrates that moderate renal impairment is not a contraindication for EVAR. Nguyen et al. (2013) identified 13,191 patients who underwent AAA repair: 9877 patients underwent EVAR and 3314 underwent OR. Forty percent of patients had eGFR of less than 60 mL/min. OR in patients with moderate renal dysfunction resulted in significantly higher mortality, cardiovascular events, and combined outcomes. They concluded that contrary to current practice EVAR should be the first choice in patients with moderate renal dysfunction if they have the appropriate anatomy.

In OVER (Open Versus Endovascular Repair) of the Veterans Affairs Cooperative Study Group of the United States, 444 patients with EVAR and 437 patients with OR were included, more than 99% were men, mean age 70 years, mean AAA diameter 5.7 cm (Lederle et al. 2009). Perioperative mortality was significantly higher for open repair at 30 days (0.2% vs 2.3%; P = .006), and at 30 days or during hospitalization (0.5% vs 3.0%; P = .004). This early advantage of EVAR was not offset by increased morbidity or mortality in the first 2 years after repair, mortality after the perioperative period was similar in the two groups (6.1% with EVAR vs 6.6% with OR). The perioperative survival advantage with endovascular repair was sustained for several years, after which there was no significant difference between the two groups. When the study was completed on October 15, 2011, the same percentage of patients had died in both groups (EVAR 32.9%, OR 33.4%) (Lederle et al. 2012). The rates of secondary therapeutic procedures were also similar after EVAR and OR (22.1% vs. 17.8%). In this study late aneurysm rupture remained a concern and EVAR did not yet offer a long-term advantage over open repair, particularly among older patients, for whom such an advantage was originally expected.

In the French *ACE*-study (Aneurysme de l'aorte abdominale, surgery versus endoprosthesis), 150 patients with an AAA > 50 mm in men or >45 mm in women were assigned to EVAR and 149 patients to OR. Thirty-day mortality was only 0.6% with OR and 1.3% with EVAR (Becquemin et al. 2011). At 3 years, cumulative survival rates were 86.7% with OR and 86.3% with EVAR. In the EVAR group, the crude percentage of vascular reintervention rate was higher (2.7% vs 16%) with a trend toward a higher aneurysm-related mortality (0.7% vs 4%). Incisional complications were significantly more common with OR (25.5% vs. 0.7%), whereas buttock claudication was more frequently seen after EVAR (14% vs. 2%). For patients with low to intermediate risk, these authors further argued for the open approach because it was as safe as EVAR and remained a more durable option.

4.2.2.2 Meta-analyses for Open and Endovascular Repair

The existing published randomized trials, together with information from Medicare and SwedVasc databases, were included in a meta-analysis by Stather et al. (2013). This included 25,078 patients undergoing EVAR and 27,142 undergoing open repair

Table 4.2 Endovascular (EVAR) vs. open repair (OR) for intact AAA – Results from meta-analyses of the literature

	EVAR	OR	EVAR	OR
Author	Stather et al. (2013)		Paravastu et al. (2014)	
Patients (n)	25,078	27,142	1362	1361
Hospital mortality	1.3%	4.7%	1.4%	4.2%
Overall mortality				
After 2 years	14.3%	15.2%		
After 4 years	33.8%	34.7%		
After more than 4 years			37.3%	37.8%

for AAA. There was no significant difference in aneurysm-related mortality by 2 years or longer follow-up. A significantly higher proportion of patients undergoing EVAR required reintervention ($P = 0.003$) and suffered aneurysm rupture ($P < 0.001$) (Table 4.2). A similar result was shown by the Cochrane Review of Paravastu et al. (2014): in individuals considered fit for conventional surgery, EVAR was associated with lower short-term mortality than OR. However, this benefit from EVAR did not persist at the intermediate- and long-term follow ups.

Bahia et al. (2015) assessed in a systematic review and meta-analysis whether improvements in perioperative practice have translated into better long-term mortality after elective AAA repair over the period 1969–2011. In this study, 5-year survival was 69%. Meta-regression on study midpoint showed no improvement in 5-year survival over the period 1969–2011. After adjusting for average patient age, an improvement in 5-year survival over the period that these data spanned was obtained. The study demonstrated that there has been no measurable improvement in the overall long-term survival of patients undergoing elective infrarenal AAA repair, because increasingly elderly cohorts have been treated over the time period examined. After adjustment for the increasing age of patients undergoing AAA repair, however, long-term survival improved over time.

A meta-analysis on health-related quality-of-life (HR-QoL) outcomes after open versus endovascular AAA repair was performed by Kayssi et al. (2015). SF-36 general health scores were higher for EVAR up to 12 months postoperatively. SF-36 physical functioning scores were higher for EVAR at 6 months but this advantage was lost at 12 months. EVAR was associated with a better EQ-5D score at 12 months, but not at 24 months of follow-up. In conclusion, EVAR was associated with better HR-QoL in some domains up to 12 months postoperatively, but there was insufficient data to demonstrate a HR-QoL advantage beyond 12 months.

4.2.2.3 Registry Data

The NIS of the U.S. comprises 90,690 patients that underwent repair of unruptured AAA and 11,288 with ruptured AAA in the years 2000–2010 (Dua et al. 2014a). There was a slight decrease from 2000 to 2010 in the incidence of unruptured and

rAAA (unruptured AAA, 13.93 to 12.83/ 100,000; rAAA, 2.10 to 1.39/100,000). The overall number of AAAs (unruptured and ruptured) in the U.S. population remained unchanged over this period after correcting for population growth (45,230 estimated total cases in 2000 vs. 44,005 cases in 2010). In 2000, 5.2% of all AAAs were repaired by EVAR (5.9% for unruptured and 0.8% of rAAAs). By 2010, 74.0% of all AAAs were repaired by EVAR (77.8% for unruptured and 38.4% of rAAAs). Although in-hospital mortality rates remained stable for OR in unruptured patients (3.8–4.8%), it declined for EVAR (1.8%–2.1% to 0.9%). Over the same time period, mortality rates for rAAAs repaired by means of OR decreased from 44.5% to 33.4%); those patients undergoing EVAR had a similar decrease for in-hospital mortality rate (40.0%–40.8% to 19.8%). Nearly the same results were seen in the National Surgical Quality Improvement Program (NSQIP) database (Malas et al. 2014). Of the 21,115 patients aged 50 years and older who received elective repair of infrarenal AAA between 2005 and 2011, 5308 (25.1%) received open repair while 15,807 (74.9%) received EVAR. This database showed a significant 3-fold increase in perioperative mortality with open repair compared with EVAR (30-day mortality OR, 3.7; EVAR 1.3%). This difference was independent of risk status and changes over time.

Hicks et al. (2016) used the Nationwide Inpatient Sample database (January 2007–December 2011) to describe the association of patient- and hospital-level factors with in-hospital mortality after elective AAA repair. 131,908 EVARs and 34,535 ORs were performed at 1207 hospitals. Overall in-hospital mortality was 0.7% for EVAR and 3.8% for OR. Mortality after EVAR was significantly higher among hospitals with high general surgery mortality. Mortality after OR was significantly lower among hospitals performing at least 25% of AAA repairs using open techniques. Neither hospital bed size nor teaching status was significantly associated with mortality after either EVAR or OR. Notably, the proportion of institutions performing at least 25% open cases fell from 41% in 2007 to 18% in 2011. This demonstrates the importance of adequate institutional experience with OR techniques, which appears to be critically declining.

Schermerhorn et al. (2015) identified 128,598 Medicare beneficiaries, 67 years of age or older, who had undergone elective repair of abdominal aortic aneurysm from 2001 through 2008; a total of 79,463 patients had undergone endovascular repair, and 49,135 patients had undergone open repair. Perioperative mortality was 1.6% in the endovascular-repair cohort versus 5.2% in the open-repair cohort. Long-term mortality was similar in the two repair cohorts. The rates of reinterventions related to abdominal aortic aneurysm were higher in the endovascular-repair cohort, and these were partially balanced by a higher rate of reinterventions for complications related to laparotomy in the open-repair cohort. Mortality at 2 years after endovascular repair decreased from 16.3% among patients who underwent procedures in 2001 to 14.6% among patients who underwent procedures in 2007, but mortality at 2 years after open repair did not change significantly during that period (16.8% among patients who underwent procedures in 2001 and 15.4% among patients who underwent procedures in 2007).

While the advantage of EVAR compared to OR in high risk patients is uncontroversial, the advantages of EVAR in patients at low risk for open surgical repair (OR)

remain unclear. Data of the National Surgical Quality Improvement Program of the United States demonstrate that even among those male patients at low risk for OR on the basis of comorbidities, EVAR is associated with reduced perioperative mortality and major complications. EVAR was associated with lower 30-day mortality (0.5% vs 1.5%; $p < .01$) compared with OR. The results of this national registry prove the short-term benefit of EVAR in low-risk male patients compared with OR (Siracuse et al. 2014).

Chang et al. (2015) studied the long-term survival and outcomes of EVAR and OR for AAA on a population level. An analysis of the California Office of Statewide Health Planning and Development statewide database from 2001 to 2009 was performed. A total of 23,670 patients with nonruptured AAA were included in this study, for a median follow-up of 3.3 years. EVAR was performed in 51.7% of patients. Thirty-day mortality was 1.5% with EVAR and 4.7% with OR. In this analysis, a survival advantage until 3 years postoperatively for all patients undergoing AAA repair by an endovascular technique was observed (all-cause mortality at 3 years: EVAR 19.8%, OR 19.9%). After 3 years, the mortality rate of EVAR repair patients was higher; however, these mortality differences did not reach statistical significance on adjusted analysis over the entire study (all-cause mortality at 5 years: EVAR 32.1%, OR 29.7%). Reintervention was higher from 6 months through 5 years in EVAR repair patients, which reflects the trends in management of endoleaks and technology available during the study. At 5 years, reintervention rate was 6.6% (EVAR) vs. 1.5% (OR), and AAA rupture occurred in 1.0% (EVAR) vs. 0.2% (OR).

4.2.3 Ruptured AAA (rAAA)

4.2.3.1 EVAR vs. OR – Randomized Studies and Meta-analyses

In the *Amsterdam Acute Aneurysm Trial* (Reimerink et al. 2013) a total of 116 of 520 patients with rAAA of three specialized centers were randomly assigned to either EVAR or OR. Nonrandomized patients were followed in a prospective cohort. Primary endpoint of the study was the composite of death and severe complications at 30 days. The 30-day mortality was 21% in patients assigned to EVAR compared with 25% for OR. The mortality of all surgically treated patients in the nonrandomized cohort was 30%. This trial did not show a significant difference in combined death and severe complications between EVAR and OR (EVAR 42%, OR 47%). Potential limitations of the study were the relatively small numbers of patients included, the high exclusion rate (78%) and the fact that mortality for OR was much lower than expected which could be explained by optimization of logistics, preoperative CT imaging, and centralization of care in centers of expertise.

Meanwhile, the much larger randomized controlled IMPROVE trial of the UK demonstrated no differences in the 30-day mortality between EVAR and OR for rAAA (IMPROVE Trial Investigators et al. 2014a). In this study, 316 patients were

randomized to the endovascular strategy and 297 to open repair. In this trial, a strategy of endovascular repair was not associated with significant reduction in either 30-day mortality or cost. Overall 30-day mortality was 35.4% in the endovascular strategy group and 37.4% in the open repair group. However, the endovascular strategy seemed to be more effective in women than in men. For women, 30-day mortality was 26/70 (37%) in the endovascular strategy group and 36/63 (57%) in the open repair group, compared with 86/246 (35%) and 75/234 (32%) for men. Another benefit of EVAR resulted from the fact that 94% per cent of discharges within 30 days were directly to home in the endovascular strategy group compared with only 77% in the OR group.

Two other findings of the IMPROVE study need further investigation. Patients in whom EVAR was performed under local anesthesia showed a significantly lower mortality than those in which the intervention was performed under general anesthesia. A meta-analysis of data from ten non randomized studies was not able to prove this earlier (Karthikesalingam et al. 2012). Furthermore, a systolic blood pressure below 70 mmHg was an independent factor for increased mortality. These results question whether the 70–80-mmHg threshold recommended for hypotensive haemostasis for ruptured aneurysm really should be used, particularly in an elderly cohort with aneurysm rupture (IMPROVE Trial Investigators et al. 2014b). Otherwise, in a retrospective study aggressive volume resuscitation of patients with rAAA before proximal aortic control predicted an increased perioperative risk of death, which was independent of systolic blood pressure. Therefore, volume resuscitation should be delayed until surgical control of bleeding is achieved (Dick et al. 2013).

The 1-year survival data are now available for 611/613 patients randomized in the IMPROVE trial (IMPROVE Trial Investigators 2015). After 1 year, 130 (41.1%) of patients in the endovascular strategy group had died vs. 133 (45.1%) in the open repair group. Almost half the deaths, in each group, occurred within 24 h and the majority occurred within 30 days. At 1 year, AAA-related mortality (including all deaths within 30 days) in the endovascular strategy and open repair groups, respectively, was 33.9% and 39.3% (P = 0.161). The subgroup analysis of 1-year mortality found weak evidence that the endovascular strategy was more effective in women than in men (odds ratio 0.41). At 3 months, a higher proportion of patients in the endovascular strategy group reported ‘no problems’ on the physical health dimensions. In addition, in this trial, there was no evidence of a difference in re-interventions (including those for endoleaks) at any time during the first year after rupture. There were indications that QALYs were higher and costs lower for the endovascular first strategy. In conclusion, an endovascular first strategy for management of ruptured aneurysms does not offer a survival benefit over 1 year but offers patients faster discharge with better QoL and is cost-effective.

An individual-patient meta-analysis across the three European trials (Sweeting et al. 2015a) came to a similar conclusion: there is no early survival benefit for an endovascular strategy following ruptured AAA, although there is a very weak indication in favour of EVAR at 90 days for patients with ruptured AAA, who are eligible for both treatments. This meta-analysis continued to suggest that women may

have improved early survival with an endovascular strategy and that patients in the endovascular strategy groups benefit from earlier hospital discharge. Meanwhile, the 1-year outcomes of the three recent randomized trials were assessed. In an individual patient data meta-analysis mortality across the three trials at 1-year was 38.6% for the EVAR and 42.8% for the open repair groups (Sweeting et al. 2015b). Taken together with the recent gains in health economic outcomes demonstrated at 1 year in the IMPROVE trial, the evidence suggests that endovascular repair should be used more widely for ruptured aneurysms. A Cochrane systematic review, finally, included three RCTs with a total of 761 patients with rAAA in a meta-analysis (Badger et al. 2016). They concluded that there was no clear evidence to support a difference between EVAR and OR. Longer term outcomes and cost per patient were evaluated in only a single study, thus precluding definite conclusions.

4.2.3.2 Registry Data

Edwards et al. (2014) identified all Medicare beneficiaries at the age 67 or older who were admitted to a US hospital with a primary discharge diagnosis of ruptured abdominal aortic aneurysm between 2001 and 2008. Of 10,998 patients with repaired rAAA, 1126 underwent EVAR and 9872 underwent open repair. Patients were matched by propensity score on baseline demographics, coexisting conditions, admission source, and hospital volume of rAAA repair. Propensity score matching yielded 1099 patient pairs. Perioperative mortality was 33.8% for EVAR and 47.7% for open repair ($P < .001$), and this difference persisted for >4 years. At 36 months, EVAR patients had higher rates of AAA-related reinterventions than open repair patients (endovascular reintervention, 10.9% vs 1.5%; $P < .001$), whereas open patients had more laparotomy-related complications (incisional hernia repair, 1.8% vs 6.2%; $P < .001$; all surgical complications, 4.4% vs 9.1%; $P < .001$). The study demonstrated that EVAR for rAAA was associated with lower perioperative and long-term mortality in Medicare beneficiaries. In this study, the use of EVAR for rAAA increased from 6% of cases in 2001 to 31% in 2008.

Karthikesalingam et al. (2016) compared 90-day and 5-year mortality in patients who had a rAAA in England and Sweden after matching for age and sex. Some 12.467 patients underwent rAAA repair in England, of whom 83.2% were men; the median (i.q.r.) age was 75 (70–80) years. A total of 2829 Swedish patients underwent rAAA repair, of whom 81.3% were men; their median (i.q.r.) age was 75 (69–80) years. Ninety-day mortality rate was worse in England (44.0% versus 33.4% in Sweden; $P < 0.001$), including separate analyses of patients undergoing OR (45.1 vs. 34.9%) and EVAR (33.4% vs. 25.6%). The crude 5-year survival was better in Sweden (freedom from mortality 46.3% vs. 38.6% in England). In patients who survived the first 90 days, the 5-year mortality rate was similar in the two countries (freedom from mortality 69.6% in England vs. 69.3% in Sweden). In England, lower mortality was seen in teaching hospitals with larger bed capacity, higher annual caseloads and greater use of endovascular aneurysm repair. In Sweden, lower mortality was associated with EVAR, high annual caseload, or surgery on

weekdays compared with weekends. In both countries, mortality was lowest in centres performing greater numbers of AAA repairs per annum, and more EVAR procedures.

Gunnarsson et al. (2016) analyzed the outcome of ruptured AAA repair in the Swewdvasc registry. In total, 1304 patients were identified. Three primary EVAR centers operated on 236 patients (74.6% EVAR). Twenty-six primary open repair centers operated 1068 patients (15.6% EVAR). When analyzing outcome based on operative technique, mortality was lower after EVAR when compared with open repair at 30 days (EVAR 21.6%; open repair 29.6% [p < .01]), however, there was no significant difference at 1 year (EVAR 32.2%: open repair 36.9%) or 2 years (EVAR 38.0%; open repair 39.4%). In this study, there was no early or midterm survival difference between primary open and endovascular operative strategies for rAAA. The results of this registry harmonized with the findings of the published randomized trials. These authors concluded that the improved perioperative outcome after EVAR seen in retrospective studies is likely to be due to selection bias. Whether the better results with EVAR as compared to OR are attributed only to a selection bias, must be left open. Most registries show an improved outcome with EVAR as compared to OR.

Ali et al. (2015) compared in-hospital mortality and morbidity after EVAR and OR of rAAA in patients from the Vascular Quality Initiative (2003–2013) stratified by the validated Vascular Study Group of New England RAAA risk score. Among 514 patients who underwent EVAR and 651 patients who underwent OR of rAAA, EVAR had lower in-hospital mortality (25% vs 33%, $P = .001$). The risk-stratified comparison showed that EVAR of rAAA had a lower mortality and morbidity compared with OR in low-risk and medium-risk patients and that EVAR should be used to treat these patients when anatomically feasible. For rAAA patients at the highest preoperative risk, there was no benefit to using EVAR compared with OR. The Vascular Quality Initiative database (2003–2013) was used also by Robinson et al. (2016) to determine Kaplan-Meier 1-year and 5-year mortality after EVAR and OR of rAAA. Among 590 patients who underwent EVAR and 692 patients who underwent OR of rAAA, the lower mortality seen in the hospital after EVAR (EVAR 23% vs OR 35%; P < .001) persisted at 1 year (EVAR 34% vs OR 42%; P = .001) and 5 years (EVAR 50% vs OR 58%; P = .003) after repair. However, after adjusting for patient and operative characteristics, EVAR did not independently reduce mortality at 1 year. Patient comorbidities and indices of shock on admission were the primary independent determinants of long-term mortality.

Soden et al. (2016) used the 2011–2013 American College of Surgeons National Surgical Quality Improvement Program to compare 30-day mortality and major adverse events for asymptomatic, symptomatic, and ruptured AAA repair, stratified by EVAR and open repair. There were 5502 infrarenal AAAs identified, 4495 asymptomatic aneurysms (830 open repair, 3665 [82%] EVAR), 455 symptomatic aneurysms (143 open repair, 312 [69%] EVAR), and 552 ruptured aneurysms (263 open repair, 289 [52%] EVAR). Symptomatic AAAs had intermediate 30-day mortality compared with asymptomatic and ruptured aneurysms after both EVAR (1.4% asymptomatic vs 3.8% symptomatic [P = .001]; symptomatic vs 22% ruptured

[P < .001]) and open repair (4.3% asymptomatic vs 7.7% symptomatic [P = .08]; symptomatic vs 34% ruptured [P < .001]).

The first international comparative report of unselected patients with rAAA in England and the USA was presented by Karthikesalingam et al. (2014). Data from the Hospital Episode Statistics for England and the Nationwide Inpatient Sample for the USA for patients admitted to hospital with rAAA from 2005 to 2010 were compared. The study included 11,799 patients with rAAA in England and 23,838 patients with rAAA in the USA. In-hospital mortality was lower in the USA than in England (53.1% vs 65.9%). Intervention (open or endovascular repair) was offered to a greater proportion of cases in the USA than in England (19 174 [80.4%] vs. 6897 [58.5%]) and endovascular repair was more common in the USA than in England (20.9% vs. 8.5%]. Postintervention mortality was similar in both countries (41.8% for England and 41.7% for USA). In this study, in-hospital survival from rAAA, intervention rates, and uptake of endovascular repair were lower in England than in the USA. The authors concluded that outcomes in England might be improved by reductions in rates of non-corrective treatment and increases in provision of endovascular technology for rAAA.

Crucial for result comparison is the distinction between hemodynamically stable and unstable patients as has been shown by Gupta et al. (2014). Patients who underwent repair of rAAA were identified from the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database (2005–2010). Of 1447 patients with rAAA, 65.5% underwent OR and 34.5% EVAR. 45% of patients were unstable. The 30-day mortality rate was 47.9% (OR, 52.8%; EVAR, 35.6%) for unstable rAAAs and was 22.4% for stable rAAAs (OS, 26.3%; EVAR, 16.4%). Regardless of whether the patients were stable or unstable, they survived better with EVAR than after OR. Multivariable analyses showed OR was a predictor of 30-day mortality for unstable rAAA (odds ratio, 1.74) and stable rAAA (odds ratio, 1.64).

4.2.4 Special Issues

4.2.4.1 AAA Treatment in Centres and Surgeon Specialization

Sahni et al. (2016) tested the hypothesis of a specialization-outcomes relation independent of a surgeon's volume in that specific procedure. In this retrospective analysis of Medicare data 25,152 US surgeons who performed one of eight procedures (carotid endarterectomy, coronary artery bypass grafting, valve replacement, abdominal aortic aneurysm repair, lung resection, cystectomy, pancreatic resection, or esophagectomy) on 695,987patients in 2008–13 were included. For AAA repair they found surgeon specialization to be an important predictor of mortality. Surgeon specialization was defined as procedure specific volume divided by total operative volume across all procedures. The results showed that the observed specialization-outcomes relation was independent of the surgeon's volume in that specific

procedure. The absolute risk reduction in mortality from greater specialization was 2.8% (NNT 36 patients) for AAA repair.

In their comparison of long-term mortality after rAAA repair in England and Sweden Karthikesalingam et al. (2016) saw in both healthcare systems the best outcomes in hospitals with the highest annual procedural case load (volume) and with the greatest availability of EVAR. They claimed that patients with rAAA should be managed in specialist centres with a high annual case load and proficiency in weekend working. Dua et al. (2014b) completed a retrospective analysis using the Nationwide Inpatient Sample from 1998 to 2011. A total of 128,232 patients were identified, of which 88.5% were elective procedures and 11.5% were performed acutely for rupture. Hospitals that complete fewer than five OARs or eight EVARs annually had significantly greater mortality compared with their counterparts. These are small case targets. In an analysis of Sidloff et al. (2014) Hospital Trusts in the UK meeting the National Health Service Standard Contract for Specialized Vascular Services in Adults (NHSSCSVS) target of more than 60 AAA repairs per year had a significantly lower elective AAA mortality rate (1.7% vs. 2.7%). However, 107 hospital Trusts (92.2%) did not meet all the NHSSCSVS targets of more than 60 AAA repairs and 50 CEAs per year, and at least six vascular surgeons per unit. The data supported a standard of more than 60 elective AAA repairs per Trust per year. Centralized care of patients with rAAA improved also in the region of Amsterdam the results. The overall regional admission survival rate, including both rejected patients and those operated on, was 58.5%. The admission survival rate in the vascular centres was 61.4% and that in the referring hospitals was 37% (van Beek et al. 2014). Karthikesalingam et al. (2014) compared mortality from rAAA in England and the USA: compared with non-teaching institutions, mortality, and non-corrective treatment rate was lower at teaching institutions in both countries, while EVAR was more prevalent in teaching institutions than in non-teaching institutions. In both countries, mortality and non-corrective treatment rates were better in hospitals with the highest bed capacity. Ozdemir et al. (2015) analyzed a total of 9877 patients with rAAA admitted to 153 hospital Trusts in England during 2005–2010. The overall (operative and non-operative) mortality rate at 90 days was 67.5%. The main finding of this study was that the 90-day mortality risk of patients admitted with rAAA was lower in teaching hospital Trusts with greater medical and nurse staffing, greater use of radiodiagnostics and with weekday admission, after adjusting for provider volume. These same factors were associated with a greater tendency towards intervention, rather than palliation of patients with rAAA. Hicks et al. (2015) conducted a retrospective analysis of the American College of Surgeons National Surgical Quality Improvement Program database on all patients undergoing elective OR or EVAR from July 1, 2010, to November 30, 2012. Data on 11,250 patients (2466 underwent OR and 8784 underwent EVAR) were analyzed. Overall 30-day mortality was 14.0% for OR and 4.3% for EVAR. Thirty-day mortality for OR was similar at academic hospitals compared with community hospitals (13.5% vs 14.9%). For both academic and community hospitals, mortality for OR was inversely associated with hospital size, with mortality increasing significantly as hospital size

decreased. Thirty-day mortality for EVAR was significantly lower at academic hospitals compared with community hospitals (2.6% vs 11.2%). In contrast with OR, there was no significant association between mortality and hospital size for EVAR at either academic or community hospitals.

The question therefore arises whether patients with rAAA should be transferred to a higher level of medical care. Mell et al. (2014) compared patients transferred for treatment of rAAAs with those treated without transfer, with particular emphasis on mortality and resource utilization. Of 4439 rAAA patients identified with intent to treat, 847 (19.1%) were transferred before receiving operative repair. Of those transferred, 141 (17%) died without undergoing AAA repair. Transfer was associated with a lower operative mortality but an increased overall mortality when including transferred patients who died without surgery. In addition, transferred patients used significantly more hospital resources. In this study, transfer was of limited benefit. In contrast, Warner et al. (2016) emphasized that care of r-AAA in the US should be centralized to centers equipped with available technology and vascular surgeons. In their retrospective study 451 patients with r-AAA were treated from 2002 to 2015. Three-hundred and twenty-one patients (71%) presented initially to community hospitals (CHs) and 130 (29%) presented to the tertiary medical center (MC). Of the 321 patients presenting to CH, 133 (41%) were treated locally (131 OR; 2 EVAR) and 188 (59%) were transferred to the MC. In total, 318 patients were treated at the MC (122 OR; 196 EVAR). At the MC, r-EVAR was associated with a lower mortality rate than r-OR (20% vs 37%, P = 0.001). Transfer did not influence r-EVAR mortality (20% in r-EVAR presenting to MC vs 20% in r-EVAR transferred). Overall, r-AAA mortality at the MC was 20% lower than CH (27% vs 46%). Regionalization of r-AAA repair to centers equipped for both r-EVAR and r-OR decreased mortality by approximately 20%.

4.2.4.2 Risk Stratification

Risk-adjusting published surgical outcome data is essential if fair comparisons between surgeons and hospitals are to be made, and inappropriate risk-averse clinical decisions avoided. Dua et al. (2015) developed a scoring system to estimate mortality in elective abdominal aortic aneurysms management. The Nationwide Inpatient Sample from 1998 to 2011 was used. Twenty-eight thousand, four-hundred and fourty-eight patients underwent elective repair of unruptured AAA of which 414 (1.5%) patients died during their hospital stay. Factors were identified as disproportionately contributing to patient mortality (age >60, female gender, congestive heart failure, peripheral artery disease, renal failure, malnutrition, and hypercoagulability). Conversely, the endovascular procedure was associated with reduced mortality. Grant et al. (2014) validated the British Aneurysm Repair (BAR) score, Medicare, and Vascular Governance North West (VGNW) models (Table 4.3) using an independent prospectively collected sample of multicentre clinical audit data. One thousand, one-hundred and twenty-four patients undergoing elective AAA repair at 17 hospitals in the north-west of England and Wales were analyzed.

Table 4.3 Contemporary risk scores for mortality following elective abdominal aortic aneurysm repair

BAR score	Medicare	VGNW
Open repair	Open repair	Open repair
Age (continuous)	Age (grouped)	Age (continuous)
Female sex	Female	Female
Creatinine > 120 μmol/L	Chronic renal disease	Creatinine (continuous)
Cardiac disease	End-stage renal disease	Diabetes
Abnormal ECG	Cardiac failure	Anti-platelet medication
Previous aortic surgery/stent	Vascular disease	Respiratory disease
Abnormal white cell count		
Abnormal sodium		
AAA diameter (cm)		
ASA grade (I-IV)		

By Grant et al. (2014)
Risk factors included in in the British Aneurysm Repair (BAR) Score, Medicare model, and Vascular Governance Northwest (VGNW) model

All three models demonstrated good calibration and discrimination for the prediction of in-hospital mortality following elective AAA repair and are potentially useful. The BAR score had a number of advantages, which include being developed on the most contemporaneous data, excellent overall discrimination, and good performance in procedural subgroups. Van Beek et al. (2015) assessed the performance of four prediction models: the updated Glasgow Aneurysm Score (GAS), the Vancouver scoring system, the Edinburgh Ruptured Aneurysm Score (ERAS), and the Hardman index in all consecutive surgically treated patients with a rAAA in the Amsterdam ambulance region between May 2004 and February 2011. In 57%, the pre-operative ECGs were missing. Therefore, the Hardman index was excluded from the analysis. The updated GAS predicted death most accurately for both discrimination and calibration. However, the updated GAS did not identify patients with a ≥95% predicted death rate, and therefore cannot reliably support the decision to withhold intervention. The updated GAS score was calculated with the formula: age (years) +7 for cardiac comorbidity (defined as previous history of myocardial infarction, cardiac surgery, angina pectoris or arrhythmia) +10 for cerebrovascular comorbidity (defined as previous history of stroke or transient ischemic attack) +17 for shock (defined as an in hospital systolic blood pressure < 80 mmHg) +14 for renal insufficiency (defined as a pre-operative serum creatinine >160 mmol/L) +7 for OR.

4.2.4.3 EVAR – Totally Percutaneous Versus Standard Femoral Artery Access

A Cochrane review compared the clinical outcomes of percutaneous access with standard femoral artery access in elective EVAR (Jackson et al. 2014). Only one trial met the inclusion criteria, involving a total of 30 participants, which did not

provide adequate evidence to determine the efficacy and safety of the percutaneous approach. However, surgery time was shorter with percutaneous access. Since then, the so-called PEVAR trial ("percutaneous endovascular aortic aneurysm repair") was published (Nelson et al. 2014). In this randomized multicenter trial, a total of 151 patients were allocated by a 2:1 design to percutaneous access/closure (n = 101) or open femoral exposure (n = 50). This trial demonstrated non-inferiority of the percutaneous technique compared to the open access with a significantly shorter procedure time and in trend with decreased blood loss and pain. In a further study, 50 patients were treated with PEVAR and 96 patients were treated with surgical cut down (Ichihashi et al. 2016). Technical success was obtained in all patients in the PEVAR group. One patient in the surgical cut down group needed surgical repair due to access site bleeding. Complication rates were similar between both groups. Again, the PEVAR group had significantly shorter surgery times and a shorter length of stay. The advantage of the shorter operation time is, however, counterbalanced by the additional costs of the device.

4.2.4.4 Balloon Occlusion of the Aorta with rAAA

Proximal aortic control by endovascular balloon occlusion (EBO) is an alternative to conventional aortic cross-clamping (CAC) in hemodynamically unstable patients presenting with a rAAA. Raux et al. (2015) treated 72 hemodynamically unstable patients with rAAA. CAC was performed in 40 and EBO in 32 patients. Regaining intraoperative hemodynamic stability was achieved in only 57% of CAC patients vs 85% of EBO patients, and intraoperative mortality was 43% in the CAC group vs 19% in the EBO group. However, there was no significant difference in 30-day (75% vs 62%) and in-hospital (77% vs 69%) mortality rates between groups.

4.2.4.5 EVAR in Young Patients

The role of EVAR in young patients is controversial because of concerns about durability, reinterventions, surveillance requirements, and lack of an early survival advantage. Lee et al. (2015) reported a cohort of 169 patients 60 years of age or younger who underwent elective repair (119 open repair, 50 EVAR). There were three in-hospital deaths (2.5%) in the open repair group and none in the EVAR group. Kaplan-Meier survival analysis showed that the survival rate at 5 years (EVAR, 86% vs open repair, 88%), and 10 years (EVAR, 54% vs open repair, 75%) did not differ between EVAR and open groups. Most common causes of long-term mortality were malignant disease and cardiovascular-related deaths. There were no aneurysm ruptures or late aneurysm-related deaths in either repair group. The study showed that younger patients who undergo elective EVAR have survival, durability, and reintervention rates similar to those of open repair patients as long as aneurysm anatomy is considered and endograft instructions for use are strictly adhered to. Sandford et al. (2014), too, questioned whether young patients are better served

with endovascular or open repair of an abdominal aortic aneurysm in the elective setting. There were 99 OR and 59 EVAR patients aged 65 years or younger who underwent aneurysm repair. There was one perioperative (<30 days) death after OR and no deaths after EVAR. Fifteen (15%) patients suffered a complication after OR and seven (12%) after EVAR. Most complications encountered following EVAR were endoleaks; however, in contrast to this, the group undergoing OR experienced more significant cardiorespiratory complication. Mean overall follow-up was 93.3 months in the OR group and 35.4 months in the EVAR group. The reintervention rate was 14% among the EVAR, approximately 50% of these were for high-risk endoleaks and were dealt with via endovascular means. The reintervention rate among the group undergoing elective OR was 7% and most of these patients had developed incisional hernia, which were subsequently repaired. This data, too, support the use of EVAR in younger patients.

4.2.4.6 Bowel Ischemia After AAA Repair

Ultee et al. (2016) assessed the incidence of postoperative bowel ischemia after AAA repair. All patients undergoing intact or ruptured AAA repair in the Vascular Study Group of New England (VSGNE) between January 2003 and November 2014 were included in this analysis. There were 7312 patients, with 6668 intact (67.0% EVAR) and 644 ruptured AAA repairs (31.5% EVAR). The incidence of bowel ischemia after intact repair was 1.6% (open repair, 3.6%; EVAR, 0.6%) and 15.2% after ruptured repair (open repair, 19.3%; EVAR, 6.4%). Ruptured AAA was the most important determinant of postoperative bowel ischemia (odds ratio, 6.4), followed by open repair (odds ratio, 2.9). Bowel ischemia patients compared with no bowel ischemia had a significantly higher perioperative mortality after intact (open repair: 20.5% vs 1.9%; EVAR: 34.6% vs 0.9%) as well as after ruptured AAA repair (open repair: 48.2% vs 25.6%; EVAR: 30.8% vs 21.1%).

4.2.4.7 Reinforcement of Midline Laparotomies for AAA

Muysoms et al. (2016) conducted a multicenter randomized trial on patients undergoing elective AAA repair through a midline laparotomy. In the study group, retromuscular mesh-augmented reinforcement (MAR) was performed with a large-pore polypropylene mesh. The primary endpoint was the incidence of incisional hernias at 2-year follow-up. A total of 120 patients were enrolled in the study, 114 received the allocated treatment and formed the intention-to-treat population. Operative and postoperative characteristics showed no difference in morbidity or mortality. The cumulative incidence of incisional hernias at 2-year follow-up after conventional closure was 28% versus 0% after MAR. No adverse effect related to MAR was observed, apart from an increased mean time to close the abdominal wall for MAR compared with the control group: 46 min (SD, 18.6) vs 30 min (SD, 18.5), respectively.

4.2.4.8 Rupture Rates of Untreated Large AAA

Parkinson et al. (2015) conducted a systematic review with the aim to determine the contemporary rupture rates of AAA >5.5 cm in patients unfit for repair at 5.5 cm. The search identified 11 studies suitable for inclusion. The overall incidence of ruptured AAA in patients with an AAA > 5.5 cm was 5.3% per year. Pooled risk of rupture was 3.5% for AAAs 5.5–6.0 cm, 4.1% for AAAs 6.1–7.0 cm, and 6.3% for AAAs >7.0 cm. Quoted yearly rupture rates were cumulative; that is, a 7.5-cm AAA would have a 63% 10-year risk of rupture. Emergency repair was offered to 32% of patients unfit for elective AAA repair, with an overall perioperative mortality of 58%. This meta-analysis showed that the rupture rate in patients with large aneurysms unfit for elective repair is lower than is commonly quoted. The risk of rupturing a large AAA was half that of death from any other cause during the combined study periods (19% vs 42%).

4.3 Conclusions for Clinical Practice

1. Patients with infrarenal or juxtarenal AAAs measuring 5.5 cm or larger should undergo repair to eliminate the risk of rupture
2. When selecting the surgical procedure, the patient preference should be taken into account. Although EVAR has the lower procedural mortality and morbidity, this advantage is not maintained over time. In the long-term course a higher rate of secondary interventions and aneurysm-related deaths were seen with EVAR, and the overall survival after EVAR and OR did not differ significantly. However, the trend is clear: registry data shows that now more than 70% of patients with an intact AAA are treated with EVAR.
3. EVAR is not inferior to OR in the repair of ruptured AAA in terms of short-term and mid-term survival at least in randomized trials. In retrospective studies EVAR even offers a survival advantage over open repair for non-elective aneurysm procedures. It is therefore recommended to choose the same technique for rAAA repair with which one is most familiar in the repair of iAAA. This suggests that endovascular repair should be used more widely for ruptured aneurysms.
4. There is a clear relationship between annual procedural case load and outcome. This means that patients, at least with rAAA, should be managed in specialist centres with a high annual case load and proficiency in weekend working.

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Chapter 5
Renal Artery Stenosis

5.1 Guidelines

5.1.1 American College of Cardiology Foundation/American Heart Association

For diagnostic studies to identify clinically significant renal artery stenosis (RAS) the following Class I recommendations are given (Anderson et al. 2013):

1. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of hypertension before the age of 30 years (Level of Evidence: B).
2. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of severe hypertension after the age of 55 years (Level of Evidence: B).
3. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the following characteristics: (a) accelerated hypertension (sudden and persistent worsening of previously controlled hypertension); (b) resistant hypertension (defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic); or (c) malignant hypertension (hypertension with coexistent evidence of acute end-organ damage, i.e., acute renal failure, acutely decompensated congestive heart failure, new visual or neurological disturbance, and/or advanced [grade III to IV] retinopathy) (Level of Evidence: C).
4. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with new azotemia or worsening renal function after the administration of an ACE inhibitor or an angiotensin receptor blocking agent (Level of Evidence: B).
5. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with an unexplained atrophic kidney or a discrepancy in size between the two kidneys of greater than 1.5 cm (Level of Evidence: B).

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6. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with sudden, unexplained pulmonary edema (especially in azotemic patients) (Level of Evidence: B).

For renal revascularization these guidelines recommend:
Asymptomatic Stenosis:

1. Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS (Class IIb recommendation/Level of Evidence: C).
2. The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven (Class IIb recommendation/Level of Evidence: C).

Hypertension:

1. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication (Class IIa recommendation/Level of Evidence: B).

Preservation of Renal Function:

1. Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney (Class IIa recommendation/Level of Evidence: B).
2. Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS (Class IIb recommendation/Level of evidence: C).

Impact of RAS on Congestive Heart Failure and Unstable Angina:

1. Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (Class I recommendation/Level of Evidence: B).
2. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina (Class IIa recommendation/Level of Evidence: B).

Endovascular Treatment for RAS:

1. Renal stent placement is indicated for ostial atherosclerotic RAS lesions that meet the clinical criteria for intervention (Class I recommendation/Level of Evidence: B).
2. Balloon angioplasty with bailout stent placement, if necessary, is recommended for fibromuscular dysplasia lesions (Class I recommendation/Level of Evidence: B).

Surgery for RAS:

1. Vascular surgical reconstruction is indicated for patients with fibromuscular dysplastic RAS with clinical indications for interventions (same as for percutaneous

transluminal angioplasty), especially those exhibiting complex disease that extends into the segmental arteries and those having macroaneurysms (Class I recommendation/Level of Evidence: B).
2. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS and clinical indications for intervention, especially those with multiple small renal arteries or early primary branching of the main renal artery (Class I recommendation/Level of Evidence: B).
3. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS in combination with pararenal aortic reconstructions (in treatment of aortic aneurysms or severe aortoiliac occlusive disease) (Class I recommendation/Level of Evidence: C).

5.1.2 European Society of Cardiology (ESC)

Recommendations for diagnostic strategies for RAS (Tendera et al. 2011):

- Duplex ultrasonography is recommended as the first-line imaging test to establish the diagnosis of RAS (Class I recommendation/Level of Evidence: B).
- In patients with a creatinine clearance >60 mL/min, CTA (computed tomography angiography) is recommended to establish the diagnosis of RAS (Class I recommendation/Level of Evidence: B).
- In patients with a creatinine clearance > 30 mL/min, MRA (magnetic resonance angiography) is recommended to establish the diagnosis of RAS (Class I recommendation/Level of Evidence: B).
- When the clinical index of suspicion is high and the results of non-invasive tests are inconclusive, DSA (digital subtraction angiography) is recommended as a diagnostic test (prepared for intervention) to establish the diagnosis of RAS (Class I recommendation/Level of Evidence: C).
- Captopril renal scintigraphy, selective renal vein renin measurements, plasma renin activity, and the captopril test are not recommended as useful screening tests to establish the diagnosis or RAS (Class III recommendation/Level of Evidence: B).

The therapeutic recommendations of the ESC include medical, endovascular, and surgical therapy. They differ only slightly from those of the AHA, and are framed more cautiously in regard to surgical and endovascular treatment. Whereas the AHA rates a therapy as indicated, the ESC deems it “worth considering”.

Medical therapy:

- ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers are effective medications for treatment of hypertension associated with unilateral RAS (Class I recommendation/Level of Evidence: B).
- ACE inhibitors and angiotensin II receptor blockers are contraindicated in bilateral severe RAS and in the case of RAS in single functional kidney (Class III recommendation/Level of Evidence: B).

Endovascular therapy:

- Angioplasty, preferably with stenting, may be considered in the case of >60% symptomatic RAS secondary to atherosclerosis (Class IIb recommendation/Level of Evidence: A).
- In the case of indication for angioplasty, stenting is recommended in ostial atherosclerotic RAS (Class I recommendation/Level of Evidence: B).
- Endovascular treatment of RAS may be considered in patients with impaired renal function (Class IIb recommendation/Level of Evidence: B).
- Treatment of RAS, by balloon angioplasty with or without stenting, may be considered for patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema and preserved systolic left ventricular function (Class IIb recommendation/Level of Evidence: C).

Surgical therapy:

- Surgical revascularization may be considered for patients undergoing surgical repair of the aorta, patients with complex anatomy of the renal arteries, or after a failed endovascular procedure (Class IIb recommendation/Level of Evidence: C).

5.1.3 Revascularization for Renal Artery Fibromuscular Dysplasia (FMD)

5.1.3.1 Scientific Statement from the American Heart Association

The AHA has published a statement regarding renal artery revascularization in patients with renal artery FMD (Olin et al. 2014). The authors found that randomized, controlled trials of revascularization versus medical therapy in patients with renal artery FMD have not been performed. The negative trials on stent implantation for atherosclerotic renal artery disease do not apply to patients with FMD given the differing pathophysiology and natural history of these two vascular disorders.

Indications for renal artery revascularization in patients with FMD are as follows:

- Resistant hypertension
- Hypertension of short duration with the goal of a cure of hypertension
- Renal artery dissection; rarely is intervention needed, but if so, stenting is generally the procedure of choice
- Renal artery aneurysm(s); surgical resection, endovascular coiling, or placement of a covered stent is usually used
- Branch renal artery disease and hypertension; some lesions can be treated with PTA, but if this is not possible, surgical revascularization may be required, often with bench repair

- Preservation of renal function in the patient with severe stenosis, especially in the pediatric population with perimedial or intimal fibroplasia.

In younger patients with recent onset of hypertension, percutaneous angioplasty may be considered first-line therapy with the goal of cure of hypertension. PTA offers many advantages over traditional surgical repair. It is less invasive and less expensive, has a lower morbidity, can be performed on an outpatient basis in many cases, and has a markedly reduced recovery time. Consequently, PTA of the renal artery is the procedure of choice for patients with renal artery FMD and hypertension in the appropriate clinical setting. However, there are patients in whom the expected outcome from surgery may be better than that expected with PTA. Examples include patients with small renal arteries (<4 mm), branch disease, especially when associated with aneurysms, or extensive intimal or perimedial fibroplasia. Secondary surgical repair after failed PTA should be considered early in the decision process before chronic ischemia leads to loss of cortical thickness.

5.1.3.2 European Consensus on the Diagnosis and Management of Fibromuscular Dysplasia

In hypertensive patients with FMD-related RAS, revascularization is recommended (Persu et al. 2014):

1. In the case of hypertension of recent onset, as a first-line treatment to normalize blood pressure.
2. In cases of medical treatment failure (drug resistance or intolerance).
3. In case of renal insufficiency or deterioration of renal function especially after administration of an angiotensin converting enzyme inhibitor, an angiotensin II receptor blocker or a renin inhibitor.
4. In case of renal size reduction downstream of the stenosis.

The two options available for renal artery revascularization are balloon PTA and renal artery surgery. It is impossible to reliably compare the results of both revascularization techniques because they are not performed in patients with similar characteristics. Furthermore, surgical revascularization has been performed for a longer time than PTA revascularization, and the assessment methods therefore also differ in series using surgery or PTA.

- In view of its less invasive character and of the large experience acquired, PTA without stenting is currently the first-line revascularization technique in FMD-related RAS. Indeed, there is no evidence of superiority of renal artery PTA followed by stenting vs. PTA alone in FMD patients. Furthermore, several cases of stent fracture have been reported in patients with renal FMD, possibly owing to an increased kinetic stress related to severe kidney ptosis. Accordingly, stenting is not indicated after primary PTA unless needed because of a significant per-procedural dissection.

- Surgery remains the primary approach for patients with complex lesions of arterial bifurcation or branches, stenoses associated with complex aneurysms, or following PTA failure.
- Cutting balloons, proposed by some authors as an alternative to surgery in case of PTA failure, are not recommended in patients with FMD because of the risk of renal artery rupture and subsequent pseudoaneurysm formation.

5.1.4 Addendum

The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension are (Daskalopoulou et al. 2015):

1. Renal artery stenosis (RAS) should be primarily managed medically.
2. Renal artery angioplasty and stenting could be considered for patients with RAS and complicated, uncontrolled hypertension.

Expert consensus statement for renal artery stenting appropriate use by the Society for Cardiovascular Angiography and Interventions (SCAI) (Parikh et al. 2014). Appropriate care of significant RAS:

- Cardiac Disturbance Syndromes (Flash Pulmonary Edema or acute coronary syndrome (ACS)) with severe hypertension.
- Resistant HTN (Uncontrolled hypertension with failure of maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic, or intolerance to medications).
- Ischemic nephropathy with chronic kidney disease (CKD) with eGFR < 45 cc/min and global renal ischemia (unilateral significant RAS with a solitary kidney or bilateral significant RAS) without other explanation.

5.2 Results

5.2.1 Endovascular Therapy

5.2.1.1 Systematic Reviews/Meta-analyses

Riaz et al. (2014) performed a meta-analysis to compare the efficacy of revascularization versus medical therapy in patients with atherosclerotic renal artery stenosis. Two thousand, one-hundred and thirty-nine patients were included in the final analysis. Angioplasty with or without stenting was not superior to medical therapy with respect to any outcome. The incidence of nonfatal myocardial infarction was 6.74% in both the stenting and medical therapy group, and incidence of renal events in stenting population was found to be 19.58% versus 20.53% in medical therapy

population. In conclusion, PTA +/− stent placement did not improve outcomes compared with medical therapy in patients with atherosclerotic RAS. Jenks et al. (2014) addressed the same question. They updated a Cochrane review first published in 2003. Eight randomized controlled trials, involving 2111 participants, comparing balloon angioplasty with medical therapy in hypertensive patients with haemodynamically significant renal artery stenosis (greater than 50% reduction in luminal diameter) and with a minimum follow-up of 6 months were included in this meta-analysis. They stressed that the available data are insufficient to conclude that revascularization in the form of balloon angioplasty, with or without stenting, is superior to medical therapy for the treatment of atherosclerotic RAS in patients with hypertension. However, balloon angioplasty results in a small improvement in diastolic blood pressure and a small reduction in antihypertensive drug requirements. Balloon angioplasty appears safe and results in similar numbers of cardiovascular and renal adverse events to medical therapy.

In a further updated meta-analysis with the CORAL Trial (including 8 studies in 2223 patients) renal artery revascularization was not associated with a change in systolic blood pressure from baseline when compared with medical therapy (Bavry et al. 2014). Mortality incidence was 14.0% for revascularization vs 15.3% for medical therapy (P = .37), hospitalization for heart failure was 9.4% vs 10.4% (P = .40), incidence for stroke was 4.1% vs 5.1% (P = .30), and for worsening renal function 15.3% vs 16.1% (P = .67), respectively. In conclusion, among patients with renal artery stenosis and hypertension and/or chronic kidney disease, revascularization was of marginal benefit. This therapy slightly reduced the need for antihypertensive medications. However, revascularization did not reduce adverse cardiovascular or renal outcomes compared with medical therapy over a mean follow-up of 34 months. This meta-analysis was commented as follows (Morgan et al. 2015): Do not perform renal artery revascularization in patients with clinically relevant RAS. Furthermore, testing for RAS has little benefit. Consistent randomized evidence shows that optimizing medical therapy is the best approach to management of hypertension and chronic kidney disease, with or without RAS.

In addition, Zhu et al. (2015) conducted a meta-analysis to evaluate the outcomes of percutaneous revascularization versus medication alone for atherosclerotic RAS. They came to an identical conclusion: percutaneous revascularization is equally effective to medical management in the treatment of RAS. Therefore, patients with atherosclerotic RAS along with hypertension or chronic kidney disease should receive medical therapy to control blood pressure, but they should not be considered for a renal artery stent.

5.2.1.2 Randomized Studies

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial was designed to determine reliably whether revascularization together with medical therapy improves renal function and other outcomes, as compared with medical therapy alone, in patients with atherosclerotic renal-artery stenosis (ASTRAL Investigators et al.

2009). A total of 806 patients were enrolled in this multicenter trial. The majority of patients had severe renal-artery stenosis (59% had stenosis of more than 70%) or clinically significant renal impairment (60% had a serum creatinine level of 150 μmol per liter [1.7 mg per deciliter] or more) or both. In the revascularization group, the procedure was attempted in 335 of the 403 patients (83%), with the procedure deemed to be a technical success in 317 of the 335 patients (95%). The primary outcome was renal function. Renal events were defined as a new onset of acute kidney injury, the initiation of dialysis, renal transplantation, nephrectomy, or death from renal failure. Secondary outcomes were blood pressure, the time to renal and major cardiovascular events, and mortality. The median follow-up was 34 months. A total of 38 periprocedural complications (defined as complications occurring within 24 h after the procedure) were reported in 31 of the 359 patients (9%) who underwent revascularization (including 1 of the 24 patients in the medical-therapy group who crossed over to revascularization). Nineteen of these events (in 17 patients) were considered to be serious complications. In this trial, no evidence of a worthwhile clinical benefit in the initial years after revascularization in patients with atherosclerotic RAS was seen. Revascularization carried substantial risk but was not associated with any benefit with respect to renal function, blood pressure, renal or cardiovascular events, or mortality.

Another randomized study (Bax et al. 2009) included substantially less participants. One-hundred and forty patients with creatinine clearance less than 80 mL/min per 1.73 m^2 and atherosclerotic RAS of 50% or greater were randomly assigned to undergo renal artery stent placement combined with medical treatment or medical treatment only. The primary end point was worsening of renal function. No statistically significant difference in progression of renal failure over 2 years in those treated with stenting and medication compared with those treated with medication only were found. However, a considerable number of stent-related complications occurred, including 2 procedure-related deaths, 1 death secondary to an infected hematoma and 1 case of deterioration of renal function resulting in dialysis, suggesting that renal stenting for RAS may cause more harm than benefit in a community setting.

Marcantoni et al. (2012) tested the effect of renal artery stenting versus medical therapy on left ventricular hypertrophy progression in patients affected by ischemic heart disease and RAS in a randomized clinical trial with 84 patients. After 1 year, there was no statistically significant difference between the medical therapy group vs medical therapy + revascularization group for left ventricular mass index, blood pressure, or estimated glomerular filtration rate. The number of major cardiovascular events was similar in the two groups. A clinically significant benefit of renal revascularization was not detected.

The randomized controlled Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study (Cooper et al. 2014) compared medical therapy alone with medical therapy plus renal-artery stenting in patients with atherosclerotic RAS and elevated blood pressure, chronic kidney disease, or both. The primary end point was the occurrence of a major cardiovascular or renal event — a composite of death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for

permanent renal-replacement therapy. Nine-hundred and forty-seven patients were randomly assigned to stenting plus medical therapy (467 patients) or medical therapy alone (480 patients). Over a median follow-up period of 43 months, no benefit of stenting with respect to the rate of the composite primary end point or any of its individual components, including death from cardiovascular or renal causes, stroke, myocardial infarction, congestive heart failure, progressive renal insufficiency, and the need for renal-replacement therapy was seen. This result was consistent across all prespecified subgroups, including patients with global renal ischemia and patients with other high-risk characteristics. A modest, but statistically significant, reduction of 2 mmHg in systolic blood pressure with stenting was observed, but this reduction did not translate into a reduction in clinical events. In summary, renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic RAS and hypertension or chronic kidney disease. Essential findings of this largest randomized clinical trial comparing the effects of stenting and optimal medical therapy alone in patients with RAS and hypertension and/or chronic kidney disease are shown in Table 5.1.

One of the criticisms of the CORAL study and the other clinical trials has been the inclusion of patients with milder degrees of hypertension, for whom it might be difficult to see a benefit of stenting. Murphy et al. (2015) therefore performed post-hoc exploratory analyses of the CORAL trial to determine if subsets of patients experienced better outcomes after stent placement than the overall cohort. Variables that were tested included the presence or absence of bilateral RAS or RAS with a

Table 5.1 Stenting and medical therapy for atherosclerotic RAS

End point	Stenting plus medical therapy (n = 459) no. (%)	Medical therapy only (n = 472) no. (%)
Primary end point[a], first event	161 (35.1)	169 (35.8)
Components of primary end point:		
Death from cardiovascular or renal causes	20 (4.4)	20 (4.2)
Stroke	12 (2.6)	16 (3.4)
Myocardial infarction	30 (6.5)	27 (5.7)
Hospitalization for CHF	27 (5.9)	26 (5.5)
Progressive renal insufficiency	68 (14.8)	77 (16.3)
Permanent renal-replacement therapy	4 (0.9)	3 (0.6)
Secondary clinical end points		
Death from any cause	63 (13.7)	76 (16.1)
Death from cardiovascular causes	41 (8.9)	45 (9.5)
Death from renal causes	2 (0.4)	1 (0.2)

Adopted from Cooper et al. 2014.
Clinical outcomes from the randomized trial/median follow-up 43 months
[a]Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure (CHF), progressive renal insufficiency, or permanent renal-replacement therapy

single functioning kidney, baseline systolic blood pressure, maximal renal artery percent diameter stenosis, and translesion pressure gradient (peak systolic and mean). There were no statistically significant differences in outcomes based on the examined variables nor were there any consistent nonsignificant trends. In conclusion, the CORAL study data does not support a benefit of stenting based on degree of stenosis, hemodynamic significance of the lesion, or higher pre-treatment blood pressure.

In the CORAL trial, a history of congestive heart failure (CHF) was present at enrollment in 123 of 931 subjects, 69 in the medical therapy group and 54 in the medical therapy+stenting group (Yu et al. 2015). Neither the composite event rate (41% vs. 48%), rate of CHF admission (20% vs. 26%) nor the rate of cardiovascular death (16% vs. 17%) differed between medical therapy only and the stent+medical therapy groups. At 2-years follow-up no differences were observed between medical therapy and medical therapy+stent for systolic blood pressure (136±26 vs. 136±18 mmHg) or eGFR (56±23 vs. 56±23 ml/min). Renal artery stenting and optimal medical therapy, when compared to optimal medical therapy only, did not reduce the risk of fatal and nonfatal cardio-renal events in patients that were enrolled with history of congestive heart failure in the CORAL trial. Furthermore, stent treatment of CHF patients did not affect kidney disease progression or blood pressure control.

Critics claim that the randomized clinical trials are flawed, and that with appropriate patient selection renal artery intervention improves patient outcomes. The most frequent criticisms are that prior randomized trials enrolled subjects with RAS that were not hemodynamically or clinically significant or excluded patients with uncontrolled hypertension, or alternatively that patient selection should have been done using translesional arterial pressure gradients. There were patients that were intentionally excluded in CORAL, such as those with advanced chronic kidney disease, a population that was underrepresented in the CORAL study generally (Murphy et al. 2015). Mohan and Bourke (2015) assessed the ASTRAL and CORAL trials and found that the question: "What is the influence of intervention in patients with severe high grade RAS and severe hypertension?" has not been answered in the CORAL trial. They suggested that single-centre trials and observational studies still support intervention for patients with RAS of >80% with a significant translesional pressure gradient; difficult to control blood pressure with more than three antihypertensives, especially in younger patients; and those with truncal rather than ostial stenosis; patients with a rapid deterioration of renal function; flash pulmonary oedema; and post-transplant RAS. In a further review analyzing the current literature Mousa et al. (2015) came to the recommendation that RAS stenting should be offered to patients with truly resistant hypertension (systolic blood pressure > 150 mm Hg measured by strict guidelines, patient receiving more than three blood pressure medications including a diuretic if tolerated) and hemodynamically significant RAS based on angiography (>80% stenosis) or hemodynamic assessment (>24 mm Hg systolic gradient). RAS stenting should be offered only in experienced centers with low mortality and morbidity.

5.2.1.3 Uncontrolled Studies

The prospective, uncontrolled multicenter HERCULES trial enrolled 202 patients with atherosclerotic RAS and uncontrolled hypertension (Chrysant et al. 2014). Procedural complication rate was 1.5%. At 36 months, freedom from death, nephrectomy, and target lesion revascularization were 90.1%, 100%, and 91.8%, respectively. The mean systolic blood pressure decreased from 162 ± 18 mm Hg to 146 mm Hg post procedure and through 36 months. HERCULES demonstrated that the procedure is safe. The single-arm, nonrandomized design, however, makes it difficult to make any further conclusions.

Restenosis and need for secondary intervention after renal artery stenting continue to be a frequent and significant limitation to the percutaneous treatment of RAS. Simone et al. (2013) evaluated retrospectively the outcomes of endovascular treatment of recurrent RAS. Sixty-five secondary (57 patients) renal interventions were undertaken for recurrent RAS associated with progressive hypertension or renal dysfunction and compared with outcomes after 216 primary (180 patients) renal artery stenting procedures. Primary and secondary interventions showed no difference in procedural complications. At a mean follow-up of 23 months, similar improvements in renal function and blood pressure were found between patients undergoing primary and secondary interventions. Restenosis rates were similar after secondary and primary interventions at 1 year (13% secondary vs 16% primary) and 3 years (50% secondary vs 59% primary). The findings showed that secondary interventions can be undertaken with expectations for clinical improvement that are similar to primary interventions.

Short and long-term outcomes of 43 endovascular procedures in 35 patients with RAS due to FMD were reported by Mousa et al. (2012). Thirty-two patients (91%) were women, with mean age of 61.9 years. Standard was to perform balloon angioplasty alone, and to only perform stenting of the lesion for bail-out if significant recoil failed to respond to prolonged inflation, in cases of associated aorto-ostial atherosclerotic disease, or in response to vessel dissection. Procedural success was 100% with provisional stent placement in one (2.3%) for dissection and four (9.3%) for concomitant renal artery ostial atherosclerosis. The majority of patients (69%) had an immediate clinical benefit for hypertension, 6% were cured requiring no antihypertensive medications, and 63% improved with less than or equal to preoperative blood pressure medications. The average length of follow-up was 4.8 ± 0.5 years. Compared to baseline measurements, long-term follow-up revealed a significant drop of systolic and diastolic blood pressure, systolic mean from 166.8 to 142.6 and diastolic mean from 84.1 to 76.5. Long-term renal function (GFR) was higher during follow-up, but not significantly. Primary patency was 95%, 71%, and 50% at 1, 5, and 9 years, respectively. The authors concluded that PTA for symptomatic RAS due to FMD should be the initial intervention. Surgical revascularization may be necessary when FMD is accompanied by large aneurysmal changes, but should otherwise be limited to patients who fail or do not meet the requirements for angioplasty.

Protection of renal parenchyma is a goal of therapy in renal interventions for symptomatic atherosclerotic RAS. Davies et al. (2010) examined retrospectively the impact of renal artery intervention on parenchymal preservation. Failure of preservation was considered to be a persistent 10% decrease in renal volume in two consecutive scans, which is equivalent to 1 cm decrease of a 9 cm kidney. Five-hundred and ninety-two renal artery interventions were performed. Thirty-one percent of the kidneys suffered parenchymal loss in follow-up (median 4.5 years). Parenchymal loss was associated with significantly worse 5-year survival (26% ± 4% vs 48% ± 2%; loss vs no loss) and with significantly worse freedom from renal-related morbidity (70% vs 82%) and with progression to hemodialysis.

5.2.2 Endovascular vs. Open Surgery for Treatment of RAS

5.2.2.1 Fibromuscular Dysplasia

Trinquart et al. (2010) performed a systematic review and meta-analysis of studies in which hypertensive patients with FMD renal artery stenosis underwent percutaneous transluminal renal angioplasty or surgical reconstruction. They selected 47 angioplasty studies (1616 patients) and 23 surgery studies (1014 patients). For PTA, they calculated a complication rate of 11.8% (major complication rate 6.3%) with a mortality risk of 0.9%. The rates of puncture site and kidney complications were 3.4% and 8.3%, respectively. For open surgery, they reported a higher combined complication rate of 16.9% (major complication rate 15.4%) with an estimated risk of death of 1.2%. The combined cure rate from hypertension by PTA was 45.7%, whereas open surgery provided a combined hypertension cure rate of 57.5%. However, if hypertension cure was defined as blood pressure below 140/90 mmHg without medical therapy, cure rates were only 36% (PTA) or 54% (open surgery). Patients with long-standing hypertension and older patients were less likely to benefit from renal revascularization. Meta-regression analyses showed that the probability of hypertension cure tended to decrease with increasing mean age (odds ratio associated with an increase in mean age of 10 years: 0.84). Given the young age of patients (mean age in PTA group was 42 years and in open surgery group 36 years) and the normal renal function in virtually all patients, the authors of this review did not find the results to be convincing. Most patients currently undergo PTA rather than surgery. Considering that only 1 patient in 3 has normal blood pressure after PTA with a 12% risk of complication, a randomized trial comparing PTA with medical treatment for FMD should be considered.

5.2.2.2 Registry Data

Liang et al. (2013) used the US Nationwide Inpatient Sample, 1988–2009, to identify patients with a diagnosis of renal artery atherosclerosis undergoing open surgical repair (bypass or endarterectomy) or PTA/Stent. The rate of interventions, in-hospital death, and perioperative outcomes were analyzed over time. There were 308,549

PTA/Stent and 33,147 open surgical repairs for patients with renal atherosclerosis and 6706 PTA/Stent and 595 open surgical repairs for patients with FMD. PTA/Stent interventions increased substantially from 1988 to 2006 (1.9 to 13.7 procedures per 100,000 adults), followed by a marked decrease from 2006 to 2009 (13.7 to 6.7 procedures per 100,000 adults), whereas the number of open repairs gradually decreased throughout the study period (1.3 to 0.3 procedures per 100,000 adults). From 2005 to 2009, 20,759 patients in the state inpatient databases (of New Jersey, Maryland, Florida, and California) and 13,194 patients in the state ambulatory surgery databases underwent PTA/Stent for a diagnosis of renal artery atherosclerosis. The number of PTA/Stent performed in the outpatient setting remained stable from 2005 (3.8/100,000) to 2009 (3.7/100,000), whereas the total number of inpatient procedures declined from 2006 (7.9/100,000) to 2009 (4.2/100,000). The percentage of outpatient procedures increased from 36% in 2005 to 47% in 2009. PTA/Stent had lower overall in-hospital mortality compared with open repair (0.9% vs 4.1%). The change in the rate of treatment for patients with FMD was similar to that seen for patients with renal atherosclerosis. The number of PTA/Stent interventions increased from 1994 to 2006 (0.1 to 0.3 procedures per 100,000 adults) and decreased from 2006 to 2009 (0.3 to 0.1 procedures per 100,000 adults). In patients with renal FMD, in-hospital mortality was significantly lower after PTA/Stent compared with open repair (1.6% vs 7.8%). In conclusion, interventions for RAS have declined since 2006, likely because in part of a lack of demonstrated benefit in RCTs. Analysis have shown that this decrease in PTA/Stent seen in the NIS database is only found in the inpatient setting while outpatient procedures have remained stable. Nevertheless, PTA/Stent remained the dominant procedural option compared with open interventions because of its lower rate of mortality and morbidity.

5.3 Conclusions for Clinical Practice

1. Optimizing medical therapy is the best approach to management of hypertension and chronic kidney disease, with or without RAS. Renal artery angioplasty and stenting may be considered for patients with RAS and complicated, uncontrolled hypertension.
2. PTA +/− stenting has widely superseded open surgical repair for RAS due to its lower rate of mortality and morbidity.
3. Clinical scenarios for surgical revascularization include patients with complex anatomy of the renal arteries, patients undergoing surgical repair of the aorta, or revascularization after a failed endovascular procedure.
4. In hypertensive patients with FMD-related RAS, revascularization is recommended in the case of hypertension of recent onset, as a first-line treatment to normalize blood pressure or in cases of medical treatment failure (drug resistance or intolerance).
5. PTA without stenting is currently the first-line revascularization technique in FMD-related RAS.

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Chapter 6
Visceral Artery Aneurysms (Including Renal Artery Aneurysms)

6.1 Guidelines

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) practice guidelines recommend (Anderson et al. 2013):

- Open repair (OR) or catheter-based intervention [endovascular repair, ER] is indicated for visceral aneurysms measuring 2.0 cm in diameter or larger in women of childbearing age who are not pregnant and in patients of either gender undergoing liver transplantation. (Class I, Level of Evidence: B)
- Open repair or catheter-based intervention is probably indicated for visceral aneurysms 2.0 cm in diameter or larger in women beyond childbearing age and in men. (Class IIa, Level of Evidence: B)

Renal and splanchnic artery aneurysms are rare conditions, an incidence of 0.01–0.09% and 0.1–2%, respectively has been reported (Cordova and Sumpio 2013). Due to the lack of prospective studies on this topic there is no standardized consensus regarding the indications for treatment of visceral artery aneurysms (VAAs). Generally, however, VAAs are treated if symptomatic, are larger than 2 cm in a good-risk surgical candidate, have a rapid growth of more than 0.5 cm/year, when present in a pregnant women or those of childbearing age, or in patients undergoing an orthotopic liver transplantation.

6.2 Results

6.2.1 Endovascular Repair

Fankhauser et al. (2011) reported a large series of VAAs and pseudoaneurysms treated by minimally invasive techniques. Minimally invasive management was attempted in 185 aneurysms in 176 patients. The aneurysms were mainly located in

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the splenic artery (34%), the hepatic artery (30%), the gastroduodenal artery (15%), and in the pancreaticoduodenal artery (8.6%). The most commonly used technique was coiling (162 aneurysms). It was the sole interventional technique employed in 144 (78%) of cases. Initial treatment was successful in 182 (98%) aneurysms. During repeat imaging within the first 30 days, persistent aneurysm flow was seen in five (3%) aneurysms, and subsequent successful reintervention was undertaken. There were 11 deaths in the initial 30-day period leading to an overall 30-day mortality rate of 6.2%. Aneurysm related 30-day mortality rate was 3.4%. Neither aneurysm growth nor aneurysm rupture was observed in any patient during the follow-up period (mean, 78 weeks). Major splenic infarction occurred in three of 33 patients (9%) with no underlying liver disease and normal splenic volume and in seven of 14 patients (50%) with portal hypertension.

A single-center experience with elective coil embolization of 63 splenic artery aneurysms (SAA) in 50 patients was presented by Patel et al. (2012). Ninety-eight percent of procedures were technically successful at thrombosing the aneurysm at the time of procedure. Neither aneurysm growth nor aneurysm rupture was observed in any patient during the follow-up period (mean, 78 weeks). There were no major adverse events. Major splenic infarction occurred in three of 33 patients (9%) with no underlying liver disease and normal splenic volume and in seven of 14 patients (50%) with portal hypertension. Etezadi et al. (2011) presented early and midterm results of endovascular treatment of 41 visceral and renal artery aneurysms in 40 consecutive patients. The series included 30 true aneurysms and 11 pseudoaneurysms in renal (n = 17), splenic (n = 13), hepatic (n = 4), celiac (n = 4), gastroduodenal (n = 2), and middle colic (n = 1) arteries. The most commonly used technique (93%) was coil embolization with (15%) or without (78%) other endovascular agents. Technical success rate was 98%, with no periprocedural mortality. Mean imaging follow-up was 11.7 months. End-organ partial infarction was detected in six patients, with no clinical evidence of organ insufficiency. Koganemaru et al. (2014) evaluated the outcomes of coil embolization of true visceral artery aneurysms in 23 patients. Complete aneurysmal occlusion was determined in 22 patients (96%) on follow-up MR angiography (mean follow-up period, 18 months). An asymptomatic localized splenic infarction was confirmed in one patient (4%). The correlation between packing density and the incidence of coil compaction or recanalization of VAAs after coil packing was evaluated by Yasumoto et al. (2013). Coil packing was performed for 46 true visceral aneurysms. The mean follow-up period was 37 months. Recanalization occurred in 12 aneurysms (26%). In aneurysms with a packing density of at least 24%, no compaction or recanalization occurred. Balderi et al. (2012) used an endovascular approach to treat 30 patients with 31 aneurysms (n = 18) or pseudoaneurysm (n = 13) of the splenic (n = 11), hepatic (n = 6), renal (n = 5), pancreaticoduodenal (n = 3), left gastric (n = 2), gastroduodenal (n = 1), rectal (n = 1) or middle colic (n = 1) arteries and the coeliac axis (n = 1). 26/31aneurysms were treated with metal coils. In all aneurysms and pseudoaneurysms immediate exclusion was obtained. In four patients with aneurysm and in four with pseudoaneurysm, parenchymal ischaemia occurred; one was treated with surgical splenectomy. One

patient with pseudoaneurysm of the coeliac axis died 10 days later because of new bleeding. During follow-up (12 months), all aneurysms and pseudoaneurysms remained excluded.

Dorigo et al. (2016) performed 26 consecutive elective endovascular interventions for VAAs. The site of aneurysm was splenic artery in 17 patients. Interventions consisted in coiling in 19 cases; in 4 patients a covered stent was placed, whereas the remaining 3 patients had a multilayer stent. Technical success was 89%. There were no perioperative deaths. Median duration of follow-up was 18 months. During follow-up, 1 aneurysm-unrelated death occurred. Freedom from aneurysm-related complications at 2 years was 72.9%. Nineteen consecutive patients with a total of 19 visceral artery aneurysms were electively (n = 9) or emergently (n = 10) treated with a variety of stent-grafts by Künzle et al. (2013). The in-hospital mortality rate was 11% (n = 2). CT angiography (CTA) demonstrated stent-graft patency at a mean follow-up of 28 months in 9 of 11 patients (82%) and thrombosis in two patients (one with a splenic and one with a renal artery stent-graft). These events were asymptomatic. Gandini et al. (2016) excluded 10 renal artery aneurysms (RAA) in 9 patients using covered stents. CTA up to 24 months after ER demonstrated patency of the cover stents, absence of endoleaks and re-stenosis in all patients.

Roberts et al. (2015) reviewed all patients undergoing emergency treatment (endovascular or surgical) of a symptomatic VAA in a 5-year period. Patients with RAA were not included in this study. Symptomatic VAAs were defined as those presenting with gastrointestinal haemorrhage (haematemesis, malaena, or haemobilia) and peritoneal or retroperitoneal haemorrhage due to the presence of the VAA. Interventional radiology was the initial treatment in all patients: endovascular procedures n = 47 and ultrasound guided percutaneous injection n = 1 (of an intrahepatic VAA). The initial success was 40 out of 48 (83%). Surgical intervention was required in two patients (4%). The 30-day mortality was eight out of 48 (17%).

Guo et al. (2016) reviewed the outcomes of symptomatic visceral artery aneurysms (SVAAs) and asymptomatic visceral artery aneurysms (ASVAAs) after endovascular treatment. In total, 27 patients with SVAA (mean diameter, 36.9 ± 15.3 mm) and 79 patients with ASVAA (mean diameter, 33.6 ± 36.1 mm) were treated. The most common intervention type was coil embolization (81%), followed by stent-assisted embolization (10%) and covered stent repair (9%). The immediate technical success rates of SVAA and ASVAA repair were 96.3% and 97.5%, respectively. The most common complication after endovascular treatment was end-organ ischemia (11.1% for SVAA vs 13.9% for ASVAA). Partial liver infarction was noted in two cases, and partial or complete splenic infarction was noted in five cases. None of these infarctions caused clinically significant complications within the first 30 days. The overall mortality rate for VAA was 6.6% (7/106), and the direct and indirect aneurysm-related mortality rate was 3.8% (4/106) during the first 30-day period and follow-up. All of the deaths occurred in the SVAA group. The median duration of follow-up was 39.1 ± 29.2 months. Twenty-two patients were lost to follow-up. There was a statistical difference in overall survival between the SVAA and ASVAA groups at 3 years (85.2% vs 97.5%).

6.2.2 Open Repair

Ghariani et al. (2013) reported long-term results of open repair of 78 VAAs in 60 patients. The aneurysms involved the coeliac trunk (30%), hepatic artery (26%), splenic artery (24%) and the mesenteric superior artery (14%). Twenty patients (33%) were symptomatic, 1 of whom presented with aneurysmal rupture (1.7%). Hospital mortality was 1.7%. Five reintervention procedures (8%) were necessary. The actuarial survival rates were 98% at 1 month and 1 year, and 97% at 5 and 10 years, respectively. The primary patency rate of the revascularizations was 98% at 1 month and 1 year, and 95% at 5 and 10 years. The authors emphasized that those results were the standard which endovascular treatment of VAAs has to match.

6.2.3 Endovascular and Open Repair

Hogendoorn et al. (2014) performed a systematic review of all studies describing the outcomes of splenic artery aneurysms treated with open (OR), endovascular (ER), or conservative management. They identified 1321 patients (OR n = 511 (38.7%); conservative n = 425 (32.2%); ER n = 385 (29.1%)) in 47 articles. The conservative group had fewer symptomatic patients (9.5% vs 28.7% in OR and 28.8% in ER) and fewer ruptured aneurysms (0.2% vs 18.4% in OR and 8.8% in ER). OR had a higher 30-day mortality than ER (5.1% vs 0.6%), whereas minor complications occurred in a larger number of the ER patients. ER required more reinterventions per year (3.2%) compared with OR (0.5%) and conservative management (1.2%). The late mortality rate was higher in conservatively treated patients (4.9%) as compared to OR (2.1%) and ER (1.4%) (Table 6.1). The authors concluded that splenic artery aneurysms >2 cm should be treated, given the good short-term and long-term results. ER has the best outcomes and should be the treatment of choice if the splenic artery has a suitable anatomy for endovascular repair. In addition, Hogendoorn et al. (2015) evaluated the cost-effectiveness of OR, ER, and conservative management of splenic artery aneurysms. They found ER to be the most cost-effective treatment for most patient groups with splenic artery aneurysms, independent of the sex and risk profile of the patient. ER was superior to OR, being both cost-saving and more effective in all age groups. Elderly patients (>78 years) should be considered for conservative management, based on the high costs in relation to the very small gain in health when treated with ER.

Marone et al. (2011) reported a single center experience of OR (n = 74) and ER (n = 20) of VAAs in 94 patients. Technical success was achieved in all cases treated by open surgery. Splenectomy was performed in 11 cases, and in six, splenic autotransplantation was performed. Perioperative mortality in the surgical group was 1.3% (1/74). There was no perioperative mortality in the endovascular group, but 4 surgical conversions were recorded. Perioperative morbidity was 9.4% (7/74) in the surgical group, and 10% (2/20) in the endovascular group. Follow-up was available for 16 patients in the endovascular group (80%) and 63 in the surgical group (85%), with a mean duration of 42 months. The Kaplan-Meier estimates of survival at 1 and 5 years were 100% and 85%, respectively, for OR, and 100% and 40%, respectively, for ER, with no significant difference between the two groups.

Table 6.1 Open repair, endovascular repair, and conservative management of true splenic artery aneurysms

Characteristic and outcomes	Open (n = 511)	ER (n = 385)	Cons (n = 425)
Patient age, years	56.3	56.7	61.4
Aneurysm size, cm	3.1	3.0	2.1
Symptomatic, %	28.7	28.8	9.5
Ruptured SAA, %	18.4	8.8	0.2 (n = 1)
Splenectomy, %	56.9	1.6	Not applicable
Reconstruction, %	19.6	Not applicable	Not applicable
Ligation, %	12.3	Not applicable	Not applicable
Resection, %	10.0	Not applicable	Not applicable
Embolization, %	Not applicable	94.8	Not applicable
Stent, %	Not applicable	3.4	Not applicable
Technical success, %	97.8	95.2	Not applicable
Minor complications, %	11.3	25.1	Not applicable
Major complications, %	1.1	0.8	Not applicable
30-day mortality, %	5.1	0.6	0.5
Length of stay, days	9.8	2.03	Not applicable
Follow-up, months	61.2	30.8	61.8
Late complications, %	2.5	9.1	0.8
Late mortality, %	2.1	1.4	4.9
Reinterventions, %	2.4	7.9	5.8

According to Hogendoorn et al. (2014)
Baseline characteristics of patients and outcomes after treatment

One-hundred and twenty-eight patients with splenic artery aneurysms (SAAs) were evaluated by Lakin et al. (2011). The mean size of the SAA at diagnosis was 2.4 ± 1.4 cm. Patients with smaller SAAs (n = 66; mean size, 1.7 ± 0.6 cm) were serially observed. Sixty-two patients underwent surgical repair (n = 13) or endovascular coil/glue occlusion (n = 49). Mean initial aneurysm size was 2.9 cm for the endovascular group and 4.4 cm for the open group. Patients undergoing open surgery were treated via SAA resection/splenectomy (7), ligation (4), or arterial reconstruction (2). Six patients underwent emergent laparotomy for rupture, whereas the remaining 7 underwent elective laparotomy. There were two perioperative deaths in the OR group. Both of these deaths occurred in patients who presented with rupture, representing a 29% mortality rate for ruptured SAA (2/7). Patients undergoing endovascular therapy were all treated with endoluminal ablation under local anesthesia with sedation in 47 of 49 interventions. Coil embolization was performed in 45 of 49 patients. There were no conversions to open repair, nor was there any periprocedural mortality. ER was safe and durable with a mean 1.5-mm regression in SAA size over 2 years. The mean rate of growth for observed SAA was 0.2 mm/year. Ten-year survival was 89.4% for all patients (observed group, 94.9%; treated group, 85.1%). No late aneurysm-related mortality was identified. In conclusion, large SAAs can undergo endovascular ablation safely with durable SAA regression. Smaller SAAs (<2 cm) grow slowly and carry a negligible rupture risk.

A retrospective review of 181 patients with repaired VAAs (77 ruptured, 104 intact) has been presented by Shukla et al. (2015). The ruptured VAAs (rVAAs) were

smaller than the intact VAAs (iVAAs) (20.7 mm vs 27.5 mm). Most rVAAs (81.8%) were pseudoaneurysms. The majority of aneurysms were repaired with endovascular techniques (61.5% for iVAAs,73% for rVAAs). When ER was the chosen modality of treatment, coil embolization was the most common intervention type (80%). Immediate technical success with ER of iVAAs and rVAAs was 98.4% and 98.7%, respectively. The 30-day mortality rate was 0% for iVAAs, which was significantly lower than mortality for rVAAs (11.9%). The rVAAs had lower 30-day mortality with ER compared with OR (7.4% vs 28.6%). Overall survival between iVAAs and rVAAs at 3 years was 91.1% vs 63.1%. There was no difference in survival at 3 years with open and endovascular repair of iVAAs. However, in the rVAA group, the 2-year overall survival was higher with ER compared with OR (69.4% vs 46.4%). In this study, open and endovascular interventions were equally durable for elective repair of VAAs, but ER for rVAAs resulted in lower morbidity and mortality. Furthermore, aggressive treatment of pseudoaneurysms was recommended at diagnosis regardless of size.

Batagini et al. (2016) treated 113 patients with VAA and Pseudoaneurysms, 57 by ER and 56 by OR. Short-term technical success was achieved in 98.2% (ER) and 96.4% (OR). During the median follow-up period of 16 months, the clinical success was 91.2% and 92.9%, and the overall survival was 94.7% and 96.4% in groups ER and OR, respectively. OR and ER had similar rates of technical and clinical success, as well as mortality during follow-up. However, periprocedural morbidity was significantly higher in the OR group.

Sticco et al. (2015) identified from 2008 to 2011 in the Nationwide Inpatient Sample (NIS) database 2316 admissions with a diagnosis code present for SAA. Among these, 347 (14.9%) patients underwent ER and 112 (4.8%) patients had OR. Therefore, the majority of patients admitted with a diagnosis of SAA were discharged without intervention. Out of the 459 patients who underwent repair, 33 (7.2%) had a diagnosis of hemoperitoneum, with 20 of these undergoing endovascular repairs and 13 open surgery. There were three mortalities in this subgroup presenting with rupture, 1 (5%) in the endovascular group and 2 (15%) in the open group. In total, 8 in-hospital deaths (2%) were seen within 30 days in the ER group and 3 (3%) in the OR group, respectively. Cardiac and pulmonary complications as well as overall percentage of complications were significantly higher among those undergoing surgical repairs. The authors, therefore, would favor endovascular treatment for patients with SAA requiring repair.

6.2.4 Special Issues

6.2.4.1 Incidence and Outcome of VAA and RAA

Clinical management and outcome of patients with VAA was investigated by Pitton et al. (2015) in terms of surgical therapy, interventional treatment and watchful waiting. They identified 233 patients with a total of 253 VAAs over the course of a

decade. In the majority of cases VAA involved the splenic artery (n = 83), followed by the coeliac trunk (n = 47), the renal arteries (n = 44), the hepatic artery (n = 40), the superior mesenteric artery and its branches (n = 17), the gastroduodenal artery (n = 10), the pancreaticoduodenal artery (n = 8), the gastric artery (n = 4), and combinations of these. Thirty-seven aneurysms in 35 patients presented with rupture. One-hundred and seventy-one of the 233 patients (73.4%) had no specific symptoms. The mean overall size of the VAAs was 16.1 ± 9.8 mm. There was no significant difference between the diameters of ruptured aneurysms compared to non-ruptured aneurysms (14.8 ± 8.2 mm vs. 16.3 ± 10.0 mm, respectively). Specific aneurysm-targeted treatment was applied to 59 of the 253 VAAs (23.3%) by means of interventional techniques (n = 45) or open surgery (n = 14). The 30-day mortality after interventional treatment of VAA was in total 5% (n = 2 of 40 patients), since both deaths occurred in the emergency setting, the mortality was 6.7% (n = 2 of 30 patients) in this subgroup. There was no 30-day mortality in the 11 patients who underwent open surgery. Only five patients were lost to follow-up. Of the 228 patients included in the follow-up after 18.0 ± 26.8 months, 161 (70.6%) were alive and 67 (29.4%) were deceased. Causes of death were mainly progressive tumor (n = 33), cardiovascular events (n = 12), post-transplantation complications (n = 6), and infection (n = 5). Retrospectively, it remained unclear whether any of the inconclusive deaths were related to VAA complications. In this study, the mean diameter of ruptured aneurysms did not significantly differ from that of non-ruptured aneurysms. Thus, treatment indications should not be based primarily on the aneurysm diameter, but in the first instance on the aneurysm etiology. Pseudoaneurysms need emergency treatment, but the vast majority of true aneurysms can probably be managed conservatively.

Buck et al. (2016) identified all patients undergoing OR or ER of isolated renal artery aneurysms (RAA) in the Nationwide Inpatient Sample (NIS) from 1988 to 2011 for epidemiologic analysis. They identified 6234 RAA repairs between 1988 and 2011. Total repairs increased after the introduction of ER (8.4 in 1988 to 13.8 in 2011 per 10 million U.S. population). ER increased from 0 in 1988 to 6.4 in 2011 per 10 million U.S. population. However, there was no concomitant decrease in open surgery (5.5 in 1988 to 7.4 in 2011 per 10 million U.S. population). From 2000 to 2011, there were 1627 open and 1082 endovascular elective repairs. In-hospital mortality was 1.8% for ER, 0.9% for OR, and 5.4% for nephrectomy ($P < .001$ compared with all revascularization). Complication rates were 12.4% for OR vs 10.5% for ER, including more cardiac (2.2% vs 0.6%) and peripheral vascular complications (0.6% vs 0.0%) with OR (Table 6.2). This retrospective review demonstrated that more RAAs are being treated after the introduction of ER. Although there is evidence supporting a significantly lower rate of postoperative complications and a shorter length of stay with ER, there has not been a reduction in operative mortality, nor has there been a reduction in open surgical procedures. Therefore, the authors concluded, re-evaluation of the indications for repair of isolated RAAs, in particular by ER but also by OR, is warranted.

Table 6.2 In-hospital outcomes of elective endovascular and open renal artery aneurysm repairs from 2000 to 2011

Postoperative outcomes	Open (n = 1627)	Endovascular (n = 1082)
In-hospital mortality (%)	0.9	1.8
Cardiac complications (%)	2.2	0.6
Respiratory complications (%)	4.6	4.3
Peripheral vascular complications (%)	0.6	0.0
Acute renal failure (%)	10	6.8
Wound dehiscence (%)	0.3	0.0
Bleeding complications (%)	5.2	5.0
Infection (%)	0.9	0.8
Any complication (%)	12.4	10.5
Length of stay (days)	6.0	4.6

According to Buck et al. (2016)
Nationwide Inpatient Sample

6.2.4.2 Renal Artery Aneurysms – Natural History

RAAs are uncommon, and rates of growth and rupture are unknown. Wayne et al. (2014) therefore studied anatomic characteristics and changes in diameter during imaging surveillance. Sixty-eight RAAs in 55 patients were analyzed. Median follow-up was 19.4 months. The patients mean age was 61.8 years, 73% were female. Multiple RAAs were present in 18% of patients, and 24% also had arterial aneurysms of other splanchnic or iliac vessels. Mean initial aneurysm diameter was 16.0 ± 6.4 mm. Median annualized growth rate was 0.06 mm. No RAA ruptures or acute symptoms occurred during surveillance, and 10.3% of RAAs were repaired electively. These findings suggest that annual (or less frequent) imaging surveillance is safe in the majority of patients and do not support pre-emptive repair of asymptomatic, small-diameter RAAs. This observation corresponds with the experiences of Klausner et al. (2014), who reviewed in a single-institution study retrospectively 59 RAAs in 40 patients. Twenty-nine patients (73%) were asymptomatic; the remainder of patients presented with hematuria (n = 4), abdominal pain (n = 3), difficult-to-control hypertension (n = 3), or flank pain (n = 2). Eight asymptomatic RAAs were treated surgically (mean RAA diameter = 2.4 ± 0.1 cm), with the remaining 33 asymptomatic RAAs being managed conservatively (mean RAA diameter = 1.4 ± 0.1 cm). Non-operated patients were followed for a mean of 36 ± 9 months, with no late acute complications and 0% mortality. Mean RAA growth rate of patients with multiple imaging studies was 0.60 ± 0.16 mm/year. There were no adverse outcomes in asymptomatic RAAs >2 cm that were observed. The authors wondered whether we may currently be too aggressive in treating asymptomatic RAAs. Consequently, they conducted a multi-institutional study to define the clinical features of RAA, including the precise growth rate and risk of rupture, and to examine the appropriateness of current criteria for repair of asymptomatic RAA (Klausner et al. 2015). They identified a total of 865 RAAs in 760 patients at 16 institutions. Of these, 75% were asymptomatic; symptomatic patients

had difficult-to-control hypertension (10%), flank pain (6%), hematuria (4%), and abdominal pain (2%). The RAAs had a mean maximum diameter of 1.5 ± 0.1 cm. Elective repair was performed in 213 patients with 241 RAAs, usually for symptoms or size >2 cm; the remaining 547 patients with 624 RAAs were observed. Major operative complications occurred in 10%, including multisystem organ failure, myocardial infarction, and renal failure requiring dialysis. RAA repair for difficult-to-control hypertension cured 32% of patients and improved it in 26%. Three patients had ruptured RAA; all underwent emergency repair, with no deaths. Conservatively treated patients were monitored for a mean of 49 months, with no acute complications. Aneurysm growth rate was 0.086 cm/y, with no difference between calcified and noncalcified aneurysms. The conclusions of this study are that rupture of asymptomatic RAAs is exceedingly rare, growth rate of RAAs is very slow, and OR is associated with significant minor morbidity but rarely with major morbidity or mortality. This study questioned current size criteria for repair of asymptomatic RAAs at 2 cm.

6.2.4.3 Splenic Artery Aneurysms – Rupture and Pregnancy

Pregnancy is cited as the most important risk factor for SAA rupture, but the true rupture rate of SAAs during pregnancy is unknown. Nanez et al. (2014) identified retrospectively 35 patients with SAA during a 5-year period. Patients had a median age of 63 years, and 28 (80%) were women who were a median age of 62 years. The SAAs in the 35 patients were a median size of 1.3 cm, and eight (23%) were >2 cm. Despite the very large number of deliveries recorded during the study period (67,616 births), no ruptured SAA were identified during pregnancy in this study. However, 89% of women with an SAA had previous pregnancies. Two women and one man (8.6%) experienced rupture, resulting in one death (2.9%). Ruptured SAAs are exceedingly rare in young women and during pregnancy.

6.2.4.4 Laparoscopic Treatment of Splenic Artery Aneurysms

Tiberio et al. (2012) designed a prospective, randomized comparison between open and laparoscopic surgery for asymptomatic SAAs. Fourteen patients were allocated to laparotomy and 15 to laparoscopy. The conversion rate from laparoscopic to open surgery was 13.3% (two cases). The type of surgical procedure performed on the splenic artery was similar in the two study groups. Aneurysmectomy + artery ligation was performed in 7 (open surgery) and 9 (laparoscopy) patients, respectively, aneurysmectomy + end-to-end anastomosis in 3 cases in each group, and aneurysmectomy + splenectomy in 2 and 3 cases, respectively. No patient died postoperatively. Laparoscopy was associated with lower postoperative morbidity (25% vs. 64%) and shorter hospital stay. The authors recommended laparoscopic treatment of SAAs when ablative procedures are required, but laparoscopic anastomoses showed poor results during long-term follow-up (mean period 50 months).

6.3 Conclusions for Clinical Practice

1. Visceral artery aneurysms can be treated by open or endovascular techniques. There are no evidence-based treatment recommendations. However, over the last years case series with open repair have been comparatively rare.
2. In the majority of cases visceral artery aneurysms involve the splenic artery. Splenic artery aneurysms >2 cm should be treated, given the good short-term and long-term results. ER has the best outcomes and should be the treatment of choice if the splenic artery has a suitable anatomy for endovascular repair.
3. Rupture of asymptomatic renal artery aneurysms is exceedingly rare, growth rate of RAAs is very slow, and OR is associated with significant minor morbidity but rarely with major morbidity or mortality. The available data question current size criteria for repair of asymptomatic RAAs at 2 cm.

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Chapter 7
Chronic Mesenteric (Intestinal) Ischemia

7.1 Clinical Diagnostics and Therapy/Medical Guidelines

Note: The terms "chronic intestinal ischemia" and "chronic mesenteric ischemia" will be used synonymously, according to literature (MEDLINE, PubMed). Chronic mesenteric ischemia (CMI) is used more commonly and will be the preferred term hereafter.

7.1.1 American College of Cardiology Foundation/American Heart Association

Guidelines of the American Heart Association (AHA) (Anderson et al. 2013) present the following recommendations regarding the diagnosis of chronic intestinal ischemia (Class I):

1. Chronic intestinal ischemia should be suspected in patients with abdominal pain and weight loss without other explanation, especially those with cardiovascular disease. (Level of Evidence: B)
2. Duplex ultrasound, CTA, and gadolinium-enhanced MRA are useful initial tests for supporting the clinical diagnosis of chronic intestinal ischemia. (Level of Evidence: B)
3. Diagnostic angiography, including lateral aortography, should be obtained in patients suspected of having chronic intestinal ischemia for whom noninvasive imaging is unavailable or indeterminate. (Level of Evidence: B)

Guidelines for therapy:

1. Percutaneous endovascular treatment of intestinal arterial stenosis is indicated in patients with chronic intestinal ischemia. (Class-I-recommendation/Level of Evidence: B)

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2. Surgical treatment of chronic intestinal ischemia is indicated in patients with chronic intestinal ischemia. (Class-I-recommendation/Level of Evidence: B)
3. Revascularization of asymptomatic intestinal arterial obstructions may be considered for patients undergoing aortic/renal artery surgery for other indications. (Class-IIb-recommendation/Level of Evidence: B)
4. Surgical revascularization is not indicated for patients with asymptomatic intestinal arterial obstructions, except in patients undergoing aortic/renal artery surgery for other indications. (Class-III-recommendation/Level of Evidence: B)

Apparent from the guidelines above, endovascular and open surgical treatment of chronic intestinal ischemia are equally recommended.

7.1.2 European Society of Cardiology (ESC)

ESC guidelines refer to mesenteric artery disease. Recommendations for diagnosis of symptomatic chronic mesenteric ischemia are as follows (European Stroke Organisation et al. 2011):

1. Duplex ultrasonography (DUS) is indicated as the first-line diagnostic test in patients suspected of mesenteric artery disease. (Class-I-recommendation/Level of Evidence: A)
2. When DUS is inconclusive, CTA or gadolinium-enhanced MRA are indicated. (Class-I-recommendation/Level of Evidence: B)
3. Catheter-based angiography is indicated exclusively during the endovascular therapy procedure. (Class-I-recommendation/Level of Evidence: C)

Guidelines for management:

1. Mesenteric revascularization should be considered in patients with symptomatic mesenteric artery disease. (Class-IIa-recommendation/Level of Evidence: B)
2. In the case of revascularization, endovascular treatment should be considered as the first-line strategy. (Class-IIa-recommendation/Level of Evidence: C)

ESC guidelines do not match AHA guidelines. Here, in contrast to AHA guidelines, the endovascular approach has explicit priority over the surgical procedure.

7.2 Results

7.2.1 Systematic Overview of Literature

A systematic literature review of the last 25-years was conducted by Pecoraro et al. (2013) to identify studies reporting on chronic mesenteric ischemia (CMI) treatment with more than 10 patients. Randomized studies were not available for

treatment recommendations. Patients were divided into endovascular treatment (ER) or open treatment (OR) groups. Forty-three articles with 1795 patients were included. Perioperative morbidity and mortality rates were lower in the ER group. No difference in survival rate was observed. Primary and secondary patencies were superior in the OR group. A greater number of vessels were revascularized in the OR group. CMI recurrence was more frequent in the ER group. Follow-up was longer in the OR group. Technical success was superior in the OR group and in-hospital length of stay was shorter in the ER group. Considering the lower periprocedural mortality and morbidity after ER, according to the authors this approach should be considered as the first treatment option in most CMI patients, especially in those with severe malnutrition. Primary OR should be restricted to cases that do not qualify for ER or good surgical risk patients with long life expectancy.

A systematic review of 12 studies comparing ER and OR in CMI was given by Saedon et al. (2015). A total of 4255 patients were treated primarily with ER and a total of 3110 with OR. In this meta-analysis there were no differences in mortality and morbidity, but patency rates were better following OR. In a further meta-analysis, 8 studies (569 cases) were included (Cai et al. 2015). This meta-analysis showed that there was no difference in 30-day mortality and 3-year cumulative survival rate between the ER group and the OR group; compared with the OR group, the ER group resulted in significantly lower rate of in-hospital complication, while recurrence rate within 3 years after revascularization was significantly greater in the ER group.

7.2.2 Registry Data

Schermerhorn et al. (2009) identified all patients undergoing surgical (bypass, endarterectomy, or embolectomy) or PTA/S (angioplasty, with and without stenting) mesenteric revascularization from the Nationwide Inpatient Sample (NIS) from 1988 to 2006. There were 6342 PTA/S and 16,071 open surgical repairs overall (acute and chronic mesenteric ischemia included). Three thousand four-hundred and fifty-five (61.9%) patients with CMI were treated via angioplasty ± stent (ER), 2128 (38.1%) patients were treated via bypass, endarterectomy or embolectomy (OR). The vast majority of OR procedures were bypasses (93%). Endarterectomy (4%) and embolectomy (3%) did not play a decisive role. Crucial results of this analysis are summarised in Table 7.1. Patients undergoing ER were older and had higher rates of comorbidities as compared to patients of the OR group. According to this study, ER is the acceptable first-line therapy for patients with CMI due to significantly reduced hospital mortality rates and fewer complications compared to OR. This was confirmed by the presented multivariate analysis concerning predictors of hospital mortality: mortality was 5- to 6-fold higher in OR compared to ER (odds ratio 5.1). Additional predictors for increased mortality were increasing age (odds ratio 1.6 per decade, meaning that mortality relatively increased by 50% with every decade), atrial fibrillation and atrial flatter (odds ratio 2.5) and congestive

Table 7.1 Treatment of patients with CMI

	ER (n = 3455)	OR (n = 2128)
Age, years (median, range)	74, 24–97	68, 29–99
Female	74%	79%
Comorbidities		
Hypertension	66%	51%
Peripheral Vascular Disease	40%	32%
Coronary Artery Disease	39%	26%
Congestive Heart Failure	17.5%	10.5%
Diabetes mellitus	19%	12%
Chronic renal disease	6.3%	1.2%
Perioperative complications		
Any complication	20.2%	39.7% (38.4%)[a]
Bowel resection	3.0%	8.0% (6.6%)[a]
Acute Renal Failure	6.0%	10.5% (9.7%)[a]
Acute Myocardial Infarction	3.0%	4.8% (3.6%)[a]
Stroke	0%	0.7% (0.8%)[a]
Respiratory	0.3%	5.3% (5.7%)[a]
Mortality	3.7%	15% (13%)[a]
Length of stay, days (median, range)	5 (0–94)	11 (1–135)

Analysis of the Nationwide Inpatient Sample (USA) for years 2000 through 2006 (Schermerhorn et al. 2009)
ER PTA +/− Stent, *OR* Bypass, endarterectomy or embolectomy
[a]Bypass only

heart failure (odds ratio 2.8). The NIS database was also used by Moghadamyeghaneh et al. (2015) to identify patients admitted for the diagnosis of CMI between 2002 and 2012. Seven-thousand nine-hundred and six patients underwent surgical (62%) or endovascular treatment (38%) for CMI. Open vascular treatment had higher mortality (adjusted odds ratio, AOR: 5.07) and morbidity (AOR: 2.14).

7.2.3 Endovascular Therapy – Case Series

Oderich et al. (2012) retrospectively reviewed the clinical data of 156 patients treated with 173 mesenteric artery stent placements for CMI (1998–2010). Eleven patients (7%) developed 14 mesenteric artery complications (distal embolization n = 6/branch perforation n = 3/dissection n = 2/stent dislodgement n = 2/stent thrombosis n = 1). Five patients required conversion to open surgical repair, including after failed endovascular treatment in one. There were four procedure-related deaths (2.5%). Any complications were seen in 46 (30%) patients. The same group presented follow-up data of patients with CMI and mesenteric artery angioplasty and stenting (Tallarita et al. 2011). 57/157 patients developed mesenteric artery in-stent restenosis (MAISR) after a mean follow-up of 29 months. There were 30 patients treated with reintervention for MAISR. Twenty-six patients (87%)

underwent redo endovascular revascularization. The other four patients (13%) had open bypass, one for acute ischemia. There was one death (3%) in a patient treated with redo stenting for acute mesenteric ischemia. After a mean follow-up of 29 months, 15 patients (50%) developed a second restenosis, and seven (23%) required another reintervention. In this study, mesenteric reinterventions were associated with low mortality (3%), high complication rate (27%), and excellent symptom improvement (92%).

Grilli et al. (2014) performed a retrospective review of 47 consecutive patients who underwent endovascular stent placement for chronic total occlusions of the superior mesenteric artery. All patients had symptoms of CMI. Technical success was achieved in 41 of 47 patients (87%). All patients who underwent successful recanalization reported symptomatic improvement. Kaplan-Meier analysis revealed primary freedom from symptomatic recurrence of 95% at 12 months and 78% at 24 months. Secondary freedom from symptomatic recurrence rates were 100% at 12 months and 88% at 24 months.

The outcomes in patients treated for CMI with mesenteric stenting using bare metal stents (BMS, n = 164 patients/197 vessels) or covered stents (CS, n = 61 patients/67 vessels) in two academic centers were presented by Oderich et al. (2013). The mean follow-up was 29 months and was significantly longer for patients treated by BMS (32 months) compared with those who had CS (19 months; $P < .05$). Technical success was achieved in 141 patients (95%) treated by BMS and 41 (98%) who had CS. Restenosis occurred in 62 patients (42%) treated by BMS and in five (12%) who had CS. This nonrandomized study suggested that CS used to treat mesenteric artery stenosis were associated with less restenosis, recurrences, and reinterventions in patients with CMI.

Forty patients undergoing ER for CMI were included in a retrospective study by Christofi et al. (2015). Fifty-two of 62 visceral arteries (18 occlusions and 34 stenoses) were successfully treated by ER (technical success rate 84%). The 12-month symptom free survival was 60%. The overall 12-month primary and secondary patency rates were 71% and 94%, respectively. No significant differences were observed between occluded and stenotic vessels concerning the primary patency rates. In this study ER was associated with high incidence of symptoms recurrence despite satisfying patency rates.

7.2.4 Endovascular Revascularization of the Superior Mesenteric Artery (SMA) and Celiac Artery – Comparison of Outcomes

A study from Ahanchi et al. (2013) compared the outcomes of superior mesenteric artery (SMA) and celiac artery (CA) stenting in patients with CMI. One-hundred and twenty-one patients received 140 visceral stents in the SMA (n = 92; 65.7%), the CA (n = 40; 28.6%), and the inferior mesenteric artery (n = 8; 5.7%). Overall mean follow-up was 12.8 months. The overall clinical patency rate was 63% at 1 year. The

SMA stent group had a significantly higher primary patency than the CA stent group, with a 1-year primary patency of 55% for the SMA stents and only 18% for the CA stents. Thirty-two (34.8%) SMA stents and 12 (30%) CA stents required reintervention. The overall survival of all patients at 1 year was 85%. Overall freedom from reintervention at 1 year was 54%, and at 4 years, 18%. The 1-year survival free from symptom recurrence for the SMA group was 63% versus 53% for the CA group. This retrospective study brings into question the utility of stenting the CA artery. CA stenting had a very high in-stent restenosis rate, significantly poorer clinical patency rates, and a trend toward a higher reintervention rate compared with SMA stenting.

Patients with symptoms of CMI treated with stenting of the CA and SMA were also presented by Aburahma et al. (2013). Eighty-three patients underwent 105 stentings of the CA or SMA. There were 51 SMA stentings and 54 CA stentings (22 had both SMA and CA stenting). Nineteen patients had open bypass to SMA/CA during the same period with a perioperative mortality rate of 10.5% (2/19). The initial technical success rate was 97%, with 2% procedure morbidity and 2% mortality. Thirty of 73 (41%) patients with long-term follow-up had late recurrent clinical symptoms at a mean of 31 months. In contrast to the aforementioned study, no significant differences in either primary or assisted primary patency between the SMA and CA groups were seen. Primary patency of the SMA at 1, 2, 3, 4, and 5 years was 71%, 47%, 37%, 28%, and 18%, respectively; and assisted primary patency was 82%, 64%, 57%, 45%, and 32%, respectively. Primary patency of the CA was 68%, 50%, 40%, 29%, and 21%, and assisted primary patency was 79%, 58%, 52%, 42%, and 36%, at 1, 2, 3, 4, and 5 years, respectively. Freedom from ≥70% in-stent stenosis for the SMA was 82% and 34%, and that for the CA was 73% and 25%, at 1 and 5 years, respectively.

7.2.5 Endovascular vs. Open Revascularization

Hogendoorn et al. (2014) evaluated the comparative effectiveness and cost-effectiveness of ER and OR in patients with CMI refractory to conservative management in a Markov decision model. The results of this decision analysis model suggested that ER is favored over OR for patients with CMI in all age groups. Although ER is associated with more expected reinterventions, ER appears to be cost-effective for all age groups.

The clinical data of 343 patients from the Mayo Clinic treated with mesenteric revascularization for chronic mesenteric ischemia between 1991 and 2010 were retrospectively reviewed by Tallarita et al. (2013). One-hundred and eighty-seven patients were treated by OR and 156 patients by ER. Procedure-related early mortality was 2.7% (OR) and 2.6% (ER), respectively. Median follow-up was 96 ± 54 months. There were 144 late deaths, most commonly from cardiac causes in 35% (51/144), followed by cancer in 15% (21/144), pulmonary complications in 13% (19/144), and mesenteric ischemia in 11% (16/144). Patient survival was analyzed using Society for Vascular Surgery (SVS) comorbidity scores and propensity score-matched comparison based on independent predictors of any-cause mortality. Late

patient survival at 5 years in the OR and ER groups was 75% ± 4% and 60% ± 9% for low SVS risk (<9), 52% ± 8% and 43% ± 9% for intermediate SVS risk (9–16), and 67% ± 15% and 30% ± 8% for high SVS risk (>16). Using propensity matched scores, 5-year survival was nearly identical for patients treated by OR (60%) or ER (57%). In this study, long-term patient survival after mesenteric revascularization was not influenced by type of arterial reconstruction. Age >80 years, diabetes, chronic kidney disease stage IV or V, and home oxygen were independent predictors of any-cause mortality.

Outcomes of 116 patients with CMI who were first treated with ER (72%) and 45 patients with OR (28%) were presented by Zacharias et al. (2016). Perioperative mortality (30-day) was not statistically significant different between the groups (ER 5.2% vs OR 11%; P = .165). Mean follow-up was 37 months. Primary patency at 3 years was higher in the OR group compared with the ER group (91% vs 74%). Among the ER patients, 27 developed restenosis and required OR (23%). Long-term survival rates were higher in the ER group (95% vs 78%). On outcome comparison between the ER success group (n = 89) and the ER group requiring OR (n = 27), patients with successful ER appeared to have shorter hospital length of stay and intensive care unit length of stay as well as lower perioperative mortality (2% vs 15%). Long-term survival was higher in the successful ER group (96% vs 81%). In this study, patients with short lesions ≤2 cm who have higher operative risk were those who benefit the most from ER. On the other hand, patients with heavily diseased visceral aortas and long lesions ≥2 cm in the celiac artery and SMA that are close to the mesenteric takeoff from the aorta may benefit from primary OR.

Early and late outcomes of patients with CMI who underwent bypass or percutaneous angioplasty (PTA) in 12 centres in the UK were compared on an intention-to-treat basis by Rawat et al. (2010). A total of 76 patients underwent 101 procedures (PTA 49; bypass 52). Of these, 36 had a PTA first, and 40 had a bypass first. Patients who underwent a primary PTA were found to be significantly older and tended to have greater comorbidities. Perioperative morbidity for bypass was significantly greater than that for PTA (32% vs. 6%). Overall, 30-day mortality for bypass tended to be greater than that for PTA (13% vs. 4%; n.s.), but was similar for patients treated electively in the two groups (4% vs. 3%). Cumulative 1- and 5-year survival (bypass: 85%, 63%; PTA: 67%, 31%) and primary patency (bypass: 81%, 69%; PTA: 54%, 32%) rates were found to be significantly better after primary bypass.

7.2.6 Open Revascularization

Davenport et al. (2012) evaluated short-term outcomes of patients who underwent aortomesenteric bypass for CMI, with specific attention given to the conduit used – prosthetic versus vein. Data from the American College of Surgeons National Surgical Quality Improvement Program were analyzed. One-hundred and fifty-six patients underwent mesenteric revascularization – 119 (76%) women and 37 (24%) men with an average age of 65 ± 13 years. The conduit used was vein in 44 (28%) and prosthetic graft in 112 (72%). Patients with a vein graft had a higher percentage

of a contaminated surgical site (30% vs. 7%) and underwent emergent surgery more frequently (16% vs. 4%). Mortality was higher in patients in whom a vein graft was used (16% vs. 5%). The higher mortality was likely due to patient factors, such as the extent of bowel ischemia at the time of operation, rather than the type of conduit used. If expeditious revascularization is done before development of bowel infarction, vein or prosthetic conduit would be expected to function equally well.

The first study that included a large sample of patients presenting exclusively with CMI, with a median follow-up longer than 5 years was presented by Lejay et al. (2015). Eighty-six patients with median age 62 years were included. Median follow-up was 6.9 years. The number of treated arteries was one in 49 patients (57%), and two in 37 patients (43%), with a mean number of 1.43. Revascularization was complete in 46 cases (53%), and anterograde in 79 cases (92%). The 30-day mortality and morbidity rates were 3.5% and 13.9%. Ten-year survival was 88% for complete revascularization and 76% for incomplete revascularization. The primary patency rate was 84.4% at 10 years for complete revascularization, and 88.1% for incomplete revascularization. Freedom from digestive symptoms was achieved significantly better with complete revascularization (80.3% at 10 years for complete revascularization, and 65.7% for incomplete revascularization). The authors concluded that open surgery is still associated with significant morbidity and mortality, but nevertheless the durability and efficacy of open surgical repair in CMI are convincing over time.

Outcomes of reinterventions for failing open mesenteric reconstructions for mesenteric ischemia have been described by Kanamori et al. (2014). Reinterventions included reoperative OR (R-OR) in 28 patients (19 with CMI and nine with acute mesenteric ischemia, AMI) and ER in 19, all for CMI. Early mortality was 22% in patients treated by R-OR for AMI. There were no early deaths among patients treated for CMI with R-OR or ER. Morbidity was significantly higher for R-OR than for ER in patients with CMI (63% vs 16%). Survival in patients treated for CMI at 1 year was similar for ER (89% ± 8%) and R-OR (79% ±10%). Compared with the first-time OR group, patients treated by R-OR had similar 30-day morbidity (OR 40% vs R-OR 63%), 30-day mortality (3% vs 0%), and 1-year freedom from symptom recurrence (97% vs 88%) and reintervention (93% vs 77%). Primary patency at 1 year was significantly lower for R-OR (66%) than for OR (93%). The authors concluded that mesenteric R-OR and ER for failing grafts are safe and provide equivalent secondary patency to first-time interventions. Primary stenting or angioplasty should be considered the first treatment option when possible because of lower morbidity and similar rates of restenosis and reintervention compared with R-OR.

7.3 Conclusions for Clinical Practice

The American College of Radiology Appropriateness Criteria® (2011) provide a consistent summary of the available data:

1. Chronic mesenteric ischemia most commonly occurs due to atherosclerotic occlusive disease of the mesenteric arteries (celiac axis, SMA, inferior mesenteric

artery). Given the relatively rich collateral supply to bowel, signs and symptoms of ischemia typically occur when at least two arteries (and often all three) are affected.
2. Endovascular therapy, particularly angioplasty and stenting, has supplanted open surgical repair as the preferred therapy for mesenteric origin stenoses in patients without bowel infarction.
3. Mortality and morbidity are believed to be lower for endovascular interventions compared to open repair; however, more patients develop recurrent symptoms and require reintervention following endovascular treatment than after open repair.

We therefore conclude that patients with short lesions <2 cm who have higher operative risks are those who benefit the most from endovascular interventions. On the other hand, in patients with heavily calcified or long lesions, particularly long occlusions and patients who fail endovascular therapy open reconstruction should be considered.

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Chapter 8
Intermittent Claudication

8.1 Treatment Indications/Guidelines

8.1.1 American College of Cardiology Foundation/American Heart Association

Recommendations (Anderson et al. 2013):

Exercise training
Class I

- A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication (IC). (Level of Evidence: A)
- Supervised exercise training should be performed for a minimum of 30–45 min, in sessions performed at least 3 times per week for a minimum of 12 weeks. (Level of Evidence: A)

Class IIb

- The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with IC. (Level of Evidence: B)

Endovascular treatment for claudication
Class I

- Endovascular procedures are indicated for individuals with a vocational or lifestyle-limiting disability due to IC when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (a) there has been an inadequate response to exercise or pharmacological therapy and/or (b) there is a very favorable risk-benefit ratio (e.g., focal aortoiliac occlusive disease). (Level of Evidence: A)

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- Endovascular intervention is recommended as the preferred revascularization technique for TASC type A and femoropopliteal arterial lesions. (Level of Evidence: B)
- Provisional stent placement is indicated for use in the iliac arteries as salvage therapy for a suboptimal or failed result from balloon dilation. (Level of Evidence: B)
- Stenting is effective as primary therapy for common iliac artery stenosis and occlusions. (Level of Evidence: B)
- Stenting is effective as primary therapy in external iliac artery stenoses and occlusions. (Level of Evidence: C)

Class IIa

- Stents (and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g, persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection). (Level of Evidence: C)

Class IIb

- The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well-established. (Level of Evidence: A)
- The effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilation) is not well established. (Level of Evidence: C)

Class III

- Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries. (Level of Evidence: C)
- Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD. (Level of Evidence: C)

Surgical Interventions

Class I

- Surgical interventions are indicated for individuals with claudication symptoms who have a significant functional disability that is vocational or lifestyle limiting, who are unresponsive to exercise or pharmacotherapy, and who have a reasonable likelihood of symptomatic improvement. (Level of Evidence: B)

Class IIb

- Because the presence of more aggressive atherosclerotic occlusive disease is associated with less durable results in patients younger than 50 years of age, the effectiveness of surgical intervention in this population for IC is unclear. (Level of Evidence: B)

Class III

- Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with IC. (Level of Evidence: B)

Inflow procedures: aortoiliac occlusive disease:
Class I

- Aortobifemoral bypass is beneficial for patients with vocational- or lifestyle-disabling symptoms and hemodynamically significant aortoiliac disease who are acceptable surgical candidates and who are unresponsive to or unsuitable for exercise, pharmacotherapy, or endovascular repair. (Level of Evidence: B)
- Iliac endarterectomy and aortoiliac or iliofemoral bypass in the setting of acceptable aortic inflow should be used for the surgical treatment of unilateral disease or in conjunction with femoral-femoral bypass for the treatment of a patient with bilateral iliac artery occlusive disease if the patient is not a suitable candidate for aortobifemoral bypass grafting. (Level of Evidence: B)

Class IIb

- Axillofemoral-femoral bypass may be considered for the surgical treatment of patients with IC in very limited settings, such as chronic infrarenal aortic occlusion associated with symptoms of severe claudication in patients who are not candidates for aortobifemoral bypass. (Level of Evidence: B)

Class III

- Axillofemoral-femoral bypass should not be used for the surgical treatment of patients with IC except in very limited settings. *(Level of Evidence: B)*

Outflow procedures – Infrainguinal disease:
Class I

- Bypasses to the popliteal artery above the knee should be constructed with autogenous vein when possible. (Level of Evidence: A)
- Bypasses to the popliteal artery below the knee should be constructed with autogenous vein when possible. (Level of Evidence: B)

Class IIa

- The use of synthetic grafts to the popliteal artery below the knee is reasonable only when no autogenous vein from ipsilateral or contralateral leg or arms is available. (Level of Evidence: A)

Class IIb

- Femoral-tibial artery bypasses constructed with autogenous vein may be considered for the treatment of claudication in rare instances for certain patients. (Level of Evidence: B)
- Because their use is associated with reduced patency rates, the effectiveness of the use of synthetic grafts to the popliteal artery above the knee is not well-established. (Level of Evidence: B)

Class III

- Femoral-tibial artery bypasses with synthetic graft material should not be used for the treatment of claudication. (Level of Evidence: C)

8.1.2 National Institute for Health and Care Excellence (NICE)

The British NICE (NICE 2012) has the following recommendations identified as priorities for implementation:

Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease on:

- Smoking cessation
- Diet, weight management and exercise
- Lipid modification and statin therapy
- Prevention, diagnosis and treatment of diabetes
- Prevention, diagnosis and treatment of high blood pressure
- Antiplatelet therapy

Supervised exercise programme

- Offer a supervised exercise programme to all people with intermittent claudication.
- Consider providing a supervised exercise programme for people with IC which involves:
  - 2 h of supervised exercise a week for a 3-month period
  - Encouraging patients to exercise to the point of maximal pain.

Angioplasty and stenting

- Offer angioplasty for treating people with IC only when:
  - advice on the benefits of modifying risk factors has been reinforced **and**
  - a supervised exercise programme has not led to a satisfactory improvement in symptoms **and**
  - imaging has confirmed that angioplasty is suitable for the person.
- Do not offer primary stent placement for treating people with IC caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.
- Consider primary stent placement for treating people with IC caused by complete aorto-iliac occlusion (rather than stenosis).
- Use bare metal stents when stenting is used for treating people with IC.

Bypass surgery and graft types

- Offer bypass surgery for treating people with severe lifestyle-limiting intermittent claudication only when:
  - angioplasty has been unsuccessful or is unsuitable **and**
  - imaging has confirmed that bypass surgery is appropriate for the person.
- Use an autologous vein whenever possible for people with IC having infrainguinal bypass surgery.

Naftidrofuryl oxalate

- Consider naftidrofuryl oxalate for treating people with IC, starting with the least costly preparation, only when:
  - supervised exercise has not led to satisfactory improvement **and**
  - the person prefers not to be referred for consideration of angioplasty or bypass surgery.
- Review progress after 3–6 months and discontinue naftidrofuryl oxalate if there has been no symptomatic benefit.

8.1.3 European Society of Cardiology (Tendera et al. 2011)

Recommendations for revascularization in patients with aortoiliac lesions

- When revascularization is indicated, an endovascular-first strategy is recommended in all aortoiliac TASC A—C lesions (Class I/Level of Evidence: C)
- A primary endovascular approach may be considered in aortoiliac TASC D lesions in patients with severe comorbidities, if done by an experienced team. (Class IIb/ Level of Evidence: C)
- Primary stent implantation rather than provisional stenting may be considered for aortoiliac lesions (Class IIb/ Level of Evidence: C)

Recommendations for the revascularization in patients with femoropopliteal lesions

- When revascularization is indicated, an endovascular-first strategy is recommended in all femoropopliteal TASC A—C lesions (Class I/ Level of Evidence C)
- Primary stent implantation should be considered in femoropopliteal TASC B lesions (Class IIa/ Level of Evidence: A)
- A primary endovascular approach may be considered in TASC D lesions in patients with severe comorbidities and the availability of an experienced interventionist. (Class IIb/ Level of Evidence C)

Recommendations for revascularization in patients with infrapopliteal lesions

- When revascularization in the infrapopliteal segment is indicated, the endovascular-first strategy should be considered (Class IIa/ Level of Evidence C)
- For infrapopliteal lesions, angioplasty is the preferred technique, and stent implantation should be considered only in the case of insufficient PTA. (Class IIa/ Level of Evidence: C)

8.1.4 *Society for Vascular Surgery Practice Guidelines (Conte et al. 2015)*

Interventions for aortoiliac occlusive disease (AIOD) in intermittent claudication (*IC*)

- We recommend endovascular procedures over open surgery for focal AIOD causing IC. (Grade 1/Level of Evidence: B)
- We recommend endovascular interventions as first-line revascularization therapy for most patients with common iliac artery or external iliac artery occlusive disease causing IC. (Grade 1/Level of Evidence: B)
- We recommend the selective use of BMS or covered stents for aortoiliac angioplasty for common iliac artery or external iliac artery occlusive disease, or both, due to improved technical success and patency. (Grade 1/Level of Evidence: B)
- We recommend the use of covered stents for treatment of AIOD in the presence of severe calcification or aneurysmal changes where the risk of rupture may be increased after unprotected dilation. (Grade 1/Level of Evidence: C)
- We recommend direct surgical reconstruction (bypass, endarterectomy) in patients with reasonable surgical risk and diffuse AIOD not amenable to an endovascular approach, after one or more failed attempts at EVT, or in patients with combined occlusive and aneurysmal disease. (Grade 1/Level of Evidence: B)

Interventions for femoropopliteal occlusive disease in (IC)

- We recommend endovascular procedures over open surgery for focal occlusive disease of the superficial femoral artery (SFA) not involving the origin at the femoral bifurcation. (Grade 1/Level of Evidence: C)
- For focal lesions (<5 cm) in the SFA that have unsatisfactory technical results with balloon angioplasty, we suggest selective stenting. (Grade 2/Level of Evidence: C)
- For intermediate-length lesions (5–15 cm) in the SFA, we recommend the adjunctive use of self-expanding nitinol stents (with or without paclitaxel) to improve the midterm patency of angioplasty. (Grade 1/Level of Evidence: B)
- We recommend against EVT of isolated infrapopliteal disease for IC because this treatment is of unproven benefit and possibly harmful. (Grade 1/Level of Evidence: C)
- We recommend surgical bypass as an initial revascularization strategy for patients with diffuse femoropopliteal disease, small caliber (<5 mm), or extensive calcification of the SFA, if they have favorable anatomy for bypass (popliteal artery target, good runoff) and have average or low operative risk. (Grade 1/Level of Evidence: B)
- We recommend using the saphenous vein as the preferred conduit for infrainguinal bypass grafts. (Grade 1/Level of Evidence: A)
- In the absence of suitable vein, we suggest using prosthetic conduit for femoropopliteal bypass in claudicant patients, if the above-knee popliteal artery is the target vessel and good runoff is present. (Grade 2/Level of Evidence: C)

BMS, Bare-metal stent; EVT, Endovascular therapy; SFA, superficial femoral artery.

8.1.5 Reporting Standards of the Society for Vascular Surgery (Stoner et al. 2016)

8.1.5.1 Claudication Reporting

1. An ankle-brachial index (ABI) ≤ 0.90 is the threshold for diagnosis of PAD. As stated in the recently published SVS guidelines, when the ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive, we recommend exercise ABI.
2. Baseline functional characterization with treadmill testing or preferably ambulatory testing by 6-min walk test.
3. Quality of life assessment by validated scoring system, such as the Walking Impairment Questionnaire.
4. Classification of severity based on previously published SVS guidelines.

8.1.5.2 Outcome Measures: Procedural

1. Technical success is defined as successful use of a device or technique to establish vessel patency with a residual stenosis <30%. Procedural success is defined as technical success and completion of the procedure without complications.
2. Hemodynamic success is defined as a pressure gradient <10 mm Hg across a lesion or corresponding increase in ABI of 0.10 or toe pressure of 0.10. Other measures of hemodynamic success (such as pulse volume recording amplitude) may be acceptable.
3. Patency is evaluated by an accepted imaging technique of the specific arterial site treated that clearly shows flow through the lesion.
4. Within the context of a clinical trial, duplex ultrasound should be considered the standard for patency and restenosis surveillance. A peak systolic velocity >300 cm/s or peak systolic velocity ratio >3.0 indicates restenosis.
5. Target lesion revascularization can be driven by clinical, anatomic, and hemodynamic indications and as such does not always contribute to the assessment of clinical failure. It should not be used as a primary end point.

8.1.5.3 Outcome Measures: Disease Specific

1. In addition to anatomic and hemodynamic measures of success, claudication trials should include disease-specific quality of life outcome measures and functional assessment.
2. Critical limb ischemia trials should use the objective performance goals as measures of efficacy and safety in addition to disease-specific and overall quality of life measures.
3. Lower extremity endovascular therapy for PAD should be reported at minimum for 30-day, 1-year, and 2-year follow-up, promoting standardization and hence more clinically meaningful comparisons of peripheral vascular interventions. Five-year follow-up is preferable.

8.2 Results

8.2.1 Exercise Training

8.2.1.1 Meta-analysis/Systematic Reviews

Supervised vs. unsupervised exercise therapy
A Cochrane review (Lane et al. 2014) determined whether an exercise programme in people with IC was effective in alleviating symptoms and increasing walking treadmill distances and walking times. Any exercise programme or regimen used in the treatment of IC was included, such as walking, skipping and running. Thirty trials were included in this review, involving a total of 1816 participants with stable leg pain. Exercise programmes were of significant benefit compared with placebo or usual care in improving walking time and distance in people with leg pain from IC who were considered to be fit for exercise intervention. The effect of exercise, when compared with placebo or usual care, was inconclusive on mortality, amputation and peak exercise calf blood flow due to limited data. No data were given on non-fatal cardiovascular events.

This poses the question whether exercise therapy should be conducted in a supervised or unsupervised setting. Al-Jundi et al. (2013) compiled a systematic review on this topic. The 17 included studies for home-based exercise programmes (HEPs) were mostly of low methodological quality. There was "low-level" evidence that HEPs can improve walking capacity and quality of life in patients with IC when compared with baseline or in comparison to usual care or observation only. In addition, improvements with HEPs may be inferior to those resulting from supervised exercise programmes. In conclusion, clinicians should consider using HEPs to promote walking in patients with IC, as opposed to basic "go home and walk" advice, when supervised training is unavailable or impractical.

The effects of supervised versus non-supervised exercise therapy on maximal walking time or distance on a treadmill for people with IC were analyzed in a further Cochrane review (Fokkenrood et al. 2013). According to this review, supervised exercise therapy (SET) has statistically significant benefit on treadmill walking distance (maximal and pain-free) compared with non-supervised regimens. However, the clinical relevance of this has not been demonstrated definitively. A further systematic review and meta-analysis came to a similar result: in claudication patients, supervised exercise (SE) is more effective than unsupervised exercise (UE) at improving maximal walking and claudication distances, yet there is no difference in general quality of life or patient-reported community-based walking (Vemulapalli et al. 2015).

In a fourth meta-analysis it was hypothesized that there is a positive treatment effect in relation to the intensity of supervision and improvement in walking capacity (i.e., a "dose–response" hypothesis) (Gommans et al. 2014). The authors found that SET for IC is superior to all other forms of exercise therapy. Intensity of supervision was related to improved walking distance. A 3-month SET programme

appeared to be the most preferable. After 3 months of training, supervision might be replaced by a home-based programme, as this meta-analysis demonstrated an equivalent effect of SET and home-based exercise therapy after 6 months.

Parmenter et al. (2015) performed the first meta-analysis limited to RCTs to analyse perceived walking impairment, general health and quality of life outcomes for exercise interventions in PAD. In analysing the findings, it is important to take into account the quality of the trials included in the review and the limited study of exercise modes other than walking. Nevertheless, this review suggests that walking training to various levels of claudication pain improves perceived walking speed, distance and stair-climbing performance as measured by the Walking Impairment Questionnaire, and self-reported physical function (SF-36) in patients with PAD.

Specific problems

In most studies, SET consists of treadmill or track walking. However, alternative modes of exercise therapy have been described. Lauret et al. (2014) assessed the effects of different modes of SET on the maximum walking distance of patients with IC in a Cochrane review. Five studies comparing supervised walking exercise and alternative modes of exercise were found. The alternative modes of exercise therapy included cycling, strength training, and upper-arm ergometry. The studies represented a sample size of 135 participants with a low risk of bias. Overall, there was no clear evidence of a difference between supervised walking exercise and alternative modes of exercise in maximum walking distance on a treadmill or in pain-free walking distance. The results indicate that alternative exercise modes may be useful when supervised walking exercise is not an option for the patient.

Occasionally, there is concern regarding the safety of performing SET because IC patients are at risk for untoward cardiovascular events. Gommans, Fokkenrood et al. (2015a) found 74 studies representing 82,725 h of training in 2876 IC patients. Eight adverse events were reported, six of cardiac and two of noncardiac origin, resulting in an all-cause complication rate of one event per 10,340 patient-hours. Thus, supervised exercise therapy can safely be prescribed in patients with IC because an exceedingly low all-cause complication rate was found. Routine cardiac screening before commencing SET is not required.

8.2.1.2 Studies

In a prospective, randomized controlled clinical trial Gardner et al. (2012) determined whether an optimal exercise program length exists to efficaciously change claudication onset time (COT) and peak walking time (PWT) in patients with peripheral arterial disease (PAD) and claudication. The primary finding of this investigation was that exercise-mediated gains in COT and PWT occur rapidly within the first 2 months of exercise rehabilitation and are maintained with further training. This finding has major implications for patients, exercise program personnel, and utilization of resources and facilities. From the patient's viewpoint, claudication severity can be improved with relatively little effort by walking an average of

1.5 miles per week for 2 months. The clinical significance is that a relatively short 2-month exercise program may be preferred to a longer program to treat claudication because adherence is higher, costs associated with personnel and use of facilities are lower per patient, and more patients can be trained for a given amount of personnel time and resource utilization.

In a further prospective study, Gardner et al. (2014) determined whether sex and diabetes were factors associated with the response to exercise rehabilitation in patients with claudication. Eighty patients were randomized to home-based and supervised exercise programs, and 60 finished with complete exercise intervention data. The primary finding was that the only subgroup of patients with PAD and claudication who did not significantly improve their COT and PWT after 3 months of exercise rehabilitation was diabetic women, only 37% of diabetic women increased their COT. Of the two factors, sex was more closely related to the exercise response than diabetes, as the mean change scores for COT and PWT in women were less than half of those in men, and fewer women responded to exercise. Gender differences following SET in patients with IC were also observed by Gommans, Scheltinga et al. (2015b). In this study, absolute claudication distance increase was significantly lower for women than for men during the first 3 months of therapy. Moreover, absolute walking distance was significantly shorter for women compared with men after 1 year, women with IC benefit less from SET than men.

A randomized clinical trial was performed by Spafford et al. (2014) to determine whether Nordic pole walking (NPW) is more effective in improving walking distance than a standard home exercise programme in patients with IC. After 12 weeks the walking distance of patients in the NPW group was significantly longer than of patients in the control group. The efficacy of NPW has been confirmed by Bulińska et al. (2016). In a randomized trial they found NPW as effective as the standard traditional treadmill training and much less expensive. It should be the preferred method of exercise in IC patients.

Saxton et al. (2011) investigated the effects of upper- and lower-limb aerobic exercise training on disease-specific functional status and generic health-related quality of life (QOL) in patients with IC in a randomized controlled trial. Improvements in patient perceptions of disease-specific functional status and generic health-related QOL domains were observed after both the upper-limb and lower-limb exercise training regimens. Both forms of exercise training were well tolerated; however, because upper-limb exercise training avoids the ischemic pain that is experienced during lower-limb exertion, it could be used in the early stages of an exercise rehabilitation program until patients feel more able and confident to engage in lower-limb exercise. It might also be a preferred exercise option for patients with increased disease severity.

Supervised exercise therapy (SET) is known to increase the walking capacity of patients with IC. However, it is unclear whether SET increases physical activity. Therefore, Fokkenrood et al. (2015) investigated the effect of SET on physical activity levels and ambulatory activities in patients with IC. All participants of this study received a move monitor, and were asked to wear the device correctly for 7 consecutive days. A 3-month period of SET was commenced immediately after a

1 week monitoring period. After 3 months, SET outcome was discussed with the patient followed by a second 7-day period of wearing the move monitor again. Despite significant increases in pain free walking distance, maximal walking distance and physical functioning score (SF-36) following SET, no increase in the mean daily physical activity level was found. Furthermore, the total number of steps and time spent in ambulatory activities did not change following SET.

SET is the first-choice symptomatic treatment for patients with IC. Unfortunately, SET has been largely underused in clinical practice. There seem to be three reasons why this safe and cost-effective treatment has not been widely adopted (Gommans & Teijink 2015). SET places a particular burden on patients in terms of effort and responsibility, rather than offering a quick fix for their discomfort, so there is some patient resistance to it. A second category of answers involves clinicians. Self-interest of doctors performing interventions that involve fee-for-service is undoubtedly a contributor. However, the most important factors hindering the wider implementation of SET are lack of access and reimbursement issues. Limited availability of qualified therapists and financial barriers in health-care systems can add to this underuse. As a result, even clinicians who fully endorse SET as initial treatment for IC may end up performing invasive interventions if their patients cannot find a qualified SET practitioner (Gommans & Teijink 2015). In this context, Dutch vascular surgeons and fellows in vascular surgery were asked by Lauret et al. (2012) to complete a 25-question survey regarding SET as treatment option for PAOD. The study showed that the criteria not to refer for SET are largely based on existence of major co-morbidity (e.g., pulmonary and cardiac) or a significant iliac stenosis causing IC. This could be explained by concern of major complications or the belief that SET is ineffective to improve walking ability or quality of life in these particular patients. Conditions that are perceived as contraindications for SET, including cardiopulmonary morbidity, are in fact additional indications for participation in an exercise programme.

8.2.2 Endovascular Therapy

8.2.2.1 Meta-analyses/Systematic Reviews

The ACC/AHA and ESC guidelines are in conflict over the use of primary stent placement in the femoral-popliteal arteries, with the ACC/AHA guideline giving it a Class III recommendation (do not do) and the ESC guideline making primary femoral stenting reasonable first-line therapy (Class IIa) for intermediate-length lesions. The current evidence from several randomized controlled trials supports primary stenting in intermediate length femoral stenoses and occlusions. In current practice, the standard is to primarily stent intermediate long superficial femoral artery (SFA) lesions (Olin et al. 2016).

A Cochrane review (Chowdhury et al. 2014) determined the effect of PTA compared with PTA with bare metal stenting for SFA stenoses on vessel patency in

people with symptomatic (Rutherford categories 1–6; Fontaine stages II to IV) lower limb peripheral vascular disease. Eleven randomized trials (1387 patients) of angioplasty alone versus angioplasty with bare metal stenting for the treatment of SFA stenoses were analyzed. At 6 months follow-up both primary duplex and angiographic patency were higher in the PTA plus stent group than the PTA alone group. The overall effect was significant (odds ratio 2.90). This significant finding was only sustained at 12 months of follow-up with regard to duplex patency. The significantly higher angiographic patency in the stent group at 6 months was lost by 12 months. Twenty-four months follow up also showed no significant difference in duplex or angiographic patency. In addition, a more pronounced improvement in treadmill walking distance in participants with PTA with stent insertion was observed at 6 months, but not at 12 months and 24 months.

Jens et al. (2014) also performed a systematic review of the 1–36 months follow-up outcomes of RCTs comparing different endovascular treatment strategies in above the knee arterial segments. The population evaluated had IC in 85% and CLI in 15%. Overall, quality of evidence was low to moderate. The 15 trials comparing bare stent (BS) with PTA (with optional bailout stenting) showed, in general, that clinical outcomes did not differ between both interventions after 6–36 months follow-up. Only for treadmill walking capacity did BS show some beneficial effect over PTA. According to this data, endovascular treatment of above the knee lesions in patients with IC should initially be performed using PTA, especially as PTA is much less expensive compared with the other treatment strategies. When PTA does not result into less than 30% residual stenosis, or flow-limiting dissection occurs, bailout stenting may be performed.

A further systematic review (Simpson et al. 2014) aimed to answer the question: What are the clinical effectiveness and cost-effectiveness of additional techniques designed to improve the results of endovascular treatment (standard transluminal balloon angioplasty) for peripheral arterial disease? The population was participants with symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament. Patients with either IC or CLI were included. In total, 40 RCTs were analyzed, many of which had small sample sizes. Significantly reduced restenosis rates were shown in meta-analyses of self-expanding stents (relative risk, RR 0.67), endovascular brachytherapy (EVBT) (RR 0.63) at 12 months and drug-coated balloons (DCBs) at 6 months (RR 0.40), and single studies of stent-graft or drug-eluting stent (DES), compared with PTA; a single study showed improvements with DES versus bare-metal stents (BMSs). Compared with PTA, walking capacity was not significantly affected by cutting balloon, balloon-expandable stents or EVBT; in self-expanding stents, there was evidence of improvement in walking capacity after up to 12 months. The use of DCBs dominated both the assumed standard practice of PTA with bailout BMS and all other interventions because it lowered lifetime costs and improved quality of life (QoL). These results were seen for both patient populations (IC and CLI). Furthermore, the positive finding for self-expanding stents in this report concurs with ESC and SVS guidelines, which recommend primary nitinol stenting as the first-line intervention for intermediate length, superficial femoral artery lesions.

Katsanos et al. (2014) conducted a network meta-analysis of RCTs comparing bare nitinol stents, covered nitinol stents, paclitaxel- or sirolimus-eluting stents (PES or SES), and paclitaxel-coated balloons (PCB) with plain balloon angioplasty or with each other in the femoropopliteal artery. Technical success was highest with covered stents (pooled odds ratio 13.6; probability best 82%) followed by uncovered stents (pooled odds ratio 7.0; probability best 18%) when compared with balloon angioplasty (reference treatment). Vascular restenosis was lowest with PES (rate ratio 0.43; probability best 45%) followed by PCB (rate ratio 0.43; probability best 42%). Target lesion revascularization was lowest with PCB (rate ratio 0.36; probability best 56%) followed by PES (rate ratio 0.42; probability best 33%). Major amputations were rare in all treatment and control groups (pooled amputation rate of 0.7 events per 100 person-years). In summary, immediate technical success is more likely with the use of either covered or uncovered stents, whereas paclitaxel-eluting stents and paclitaxel-coated balloons offer the best long-term results in occlusive disease of femoropopliteal artery. In addition, Katsanos, Spiliopoulos et al. (2016b) provided a qualitative analysis and quantitative synthesis of RCTs investigating PCBs in the femoropopliteal artery. Eleven RCTs with 1609 subjects (1403 claudicants and 206 patients with critical limb ischemia) with medium-length femoropopliteal lesions (mean range 5.1–11.9 cm) were included. According to this systematic review and meta-analysis PCBs reduce by more than half the rates of restenosis and target lesion revascularization in the femoropopliteal artery regardless of stent placement. Biologic effect size may vary according to paclitaxel bioavailability. In a further analysis, Katsanos, Geisler et al. (2016a) estimated the per-patient cost impact on the NHS of these competing endovascular treatment strategies. Over 24 months, DCB, DES and BMS reduced target lesion revascularisations (TLRs) of de novo lesions from 36.2% to 17.6%, 19.4% and 26.9%, respectively, at an increased cost of £43, £44 and £112. Numbers needed to treat (NNTs) to avoid 1 TLR in 24 months were 5.4, 6.0 and 10.8, resulting in cost per TLR avoided of £231, £264 and £1204. In conclusion, widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS. Based on currently available data, DCBs offer the highest clinical and economic value.

Ambler et al. (2014) compiled a Cochrane review with the objective to analyze RCTs comparing atherectomy by a rotating cutting blade against any established treatment for peripheral arterial disease in order to evaluate the effectiveness of atherectomy. Four trials were included with a total of 220 participants. All participants had symptomatic peripheral arterial disease with either claudication or critical limb ischaemia. The review identified poor quality evidence to support atherectomy as an alternative to balloon angioplasty in maintaining primary patency at any time interval. There was no evidence for superiority of atherectomy over angioplasty on any outcome, and distal embolisation was not reported in all trials of atherectomy.

Last, but not least a Cochrane review (Andras et al. 2014) assessed the efficacy of, and complications associated with, intravascular brachytherapy (IVBT) for maintaining patency after angioplasty or stent insertion in native vessels or bypass grafts of the iliac or infrainguinal arteries. Eight RCTs with a combined total of 1090 participants were included in this review. The evidence for using peripheral

artery brachytherapy as an adjunct to percutaneous transluminal angioplasty to maintain patency and for the prevention of restenosis in people with peripheral vascular disease is limited, mainly due to the inconsistencies of assessment and reporting of clinically relevant outcomes. Use of brachytherapy may be recommended for a medium-term 1-year reduction in restenosis rate. In particular, more data on long-term outcomes and comparisons with other techniques such as drug eluting balloons and stents, together with health economics and cost-effectiveness data, are required before the procedure could be recommended for widespread use.

8.2.2.2 Studies

Laird et al. (2012) presented the 3-year outcomes of the RESILIENT-Study. Two hundred and six patients (143 men; mean age 67 years) with IC due to superficial femoral and proximal popliteal artery lesions up to 15 cm long were randomized (2:1) to treatment with nitinol stents or balloon angioplasty at 24 US and European centers and followed for 3 years. In this multicenter trial, primary implantation of a nitinol stent for moderate-length lesions in the femoropopliteal segment of patients with claudication was associated with better long-term results vs. balloon angioplasty alone. The 12-month freedom from target lesion revascularization (TLR) was 87.3% for the stent group vs. 45.2% for the angioplasty group ($p < 0.0001$). At 3 years, there was no difference in survival (90.0% vs. 91.7%) or major adverse events (75.2% vs. 75.2%) between the stent and angioplasty groups. Freedom from TLR at 3 years was significantly better in the stent group (75.5% vs. 41.8%), as was clinical success (63.2% vs. 17.9%). At 18 months, a 4.1% stent fracture rate was documented.

The VIASTAR trial is a prospective, randomized, single-blind, multicenter study (Lammer et al. 2015). The major inclusion criteria were moderate to severe claudication and CLI, de novo arteriosclerotic stenosis or occlusion of the SFA and proximal popliteal artery 10–35 cm in length (TASC II C and D). A total of 141 patients were included; 72 patients were allocated to treatment with the VIABAHN endoprosthesis and 69 patients to BMS. The 24-month primary patency rate was significantly higher in the VIABAHN versus BMS group (63.1 versus 41.2), whereas the difference was not significant at the 12-month follow-up. The driver of significance was lesions C 20 cm with significantly higher primary patency rates at 24 months in favor of the VIABAHN compared with BMS (65.2 versus 26.7%). The difference in freedom from TLR was not significant (79.4 versus 73.0%). At 24-month, this trial in PAD patients with long femoropopliteal lesions demonstrated a significantly improved primary patency rate for heparin-bonded covered stents compared to BMS, however, without a significant impact on clinical outcomes and TLR. Geraghty et al. (2013), too, compared the long-term outcomes of complex superficial femoral artery disease intervention using the VIABAHN endoprosthesis to those obtained with bare nitinol stent implantation. The primary end point of this randomized VIBRANT trial was primary patency of the treated arterial segment. There was no significant difference between 3-year primary patency for the VIABAHN device (24.2%) or bare nitinol stent (25.9%). At the 3-year end point, bare nitinol stents

demonstrated a statistical advantage over the VIABAHN endoprostheses with regard to primary-assisted patency (88.8% vs 69.8%). No study patient required major amputation during the trial. Thus, at 3 years, substantially equivalent safety and efficacy were demonstrated between the VIABAHN endograft and bare nitinol stent treatment arms.

The randomized controlled Zilver PTX trial evaluated clinical durability of a paclitaxel-coated drug-eluting stent (DES) for femoropopliteal artery lesions (Dake et al. 2016). Outcomes compared primary DES versus PTA, overall DES (primary and provisional) versus standard care (PTA and provisional Zilver bare metal stent [BMS]), and provisional DES versus provisional BMS. Patients with symptomatic femoropopliteal artery disease were randomly assigned to DES (n = 236) or PTA (n = 238). Approximately 91% had claudication; 9% had CLI. Patients experiencing acute PTA failure underwent secondary randomization to provisional BMS (n = 59) or DES (n = 61). The 1-year primary end points of event-free survival and patency showed superiority of primary DES in comparison with PTA; these results were sustained through 5 years. These results represent >40% relative risk reduction for restenosis and target lesion revascularization through 5 years for the overall DES in comparison with standard care and for provisional DES in comparison with provisional BMS.

Zeller et al. (2014) compared retrospectively the performance of DCB and DES in long femoropopliteal lesions in 228 patients (139 men; median age 69 years) with femoropopliteal lesions ≥10 cm suffering from peripheral artery disease (Rutherford categories 1–5). Propensity score stratification was used to minimize bias. In the DCB cohort, provisional stent placement was performed in 24 (18.3%) lesions for refractory stenosis (3.8%), flow-limiting dissection (9.9%), and other reasons (4.6%). The binary restenosis rates were 23.9% and 30.4% in the DCB and DES cohorts, respectively, and clinically driven TLR rates were 15.6% vs. 19.0%, respectively. Estimates for freedom from clinically driven TLR and event-free survival were not different between the study cohorts nor were outcomes regarding the ankle-brachial index and Rutherford category.

The THUNDER trial was the first study to investigate the treatment of femoropopliteal arteries with a paclitaxel-coated balloon. Over the 5-year period, the cumulative number of patients with TLR remained significantly lower in the PCB group (21%) than in the control group (uncoated balloon, 56%) (Tepe et al. 2015b). The IN.PACT SFA trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with IC or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA (Tepe et al. 2015a). In the intention-to-treat population, the 12-month primary patency rate was 82.2% in the DCB arm versus 52.4% in the PTA arm. The DCB-treated patients demonstrated lower rates of clinically driven target lesion revascularization versus PTA-treated patients through 12 months (2.4% versus 20.6%). A significantly higher primary sustained clinical improvement (85.2%) was observed in the DCB arm in comparison with the PTA arm (68.9%). Implantation of provisional stents was similar in the DCB and PTA arms (7.3% versus 12.6%). In conclusion, in this trial DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic superficial femoral and proximal

popliteal artery PAD. Meanwhile the longer-term outcomes from this trial have been published (Laird et al. 2015). The 24-month outcomes demonstrated a durable and superior treatment effect of DCB versus PTA. Patients treated with DCB showed significantly higher primary patency when compared with PTA (78.9% vs. 50.1%). Clinically driven target lesion revascularization rates were 9.1% and 28.3% for the DCB and PTA groups, respectively. The primary safety composite endpoint of freedom from 30-day device- and procedure-related death and target limb major amputation and clinically driven-TVR within 24 months was 87.4% in the DCB group versus 69.8% in the PTA group.

LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) was a prospective, single blind (to patient), randomized (1:1) trial comparing late lumen loss in femoropopliteal lesions treated with the Lutonix DCB versus an uncoated balloon (Scheinert et al. 2014). At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 mm) than for the control group (1.09 mm), with similar safety as has been reported for uncoated balloon angioplasty. The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT II) trial was a prospective, multicenter, randomized, controlled trial (Rosenfield et al. 2015). Patients eligible for inclusion in the trial had Rutherford stage 2–4 of PAD and an angiographically significant atherosclerotic lesion (diameter of stenosis, ≥70%) in the superficial femoral or popliteal artery (or both). Four hundred and seventy six patients were randomly assigned, in a 2:1 ratio, to undergo PTA with the use of either a paclitaxel-coated balloon (Lutonix) or a standard angioplasty balloon. The proportion of patients who had primary patency at 12 months (the primary efficacy end point) was significantly greater with the drug-coated balloon than with the standard angioplasty balloon (65.2% vs. 52.6%). There were fewer events of target-lesion revascularization in the drug-coated–balloon group than in the standard-angioplasty group, but this difference did not reach statistical significance. The safety of the drug-coated balloon was noninferior to that of the standard balloon.

8.2.3 Exercise Therapy and Endovascular Therapy

8.2.3.1 Meta-analysis/Systematic Reviews

Frans et al. (2012) performed a systematic review to summarize the results of all randomized clinical trials comparing PTA with (supervised) exercise therapy ((S)ET) in patients with IC. Although the endpoints in most trials comprised walking distances and QoL, pooling of data was impossible owing to heterogeneity. Generally, the effectiveness of PTA and (S)ET was equivalent. A combination of PTA and exercise (SET or ET advice) may be superior to exercise or PTA alone. A further review came to a similar conclusion (Aherne et al. 2015).

The relative effectiveness of the available treatments for patients with IC, such as exercise therapy and revascularization (either by surgical bypass or endovascular interventions), is not well established. Malgor et al. (2015) conducted a systematic

review to evaluate the available modalities. Eight systematic reviews and 12 trials enrolling 1548 patients were included in this analysis. Compared with medical management, each of the three treatments (surgery, endovascular therapy, and exercise therapy) was associated with improved walking distance, claudication symptoms, and quality of life (high-quality evidence). Evidence supporting superiority of one of the three approaches was limited. However, blood flow parameters improved faster and better with both forms of revascularization compared with exercise or medical management (low- to moderate-quality evidence). Compared with endovascular therapy, open surgery may be associated with longer length of hospital stay and higher complication rate but resulted in more durable patency (moderate-quality evidence). Data on which intervention is best suited for a particular patient to obtain the best outcome are lacking. Therefore, patients should be informed of the current uncertainty and the pros and cons of these treatments. Patients' values and preferences and availability of operative expertise should help guide this decision.

8.2.3.2 Studies

The CLEVER study was a randomized, multicenter clinical trial designed to test the hypothesis that stent revascularization (ST) plus optimal medical care (OMC) and supervised exercise (SE) plus OMC would be associated with a greater improvement in peak walking time (PWT) on a graded treadmill test than with OMC alone (Murphy et al. 2015). One hundred and eleven patients were included. In this study, patients with aortoiliac artery PAD and moderate-to-severe claudication, a population widely regarded as optimal for ST, achieved significant improvements in clinical outcomes when treated with either SE or ST compared with OMC alone, and this benefit was durable for at least 18 months. The benefit of SE was equal to the invasive stent strategy and was maintained for a full year after completion of the supervised training phase. These data provide strong support in favor of comparable access to both SE and ST to improve the primary ischemic symptom of PAD, claudication. Reynolds et al. (2014) defined the cost-effectiveness of the three strategies tested in the CLEVER study. They found that both SE and ST are economically attractive by conventional US standards relative to OMC for the treatment of claudication due to aortoiliac stenosis. Because ST is more costly and provides marginal additional benefit over SE, SE may provide better value, at least in the short term.

The CETAC trial was a single-centre randomized trial comparing the clinical effectiveness of SET versus endovascular revascularization (ER) as initial treatment for patients with IC due to aortoiliac or femoropopliteal disease (Fakhry et al. 2013). A total of 151 patients were initially assigned randomly to SET (n = 75) or ER (n = 76). This report examined the long-term clinical effectiveness of SET and ER as initial treatment for patients with IC. During follow-up, 17 patients in the SET group and 15 in the ER group died. The cumulative survival probability for 7 years after randomization was 68 per cent in the SET group and 74% in the ER group (not significant). After a median follow-up of approximately 7 years, SET-first treatment was equivalent to ER-first treatment in achieving improvements in functional performance and QoL. Although the secondary intervention rate was

higher in patients who had SET as initial treatment, the total number of invasive interventions (primary and secondary) remained substantially lower, and hence this study supports the use of a SET-first approach for patients with IC.

Mazari et al. (2012) recruited over a 6-year interval 178 patients with IC and femoropopliteal arterial lesions. The patients were randomized into one of three treatment arms (PTA, 60; SE, 60; PTA plus SE, 58). There were no significant differences in outcomes between the groups. At 12 months after treatment in the PTA group, 37 (71%) of 52 patients had improved, nine (17%) demonstrated no change, and six (12%) had deteriorated. In the SE group, 32 (70%) of 46 patients had improved, 6 (13%) demonstrated no change, and 8 (17%) had deteriorated. In the PTA plus SE group, 40 patients (85%) had improved, and seven (15%) demonstrated no change. No patient in this treatment arm reported any deterioration at 1 year. PTA and PTA plus SE resulted in a significantly higher median postexercise ABPI compared with SE alone at 12 months. However, there were no statistically significant differences between the three treatment arms in any other clinical indicator. For patients with IC due to femoropopliteal disease, PTA, SE, and PTA plus SE were all equally effective in improving walking distance and QoL after 12 months. PTA was associated with a high incidence of restenosis, adding both the costs of reintervention and the potential for complications. In this study, SE was the most cost-effective first-line treatment for IC, and when combined with PTA was more cost-effective than PTA alone (Mazari et al. 2013). The cost per QALY was significantly higher for PTA (€11,777.00) compared with SE (€6147.04) and PTA + SE (€10,649.74). QALYs were lost when PTA alone was used as first-line treatment in comparison with SE or PTA + SE. Already before, the cost-effectiveness of endovascular revascularization was compared to supervised hospital-based exercise in patients with intermittent claudication after 12-month follow-up (Spronk et al. 2008). In this prospective RCT no significant difference in the 6- and 12-month EuroQol rating scale, SF36 physical functioning, and QALYs between the treatment groups was seen. Revascularization was significantly more expensive, which favors exercise.

The ERASE study was a parallel-design RCT conducted in the Netherlands at 10 sites comparing endovascular revascularization plus supervised exercise (SE) for IC with SE only (Fakhry et al. 2015). Two hundred and twelve patients were randomly assigned to SE (n = 106) or endovascular revascularization plus SE (n = 106; combination therapy group). All participants had one or more vascular stenoses at the aortoiliac level, the femoropopliteal level, or both. During follow-up, the maximum treadmill walking distance improved significantly in both groups. Compared with the SE only group, the improvement was significantly greater in the combination therapy group. One year after randomization, endovascular revascularization plus SE led to greater improvement in pain-free walking distance compared with SE. Similarly, ABI at rest and after exercise showed significantly greater improvement in the combination therapy group. Twenty-three patients (22%) in the SE group needed an intervention during follow-up due to deterioration of symptoms or persisting disabling symptoms. In the combination therapy group, eight patients (8%) required a secondary intervention. One year after randomization, the disease-

specific VascuQol score significantly improved in both groups. The improvement was significantly greater for the combination therapy group.

8.2.4 Endovascular and Surgical Intervention

In spite of recommendations advocating conservative best medical treatment, many patients with infrainguinal IC are treated by invasive open and endovascular methods. Lindgren et al. (2014) evaluated the incidence and 1-year results of all such treatments during 2009 in Sweden. The design was a 1-year follow-up through the Swedish Vascular Registry (Swedvasc) of all 775 patients in whom 843 invasive infrainguinal procedures (796 index procedures and 47 secondary procedures) were performed for IC in 2009. The index procedures were open surgery in 37% of patients, endovascular treatment in 58%, and hybrid treatment in 5%. Improvement at 1 year was reported by 77.6% of patients in the open surgery group, 71.6% in the endovascular treatment group, and 57.9% in the hybrid treatment group; 7.3% of patients reported unchanged limb function, and 4.1% reported deterioration. The 12-month amputation rate was 1.4%. New interventions were performed in 5.9%. Reintervention on the index side was performed in 3.3% of cases in the open surgery group and in 2.8% in the endovascular treatment group. The identified results of satisfactory outcome in three out of four patients warrant further studies of whether or not invasive treatment of infrainguinal IC is appropriate.

Sachs et al. (2011) offered an overview of the treatment of PAD patients in the U.S. between the years 1999 and 2007 based on the Nationwide Inpatient Sample (NIS) database. During this time period, the number of annually performed procedures for claudication increased by 58%, from 24,488 to 38,785. PTA ± Stent procedures increased approximately threefold between 1999 and 2007, for claudication from 6416 to 26,671. Peripheral bypass graft (BPG) operations dropped by a third for claudication (from 13,625 to 9108). Aortoiliac-femoral bypass (ABF) procedures decreased by 38% for claudication (3184 to 1967). Average costs per case involving PTA ± Stent procedures for claudication rose from $8670 ± $5125 in 2001 to $14,084 ± 9922 in 2007 (62.5% increase). For BPG, average costs for claudication rose from $9322 ±$7353 to $12,681 ± $8427. In claudicants, the PTA ± Stent group had similar, albeit slightly lower rates of adjusted in-hospital mortality than BPG (0.2% vs 0.4%) and both were lower than ABF (1.5%). In claudicants, amputation was rare, irrespective of the type of intervention (PTA ± Stent: 0.1%; BPG: 0.2%; ABF: 0.1%) and event rates did not differ between groups. Length of stay was lowest in the PTA± Stent group (1.0 day ± 0.02 days), followed by BPG (4.52 days ± 0.31 days), and ABF (5.88 days ± 0.05 days). The authors concluded that better data are necessary in order to justify this increase in both the use and the costs of PTA ± Stent for claudication. Crucial data of this largest study about the surgical/endovascular treatment of IC patients can be found in Table 8.1.

Table 8.1 Demographics and comorbidities of patients in the US nationwide inpatient sample with claudication, by intervention: 1999–2007 (Sachs et al. 2011)

	PTA ± Stent	Aortofemoral bypass	Peripheral bypass
Total patients (n)	128,937	24,033	102,604
Mean patient age (years)	69	60	67
Female gender (%)	43.1	44.9	37.1
Comorbidities			
Congestive heart failure (%)	6.7	7.7	6.3
Renal failure (%)	6.1	2.4	3.2
Hypertension (%)	69.8	61.0	67.8
Diabetes (%)	29.5	16.2	26.4
Chron. pulmonary disease (%)	17.1	33.4	25.3
In-hospital mortality (%)	0.2	1.5	0.4
Length of stay (days)[a]	1.0 ± 0.02	5.88 ± 0.05	4.52 ± 0.31
Discharged home (%)[a]	80.2	73.9	55.2

Note: [a]Combined values for patients with IC and CLI

8.2.5 Antiplatelet Therapy After Endovascular Arterial Procedures

Peeters Weem et al. (2016) performed a systematic review and meta-analysis to summarize the available evidence for Dual antiplatelet therapy (DAPT) after endovascular revascularization throughout the arterial system. Included in the search were randomized controlled trials (RCTs) comparing DAPT with mono antiplatelet therapy (MAPT). The primary outcome was restenosis or stent thrombosis, and secondary outcomes were major adverse cardiac events (MACE), target lesion revascularization, cerebrovascular accident or transient ischemic attack, bleeding, and death. Nine articles were included in this study, involving lower limb peripheral arteries (1), carotid arteries (2), and coronary arteries (6). The pooled results of coronary trials showed a risk ratio (RR) for restenosis with DAPT of 0.60 and for myocardial infarction 0.49. In the carotid artery trials the RR for restenosis was 0.22 and for peripheral arteries 1.02. A meta-analysis of bleeding risk of all the included trials showed a RR of 1.06 with DAPT. The available evidence comparing DAPT with mono antiplatelet therapy (MAPT) after endovascular arterial revascularization is limited and the majority of trials were conducted in the cardiology field. No significant evidence for superiority of DAPT compared with MAPT was found, but there was also no evidence of an increased bleeding risk with DAPT over MAPT.

8.3 Conclusions for Clinical Practice

1. In patients with IC, the most important management options are information, advice, support and treatment regarding the secondary prevention of cardiovascular disease and modification of risk factors.

2. In a step-by-step approach patient should be initially recommended supervised exercise therapy. In most studies, supervised exercise therapy consists of treadmill or track walking. Alternative exercise modes may be useful when supervised walking exercise is not an option for the patient.
3. Next in the management algorithm is an endovascular strategy. Offer bypass surgery for treating people with severe lifestyle-limiting IC only when angioplasty has been unsuccessful or is unsuitable.
4. A combination of PTA and exercise may be superior to exercise or PTA alone.

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Chapter 9
Critical Limb Ischemia

9.1 Classification and Prognosis

The term "critical limb ischemia" (CLI) is defined by clinical manifestations of rest pain, ischemic ulcers, and gangrene, corresponding to stages III and IV or 4–6 of the Fontaine and Rutherford classification systems, respectively. A more thorough classification system, however, is required (in part due to the dramatic rise of diabetes) in order to more accurately assess and describe the extent of infection and/or tissue loss. The Society for Vascular Surgery's recently developed "Threatened Limb Classification System" categorises the condition according to the extent of wound size, ischemia and foot infection ("WIFI"), while also taking the ankle-brachial index (ABI), toe pressure and transcutaneous O_2 measurements into account (Mills et al. 2014) (for details, see Chap. 13, *Diabetic Foot*).

Upon review of 50 studies, Rollins et al. (2013) were able to collect and present data regarding the general prognosis and mortality of patients suffering from CLI. The resulting numbers can be used to assess study results; they confirm the poor outcome of this disease. According to their estimations, the current predicted probability of death from any cause in CLI patients is 3.7% after 30 days, 17.5% after 1 year, 35.1% after 3 years, and 46.2% following 5 years.

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9.2 Guidelines

9.2.1 American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA)

The ACCF/AHA guidelines (Anderson et al. 2013) provide the following Class I recommendations for treatment of patients with CLI:

1. Patients with critical limb ischemia (CLI) should undergo expedited evaluation and treatment of factors that are known to increase the risk of amputation. *(Level of Evidence: C)*
2. Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk. *(Level of Evidence: B)*
3. Patients with a prior history of CLI or who have undergone successful treatment for CLI should be evaluated at least twice annually by a vascular specialist owing to the relatively high incidence of recurrence. *(Level of Evidence: C)*
4. Patients at risk of CLI (ABI <0.4 in an individual with diabetes, or any individual with diabetes and known lower extremity PAD) should undergo regular inspection of the feet to detect objective signs of CLI. *(Level of Evidence: B)*
5. The feet should be examined directly, with shoes and socks removed, at regular intervals after successful treatment of CLI. (*Level of Evidence: C*)
6. Patients with CLI and features to suggest atheroembolization should be evaluated for aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms). (*Level of Evidence: B*)
7. Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection. (*Level of Evidence: B*)
8. Patients with CLI and skin breakdown should be referred to healthcare providers with specialized expertise in wound care. (*Level of Evidence: B*)
9. Patients at risk for CLI (those with diabetes, neuropathy, chronic renal failure, or infection) who develop acute limb symptoms represent potential vascular emergencies and should be assessed immediately and treated by a specialist competent in treating vascular disease. (*Level of Evidence: C*)
10. Patients at risk for or who have been treated for CLI should receive verbal and written instructions regarding self-surveillance for potential recurrence. (*Level of Evidence: C*)

Medical and Pharmacological Treatment for CLI

- Parenteral administration of PGe-1 or iloprost for 7–28 days may be considered to reduce ischemic pain and facilitate ulcer healing in patients with CLI, but its efficacy is likely to be limited to a small percentage of patients. (*Class IIb recommendation/Level of Evidence: A*)
- Oral iloprost is not an effective therapy to reduce the risk of amputation or death in patients with CLI. (*Class III recommendation/Level of Evidence: B*)
- The efficacy of angiogenic growth factor therapy for treatment of CLI is not well established and is best investigated in the context of a placebo-controlled trial. *(Class IIb recommendation/Level of Evidence: C)*

Endovascular Treatments and Surgery for CLI

- For individuals with combined inflow and outflow disease with CLI, inflow lesions should be addressed first. (*Class I recommendation/Level of Evidence: C* (endovascular) and *B* (surgery), respectively)
- For individuals with combined inflow and outflow disease in whom symptoms of CLI or infection persist after inflow revascularization, an outflow revascularization procedure should be performed. (*Class I recommendation/Level of Evidence: B*)
- For patients with limb-threatening lower extremity ischemia and an estimated life expectancy of 2 years or less in patients in whom an autogenous vein conduit is not available, balloon angioplasty is reasonable to perform when possible as the initial procedure to improve distal blood flow. (*Class IIa recommendation/Level of Evidence: B)*
- For patients with limb-threatening ischemia and an estimated life expectancy of more than 2 years, bypass surgery, when possible and when an autogenous vein conduit is available, is reasonable to perform as the initial treatment to improve distal blood flow. (*Class IIa recommendation/Level of Evidence: B)*
- Surgical and endovascular intervention is not indicated in patients with severe decrements in limb perfusion (eg, ABI <0.4) in the absence of clinical symptoms of CLI. (*Class III recommendation/Level of Evidence: C*)

Outflow Procedures: Infrainguinal Disease

- Bypasses to the above-knee popliteal artery should be constructed with autogenous saphenous vein when possible. (*Class I Recommendation/Level of Evidence: A)*
- Bypasses to the below-knee popliteal artery should be constructed with autogenous vein when possible. *(Class I recommendation/Level of Evidence: A)*
- The most distal artery with continuous flow from above and without a stenosis greater than 20% should be used as the point of origin for a distal bypass. *(Class I recommendation/Level of Evidence: B)*
- The tibial or pedal artery that is capable of providing continuous and uncompromised outflow to the foot should be used as the site of distal anastomosis. (*Class I recommendation/Level of Evidence: B*)
- Femoral-tibial artery bypasses should be constructed with autogenous vein, including the ipsilateral greater saphenous vein, or if unavailable, other sources of vein from the leg or arm. (*Class I recommendation/Level of Evidence: B*)
- Composite sequential femoropopliteal-tibial bypass and bypass to an isolated popliteal arterial segment that has collateral outflow to the foot are both acceptable methods of revascularization and should be considered when no other form of bypass with adequate autogenous conduit is possible. (*Class I recommendation/Level of Evidence: B*)
- If no autogenous vein is available, a prosthetic femoral-tibial bypass, and possibly an adjunctive procedure, such as arteriovenous fistula or vein interposition or cuff, should be used when amputation is imminent. (*Class I recommendation/Level of Evidence: B*)
- Prosthetic material can be used effectively for bypasses to the below-knee popliteal artery when no autogenous vein from ipsilateral or contralateral leg or arms is available. (*Class IIa recommendation/Level of Evidence: B*)

9.3 Objective Performance Goals (OPG) for Evaluating New Catheter-Based Treatments in CLI

Conte et al. (2009) developed a set of suggested objective performance goals (OPG) for evaluating new catheter-based treatments in CLI, based on evidence from historical controls. The work was supported by funding from the Society for Vascular Surgery (SVS). They proposed the use of risk-adjusted surgical controls to generate OPG for endovascular devices seeking pre-market approval for the treatment of CLI. They restricted the analysis to infrainguinal disease, and to open surgical bypass performed with autogenous vein, considered as the standard of care for CLI. Patients who received prosthetic grafts or test drugs, in addition to those with end-stage renal disease were excluded from analysis.

(a) Safety outcomes (30-day-event-rates and 95% confidence intervals) for the open surgery control group and suggested OPG:

- MACE, Major Adverse Cardiovascular Event, included myocardial infarction and stroke in addition to death from any cause: 6.2% (4.7–8.1%); safety OPG 8%.
  - death 2.7%; myocardial infarction 3.1%; cerebrovascular accident 1.0%
  - clinical high risk (age ≧ 80 and tissue loss) subgroup: safety OPG 18%
  - anatomic high risk (infra-popliteal) subgroup: safety OPG 10%
- MALE, Major Adverse Limb Event, above ankle amputation of the index limb or major reintervention (new bypass graft/jump/ interposition-graft revision, or thrombectomy/thrombolysis): 6.1% (4.6–7.9%); safety OPG 8%
  - clinical high risk (age > 80 and tissue loss) subgroup: safety OPG 10%
  - anatomic high risk (infra-popliteal) subgroup: safety OPG 9%
- Amputation: 1.9% (1.1–3.1%); safety OPG 3%
  - clinical high risk (age > 80 and tissue loss) subgroup: safety OPG 7%
  - anatomic high risk (infra-popliteal) subgroup: safety OPG 4%

(b) Efficacy outcomes (1 year) for overall CLI cohort and suggested OPG for each endpoint

- Freedom from MALE or postoperative death: 76.9%

  OPG: overall 71%; patients ≧ 80 years and tissue loss 61%; infra-popliteal subgroup 67%
- Amputation-free survival: 76.5%

  OPG: overall 71%; patients ≧ 80 years and with tissue loss 53%; infra-popliteal subgroup 68%
- Freedom from any reintervention or above ankle amputation of the index limb, or stenosis: 46.5%

OPG: overall 39%; patients ≧ 80 years old and with tissue loss 29%; infrapopliteal subgroup 36%

- Freedom from any reintervention or above ankle amputation of the index limb: 61.3%

  OPG: overall 55%; patients ≧ 80 years old and with tissue loss 54%; infrapopliteal subgroup 51%

- Limb salvage: 88.9%

  OPG: overall 84%; patients ≧ 80 years old and with tissue loss 80%; infrapopliteal subgroup 81%

- Survival: 85.7%

  OPG: overall 80%; patients ≧ 80 years old and with tissue loss 63%; infrapopliteal subgroup 80%

9.4 Results

9.4.1 Endovascular Therapy

9.4.1.1 Endovascular Techniques

Jens et al. (2014) performed a systematic review to determine overall 1 to 48-month follow-up outcomes of RCTs (published up until November 2013) comparing different endovascular treatment strategies in below-the-knee arterial lesions in patients with CLI. Twelve studies with a total of 1145 patients were included, in which 90% of the patients suffered from CLI. On the basis of moderate evidence, the authors recommended PTA with optional bailout stenting as the preferred strategy. According to the authors, alternative strategies, including drug-eluting stents (DES) and balloons (DEB), must be first tested in larger and high quality randomised controlled trials before being considered as viable and safe treatment options. Along these lines, Canaud et al. (2014) identified 26 studies (11 of which were randomised controlled trials) concerning infrainguinal angioplasty with a total of 2407 limbs, with the goal of comparing the treatment outcomes of varying endovascular devices. Meta-analysis of studies comparing DEB with standard balloon angioplasty demonstrated a result in favour of DEB for preventing binary primary restenosis (odds ratio 0.27). The meta-analysis comparing DES with bare-metal stents favoured DES with regard to target lesion revascularization (OR 0.15), as well as binary primary restenosis (OR 0.23). Overall, however, drug-eluting technology did not prevent more deaths or amputations. Therefore, whether or not the short-term success of such treatment methods will be reflected in long-term clinical outcome (mortality/rate of amputation) remains to be seen.

In the randomised IN.PACT DEEP trial, Zeller et al. (2014) assessed the efficacy and safety of a special drug-eluting balloon (IA-DEB) compared to PTA for infrapopliteal arterial revascularization in patients with CLI. Twelve months following intervention, no significant difference regarding the primary efficacy and safety endpoints was seen. However, a trend towards an increased major amputation rate was observed in the IA-DEB group versus the PTA-arm (8.8% vs. 3.6%). As a result, this particular study was not able to demonstrate an advantage of IA-DEB treatment strategies over PTA for infrapopliteal lesions. In a second RCT including 72 patients this group compared the safety and efficacy of a novel paclitaxel-coated drug-eluting balloon (DEB) versus an uncoated balloon in PTA of de novo or native restenotic lesions of the infrapopliteal arteries in patients with claudication and critical limb ischemia (Zeller et al. 2015). In this trial, the primary performance endpoint (patency loss at 6 months) was 17.1% in the DEB group versus 26.1% in the PTA group ($p = 0.298$), and major amputations of the target extremity occurred in 3.3% versus 5.6% of the patients at 12 months, respectively. The authors concluded that the novel Passeo-18 Lux DEB has been proven to be safe and effective in infrapopliteal lesions with comparable outcomes to PTA.

Todd et al. (2013) analysed 418 endovascular tibial interventions in patients with CLI (333 PTA alone, 6 PTA + stent, 11 artherectomy only, 68 artherectomy + PTA). The results of artherectomy, PTA and artherectomy-assisted procedures (i.e., artherectomy + PTA) were compared. TASC D lesions were more frequent in the PTA alone group than in the artherectomy cohort (25% vs. 13%). No significant differences existed with respect to the early (30-day) outcomes of loss of patency (11% vs 13%), complications (8% vs 13%), or major amputation (17% vs 13%) in the PTA-alone group vs the atherectomy-assisted group. This was also true for the 3-year follow-up (PTA vs. artherectomy + PTA: primary patency rate 55% vs. 46%; secondary patency rate 89% vs. 89%; limb salvage 70% vs. 77%; patient survival 56% vs. 50%). Considering the additional cost and increased procedural time, these findings put into question the routine use of adjunctive atherectomy.

Shammas et al. (2012) performed a similar analysis of a randomised controlled trial, however with a population size of only 50 patients. They investigated whether or not patients with CLI and calcified stenoses in the infrapopliteal area benefit from artherectomy with a rotation catheter before angioplasty. Indeed, their data appear to support this hypothesis; 1 year following intervention, 93.3% of the artherectomy + PTA group were free from revascularisation of the target vessel, compared with 80% in the PTA-alone group. However, the reason the first group demonstrated a mortality rate of 0% after 1 year and the PTA group a mortality rate of 32% remains to be determined, as the additional artherectomy alone is not enough to account for such a difference, particularly when the rate of amputation between the two groups did not differ.

SCAI expert consensus statement for infrapopliteal arterial intervention

The Society for Cardiovascular Angiography and Interventions has published an expert consensus statement for infrapopliteal arterial intervention appropriate use (Gray et al. 2014). They recommend:

PTA is the current standard for endovascular therapy for clinically significant infrapopliteal disease. Bailout bare metal and drug eluting stents in the tibial arteries should be considered for failures of balloon angioplasty. Studies are currently enrolling patients to address the use of combined strategies (i.e., atherectomy and drug-coated balloons). Further data are needed regarding the utility of atherectomy devices, drug-coated balloons, DES, and bioabsorbable stents in infrapopliteal interventions. However, until these results are available, given the increased costs of other modalities (e.g., cutting balloons, cryoplasty, laser, orbital, rotational, and directional atherectomy catheters), and the lack of comparative data to support their efficacy, balloon angioplasty should remain the initial endovascular therapy for most infrapopliteal disease.

9.4.1.2 Studies and Registry Data

Lo et al. (2013) performed a retrospective chart review using prospectively collected data on all consecutive patients undergoing an attempt at infrapopliteal angioplasty for critical limb ischemia from 2004 to 2012. Infrapopliteal PTA (stenting 14%, multilevel intervention 50%) was performed in 459 limbs of 413 patients (59% male). The majority (79%) of interventions were performed for tissue loss with fewer performed for rest pain (12%), ALI (3%), or to treat a stenosis in the native outflow vessel of a previous bypass graft performed for CLI (6%). Technical success was achieved in 427 of 459 (93%) limbs. Postoperative complications developed in 52 patients (11%), 30-day mortality rate was 6%. Technical failures were only observed in TASC D- lesions. Survival at 1, 3, and 5 years was 83%, 64%, and 49%, respectively. One- and 5-year primary patency was 57% and 38% and limb salvage was 84% and 81%, respectively. Freedom from restenosis was 56% and 34% at 1 and 5 years, respectively, and freedom from any subsequent revascularization was 74% and 50% at 1 and 5 years, respectively. The authors concluded that infrapopliteal angioplasty can achieve limb salvage and survival rates at 5 years comparable to those of surgical bypass and thus can be considered a reasonable first-line therapy in the treatment of TASC A, B, and perhaps C lesions even in a patient with adequate conduit available. TASC D lesions should preferably be treated with bypass in patients who are suitable candidates for surgery.

The OLIVE registry is a prospective multicenter registry study that consecutively enrolled patients who received infrainguinal endovascular treatment for CLI (Iida et al. 2015). A total of 314 patients were enrolled, with 312 evaluable patients remaining. Mean age of the patients was 73 ± 10 years, and 65% of the patients were male. Diabetes mellitus and hemodialysis were observed in 71% and 52% of patients, respectively. With respect to limb condition, tissue loss and wound infection were 88% (Rutherford 5: 73%, Rutherford 6: 15%) and 15%, respectively. At 3 years, overall survival rate was 63.0%, freedom from major amputation was 87.9%, and freedom from reintervention was 43.2%. Three-year freedom from MALE was 84.0% and rate of wound recurrence at 3 years was 43.9%. After multivariable analysis, age, body mass index ≤18.5, dialysis, and Rutherford 6 were

identified as predictors of 3-year major amputation or death. With respect to the results it is noteworthy that in this registry 50% of patients were on hemodialysis. Nevertheless, the OLIVE registry demonstrated that the 3-year clinical results of endovascular treatment were reasonable, despite high reintervention and moderate ulcer recurrence rates.

Vierthaler et al. (2015) reviewed 1244 patients undergoing 1414 peripheral endovascular interventions for CLI (rest pain, 29%; tissue loss, 71%) within the Vascular Study Group of New England (VSGNE) from January 2010 to December 2011. The overall survival rate (OS), amputation-free survival rate (AFS), and freedom from major amputation rate (FFA) were lower for patients treated for tissue loss than for patients treated for rest pain, with 1-year estimates of 80% vs.87%, 71% vs. 87%, and 81% vs. 94%, respectively. In this study, the independent factors associated with OS, AFS, and FFA after peripheral endovascular intervention differed. In a multivariable model the authors identified eight factors associated with reduced survival at 1 year and six variables predictive of major amputation at 1 year (Tables 9.1 and 9.2). The only common risk factor for OS, AFS, and FFA was dialysis, emphasizing the importance of renal function in patient prognosis. In contrast, congestive heart failure was associated with decreased OS and AFS. The differences in risk factors for survival vs amputation highlighted the difficulty in predicting composite end points such as AFS. Causes of death may range from cardiovascular causes, such as myocardial infarction, to stroke and to cancer. Conversely, prior major amputation was associated with a later major amputation but not with survival.

A further database of 728 patients undergoing endovascular treatment of the lower extremity for CLI was queried by Davies et al. (2015). Patients had an average

Table 9.1 Hazards model of factors associated with 1-year survival after peripheral endovascular intervention for CLI

Preoperative characteristic	Hazard ratio
Dialysis dependence	3.8
Emergency procedure	2.5
Age >80 years	2.2
Not living at home preoperatively	2.0
Creatinine >1.8 mg/dL	1.9
Congestive heart failure	1.7
Chronic β-blocker use	1.4
Independent ambulation preoperatively	0.7

According to Vierthaler et al. (2015)

Table 9.2 Hazards model of factors associated with freedom from major amputation after peripheral endovascular intervention for CLI

Variable	Hazard ratio
Dialysis dependence	2.7
Tissue loss	2.0
Prior major contralateral amputation	2.0
Nonwhite race	1.7
Male gender	1.6
Current or former smoker	0.6

According to Vierthaler et al. (2015)

age of 68 years. Tissue loss was the indication in 66% of the interventions, the other patients were treated for rest pain. The SFA was the site for 49% of the interventions, 17% were in one or more tibial arteries, and 34% were performed at the level of the SFA and tibial arteries. The overall technical failure rate was 4%. In this study, the outcomes of lower extremity endovascular intervention for CLI using the OPG proposed by the SVS (s.o.) were reported. The 30-day MACE rate was 3%, which was less than the stated OPG of 8%, but the 30-day MALE rate was 12%, which was much higher than the stated OPG of 8%. In the clinical high-risk group (age >80 years and tissue loss), the 30-day MACE rate was 3%, which was superior to the OPG of 18%, but the 30-day MALE rate was 19%, which was inferior to the OPG of 10%. In the anatomic high-risk group (infrapopliteal distal target), the 30-day MACE rate was 1%, which was superior to the OPG of 10% for this subgroup, but the 30-day MALE rate was 13%, which was inferior to the OPG of 9% for this subgroup. Overall mortality during follow-up was high, with patient survival rates of 49% ± 2% at 5 years. Median follow-up was 2.5 years. Major amputation occurred in 23% of the patients, with above-knee amputation occurring in 16% and below-knee amputation occurring in 7%. Overall freedom from MALE was 51% ± 2% at 5 years. In this study, endoluminal therapy for CLI was associated with an early low MACE rate but a high MALE rate. Longer-term outcomes after endovascular intervention for CLI remained relatively poor, with <40% success in objective performance outcomes at 5 years.

9.4.2 Surgical Intervention

9.4.2.1 Studies and Registry Data

A total of 2110 infrainguinal bypasses performed on patients with CLI between 2003 and 2009 were identified in the VSGNE database (Simons et al. 2012). The mean patient age was 69.9 years, 5 years older than that of the simultaneously analysed cohort of patients with intermittent claudication (IC). 24.7% of CLI patients received a prosthetic conduit. Hospital mortality was low, at 2.1%, however reoperation was necessary in 15% of the cases, and the rate of wound infection was at 5.6%. One year after surgery, 13.6% of the patients had died and the rate of major amputations was at 12.2%. The primary graft patency was calculated to be 66.4%, while the secondary patency was 77.4%. The results for patients with CLI were therefore considerably worse than those with IC (Table 9.3).

One thousand two hundred and twenty seven patients who underwent below-knee bypass in the years 2003–2009 for CLI were studied by Suckow et al. (2013) utilizing the same registry. One thousand and four patients (82%) received greater saphenous vein (GSV) and 223 (18%) received a prosthetic graft to the below-knee popliteal artery (70%) or more distal target (30%). Patients receiving prosthetic conduit were more likely to be treated with warfarin than those with greater saphenous vein (57% vs. 24%). Primary graft patency at 1 year was maintained in 70% of

Table 9.3 Outcomes of infrainguinal lower extremity bypass by indication. Intermittent claudication (IC) vs. Critical Limb ischemia (CLI)

	IC (n = 797)	CLI (n = 2110)
Age (years)	64.3 ± 10.4	69.9 ± 11.4
% Female	25.7	33.0
Previous ipsilateral endovascular intervention (%)	18.8	18.7
Previous arterial bypass of any kind (%)	30	32.2
Perioperative mortality (%)	0.3	2.1
Need for reoperation (%)	5.4	15.0
Myocardial infarction or dysrhythmia (%)	3.0	8.7
Wound infection (%)	4.5	5.6
Length of stay, means ± SD (days)	4.0 ± 4.3	9.2 ± 8.2
1 year follow-up/mortality (%)	3.7	13.6
1 year follow-up/major amputations (%)	1.6	12.2
1 year follow-up/graft patency (%)		
Primary	78.9	66.4
Secondary	89	77.4

Vascular Study Group of New England 2003–2009
Adapted from Simons et al. (2012)

GSV patients and in 72% of prosthetic patients. Within the first year after bypass, major limb amputation occurred in 11% of patients with GSV and 16% of patients with a prosthetic graft. Following risk adjustment, however, there was no difference in 1-year survival between propensity-matched subjects with GSV (89%) and prosthetic conduit subjects (81%). These results provide justification for the use of a synthetic graft in conjunction with appropriate antithrombotic therapy, when a suitable vein conduit is not available.

The Vascular Study Group of New England registry was also used to study the associations between statin use and long-term mortality, graft occlusion, and amputation after infrainguinal bypass in patients with CLI (Suckow et al. 2015).

Of 2067 patients, 1537 (74%) were taking a statin perioperatively and at the 1-year follow-up, whereas 530 (26%) were never on a statin. In subgroup analysis, a survival advantage was evident in patients on statins with CLI (5-year survival rate, 63% vs 54%) but not claudication (5-year survival rate, 84% vs 80%). However, although overall survival differed by statin treatment groups, a difference in graft-specific or limb-specific outcomes (graft occlusion or major amputation rates) at 1 year after bypass between individuals who were and were not on prolonged postoperative statin therapy could not be demonstrated. Statin therapy was not associated with reduced 1-year rates of major amputation (12% vs 11%) or graft occlusion (20% vs 18%) in CLI patients.

Dermody et al. (2015) studied all patients in the Vascular Study Group of New England database undergoing infrainguinal bypass for PAD between 2003 and 2013. Age was grouped by <50 years, 50–79 years, and ≥80 years. A subgroup analysis of CLI patients included 171 (52.8%) in the <50 years group, 2498 (61.6%) in the 50–79 years group, and 702 (79.5%) aged ≥80 years. Their MALE-free rates

at 1 year were 62%, 69.6%, and 68.7%, respectively. Amputation-free survival (AFS) rates among the CLI subgroup were 68.5%, 74.7%, and 58.8%, respectively. When looking at AFS alone, the <50 years group had a significantly lower rate of 76.5% than both older cohorts at 1 year (87.4% for 50–79 years, P = .006; 86.9% for ≥80 years, P = .035), and therefore more amputations compared with the older cohorts. Knowing that older patients have a higher mortality rate, they are likely to die before a major amputation is required, which may ultimately skew the finding of higher amputation rates in younger patients. However, a major amputation rate of 23.5% in the <50 years CLI subgroup correlates with previous studies in which rates ranged from 20.7% to 31% in patients with premature PAD. It was concluded that patients with premature PAD may have fewer comorbidities and better survival compared with older patients undergoing infrainguinal bypass, but their amputation rates are higher when faced with CLI.

Prospectively collected data from the Society for Vascular Surgery Vascular Quality Initiative (VQI) database was retrospectively reviewed by Simons et al. (2016) to identify all patients who underwent infrainguinal lower extremity bypass (LEB) between January 1, 2003, and December 31, 2012. Seven thousand seven hundred and fifty patients who underwent nonemergency LEB for CLI were identified. Most patients were male (65%), white (84%), and 60–80 years old (76%). More than one-third of patients (37%) had already been treated with a prior ipsilateral endovascular intervention, and 51% of the bypasses were to a tibial vessel. Single-segment great saphenous vein was used in 62% of patients. The overall 1-year amputation-free survival (AFS) was 74%, the 1-year freedom from major amputation was 86% and the 1-year survival was 89%. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL), Finland National Vascular (FINNVASC) registry, and the modified Project of Ex-vivo vein graft Engineering via Transfection III (PREVENT III [mPIII]) risk scores were applied to the VQI cohort. Existing scoring systems performed modestly for prediction of 1-year AFS. A novel model for risk-adjusting outcomes after LEB was derived from the data. When entered into a Cox regression model of 1-year AFS, bedbound status (hazard ratio, 4.4), followed by dialysis dependence (hazard ratio, 2.5) had the largest magnitude of effect on the hazard of amputation or death. The authors concluded that national registries such as VQI should begin using this novel model for benchmarking quality of care.

The SVS established objective performance goals (OPG) (Conte et al. 2009) for lower extremity bypass in patients with CLI are based on pooled data from previously performed prospective studies. However, patients with a prosthetic conduit and end-stage renal disease were excluded from this cohort. Saraidaridis et al. (2015) established safety and efficacy measures for patients who were excluded from the original SVS OPG analysis. They identified 3609 patients: 2360 OPG (65%) vs 1249 non-OPG (35%). The 30-day major adverse limb event rate was 5.0% (5.5% non-OPG vs 4.4% OPG), and the 30-day major adverse cardiovascular event rate was 7.3% (9.2% non-OPG vs 6.2% OPG). At 1 year, survival was 84% (75.9% non-OPG vs 88.3% OPG), and freedom from amputation was 86.9% (80.9% non-OPG vs 90.1% OPG). In this analysis 35% of patients who underwent lower extremity

bypass for CLI in the last 10 years fell outside the OPG criteria by having end-stage renal disease or requiring a prosthetic conduit. This makes generalization of the SVS OPG difficult and suggests new benchmarks for these high-risk populations.

Lejay et al. (2015) evaluated gender-specific differences in patient characteristics and long-term clinical outcomes among patients undergoing infrainguinal open surgery for CLI. Five hundred and eighty four patients (269 women and 315 men, mean age 76 and 71 years respectively) underwent 658 infrainguinal open interventions (313 in women and 345 in men). The 30-day mortality rates were 2.9% and 2.6% in women and men respectively, without any difference. The 30-day morbidity was higher in women (10.2%) than in men (5.8%). Survival rate at 6 years was lower among women compared to men with 53.5% vs 70.9%. Adjusted for age and gender, at 6 years primary patency rate and limb salvage rate, respectively, were lower in the female group: 35.9% versus 52.4%, and 54.3% versus 81.1%, respectively. This retrospective study evaluating infrainguinal open surgery performed in a consecutive series of CLI patients showed that female gender is a risk factor for adverse outcomes. However, female gender might be considered a risk factor also because women are more often older at presentation and present with bilateral lesions.

9.4.2.2 Bypass Surgery Following Endovascular Intervention

The Vascular Study Group of New England registry has documented 1880 infrainguinal bypass grafts performed between January 2003 and December 2009 for CLI (rest pain or tissue loss) in ten centers (Nolan et al. 2011). Thirty two percent (n = 603) of patients had undergone an infrainguinal revascularization procedure at some time prior to the index bypass procedure. Prior endovascular intervention or bypass did not alter 30-day major adverse events and 1-year mortality after the index bypass. In contrast, 1-year major amputation and 1-year graft occlusion rates were significantly higher in patients who had prior ipsilateral endovascular intervention than those without (31% vs 20% and 28% vs 18%), similar to patients who had a prior ipsilateral bypass (1-year major amputation 29% vs 20%; 1-year graft occlusion 33% vs 18%). While it is well known that a prior failed ipsilateral infrainguinal bypass is a negative predictor for future lower extremity bypass success, this study demonstrated that a prior failed infrainguinal ipsilateral endovascular intervention has a similar negative prognostic effect on subsequent lower extremity bypass.

Santo et al. (2014) were unable to confirm the above observations. They described the long-term results in 314 autogenous vein lower extremity bypasses, 60% of which were infrapopliteal, in patients with CLI. The 30-day mortality rate was 3.5%. The 5-year follow-up results were as follows: primary patency rate 45%, secondary patency rate 64%, limb salvage rate 89%, and amputation-free survival 49%. Significant differences in patients who had prior endovascular treatment compared to those who had not were not seen.

Uhl et al. (2015a) came to the same conclusion. They compared retrospectively 40 patients who had undergone tibial or peroneal bypass surgery after prior endovascular interventions (PEI-group) with 93 patients who had received a tibial

or peroneal bypass as primary revascularization procedure (bypass first group, BF). Primary patency for the BF-group was 74.3% vs. 55.1% for the PEI-group at 2 years, secondary patency was 74.6% vs. 59.1%. These differences were not significant. Furthermore, the groups did not differ with respect to limb salvage (83.7% vs. 83.6%) or survival (61.0% vs. 65.0%), both observed 2 years following intervention. The authors concluded that prior endovascular femoro-tibial intervention has no negative impact on the outcome of subsequent tibial or peroneal bypass surgery in patients with CLI.

9.4.2.3 Biological Bypass Material

Avgerinos et al. (2015) analyzed a total of 407 infrainguinal bypasses to below-knee targets; 255 patients (63%) received a single-segment great saphenous vein (GSV), 106 patients (26%) received an alternative autologous vein (AAV), and 46 patients (11%) received a prosthetic conduit which included five ePTFE and 41 heparin-bonded PTFE. Primary patency at 2 and 5 years was estimated at 47% and 32%, respectively, for the GSV group; 24% and 23% for the AAV group; and 43% and 38% for the prosthetic group. Secondary patency at 2 and 5 years was estimated at 75% and 60%, respectively, for the GSV group; 57% and 55% for the AAV group; and 46% and 41% for the prosthetic group. Limb salvage at 2 and 5 years was estimated at 86% and 80%, respectively, for the GSV group; 78% and 76% for the AAV group; and 72% and 72% for the prosthetic group. In this study, single-segment GSV has been the optimal conduit for below-knee popliteal and infrapopliteal targets in patients with CLI. However, when GSV is not available, AAV conduits may not offer any significant advantage over prosthetic bypass for below-knee targets at midterm follow-up.

Moreira et al. (2016) came to a similar conclusion. They queried the Vascular Study Group of New England database (2003–2014) for patients who underwent infrageniculate bypass originating from the femoral arteries. Conduit types were categorized as single-segment GSV, alternative autologous conduit (AAC), and nonautologous conduit (NAC). Lower extremity bypass was performed in 2148 patients, of which 1125 were to below-knee popliteal (BK-Pop) and 1023 to infrapopliteal artery (IPA) targets. In multivariable analysis, conduit type did not make a difference in 1-year MALE, MALE-free survival, or primary graft patency for BK-Pop bypasses. For IPA bypasses, NAC use was associated with higher rates of postoperative (6.4%) and in-hospital death (4.5%) compared with GSV (2.5% and 1.4%, respectively) and AAC (2.9% and 1.9%, respectively). In conclusion, conduit type did not affect outcomes in BK-Pop bypass. In the absence of single-segment GSV, the use of AAC for IPA bypass does not appear to confer any additional benefit of MALE, MALE-free survival, or graft patency compared with prosthetic grafts at 1-year follow-up.

Brochado Neto et al. (2014) performed 120 infragenicular bypasses using arm vein conduits. CLI was the main indication (87.5%) for the procedures. The indications for using arm veins were inadequacy or absence of the ipsilateral greater saphenous vein (GSV). They reported 5-year primary and secondary bypass patency

rates of 45.2% ± 5.6% and 56.5% ± 5.0%, respectively, and cumulative limb salvage of 70.6% ± 5.9% and a survival rate of 59.6 ± 5.8% at 5 years. Although these results were obtained in a non-randomized study, the authors believed that arm vein conduits may have two major advantages over prosthetic grafts: (a) higher long-term patency and limb salvage rates for below-knee bypass grafts, and (b) a lower infection rate. However, this hypothesis was not proved here.

Chang et al. (2014) examined 81 CLI patients who had undergone lower extremity bypass surgery with the use of cryopreserved cadaveric saphenous vein grafts. In all cases, autogenous vein conduits were not available. The rate of postoperative complications was 36%, and the 30-day mortality was 4%. 1- and 3-year actuarial estimated patient survival was of 84% ± 4% and 62% ± 6%. Primary patency of cadaveric vein bypass for CLI was 27% ± 6% and 17% ± 6% at 1 and 3 years, respectively. Freedom from major amputation after cadaveric vein bypass for CLI was 57% ± 6% and 43% ± 7% at 1 and 3 years, respectively. Freedom from MALE for all CLI patients was 47% ± 7% at 1 year and 25% ± 7% at 3 years. In this study, in CLI patients with no autologous conduit and prior failed infrainguinal bypass, cadaveric vein bypass outcomes were disappointing. These grafts performed best in patients with rest pain, particularly those who could be anticoagulated with warfarin.

A retrospective analysis of 118 infragenicular revascularizations performed for CLI with cold-stored venous allografts obtained from varicose vein stripping surgery was presented by Ziza et al. (2015). Venous grafts were stored at a mean temperature of 4 °C using sterile isotonic preservation saline solution and implanted within 2 months after vein harvest. Technical success was 98.3% (116 limbs). At 30 days, perioperative death rate was 6.8%, major adverse cardiovascular event rate was 7.6%, and major adverse limb event rate was 11.9%. Mean follow-up was 34 ± 29 months. During follow-up, 63 bypasses occluded (53.4%). Overall, 33 major amputations were performed (28.0%). Three major amputations were done for progressive tissue loss despite patent bypass grafts. At 1 year, 3 years, and 5 years, primary patency rates were, respectively, 47.0% ± 5.2%, 26.2% ± 5.4%, and 9.7% ± 4.7%, and secondary patency rates were 58.3% ± 5.2%, 43.5% ± 5.9% and 24.4% ± 7.2%. Reintervention for aneurysmal degeneration of the allograft was necessary in 5.1%. It was concluded that cold-stored venous allografts may be used for below-knee revascularization for CLI with acceptable results despite poor long-term patency. Their level of performance remained inferior to a single segment of GSV or alternative autologous vein sources but seemed comparable to alternative allograft sources or prosthetic conduit. Their availability was a major advantage compared with other biologic alternative sources.

Neufang et al. (2014) presented long-term results of 122 femoro-distal bypasses (117 of which were performed for CLI) with biological bypass material (human umbilical vein n = 90/Omniflow (ovine collagen prosthesis) n = 32). The 30-day mortality was 4.1%. Primary, primary assisted and secondary patency rates, as well as limb salvage 10 years after bypass, were calculated to be 26%, 46%, 54% and 77%, respectively. In four cases, a late biodegeneration of the human umbilical vein prostheses was observed. The results justify the use of biological vascular conduits in cases where autologous vein is unavailable for a distal bypass.

9.4.2.4 Synthetic Bypass Grafts in CLI

In the randomized prospective Swedish External Support Study (Lundgren & Swedish External Support Study (SWEXSUS) 2013), a total of 334 patients with CLI were included. It was examined whether external graft support improves patency and/or limb salvage in patients undergoing reconstruction with synthetic PTFE grafts to the below-knee arteries. One year following intervention, the primary and secondary patency rates of the externally supported prostheses were significantly better (55% and 58% vs. 42% and 47%). With respect to limb preservation, however, no significant differences were observed (75% and 69% after 1 year, with and without support, respectively).

Uhl et al. (2015b) examined retrospectively short- and long-term outcomes of tibial and peroneal vein and heparin-bonded expanded polytetrafluoroethylene bypasses in patients with CLI who were unsuitable for endovascular revascularization. Autologous veins were used in 109 cases and heparin-bonded PTFE grafts in 89 cases. At 3 years, primary patency for the vein group was 68.2% vs 34.1% for the heparin-bonded PTFE group (P = .000) and secondary patency was 69.8% vs 35.5% (P = .001). Limb salvage was 81.8% for the vein group vs 56.5% for the heparin-bonded PTFE group (P = .000) and survival was 62.8% versus 46.7% (P = .019). These results demonstrate that autologous vein grafts are still first choice for tibial and peroneal bypasses in patients with CLI. A retrospective comparison of heparin-bonded PTFE prostheses (HePTFE) (n = 62) and single-segment great saphenous vein (n = 50) for tibial bypasses was also reported by Neville, Capone et al. (2012b). A distal vein patch technique was used in each HePTFE bypass. 91.1% of the series presented with an indication of limb-threatening ischemia. Primary patency at 1 year was 75.4% for HePTFE and 86.0% for vein grafts. Regarding amputation, no significant differences were found. The results support the use of heparin-PTFE prostheses in patients who need a tibial bypass and in whom an autogenous vein conduit is not available. A further retrospective study comparing heparin-bonded PTFE grafts with great saphenous vein grafts (GSV) in patients with CLI was performed by Gessaroli et al. (2015). Fourty-one femorocrural bypasses using modified ringed HePTFE grafts with a handmade distal radial stretch HePTFE cuff to reduce the mismatch compliance between the graft and the artery wall were compared with 33 femorocrural vein bypasses. In this study the modified heparin-bonded PTFE grafts had 1-, 2-, and 3-year primary patency and limb salvage results which were not significantly different from those with the GSV grafts (limb salvage: HePTFE group: 87%, 87%, and 76%, respectively; the GSV group: 84%, 75%, and 75%, respectively).

Nevertheless, with uncoated PTFE prostheses, too, acceptable results can be achieved in patients with CLI, provided that the distal vein patch technique is used. Neville, Lidsky et al. (2012a) examined this technique in 270 below-knee bypasses (with tibial artery bypass comprising 94% of the bypass cohort) in patients almost exclusively suffering from CLI (9.3% claudication, 27.8% rest pain, 22.2% gangrene, and 40.7% non-healing ulceration). There was one perioperative death (0.5%). The primary graft patency after 1 year and 48 months was 79.8% and

51.2%, respectively, and the corresponding rates of limb salvage were 80.6% and 67.5%. A Cochrane review performed by Khalil et al. (2012) supports the use of vein cuffed prosthetic grafts for below knee bypass in critical limb ischaemia. There is evidence that a vein cuff at the distal anastomosis site improves primary graft patency rates for below knee PTFE graft, but this does not reduce the risk of limb loss. Pre-cuffed PTFE grafts have comparable patency and limb salvage rates to vein cuff PTFE grafts. However, evidence for a beneficial effect of vein cuffed PTFE grafts is weak and based on underpowered trials. The authors concluded that a large study with a specific focus on below knee vein cuff prosthetic grafts, including PTFE, is required.

9.4.2.5 Revascularisation in Patients with End-Stage Renal Disease

Kumada et al. (2015) investigated the limb salvage rate after infrapopliteal bypass surgery in hemodialysis (HD) patients with CLI (226 patients with 236 limbs). Ulcer/gangrene was present in 206 patients (91.2%), and 233 limbs (98.7%) were treated using autogenous vein. The 5-year amputation-free survival rate was significantly lower in HD patients than in non-HD patients (43.6% vs. 78.8%). Compared with non-HD patients, the status of HD was similarly an independent risk of major amputation (72.4% vs 92.5%) and mortality (56.9% vs 83.2%). However, freedom from reintervention was comparable between the two groups (84.3% vs 86.8%).

Fallon et al. (2015) studied the open and endovascular outcomes of 689 HD patients undergoing open surgical bypass (n = 295) or endovascular intervention (n = 394) for lower extremity revascularization. Data was collected using the Vascular Study Group of New England regional quality improvement registry. CLI was the indication for bypass surgery in 95% and for endovascular intervention in 90%. The most frequent bypass was a common femoral to a below-knee target (82%), most often vein conduit was used (70%). In the endovascular group, 55% of procedures were done at or below knee vessels. At 2 years, 76% of endovascular revascularizations were patent compared with 26% for open surgical bypass. Survival and AFS showed no clinically substantial difference between open and endovascular methods (at 2 years, survival 39% vs 48% and AFS 19% vs 12%). Long-term outcomes were especially poor, with only 20% overall survival and <5% AFS at 5 years. Death constituted the major mode of failure for both revascularization methods.

9.4.3 Comparison of Endovascular Versus Surgical Revascularisation

In a meta-analysis performed by Jones et al. (2014), 23 studies published from 1995 to 2012 were identified that evaluated the comparative effectiveness of endovascular and surgical revascularization in 12,779 patients with CLI. Meta-analysis of the observational studies showed a statistically nonsignificant reduction in all-cause

mortality at 6 months (11 studies, odds ratio 0.85) and amputation-free survival at 1 year (2 studies, odds ratio 0.76) in patients treated with endovascular revascularization. There was no difference in overall death, amputation, or amputation-free survival at ≥2 years. In conclusion, there did not appear to be significant differences in mortality or limb outcomes between endovascular and surgical revascularization in CLI patients.

Abu Dabrh et al. (2016), too, systematically reviewed the evidence to compare bypass surgery with endovascular revascularization in patients with CLI. The review compared controlled studies that enrolled patients with critical or severe limb ischemia with a follow-up of ≥1 year. Nine studies that enrolled 3071 subjects were included. They found no significant difference in mortality or amputation. However, bypass surgery was associated with higher primary patency and assisted primary patency. The quality of evidence was low for mortality and amputation outcomes and moderate for patency outcomes.

A retrospective analysis of 1053 CLI patients with first treated infrainguinal lesions who underwent bypass surgery (n = 230) or endovascular intervention (n = 823) at 14 Japanese centres was conducted by Soga et al. (2014). At 3 years, no significant differences in amputation-free survival (endovascular 60.5%/bypass 62.1%), overall survival (endovascular 65.8%/bypass 69.2%), or limb salvage (endovascular 88.7%/bypass 85.4%) were observed. An additional matched pairs analysis also revealed no significant difference in any outcome between the two intervention strategies, which possibly supports the preferential choice of less-burdensome endovascular procedures in high-risk patients with limited life expectancy.

Dosluoglu et al. (2012) presented the long-term results of a prospective database, in which 433 patients (514 limbs) with CLI were included. Seventy-one percent of the infrainguinal revascularizations were endovascular interventions, while 29% were open procedures. Patients in the endovascular group were older (73 vs. 69 years), and were more likely to have diabetes (69% vs. 40%) as well as renal insufficiency (34% vs. 25%). The rates for 30-day mortality (6.0% vs 2.8%), combined myocardial infarction/stroke/limb ischemia and mortality (11.2% vs 4.9%), and any complication (29.1% vs 7.2%) were higher in the open group than in the endovascular group. The 5-year survival rate was 36% in the endovascular group and 46% in the surgical group, the amputation-free survival was 30% vs. 39%, respectively, and limb salvage was identical (78% vs 78%). From these data, the authors concluded that endovascular intervention and bypass surgery can result in similar rates of survival, limb salvage, and amputation-free survival, and should be considered on an individual basis. Bypass surgery was more often indicated in cases of multilevel occlusions/stenoses and in infrapopliteal lesions.

Garg et al. (2014) examined the long-term outcomes of selective use of endovascular-first (endo-first) and open-first strategies in 302 patients. Endo-first was performed in 187 (62%), open-first in 105 (35%), and 10 (3%) had hybrid procedures. The endo-first group was older, with more diabetes and tissue loss. Bypass was used more to infrapopliteal targets (70% vs 50%). The 5-year mortality was comparable (open 48%, endovascular 42%), as was the rate of limb salvage (surgical 83%, endovascular 85%) and amputation-free survival (45% vs. 50%). Predictors

of death were age >75 years, end-stage renal disease (ESRD), and prior stroke. Predictors of limb loss were ESRD and below-the-knee intervention. Based on these results, the authors stressed the equivalence of both strategies, provided that certain criteria were observed with endo-first (in this study short (5-cm to 7-cm) occlusions or stenoses in crural vessels; disease in the superficial femoral artery limited to TASC II A, B, or C; and no impending limb loss).

In a community-based clinical registry Tsai et al. (2015) compared 291 patients undergoing peripheral endovascular intervention (PVI) and 633 patients undergoing lower extremity bypass (LEB) for CLI. Patients undergoing LEB were more likely to have glomerular filtration rate levels <30, to have a history of stroke, and to be on dialysis. Postoperative 30-day complication rate (any complication) was significantly higher in the LEB group (40.6% vs. 18.2%). The 3-year major amputation rate for PVI (21.2%) was not significantly different from that for LEB (25.4%). The difference in 3-year mortality rate was also not significant (PVI 26.9% vs LEB 35.9%, respectively). Target lesion revascularization rate at 3 years was greater for PVI than for LEB (31.6% vs 16.0%). How the increased perioperative risk of LEB is weighed against the benefit of decreased reinterventions requires judgment by both patients and treating physicians.

In the CRITISCH registry, the current practice of all first-line treatment strategies - endovascular revascularization (ER), bypass surgery (BS), femoral/profundal artery patchplasty (FAP), conservative treatment, and primary amputation – was determined among CLI patients in 27 German vascular centers (Bisdas et al. 2015). The main composite end point was major amputation or death, or both, during the hospital stay. The study included 1200 consecutive patients. The CRITISCH registry revealed ER as the most common first-line approach in CLI patients. First-line treatment of choice was ER in 53.4%, BS in 23.7%, FAP in 10.5%, conservative treatment in 9.8%, and primary amputation in 2.5%. The composite end point was met in 4% after ER, in 6% after BS, in 6% after FAP, and in 8% after conservative treatment. The highest rate of in-hospital death was observed after primary amputation (10%). In the multivariate regression model, coronary artery disease (odds ratio 2.96) and previous myocardial infarction (PMI) < 6 months (odds ratio 3.67) were identified as risk factors for the composite end point. Risk factors for amputation were dialysis (odds ratio 3.31) and PMI (odds ratio 3.26) and for death, BS compared with ER (odds ratio 3.32), renal insufficiency without dialysis (OR 6.34), and PMI (OR 7.41).

Agarwal et al. (2016) analysed a total of 642,433 admissions with CLI across 2003–2011 using the Nationwide Inpatient Sample. The annual rate of CLI admissions has been relatively constant across 2003–2011 (about 150 per 100,000 people in the United States). There has been a significant reduction in the proportion of patients undergoing surgical revascularization from 13.9% in 2003 to 8.8% in 2011, while endovascular revascularization has increased from 5.1 to 11.0% during the same time period. This was accompanied by a steady reduction in the incidence of in-hospital mortality and major amputation. Compared to surgical revascularization, endovascular revascularization was associated with reduced in-hospital mortality (2.34% vs. 2.73%), mean LOS (8.7 days vs. 10.7 days), and mean cost of hospitalization ($31,679 vs. $32,485).

Saarinen et al. (2015) demonstrated that revascularization of a critically ischemic leg can be justified for very elderly patients because limb preservation is likely to maintain ambulatory status and independent living. The median age of the study population was 92 years (range 90–100 years). The majority (81.1%) of the patients were female. Seventy-three percent (n = 170) of the patients had chronic CLI (rest pain n = 56, ulcer/gangrene n = 114) and 27% (n = 63) had ALI (thrombosis, embolism). Seventy percent of the patients underwent surgical revascularization (bypass, endarterectomy, or thrombectomy/embolectomy), and 30% were treated endovascularly. 72.5% of the patients maintained their independent living status; similarly, 82.0% of the patients maintained their walking ability. One-year survival, limb salvage, and AFS rates were 50.9% versus 48.6%, 85.1% versus 87.0%, and 45.7% versus 44.4% in the surgical versus endovascular group, with no significant differences. In this study, good limb salvage could be achieved by both surgical and endovascular revascularization, and independent living could be maintained in the majority of the patients. However, the benefit of revascularization was limited owing to high mortality.

9.5 Conclusions for Clinical Practice

1. In patients with CLI, endovascular intervention is the most common first-line approach.
2. There do not appear to be significant differences in mortality or limb outcomes between endovascular and surgical revascularization in CLI patients.
3. The SVS Objective Performance Goals (OPG) provide an orientation to evaluate CLI treatment results, but are not appropriate for patients with ESRD.
4. PTA with optional bailout stenting with bare metal stents is the preferred endovascular strategy for patients with CLI and below knee arterial lesions.
5. Bypasses to the above and below-knee popliteal artery should be performed with autogenous saphenous vein when possible. However, when great saphenous vein is not available, alternative autogenous vein conduits may not offer any significant advantage over prosthetic bypass for below-knee targets at midterm follow-up.
6. There is some evidence that a vein cuff at the distal anastomosis site improves primary graft patency rates for below knee PTFE graft, but this does not reduce the risk of limb loss. Pre-cuffed PTFE grafts have comparable patency and limb salvage rates to vein cuff PTFE grafts.

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Chapter 10
Acute Limb Ischemia

10.1 Classification and Prognosis

Acute limb ischemia (ALI) is any sudden decrease in limb perfusion causing a potential threat to limb viability. Presentation is normally up to 2 weeks following the acute event (Norgren et al. 2007). The most common causes for ALI are arterial thrombosis in case of peripheral artery disease (PAD), embolism, reconstruction/graft thrombosis, and peripheral aneurysms with emboli. The level of emergency and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficiencies, and the thrombotic vs. embolic cause. The grade of ischemia is clinically classified according to Rutherford. Clinical categories and prognosis as presented in the European Society of Cardiology (ESC) (2011) guidelines are listed in Table 10.1.

Table 10.1 Clinical categories of acute limb ischemia (ALI) (ESC Guidelines, Eur Heart J 2011)

Grade	Category	Sensory loss	Motor deficit	Prognosis
I	Viable	None	None	No immediate threat
IIA	Marginally threatened	None or minimal (toes)	None	Salvageable if promptly treated
IIB	Immediately threatened	More than toes	Mild/moderate	Salvageable if promptly revascularised
III	Irreversible	Profound, anaesthetic	Profound, paralysis (rigor)	Major tissue loss Amputation. Permanent nerve damage inevitable

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Table 10.2 Doppler signals of different clinical ALI categories (Norgren et al. 2007)

Category	Arterial Doppler signals	Venous Doppler signals
I. Viable	Audible	Audible
IIA. Marginally threatened	(Often) inaudible	Audible
IIB. Immediately threatened	(Usually) inaudible	Audible
III. Irreversible	Inaudible	Inaudible

10.2 Guidelines

10.2.1 TASC II Working Group

The TASC II Working Group (Norgren et al. 2007) recommends:

1. Due to inaccuracy of pulse palpation and the physical examination, all patients with suspected ALI should have Doppler assessment of peripheral pulses immediately at presentation to determine if a flow signal is present. (Level of Evidence: C) (Doppler signals of different Rutherford categories are listed in Table 10.2)
2. All patients with suspected ALI should be evaluated immediately by a vascular specialist who should direct immediate decision making and perform revascularization because irreversible nerve and muscle damage may occur within hours. (Level of Evidence: C)
3. Immediate parenteral anticoagulant therapy is indicated in all patients with ALI. In patients expected to undergo imminent imaging/therapy on arrival, heparin should be given. (Level of Evidence: C).

10.2.2 American College of Cardiology Foundation/American Heart Association

Guidelines of the American Heart Association (AHA) (Anderson et al. 2013) recommend:

1. Catheter-based thrombolysis is an effective and beneficial therapy and is indicated for patients with acute limb ischemia (Rutherford categories I and IIa) of less than 14 days' duration. (Class-I-recommendation/Level of Evidence: A)
2. Mechanical thrombectomy devices can be used as adjunctive therapy for acute limb ischemia due to peripheral arterial occlusion. (Class-IIa-recommendation/Level of Evidence: B)
3. Catheter-based thrombolysis or thrombectomy may be considered for patients with acute limb ischemia (Rutherford category IIb) of more than 14 days' duration. (Class-IIa-recommendation/Level of Evidence: B)

10.2.3 European Society of Cardiology

Recommendations for therapy are the following (European Stroke Organisation et al. 2011):

- Urgent revascularization is indicated for ALI with threatened viability (stage II). (Class-I-recommendation/Level of Evidence: A)
- In the case of urgent endovascular therapy, catheter-based thrombolysis in combination with mechanical clot removal is indicated to decrease the time to reperfusion. (Class-I-recommendation/Level of Evidence: B)
- Surgery is indicated in ALI patients with motor or severe sensory deficit (stage IIB). (Class-I-recommendation/Level of Evidence: B)
- In all patients with ALI, heparin treatment should be instituted as soon as possible. (Class-I-recommendation/Level of Evidence: C)
- Endovascular therapy should be considered for ALI patients with symptom onset <14 days without motor deficit (stage IIA). (Class-IIa-recommendation/Level of Evidence: A)

10.2.4 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

These guidelines (Alonso-Coello et al. 2012) specifically refer to antithrombotic therapy of ALI:

- In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C)
- We suggest reperfusion therapy (surgery or intraarterial thrombolysis) over no reperfusion therapy (Grade 2C)
- We recommend surgery over intraarterial thrombolysis (Grade 1B)
- In patients undergoing intraarterial thrombolysis, we suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase (Grade 2C).

The latter recommendation is supported by a Cochrane Review (Robertson et al. 2013) which found some evidence to suggest that intra-arterial rt-PA is more effective than intra-arterial streptokinase or intravenous rt-PA in improving vessel patency in patients with peripheral arterial occlusion. There was no evidence that rt-PA was more effective than urokinase for patients with peripheral arterial occlusion and some evidence that initial lysis may be more rapid with rt-PA, depending on the regime. Incidences of haemorrhagic complications were not statistically significantly greater with rt-PA than with other regimes.

The preference of surgery over intra-arterial thrombolysis is justified in this guideline by the increased risk in stroke (10 per 1000 treated) and major bleeding (16 per 1000 treated) at 30 days associated with thrombolysis.

10.3 Results

10.3.1 Systematic Reviews

A Cochrane review (Berridge et al. 2013) addressed the question whether surgery or thrombolysis should be the preferred initial treatment for ALI. Five randomised trials with a total of 1283 patients were included. There was no significant difference in limb salvage or death at 30 days, 6 months or 1 year between initial surgery and initial thrombolysis. However, stroke was significantly more frequent at 30 days in thrombolysis participants (1.3%) compared to surgery participants (0%). Major haemorrhage was more likely at 30 days in thrombolysis participants (8.8%) compared to surgery participants (3.3%), and distal embolization was more likely at 30 days in thrombolysis participants (12.4%) compared to surgery participants (0%). The authors concluded that universal initial treatment with either surgery or thrombolysis cannot be advocated on the available evidence. Thrombolysis may be associated with a higher risk of ongoing limb ischaemia and haemorrhagic complications including stroke. The higher risk of complications must be balanced against risks of surgery in each person. The risks of surgery and thrombolysis in the initial treatment of ALI were elaborated in a meta-analysis which constituted the background for the clinical guidelines of the American College of Chest Physicians (Alonso-Coello et al. 2012). See Table 10.3.

Wang et al. (2016) reviewed current data for ALI management with open or endovascular surgery, their outcomes, and complications. Four randomized prospective clinical trials and five other study reports formed the basis of this evidence summary.

Table 10.3 Summary of findings: thrombolysis vs. surgery for the initial treatment of acute limb ischemia (Alonso-Coello et al. 2012)

Outcomes	Risk with surgery	Risk difference with thrombolysis (95% CI)
Total mortality at 1 year	169 per 1000	43 fewer per 1000 (from 109 fewer to 98 more)
Stroke at 30 days (includes nonfatal ischemic and haemorrhagic strokes)	0 per 1000	10 more per 1000 (from 0 fewer to 20 more)
Major extracranial bleed at 30 days	12 per 1000	16 more per 1000 (from 3 more to 37 more)
Limb salvage at 1 year	754 per 1000	0 fewer per 1000 (from 106 fewer to 128 more)
Amputation after 1 year	190 per 1000	19 more per 1000 (from 22 fewer to 72 more)

CI confidence interval

These authors recommended initial treatment of ALI with endovascular therapy if it is not contraindicated, because of its equivalence in short-term outcomes (limb salvage, amputation-free survival, overall survival) and lower morbidity and mortality rates than urgent open revascularization, while acknowledging a higher need for future intervention. Contraindications to endovascular therapy include recent neurosurgery, recent bleeding including hemorrhagic stroke, and ongoing bleeding diathesis. Once ALI is resolved and patients are systemically optimized, they may be better candidates for definitive surgical revascularization with improved longer term outcomes.

10.3.2 Thrombolysis

10.3.2.1 Catheter-Directed Thrombolysis

Acosta and Kuoppala (2015) presented results after intra-arterial thrombolysis with low dose rtPA from 2001 to 2012 in two large vascular centers in Sweden. Technical success rate for thrombolysis of occluded endoprostheses, bypasses and native artery occlusion was 91%, 89% and 73%, respectively. Amputation-free survival rate at 1 year was 73%. Major hemorrhage occurred in 104 procedures (13.9%); 43 (5.7%) were so severe that thrombolysis was discontinued in advance. All three (0.4%) hemorrhagic strokes were fatal.

Grip et al. (2014) reported 749 intra-arterial thrombolyses in 644 patients with ALI. The purpose of this study was to evaluate different thrombolytic treatment strategies. Median patient age was 73 years, 47.1% of the procedures were done in women. The aetiology of ischaemia was graft occlusion in 38.8%, acute arterial thrombosis in 32.2%, embolus in 22.3% and popliteal aneurysm in 6%. Concomitant heparin infusion was used in 63.2%. The mean dose of rt-PA administered was 21.0 mg, with a mean duration of 25.2 h. Technical success was achieved in 80.2%. Major amputation and death within 30 days occurred in 13.1% and 4.4% respectively. Bleeding complications occurred in 30.3% of treatments. Three patients (0.4%) suffered from fatal intracranial bleeding. Amputation-free survival at 30 days was 83.6%. Comparing the results of two different centres, the authors concluded that continuous heparin infusion during intra-arterial thrombolysis offers no advantage. Acosta and Kuoppala (2015) had come to the same conclusion.

Kashyap et al. (2011) assessed outcomes in 119 patients (129 limbs) treated for ALI with intra-arterial thrombolysis. Percutaneous mechanical thrombectomy was utilized in nearly half the cases (47%) in addition to thrombolysis. The mean follow-up was 16.8 months. Technical success was achieved in 82% cases. The 30-day mortality rate was 6.0% with all 30-day deaths occurring in females. One (0.76%) central nervous system haemorrhage was noted in this cohort. Eighty-two percent of patients were alive and had their limb intact at 30 days after endovascular treatment for ALI. Primary patency for the entire cohort at 12 and 24 months was 50.1% and 37.7%, respectively, while secondary patency was 74.0% and 65.3%. Survival of

the entire cohort at 12 months was 85.7%. Thrombolysis >3 days was associated with an increased risk of limb loss and should be therefore limited to < 3 days.

123 patients undergoing thrombolysis for acute graft occlusion in the lower limb were retrospectively reviewed by Koraen et al. (2011). 67% had synthetic grafts. ALI (74%) was the dominating symptom preceding thrombolytic treatment. In 29% of cases, no adjunctive interventions were required, whereas 21% underwent open surgery, 39% endovascular intervention, and 11% underwent a hybrid procedure. Technical failure of thrombolysis occurred in 18 patients (15%). Fatal myocardial infarction occurred in three patients (2.4%). There were two patients with hemorrrhagic stroke (1.6%), of which one was fatal. Major hemorrhage occurred in 13.2% of the patients. The mortality rate was 6.5% and 13% at 1 and 12 months, respectively. The amputation-free survival rate was 89% and 75% at 1 and 12 months, respectively. One advantage with successful thrombolysis over the open surgical technique was in this study that thrombolysis allowed an accurate assessment of the vascular tree and underlying causes contributing to bypass graft failure. In this study the majority of patients underwent subsequent correction of an underlying stenosis within the graft and/or of an in- or outflow stenosis. In addition, thrombolysis had been assumed to result in more patent outflow vessels compared with surgical thrombectomy.

Schrijver et al. (2016) retrospectively analyzed 159 consecutive patients with 89 native artery (56%), and 70 prosthetic bypass graft (44%) occlusions of the lower extremity. Complete (>95%) lysis was achieved in 69% of native arteries and bypass grafts. Major hemorrhagic complications occurred in 12% (4% hemorrhagic strokes, of which 2% were fatal) of native arteries and in 7% (0% hemorrhagic stroke) of bypass grafts. The 30-day mortality rate was 6% in native arteries and 1% in bypass grafts, and the 30-day amputation rate was 10% in native arteries and 13% in bypass grafts. Amputation-free survival at 1 year was 76% for native arteries and 78% for bypass grafts and at 5 years was 65% for native arteries and 51% for bypass grafts. Long-term outcome after catheter-directed thrombolysis for acute lower extremity occlusions of native arteries compared with prosthetic bypass grafts was not different in this study.

10.3.2.2 Ultrasound-Accelerated Thrombolysis

Schernthaner et al. (2014) retrospectively compared the safety and efficacy of ultrasound-accelerated thrombolysis (UAT) and standard catheter-directed thrombolysis (CDT) in patients with acute and subacute limb ischemia. UAT was performed in 75 patients, and CDT was performed in 27 patients. Complete lysis was achieved in 72.0% (UAT) and 63.0% (CDT) of patients, respectively; hemodynamic success was achieved in 91.8% (UAT) and 92.3% (CDT). Major and minor bleeding combined was lower in UAT (6.7%) versus 22.2% in CDT. Median long-term survival was not significantly different between UAT and CDT. According to this data the observed lower risk of total bleeding might be an advantage of UAT. In the Dutch randomized trial comparing standard CDT and UAT for the treatment of

arterial thromboembolic occlusions (DUET study), thrombolysis was significantly faster in the UAT group (17.7 ± 2.0 h) than in the CDT group (29.5 ± 3.2 h, $p = 0.009$) and required significantly fewer units of urokinase (Schrijver et al. 2015). Technical success was achieved in 84% of patients in the CDT group vs. 75% patients in the UAT group. The combined 30-day death and severe adverse event rate was 19% in the CDT group and 29% in the UAT group. The 30-day patency rate was 82% in the CDT group as compared with 71% in the UAT group (p = 0.35). These differences were not statistically significant.

10.3.2.3 Thrombolysis/Dosage

Alteplase (rt-PA) weight-adjusted doses have ranged in the literature from 0.02 to 0.1 mg/kg/h, whereas non–weight-based doses generally range from 0.25 to 1.0 mg/h, even though higher doses have been reported. In general, the lowest effective dose has not been determined. The recommended maximum dosing was no greater than 40 mg for catheter-directed therapy (Patel et al. 2013). To shorten treatment times, Falkowski et al. (2013) analysed safety and efficacy of ultra-high-dose, short-term thrombolysis in a prospective single-centre study. The outcome of treatment in 97 patients with acute limb ischemia (<14 days) with the use of catheter directed rt-PA infusion was evaluated. The mean total dose of rt-PA was 54.1 mg (50–60 mg) and was administered for a mean of 2.51 h (2–4 h). Thrombolytic success was defined as 95% thrombolysis of an occluded segment with return of antegrade flow. Thrombolytic success was achieved in 83.5%. Overall clinical success was 88.7%. The 30-day amputation-free survival rate was 93.8%. Major bleeding complications occurred in 10 patients (10.3%). There were two deaths (2.1%) and four amputations (4.1%). Amputation-free survival at 2 years was 70%. The study did not support the superiority of ultra-high-dose rt-PA administered over short time frames in limb salvage over other methods of thrombolytic agent administration, but there was an obvious benefit in faster restoration of limb perfusion and greater patient comfort/tolerance.

10.3.3 Percutaneous Endovascular Thrombosuction

Katsargyris et al. (2015) reported a 5-year single center experience with the use of percutaneous endovascular thrombosuction (PET) for ALI. A total of 262 patients were treated. Preoperative level of ALI was category I (viable) in 76%) of patients, category IIa (threatened marginally) in 19.4%, and category IIb (threatened immediately) in 4.6%. Initial technical success was 91% (237/262). Additional PTA was performed in 29.8% of patients, and PTA with stenting in 27.5%. Open surgery due to technical failure of PET was required in 4.2% (11/262) of patients. Thirty-day mortality was 4.6%. Perioperative complications occurred in 9.2%. Thirty-day amputation rate was 3.8%. Estimated cumulative survival was 73.7 ± 3.6% at

3 years. Estimated freedom from amputation during follow-up was 91.2 ± 2% at 3 years. Estimated freedom from reintervention was 90.4 ± 2% at 1 year, and 80 ± 3.7% at 3 years. The authors stressed the high initial technical success, low mortality and morbidity rates, and favorable early and mid-term limb salvage rates with PET.

10.3.4 Surgical Treatment

10.3.4.1 Acute Thrombembolectomy

Kempe et al. (2014) analyzed 170 patients with acute thromboembolic lower extremity ischemia. Eighty two patients (49%) had a previous history of atrial fibrillation, and four (2%) were therapeutically anticoagulated at presentation. The mean duration of symptoms before presentation was 1.7 ± 1.4 days. Common femoral artery exposure for the performance of embolectomy was the initial procedure in 86% of patients, and isolated popliteal fossa exposure for the performance of embolectomy was used in 9%. Intraoperative thrombolysis was administered in 16% because of incomplete distal arterial revascularization. Fasciotomies were performed in 39%. Ten bypass procedures were performed concurrently with the initial thromboembolectomy. Amputation within a 90-day interval occurred in 27 patients (16%), with 26 (15%) being major amputations. Median time to amputation was 1 day. Freedom from amputation was 80% at 5 years. The 30-day or in-hospital mortality was 18%. Estimated overall survival at 5 years was 41%. The data demonstrate that acute thromboembolic lower extremity ischemia remains a cause of high mortality, morbidity, and health care resource use that may be preventable in a large number of patients.

10.3.4.2 Bypass Surgery

The database of the Vascular Study Group of New England (VSGNE) covers 323 (5.7%) of 5712 lower extremity bypasses that were performed for the indication ALI and classified as an emergent or urgent procedure (Baril et al. 2013). Patients undergoing lower extremity bypass for ALI were more likely to have had undergone a previous ipsilateral endovascular intervention than those undergoing bypass for all other indications (41.1% vs. 28.8%). Additionally, these patients were more likely to have undergone a prior ipsilateral bypass (32.8% vs. 23.5%). Patients with ALI had longer operative times than those undergoing lower extremity bypass for all other indications (270 min vs. 244 min), had more common use of prosthetic conduit (40.6% vs. 32.6%), and had an increased rate of in-hospital major adverse events (19.8% vs. 11.6%). Although patients undergoing lower extremity bypass for ALI experienced no difference in rates of graft occlusion at 1 year compared with patients undergoing bypass for all other indications (18.1% vs. 18.5%), these

patients did experience higher rates of both major amputation (22.4% vs. 9.7%) and mortality at 1 year (20.9% vs. 13.1%). In multivariable analysis, ALI was an independent predictor of both amputation and mortality at 1 year. The question which patient subgroups might benefit more from an endovascular approach compared with an open surgical bypass, however, could not be answered in this paper.

Marqués de Marino et al. (2016) assessed the outcomes of infrainguinal bypass performed for ALI in a retrospective cohort study. The cohort was stratified according to the indication for surgery into two groups: group A (acute limb ischaemia) and group B (chronic lower extremity ischaemia). In total, 702 bypasses were performed (group A, n = 107; group B, n = 595). Patients with acute limb ischaemia more often required general anaesthesia (47% vs. 12%) and a short bypass was more often performed (32% vs. 7%). No differences were found in patency rates at 1, 12, and 24 months between groups, but group B had a higher re-intervention rate during follow up. Primary patency in group A was 84%, 63%, and 58%, and in group B it was 88%, 62%, and 53% at 1, 12, and 24 months, respectively. Acute limb ischaemia was an independent risk factor for amputation (odds ratio [OR] 4.96) and mortality (OR 4.13) at 30 days. In group A, female sex, prosthetic conduit, and need of distal thrombectomy were independently associated with worse patency rates. Poor intra-operative runoff was correlated with higher amputation rates.

10.3.5 Registry Data on Treatment of ALI

The largest retrospective analysis of admissions for severe limb-threatening ischemia in the USA was performed by Korabathina et al. (2013). Data from 1988 through 2007 from the National Hospital Discharge Survey were analysed and all admissions for patients with lower-extremity arterial thromboembolism (LET) were extracted. Over the 20-year span, there were 1.76 million cases of LET. The incidence of LET decreased significantly from 42.4 per 100,000 persons between 1988 and 1997 to 23.3 per 100,000 persons between 1998 and 2007. The in-hospital mortality for LET decreased significantly from 8.28% between 1988 and 1997 to 6.34% between 1998 and 2007, and male patients achieved greater mortality reduction compared with female patients. Treatments for ALI showed decreasing use of surgical bypass and amputation and increasing rates of catheter-based thrombolysis. An overview of the data from the last decade (1998 to 2007) is given in Table 10.4.

Trends in the incidence and treatment of ALI in Medicare fee-for-service beneficiaries 65 years or older from the years 1998–2009 were presented by Baril et al. (2014). Within this population, hospitalizations for ALI decreased from 45.7 per 100,000 in 1998 to 26.0 per 100,000 in 2009. The proportion of patients undergoing intervention for limb salvage during their ALI hospitalization increased from 66.6% in 1998 to 74.9% in 2009. There was a marked shift from open to endovascular limb salvage procedures during the study period. The proportion of patients undergoing open surgery declined from 57.1% in 1998 to 51.6% in 2009. Concomitantly, the

Table 10.4 Admissions with the primary diagnosis lower-extremity arterial thromboembolism in the USA, 1998 to 2007 (Korabathina et al. 2013)

	Total	Men	Women
Estimated total admissions, n	670,704	357,598	313,106
Age, mean (SD), years	67 (14)	65 (14)	70 (16)
Mean (SD) length of stay	8.1 (10.5)	7.7 (8.4)	8.6 (12.5)
Atrial fibrillation (%)	15.6	12.4	19.3
Coronary artery disease (%)	21,6	26.3	16.3
Diabetes mellitus (%)	21.6	19.9	23,5
Peripheral arterial disease (%)	24.8	26.9	22.4
Aortic aneurysm/dissection (%)	4.6	5.8	3.2
Tissue loss (%)	19	21.4	16.1
Estimated age-adjusted incidence of lower-extremity arterial thromboembolism per 100,000 persons	23.3	25.3	21.4
In-hospital mortality (%)	6.34	5.01	7.86
Revascularisation procedures			
Surgical bypass (%)	29.6		
Endarterectomy (%)	7.6		
Thromboembolectomy (%)	15.8		
Amputation (%)	7.3		
Fasciotomy (%)	2.6		
Thrombolysis (%)	7.1		
Percutaneous angioplasty (%)	15.4		

SD standard deviation

percentage of patients undergoing endovascular therapy increased from 15.0% in 1998 to 33.1% in 2009. In-hospital amputations rates did not change over time and were 8.1% in 1998 and 6.4% in 2009, but in-hospital mortality for patients with ALI decreased over time from 12.1% in 1998 to 9.0% in 2009. However, 30-day amputation-free survival remained stable (73.5% in 1998 to 74.5% in 2008), as did 1-year amputation-free survival (51.8% in 1998 to 52.3% in 2009). Furthermore, although in-hospital mortality rates declined after presentation with ALI, the overall risk-adjusted 1-year mortality for ALI remained unchanged at 41.0% in 1998 to 42.0% in 2008.

Von Allmen et al. (2015) determined recent hospital trends for ALI in England using Hospital Episode Statistics for the years 2000 to 2011 and mortality data from the Office for National Statistics. Hospital admissions have risen significantly from 60.3 to 94.3 per 100,000 of the population, with an average annual increase of 6.2% since 2003. The rise was greater in the older age group and yet procedures for ALI have shown a significant decrease since 2000 from 14.3 to 12.4 per 100,000, independent of age and sex. Open embolectomy of the femoral artery remained the most common procedure and the proportion of endovascular interventions showed only a

small increase. Over the decade, the relative proportion of endovascular procedures compared with surgery for ALI was 14.3% in 2000 and 16.8% in 2011.

10.3.6 Endovascular and Surgical Revascularisation in ALI

Taha et al. (2015) retrospectively reviewed all patients with lower extremity ALI who underwent endovascular revascularization (ER) or open revascularization (OR) at the University of Pittsburgh Medical Center from January 2005 through May 2011. Patients with ALI due to embolism or thrombosis of a native artery, bypass graft, or previous stent were considered in the study. A total of 154 limbs (147 patients) in the ER group were compared with 326 limbs (296 patients) in the OR group. Cardiac embolism was more common in the OR group, whereas failed stent was more common in the ER group. The overall technical success rate was better with OR (88%) than with ER (81%). OR was associated with a higher incidence of wound infection (9% vs. 0.7%), rethrombosis (14.7% vs. 1.3%), fasciotomy (29.1% vs. 7.3%), or unplanned return to the operating room (25.5% vs. 1.3%) compared with ER. Also, OR had a higher incidence of reversible postoperative acute renal failure (12% vs. 4%) and new-onset postoperative hemodialysis (4% vs. 0.7%) as well as a more prolonged hospital stay compared with ER (11.5 ± 12 vs. 8 ± 7 days). On the other hand, ER was associated with a higher incidence of systemic bleeding events than OR was (5.8% vs. 0%). The overall 30-day amputation rate was significantly higher with OR (13.5%) than with ER (6.5%). Excluding Rutherford III patients, rates were 11.5% for OR vs. 6.5% for ER. Amputation rates specific to patients presenting with Rutherford II ischemia were comparable between the two groups (10% for OR vs. 7%). At 1 year, no significant differences were noted between the OR and ER groups in the overall amputation rates or in rates specific to Rutherford II patients as well. The overall mortality rates were significantly lower with ER than with OR at 30 days (5.4% vs. 13.2%), 1 year (12.9% vs. 33.8%), and 2 years (18.7% vs. 40.5%). The mean follow-up time was 14 months. The primary patency rates, the primary-assisted patency rates for OR and ER (96% and 100% at 1 year, 92% and 97% at 2 years), and secondary patency rates were comparable. The authors concluded that OR as an initial treatment of ALI results in improved technical success rates in patients with Rutherford II ischemia, especially when it is caused by a failed stent or bypass graft. This was at the expense of a higher mortality rate compared with ER, without the added advantage of improved patency or limb salvage at 30 days and at 1 year. In patients with Rutherford II ischemia secondary to stent failure or native artery thrombosis, the observed trend toward improved limb salvage with thrombolysis (at 30 days and 1 year) might suggest that ER may be considered the initial treatment for this particular group of patients. In contrast, patients with failed bypass grafts had a trend toward improved limb salvage with OR, which might suggest that surgery should be the preferred initial treatment for those patients. Predictors of overall mortality in this study are given in Table 10.5.

Table 10.5 Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia/ predictors of mortality (Taha et al. 2015)

Variable	HR, hazard ratio
Endovascular intervention	0.687
Age	1.031
Cancer	1.646
End-stage renal disease/dialysis	7.278
Chronic renal insufficiency	1.449
Chronic obstructive pulmonary disease	1.609
Severity of ischemia[a]	
Category IIa	5.973
Category IIb	7.995
Category III	38.675

[a]Reference category is Rutherford I category

The same group (Genovese et al. 2016) reported 5-year mortality and amputation rates in a total of 411 patients (445 limbs) treated for ALI. Interventions included surgical thrombectomy (48%), emergent bypass (18%), and endovascular revascularization (34%). Most patients presented with Rutherford classification IIa (54%) or IIb (39%). The etiology of ALI included embolism (27%), in situ thrombosis (28%), thrombosed bypass grafts (32%), and thrombosed stents (13%). Excluding Rutherford class III patients (n = 12), overall 5-year mortality was 54% (stratified by treatment, 65% for thrombectomy, 63% for bypass, and 36% for endovascular, $P < 0.001$); 5-year amputation was 28% (stratified by treatment, 18% for thrombectomy, 27% for bypass, and 17% for endovascular, $P = 0.042$). In this study, long-term mortality and amputation rates were greater in patients treated with open techniques. However, OR patients presented with a higher number of comorbidities and advanced ischemia, while also experiencing a higher rate of major postoperative complications.

Donato et al. (2014) described the role of the combination of surgical embolectomy and endovascular techniques (so-called "hybrid procedures," HP) for treatment of patients presenting with ALI. They compared outcomes of surgical thromboembolectomy (TE) vs. HP in patients with ALI. Patients received urgent surgical treatment using only a Fogarty balloon catheter (TE group = 112) or in conjunction with endovascular completion (HP group = 210). HPs following surgical TE consisted of angioplasty (PTA) ± stenting in 90 cases, catheter-directed intra-arterial thrombolysis + PTA ± stenting in 24, thrombus fragmentation and aspiration by large guiding catheter + PTA ± stenting in 67, vacuum-based accelerated thromboaspiration by mechanical devices in 9, and primary covered stenting in 12. Estimated primary patency was 87.1% vs. 66.3% at 5-year follow-up, respectively, for HP and TE patients. Estimated freedom from reintervention at 1 year was 94.4% for HP vs. 82.1% for TE patients, and 89% vs. 73.7% at 5 years, respectively (P = .04). The authors believed that surgical TE is still the most effective and less time-consuming solution in removing a large clot from the femoropopliteal arterial segment. However, percutaneous pharmacological or mechanical thrombolysis, applied as an adjuvant procedure to surgery, may improve results by clearing a reasonable amount of clot from distal vessels, with remarkable primary technical success (99.1%).

10.3.7 Specific Issues

Paediatrics

ALI is an infrequent but potentially devastating condition in the pediatric population. It is usually post-traumatic or iatrogenic and is rarely secondary to arterial occlusive disease as in the adult population. Kayssi et al. (2014) reviewed the medical records of 151 inpatients diagnosed with ALI of the upper or lower limb. Patients were an average age of 1.51 ± 3.72 years, with 57 (38%) ≤30 days old, 70 (46%) 1 to 12 months old, and 24 (16%) > 1 year old. Injuries in 137 patients (91%) were iatrogenic secondary to catheterization mostly for cardiac indications. Most injuries occurred in the lower extremity (94%) and included the external iliac (42%) or common femoral (30%) arteries. One hundred and twenty nine of the patients with postcatheterization ALI (94%) were treated with anticoagulation alone, eight patients (6%) showed no clinical improvement after 24 h of anticoagulation therapy and received a course of tissue plasminogen activator (tPA). Twenty nine patients (19%) died of causes that were not directly related to limb ischemia such as cardiopulmonary failure or multiple organ dysfunction. Of the patients followed up as outpatients, 13 (15%) developed claudication or limb length or limb circumference discrepancy. The data demonstrate that ALI in children can generally be managed nonoperatively with anticoagulation, likely because of their greater ability to develop arterial collaterals. Matos et al. (2012) confirmed in a smaller patient cohort of 12 infants less than 1 year of age the conservative treatment approach in the infant population. Supportive care and the use of systemic anticoagulation with heparin was the best management for most patients. Limb viability was 100% in this series of infants with ALI managed nonoperatively.

Cancer Patients

Should the indications for surgery or catheter-based intervention in cancer patients with ALI differ from patients without cancer due to their worse prognosis and coagulation behavior? According to an analysis of patients of the MD Anderson Cancer Center (Mouhayar et al. 2014), the answer is no. In a total of 74 cancer patients with concomitant ALI, surgery was the most common therapy (36 patients; 49%). Percutaneous catheter-based interventions were used in 21 patients (28%); 7 failed, referred to surgery. Eighteen patients (24%) received anticoagulation therapy only, and 6 patients (8%) received no therapy. The 30-day, 6-month, and 1-year overall survival rates were 80%, 59%, and 48%, respectively. Eight patients (11%) underwent amputation. The 1-year amputation-free survival rate was 47%. According to this study conservative management as the main therapeutic modality would only be justified in cases of terminal cancer where palliative care supersedes. Aggressive treatment of ALI in cancer patients was also advocated by Tsang et al. (2011) based on 16 cases of thromboembolectomy. In this study 44% of patients were still alive at 1 year after intervention. In addition, Silverberg et al. (2015) presented 24 cancer patients treated for ALI. Perioperative mortality rates were similar among cancer and non-cancer patients (20% vs. 16%). Nevertheless, long-term survival rates of cancer patients were significantly lower compared to non-cancer patients (45% vs. 77%) with a mean follow-up of 9.8 months for the malignancy group. However, there are also contrary attitudes. Morris-Stiff and Lewis (2010) compared 14 patients with ALI and malignancy to 102 patients with ALI but without malignancy. 30-day

(50% vs. 30%) and 60-day mortality rates (100% vs. 35%) were significantly higher in the malignancy group. The performance of emergency vascular surgery for patients with advanced malignant disease appeared to be of limited benefit. Indeed, in cases where patients are known to have metastatic disease at the time of presentation with ALI, it may be advocated that operative intervention is not undertaken.

Controlled Reperfusion

Despite the fact that ischemia-reperfusion injury has to be expected after revascularisation of an ischemic limb, only a few studies have been published about its prevention in patients with ALI. In a prospective randomized trial a total of 174 ALI patients from 14 centers were randomized between conventional treatment (CT) by thromboembolectomy and normal blood reperfusion and thromboembolectomy followed by controlled reperfusion (CR) with a crystalloid reperfusion solution supplemented with allopurinol (Heilmann et al. 2013). Adult patients (aged ≥18 years) with acute arterial occlusion of one or both legs and uncompensated ischemia (Rutherford classification of ALI, stages IIA–III) were eligible for the study. The primary end point was amputation-free survival (AFS) after 4 weeks (CT, 82.4%; CR, 82.6%). Secondary end points were AFS (CT, 62.4%; CR, 63.1%) and overall survival (CT, 71.6%; CR, 76.3%) after 1 year. In this study, no differences between treatment groups CT and CR were found, neither overall nor in the per-protocol population nor in patient subgroups defined by other pre- and intraoperative factors. The benefit of controlled reperfusion in the treatment of ALI is therefore not proven. This applies also to another study (Schmidt et al. 2015). In this retrospective single-center study, controlled limb reperfusion was applied in 36 patients with ALI of category IIA to III. 52.8% had central (aortic and bifurcation) and 47.2% had peripheral (common iliac artery and distal) vascular occlusions. The common femoral artery and vein were cannulated, and a hypothermic (22 °C), initially oxygen-free, potassium-free ringer's solution was perfused using a heparin-coated extracorporeal membrane oxygenation (ECMO) and hemofiltration system with low-dose heparinization. Average perfusion time was 94 ± 35 min. Thirty-day mortality was 27.8%. 55.5% of patients showed complete recovery of motor and sensory dysfunction. A total of 27.8% of patients developed a compartment syndrome and required fasciotomy. Lower leg amputation was necessary in 11.1% of patients. Whether this procedure might reduce mortality and morbidity is unknown, as long as data from randomized controlled studies are not available.

10.4 Conclusions for Clinical Practice

1. Urgent revascularization is indicated for ALI with threatened viability (stage II).
2. A general recommendation for initial treatment of ALI with open surgery or thrombolysis cannot be given. In case of doubt, surgical treatment should be preferred due to the increased risk in stroke and major bleeding associated with thrombolysis.

3. Catheter-based thrombolysis is an effective and beneficial therapy and is indicated for patients with ALI (Rutherford categories I and IIa) of less than 14 days' duration. Surgery is indicated in ALI patients with motor or severe sensory deficit (stage IIb).
4. CIRSE and SIR Standards of Practice Committees (Patel et al. 2013) published detailed guidelines for percutaneous management of acute lower-extremity ischemia. These guidelines include a treatment algorithm regarding ALI. The algorithm may be seen as a synopsis of the present statements (Fig. 10.1).

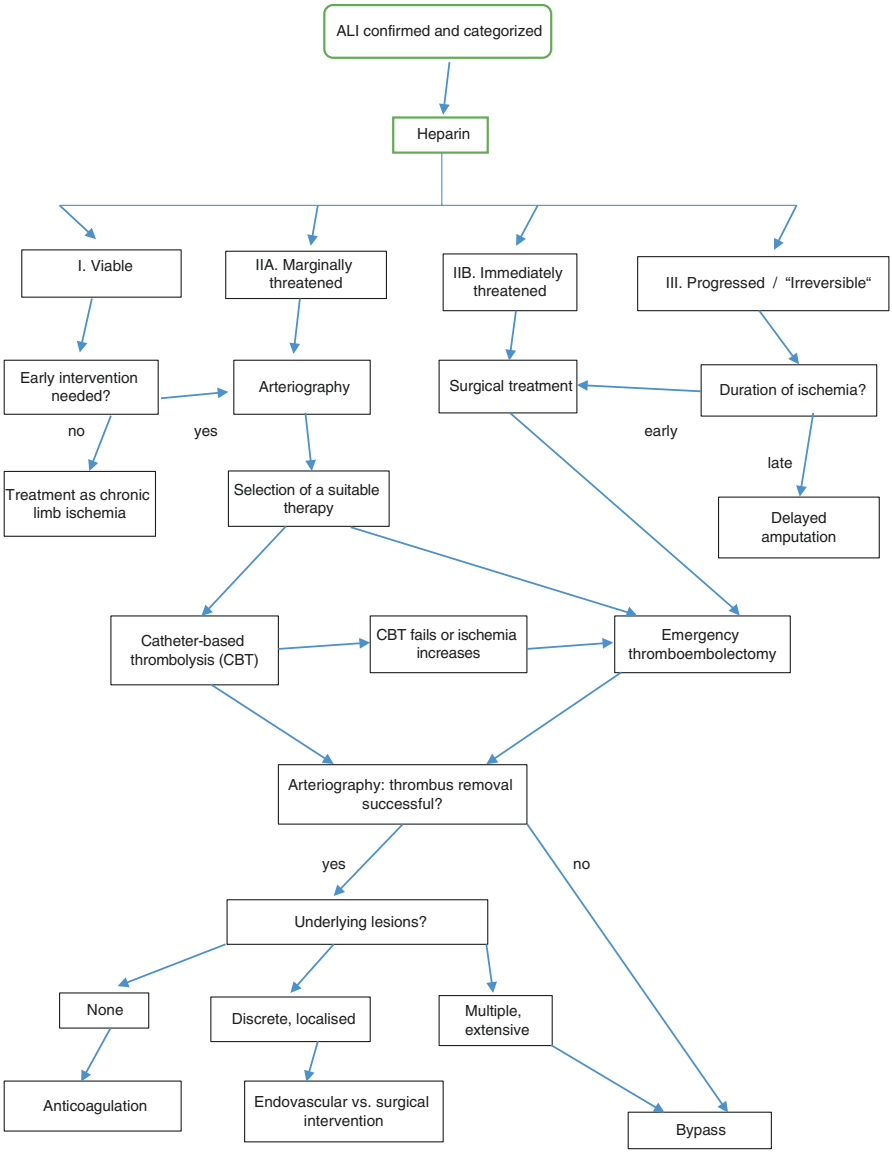

Fig. 10.1 Proposed algorithm for management of ALI (Patel et al. 2013)

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Chapter 11
Popliteal Artery Aneurysm

11.1 Guidelines

Treatment of symptomatic popliteal artery aneurysms (PAA) is undisputed. In asymptomatic PAA, the indication for repair depends on aneurysm diameter. The American College of Cardiology Foundation/American Heart Association recommends (Anderson et al. 2013):

Class-I

- Patients with a palpable popliteal mass should undergo an ultrasound examination to exclude popliteal aneurysm. (Level of Evidence: B)
- Patients with popliteal aneurysms 2.0 cm in diameter or larger should undergo repair to reduce the risk of thromboembolic complications and limb loss. (Level of Evidence: B)
- Patients with anastomotic pseudoaneurysms or symptomatic femoral artery aneurysms should undergo repair. (Level of Evidence: A)

Class IIa

- Surveillance by annual ultrasound imaging is suggested for patients with asymptomatic femoral artery true aneurysms smaller than 3.0 cm in diameter. (Level of Evidence: C)
- In patients with acute ischemia and popliteal artery aneurysms and absent runoff, catheter-directed thrombolysis or mechanical thrombectomy (or both) is suggested to restore distal runoff and resolve emboli. (Level of Evidence: B)
- In patients with asymptomatic enlargement of the popliteal arteries twice the normal diameter for age and gender, annual ultrasound monitoring is reasonable. (Level of Evidence: C)
- In patients with femoral or popliteal artery aneurysms, administration of antiplatelet medication may be beneficial. (Level of Evidence: C)

The AHA-guidelines do not set whether PAA should be treated by open repair (OR) or endovascular repair (ER). There is a lack of evidence on this subject.

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11.2 Results

11.2.1 Meta-analysis and Systematic Overviews

A Cochrane Review (Joshi et al. 2014) assessed the effectiveness of an endovascular stent graft versus conventional open surgery for the treatment of asymptomatic PAA on primary and assisted patency rates, hospital stay, length of the procedure and local complications. Due to the limitations of the current evidence from one small underpowered study, this review was unable to determine the effectiveness of endovascular stent graft versus conventional open surgery for the treatment of asymptomatic PAAs. However, it seemed reasonable to suggest that endovascular repair should be considered as a viable alternative to open repair of PAA on a case by case basis.

In a systematic review of data published between 1994 and 2009, Cina (2010) came to the same conclusion. In his paper, the pooled estimate of patency rate for ER of PAA showed that primary and secondary patency rates at 1 year were 83% and 86%; and at 3 years 74% and 85%, respectively. These results were comparable with that obtainable with open surgery: pooled estimates of 5-year patency for OR was 72%. From this, Cina concluded that ER in the presence of a suitable anatomy and with good tibial run-off is not only feasible, but also safe and with midterm results that are clinically acceptable and probably not different from open repair.

More recently, a further metaanalysis including five studies with a total of 652 PAA repairs (236 ER, 416 OR) in 597 patients with a mean age of 71 years has been published (von Stumm et al. 2015). They, too, found no statistically significant differences between open and endovascular treatment in the categories of patient survival, limb loss, and primary patency when calculated as the hazard ratios (HR) in a random model. The conclusion was that midterm primary patency rates did not differ between ER and OR, but 30-day reintervention and thrombosis following ER was more frequent than after OR. Yet the evidence of this conclusion was low.

11.2.2 Registry Data

The treatment of PAA is not standardised. A considerable variability exists in terms of the incidence of procedures, the operative indicators and the choice of operative procedure. This is shown by the data from the multinational VASCUNET Collaboration (Björck et al. 2014). The incidence of procedures in the 8 participating countries ranged from 3.4 (Hungary) to 17.6 (Sweden) per 1 million inhabitants per year. Selective procedures made up, depending on the country, 26.2 to 86.2% of all procedures. Of all aneurysms, 34.7% in Australia and 29.5% in Sweden were treated through endovascular repair, compared with 0% in Switzerland and Finland. The choice of operative technique depended more on surgical tradition than on the original diagnosis. The large variance in information provided and the variable

Table 11.1 Current treatment of PAA – results from the VASCUNET collaboration

Number of PAA in total	1471
Number of operations per million person years	9.59
Median patient age (years)	70
Percentage of men	95.6%
Active smokers	44%
Elective procedure	72%
Percentage of endovascular repair in total	22.2%
Percentage ER in patients with acute thrombosis	12.2%
Percentage ER in elective cases	24.1%
OR	
Usage of vein graft	87.2%
Synthetic bypass or composite graft	12.7%
Follow-up until discharge or 30 days:	
Amputation rate overall	2.0%
Amputation rate after acute thrombosis	6.5%
Amputation rate after ER	1.0%
Amputation rate after OR	1.8%
Amputation rate after hybrid repair	26.3%
Mortality overall	0.7%
Mortality after elective repair	0.1%
Mortality after acute thrombosis	1.6%
Mortality after rupture	11.1%

From Björck et al. (2014)
Values provided are average values from 8 countries

involvement in compiling the register mean that, at present, it is not possible to assess the efficacy of ER and OR. As the authors themselves emphasise, this will first be possible when longer-term post-operative examination results are analysed. Nonetheless, the averaged values of the registry do provide insight into the present state of PAA-treatment and are therefore given in Table 11.1.

Galiñanes et al. (2013) analysed data from Medicare and Medicaid services' inpatient claims from 2005 to 2007. During this period, a total of 2962 patients with PAA were registered, from which initially 11.7%, and subsequently 23.6% were treated with endovascular repair. The total rate of complications was 11.3% (OR) vs. 9.3% (ER). The 30-day and 90-day mortality did not differ between the two techniques. The re-intervention rate following ER was higher as compared to OR (after 30 days 4.6% vs. 2.1%; after 90 days 11.8% vs. 7.4%). The length of stay and charges were greater for OR than for ER. However, as a result of the high reintervention rate, there was no financial advantage for the endovascular procedure. Despite a significant increase in the utilization of endovascular repair of PAA, ER was associated with greater reinterventions over time and did not offer a mortality or cost benefit.

In the Swedish vascular registry, Swedvasc, 592 interventions for PAA (499 patients) were registered between May 2008 and May 2012 (Cervin et al. 2015). Of

the 592 PAA, 187 (31.6%) were treated emergently and 405 (68.4%) electively. The indication for treatment was: rupture 2.2%, acute ischaemia 29.4%, elective symptomatic 17.7%, and asymptomatic 50.7%. In symptomatic patients, the amputation free survival at 1 year was 73/83 (88%) with OR and 9/9 (100%) with ER. In asymptomatic patients it was 216/221 (97.8%) with OR and 48/52 (92.3%) with ER ($p < 0.048$). In patients with acute ischemia, significantly poorer results were obtained with ER as compared to OR, the amputation free survival after 1 year was 19/25 (76.0%) with ER vs. 109/122 (89.3%) with OR. These results favor OR for treatment of PAA, in particular among those treated for acute ischemia and put the use of ER for PAA outside trials in question.

11.2.3 Clinical Studies: OR

Dorweiler et al. (2014) have reported on OR of 206 PAA with an average diameter of 3 cm, in a total of 154 patients. One hundred sixty-one PAA were treated electively, and 45 were treated under emergency conditions. Vein grafts were predominantly used (82%) and a medial approach was chosen in 92%. Hospital mortality was 2% for elective procedures and 3% for emergencies. The late results in this study showed a median follow-up of 137 months with an overall survival rate of 63.5% at 5 years and 40.8% at 10 years and no significant difference between elective and emergent surgeries. Primary, assisted primary, and secondary patency rates were 88.1% (73.5%), 92.1% (84.3%), and 96.5% (89.8%) at 5 (at 10) years, respectively, with no significant difference between elective and emergent surgeries. Limb salvage rate, however, was significantly reduced in the emergent group vs the elective group with 91.1% vs 98.6% at 5 and 10 years. Freedom from any necessary reintervention was 84.3% after 5 and 69.8% after 10 years. The long-term results of this study were excellent and can be considered a standard, against which the ER of PAA can be compared and measured.

From January 1981 to December 2013, Dorigo et al. (2015) performed 234 open surgical interventions for PAA in 196 patients. The PAA was asymptomatic in 97 limbs, intermittent claudication was present in 68, and limb-threatening ischemia was present in 62 limbs. The intervention consisted of aneurysmal ligation and bypass grafting in 122 interventions, aneurysmectomy with graft interposition was used in 108, and four patients underwent aneurysmectomy with an end-to-end anastomosis. An autologous vein was used in 49 interventions, and a prosthetic graft was used in 181. In 71 interventions a posterior approach was used, and in the remaining 163, a medial approach was preferred. There were two perioperative deaths, with a cumulative mortality rate of 1%. Perioperative thrombosis occurred after 18 interventions (7.7%). The cumulative rate of amputations at 30 days was 3.8% (9 of 234 limbs). Mean duration of follow-up was 62 months. The estimated 13-year survival rate was 50.8%; during the same interval, primary patency, secondary patency, and limb preservation rates were 55.1%, 68%, and 86%.

Long-term results of the posterior approach (PA) for the treatment of popliteal artery aneurysms, compared with those operated on through a standard medial

approach (MA) were reported by Mazzacarro et al. (2015). A total of 77 aneurysms were treated in 65 patients (64 men). Thirty-six aneurysms were asymptomatic (47%). A PA was used in 43 PAAs (55%) and a MA in 34. All PA repairs consisted of aneurysmectomy with an interposition graft with end-to-end anastomoses; among MA repairs, 22 interposition grafts and 12 bypasses were performed. A polytetrafluoroethylene graft was used in 54 cases. No perioperative deaths or early amputations occurred. The median in-hospital stay was longer for MA (10 days) than for PA (7 days; P = .02). Median follow-up was 58.8 months. The differences between the two groups were small and not statistically significant. The 5-year primary and secondary patency rates were 59.6% ± 8.6% and 96.5% ± 3.4%, respectively, for PA, and 65.1% ± 11.1% and 79.4% ± 9.7%, respectively, for MA. Limb salvage was 100% at 5 years and 93.3% ± 6.4% at 10 years for PA and 91.1% ± 6.3% at both times for MA (P = .28).

11.2.4 Clinical Studies: ER

Long-term outcomes after ER of PAA (46 procedures on 42 patients) were presented by Piazza et al. (2014). In 93% of cases (n = 43) the procedure was elective. Technical success was 98%. Mean duration of follow-up was 56 ± 21 months. Primary patency at 1, 3, and 5 years was 82%, 79%, and 76%, while secondary patency was 90%, 85%, and 82% respectively; at 5 years there was 98% limb salvage and an 84% survival rate. During follow-up, 11 limbs had stent graft failure: six required conversions, one underwent amputation, and four continued with mild claudication. Of those with graft failure, 63% (7/11) occurred within the first year of follow-up. Segment coverage >20 cm was a negative predictor for patency (HR 2.76). The mean aneurysm sac volume shrinkage between preoperative and 5-year post-procedure measurement was significant (45.5 ± 3.5 mL vs. 23.0 ± 5.0 mL). In addition, Piazza et al. (2016) evaluated in a randomized study outcomes of intraoperative aneurysm sac embolization during endovascular aneurysm repair (EVAR) in patients considered at risk for type II endoleak (EII), using a sac volume-dependent dose of fibrin glue and coils. One hundred twenty-six patients underwent EVAR. One hundred seven patients (85%) were defined as at risk for EII and assigned to randomization for standard EVAR (group A; n = 55) or EVAR with intraoperative sac embolization (group B; n = 52). Freedom from EII was significantly lower for group A compared with group B at 3 months (58% vs 80%), 6 months (68% vs 85%), and 12 months (70% vs 87%), but not statistically significant at 24 months (85% vs 87%). Freedom from EII-related reintervention at 24 months was significantly lower for group A compared with group B (82% vs 96%). Patients in group B showed a significantly overall mean difference in aneurysm sac volume shrinkage compared with group A at 6 months (−11 ± 17 cm^3 vs −2 ± 14 cm^3), 12 months, and 24 months (−27 ± 25 cm^3 vs −5 ± 26 cm^3). In this study, sac embolization during EVAR was a valid method to significantly reduce EII and its complications during early and midterm follow-up in patients considered at risk.

Saunders et al. (2014) identified 34 PAAs in 26 patients, of which 32% presented with acute symptoms. PAA were repaired with either Hemobahn(®) or Viabahn(®) endografts, using an entirely percutaneous approach. At 1, 3, and 5 years follow-up, the primary graft patency was 88, 82, and 82%, respectively, and secondary patency was 90, 86, and 86%. Amputation-free survival at 1, 3, and 5 years was 97, 94, and 94%, respectively. Technical success was achieved in 100%. The authors concluded that the primary and secondary patency rates of endovascular repair of PAA are equivalent to the reported outcome of open repair.

Fifty-three consecutive PAA patients treated by endovascular procedures between January 2004 and December 2013 were retrospectively reviewed by Speziale et al. (2015). Fifty-two patients (98.1%) had at least 1 patent runoff vessel. Technical success was achieved in all patients. In-hospital mortality rate and 30-day reinterventions were null. Long-term results were satisfactory. At a mean follow-up of 37.4 ± 29.3 months, primary patency, secondary patency, and limb salvage were 73.6%, 92.4%, and 100%, respectively.

A retrospective review of 33 endovascular popliteal artery aneurysm repairs in 28 patients was conducted by Kumar et al. (2015). All repairs were performed using a self-expanding covered stent graft. Among the patients, 18% were symptomatic at the time of repair. The median number of stents used was 2 (range, 1–4). Median duration of stay was 1 day (range, 0–12). The 1-year and 2-year patency were 87% and 81%, respectively, with a mean follow-up of 23 months. In this study, loss of patency was associated with both poor distal runoff (P = .007) and increasing number of stents used (P = .03). Early complications were seen in 4 patients including: stent oversizing leading to in-folding, perforation of a tibial artery, access site hematoma, and access vessel dissection.

Data on all patients with PAA treated with a heparin-bonded polytetrafluoroethylene (ePTFE) stent graft between April 2009 and March 2014 were retrospectively analysed by Golchehr et al. (2016). A total of 72 PAA was treated in 70 patients. Mean age was 71.2 ± 8.5 years and 93% were male. The majority of PAA were asymptomatic (78%). Sixteen cases (22%) had a symptomatic PAA, of which seven presented with acute ischemia. Early postoperative complications occurred in two patients (3%). Median follow-up was 13 months. Primary patency rate at 1 year was 83% and after 3 years 69%; primary assisted patency rate was 87% at 1 year and 74% after 3 years. Secondary patency rate was 88% and 76% at 1 and 3 years, respectively. There were no amputations during follow-up.

11.2.5 Comparative Studies OR Versus ER

Eslami et al. (2015b) queried the Vascular Quality Initiative (VQI) databases (2010 to 2013) for patients undergoing asymptomatic PAA repair using OR and ER. Three hundred ninety patients with asymptomatic PAA (221 OR, 169 ER) were included in this study. Preoperative comorbidities were similar between the two groups, except for a higher rate of congestive heart failure (19.5% vs 11.8%) and chronic obstructive pulmonary disease (19.5% vs 11.8%) in the ER group. No in-hospital mortality was

observed. The crude comparison of long-term follow-up results showed lower rates of 1-year mortality (1.8% vs 0.5%), major adverse limb events, MALE (6.5% vs 5%), and MALE or perioperative death, MALEPOD (8.3% vs 5.4%) in the OR group, but none of these differences were statistically significant. However, an adjustment for confounding variables showed open surgery was associated with significantly lower hazards of MALE (HR, 0.35), MALE-POD (HR, 0.28), and of loss of primary patency (HR, 0.25) when compared with ER. The results indicated that patients who underwent OR had significantly less 1-year rates of adverse outcomes and suggest that OR should be preferentially offered to patients who can tolerate either therapeutic option. Nevertheless, the authors interpreted the data cautiously, in anticipation of the ongoing prospective randomized OVERPAR trial which might definitively answer if one procedure is superior to the other (Eslami et al. 2015a).

Huang et al. (2014) described the open (n = 107) and endovascular (n = 42) repair of 149 PAA. Primary end points were major adverse events (MAEs) including mortality, major amputation, patency, complications, and reinterventions. The technical success rate of ER was 98%; the 30-day mortality and rate of amputation were 0% for elective and 20% for emergency procedures (ER). After OR, a 30-day mortality of 1% for elective operations and 0% for emergency operations was observed. No amputations were carried out. In the follow-up at 3 years, in elective procedures a trend towards fewer MAEs following an OR became apparent. Additionally, freedom of reintervention was significantly higher in the OR group (OR 88%, ER 72%). On the other hand, emergency procedures with acute leg ischemia had an equally adverse prognosis after ER and OR (Table 11.2).

Table 11.2 Results after open (OR) and endovascular (ER) treatment of PAA

	ER	OR
Total patients (n)	35	91
Mean age (years)	81 ± 6.5	71 ± 9.6
Total PAA	42	107
Elective	32	93
Emergency	10	14
30-day MAEs		
Elective repairs	9%	5%
Emergent repairs	52%	43%
30-day mortality and amputation rate		
Elective repairs Emergent repairs	0% 20%	1% 0%
Mean follow-up (years)	2.6	3.8
3-year freedom from MAEs		
Elective repairs	66%	80%
Emergent repairs	40%	50%
3-year primary patency rate		
Elective repairs	75%	85%
Emergent repairs	54%	77%

Mayo Clinic 2005 to 2012 (Adapted from Huang et al. 2014)
MAEs major adverse events (mortality, major amputation, patency, complications, and reinterventions)

In the years 1993–2013, Serrano Hernando et al. (2015) treated 171 PAA, 53.3% of which were asymptomatic and 18.7% had acute ischemia. Good runoff (2 to 3 vessels) was present in 69% of the patients. The patients were either treated with a vein bypass (57.9%), a PTFE prosthesis (23.4%) or an endovascular stent graft (18.7%). The 30-day mortality was 1.8%. Major amputations were needed in five patients (all with previous acute ischemia). Popliteal-popliteal bypasses showed better primary patency at 24 months when saphenous vein was used vs PTFE (94.9% vs 79%). However, similar patency rates were recorded for short PTFE bypasses and stent grafts (79% vs 79.7%). On multivariate analysis, only poor run-off emerged as an independent factor for worse primary patency. Given the good midterm outcomes of endovascular treatment, the authors concluded that this may be a feasible option in selected patients.

Data concerning 178 OR and 134 ER for PAA were collected by Pulli et al. (2013). Patients of both groups were not comparable as 64% of the OR patients but only 34% of the ER patients were symptomatic. An acute limb ischemia was present in 23% of the OR group vs. 6.5% of the ER group. A run-off score of <2 was registered in 39% of OR cases vs. 26% of ER cases. Six perioperative thromboses (3.3%), 1 amputation (0.5%) and no perioperative mortality were noticed in the OR group, whereas 13 thromboses (9.7%), 1 amputation (0.5%) and 2 perioperative deaths (1.5%) were observed in the ER group. The average follow-up was 30.6 ± 27.5 months. The primary and secondary patency rates, freedom from reintervention and limb preservation rates at 48 months were for OR (ER in brackets): 63.5% (73.4%)/76.5% (85%)/72.5% (75%)/89.7% (97%). In the OR group, primary patency rates at 4 years were significantly better in patients operated on with an autologous vein (86.3%) than in patients who had a prosthetic graft (56.3%). Pointing out the different patient characteristics, the authors nonetheless concluded that treatment of PAA with either OR or ER was safe and effective.

88 PAA (72 patients) were treated by Stone et al. (2013) during 10 years (2001–2011). Indications for intervention included symptomatic presentations in 53% (n = 47) and asymptomatic in 47% (n = 41). Treatment included ER in 24, surgical repair in 63, and primary amputation in one patient. The mean length of stay was 3.9 days (ER) vs 9.5 days (OR) favoring endovascular treatment. There were no perioperative (30-day) deaths in the ER group and one in the surgical cohort. The mean patency follow-up was 21.2 vs 28.3 months. Primary patency did not differ significantly between endovascular and surgically treated patients at 1 year (92.9% vs 83.3) and 3 years (63.7% vs 77.8). The mid-term survival was 65% after ER (average follow-up period 33.9 months) and 80.8% after OR (average follow-up 42.9 months). It could be concluded that ER provides similar short-term patency to that of surgical bypass, with shorter hospitalizations in both symptomatic and asymptomatic patients. Leake et al. (2016) came to a similar statement. They considered ER a safe and durable option for PAA, with lower complication rates and a shorter length of stay compared to OR. They evaluated a total of 186 PAA in 156 patients (110 OR, 76 ER). Mean follow-up was 34.9 ±28.6 months for OR and 28.3 ±25.8 months for

ER. Technical success was 100% in all ER and OR patients. The length of stay after the procedure was significantly shorter for ER (1.6 ± 3.7 days) than for OR (5.8 ± 4.5 days). ER had significantly fewer 30-day complications (2.6%) vs OR (18.2%). At 3 years, primary, primary assisted, and secondary patency rates were 79.5%, 83.7%, and 85.0% for OR and 73.2%, 76.3%, and 83.0% for ER. In this study, a total of 130 patients, 63 OR and 67 ER, were elective cases. In this subgroup, OR had significantly better primary patency at 1 year and 3 years compared with ER (3 years: OR, 88.3% vs ER, 69.8%), but there was no difference in secondary patency between groups (3 years: OR, 90.2% vs ER, 82.0%).

11.2.6 Special Issues

11.2.6.1 Thrombolysis for Acute Thrombosed PAA

The effect of preoperative thrombolysis prior to definite surgical repair of acute thrombosed PAA could not be analysed in the Vascunet database (Björck et al. 2014). Kropman et al. (2010) performed a systematic review to summarise outcomes of acute thrombosed popliteal artery aneurysms (PAA) treated with thrombolysis or thrombectomy followed by bypass. Eight prospective studies and 25 retrospective studies with 895 patients presenting with acute ischaemia were included. No randomised trials were included. The mortality rate after surgical repair was 3.2%. The amputation rate was 14.1%. Thrombolysis before surgery did not result in a significant reduction of the number of amputations, compared with surgery (thrombectomy and bypass) alone. The mean primary patency rates of the bypasses at 1, 3 and 5 years were 79%, 77% and 74%, respectively, in the 'thrombolysis' group and 71%, 54% and 45% in the 'thrombectomy' group. No distinction could be made regarding secondary patency and limb-salvage rates between the groups owing to insufficient data. According to this review, preoperative and intraoperative thrombolyses result in a significant improvement in 1-year primary graft patency rates, but do not result in a significant reduction for amputations compared with surgery alone.

Gabrielli et al. (2015) compared retrospectively 47 patients with acute limb ischemia due to a thrombosed PAA, who were treated by immediate surgery (including intra-operative thrombolysis) with 39 patients who underwent preoperative thrombolysis before acute or elective OR. The primary and secondary patency rates after 2 years were 61.7% and 70.2% respectively when immediate surgery with intraoperative thrombolysis was performed, and only 43.6% and 53% when thrombolysis was initiated preoperatively. Additionally, the amputation rates after 1 month (18% vs. 29%) and 12 months (19% vs. 44%) were better in the group with immediate surgery. Due to this retrospective study, patients suffering from thrombosed PAA should undergo surgery immediately and thrombolytic drugs should be administered intraoperatively.

11.2.6.2 Outcome in Women

PAA requiring intervention in women is a rare clinical occurrence. Peeran et al. (2016) found 8 women with degenerative PAA (1.6% of 485 total surgical PAA repairs). The overall median follow-up was 5 years. At the time of repair, women were of similar age compared with men (73.5 vs. 71.7 years) and had similar aneurysm size (2.7 vs. 2.9 cm). Women had similar urgency (25 vs. 17.5% emergent) and symptomatic status (50% vs. 55% acute) even though 7 of the 8 women had a thrombosed PAA at the time of repair. Operative time, approach, graft type, and inflow and outflow sources were similar between genders. No women received endovascular repair (0% vs. 10%, P = 0.5). One patient of each gender underwent major amputation (one woman on post-operative day 158 and one man on post-operative day 3). Overall, women had lower survival and amputation-free survival at 2 years (51% vs. 100% and 20% vs. 94%).

Kropman et al. (2014) compared initial and long-term outcomes between men and women after endovascular and open repair of PAA. Two hundred two patients (185 men [92%]), underwent open (n = 186) or endovascular (n = 16) repair of a PAA. Data were retrospectively analysed. Significant differences in baseline characteristics were determined between men and women with regard to aneurysm diameter (men: 30 mm; women: 26 mm) and age (men: 66 ± 10 years; women: 71 ± 9 years). There were no differences in regards to the perioperative results. The 30-day mortality rate was 0% in both groups. The primary patency rates at 1, 3, and 5 years were 88%, 82%, and 76% in men compared with 64%, 64%, and 48% in women, respectively (p = 0.007). When correcting for potential confounders with multivariable regression analysis, sex was independently associated with primary patency (hazard ratio: 2.98). According to this retrospective study, women are associated with lower primary patency rates and a trend toward lower limb salvage rates compared to men. However, the large differences in group size limit the reliability of this statement.

11.2.6.3 Decision analysis Model for OR vs. ER

Hogendoorn et al. (2014) developed a Markov decision model to compare OR with great saphenous vein bypass vs. ER in patients with asymptomatic PAA on the basis of the best available and most up-to-date evidence from relevant articles. According to this model, OR should be preferred over ER for a 65-year-old male patient with a 2.0-cm asymptomatic PAA and without significant comorbidities, as it results in a win of 0.36 QALYs (Quality adjusted life years). Conversely, higher costs and more re-interventions are observed per patient in the ER group (1.03 in ER group vs. 0.52 in OR group). ER is preferred in patients who are at high risk for open repair (>6% 30-day mortality) or if the 5-year primary patency rates of stenting increase to 80%. For very old patients (>95 years) and patients with a very short life expectancy (<1.5 years), best medical treatment yields higher QALYs.

11.3 Conclusions for Clinical Practice

1. PAA can be treated with open repair or an endovascular approach. Due to the limitations of the current evidence, the effectiveness of endovascular stent graft versus conventional open surgery for the treatment of asymptomatic PAAs cannot be definitely determined.
2. It seems reasonable to suggest that endovascular repair should be considered as a feasible option in selected patients.
3. When surgical treatment is used, a vein bypass should be preferred to a prosthetic graft.
4. The effect of preoperative thrombolysis prior to definite surgical repair of acute thrombosed PAA has to be further investigated.

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Chapter 12
Vascular Access for Hemodialysis

12.1 Guidelines

12.1.1 UK Renal Association

- Preferred type of vascular access (Kumwenda et al. 2015): We recommend that all patients with end stage kidney disease who commence haemodialysis or are on long-term haemodialysis should dialyse with an arteriovenous fistula (AVF) as first choice, an arteriovenous graft as second choice, a tunnelled venous catheter as third choice and a non-tunnelled temporary catheter as an option of necessity (1A).
- We recommend that the AVF should be placed as distally as possible in the non-dominant arm. Radiocephalic and brachiocephalic AVF are preferred to brachio-basilic transposition AVF(2C).
- Audit measures:

  (a) 60% of all incident patients with established end stage kidney disease commencing planned haemodialysis should receive dialysis via a functioning arteriovenous fistula (AVF) or arteriovenous graft (AVG).
  (b) 80% of all prevalent long term dialysis patients should receive dialysis treatment via definitive access: AVF or AVG or Tenckhoff catheter.
  (c) The annual *Staphylococcus aureus* bacteraemia rate in the prevalent haemodialysis population should be less than 2.5 episodes per 100 HD patients and less than 1.0 for MRSA over 2 years.

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12.1.2 Society for Vascular Surgery

The Society for Vascular Surgery recommends the following operative strategies for the placement of autogenous accesses (Sidawy et al. 2008):

- AV accesses are placed as far distally in the upper extremity as possible to preserve proximal sites for future accesses (GRADE 1 recommendation, very low-quality evidence).
- When possible, autogenous AV accesses should be considered before prosthetic arteriovenous accesses are placed. These autogenous access configurations should include, in order of preference, the use of direct AV anastomosis, venous transpositions, and translocations (GRADE 1 recommendation, very low-quality evidence).
- Upper extremity access sites are used first, with the non-dominant arm given preference over the dominant arm only when access opportunities are equal in both extremities (GRADE 1 recommendation, very low-quality evidence).
- Lower extremity and body wall access sites are used only after all upper extremity access sites have been exhausted (GRADE 1 recommendation, very low-quality evidence).
- We recommend the placement of forearm autogenous arteriovenous access as the first choice for primary access for hemodialysis (GRADE 1 recommendation, very low-quality evidence).

  A. When arterial and venous anatomy is suitable, placement of autogenous radial–cephalic direct wrist access (Brescia-Cimino-Appel) or autogenous posterior radial branch–cephalic direct wrist access (snuffbox) is recommended.
  B. In the case where arterial or venous anatomy does not allow placement of a direct access, forearm vein transposition or translocation are recommended. These procedures should use the maximal length of adequate vein and use arterial inflow from the forearm tailored to accommodate this length of vein.

- For patients who have exhausted all forearm veins on both sides and, according to vein availability and surgical expertise, are suitable candidates for either forearm prosthetic access or upper arm access of any type, we suggest that the surgeon offer both alternatives to patients (GRADE 2, very low-quality evidence).
- Management of non-functional or failed arteriovenous access: We suggest open surgery, endovascular means, or a combination of both to maintain or restore patency in AV access (GRADE 2, very low-quality evidence).

12.1.3 National Kidney Foundation (USA)

According to the clinical practice guidelines from the National Kidney Foundation (NKF) (2006) the order of preference for placement of fistulae in patients with kidney failure who choose hemodialysis as their initial mode of kidney replacement therapy should be (in descending order of preference):

Preferred: Fistulae. (B)

- A wrist (radiocephalic) primary fistula. (A)
- An elbow (brachiocephalic) primary fistula. (A)
- A transposed brachial basilic vein fistula: (B)

Acceptable: arteriovenous grafts (AVG) of synthetic or biological material, such as: (B)

- A forearm loop graft, preferable to a straight configuration.
- Upper-arm graft.
- Chest wall or "necklace" prosthetic graft or lower-extremity fistula or graft; all upper-arm sites should be exhausted.

12.1.4 German Task Force Clinical Nephrology

Interdisciplinary guidelines for monitoring arteriovenous access and management of complications have been compiled by a German task force (Hollenbeck et al. 2009). The recommendations:

- A hemodynamically significant stenosis, suspected by clinical assessment and/or flow measurements, should be further verified as soon as possible by diagnostic imaging (evidence level III). A pre-emptive percutaneous or surgical intervention should be carried out without delay, and the imaging should occur shortly prior to the procedure (evidence level II).
- Percutaneous transluminal angioplasty (PTA) is the therapy of choice for venous outflow stenosis (evidence level III).
- Thrombosed AV fistulae or thrombosed AVG should be treated either by endovascular or surgical intervention. Clinical centres should review their results and choose the modality which provides the best outcome (evidence level III).
- Localised widening of fistula veins with rapid progression and risk of perforation, parietal stenoses, and signs of infection should be surgically corrected. Clinicians must pay attention to the possibility of downstream stenosis.
- Pseudoaneurysms from prosthetic grafts due to area puncture, which show progression, are an indication for partial graft replacement.
- In the case of suspected central venous obstruction, an angiographic examination of AVF and complete venous outflow up to the right atrium should be accomplished (evidence level III). Treatment should be performed with percutaneous endovascular intervention (evidence level III).
- Shunt-induced ischemia should be recognised through clinical examination. The cause should be identified, both through non-invasive imaging and angiography (evidence level III). Therapeutic options include the improvement of arterial inflow, restraining shunt-flow and/or the improvement of distal blood flow. When these techniques do not succeed, a shunt ligation should be considered (evidence level II).

- Infected AV fistulae accompanied by fever and/or bacteraemia should be treated with intravenous antibiotics over at least 2 weeks. In the case of septic thrombi and/or septic emboli, an excision of the fistula is required (evidence level IV).
- Locally infected prosthetic grafts can be preserved through segmental resection and circumvention of infected areas. A suitable, long-term antibiotic therapy (2 weeks intravenously and hereinafter orally over another 4 weeks) is recommended (evidence level III).
- An infected anastomosis is an indication for the total removal of the graft (evidence level II).

12.2 Results

12.2.1 Meta-analyses/Systematic Reviews

12.2.1.1 Choice of Haemodialysis Access

Al-Jaishi et al. (2014) ascertained in a systematic review and meta-analysis outcomes of AVF. Fourty-six articles met eligibility criteria (62 unique cohorts; n = 12,383). They found that in recent years, AVF had a high rate of primary failure and low to moderate primary and secondary patency rates. The rate of primary failure was 23%. When primary failures were included, the primary patency rate was 60% at 1 year and 51% at 2 years. The secondary patency rate was 71% at 1 year and 64% at 2 years. In metaregression, there was a significant decrease in primary patency rate in studies that started recruitment in more recent years. Nonetheless, patients with usable fistulas have the lowest risk for death, infections, and cardiovascular events compared with other vascular access types. This was demonstrated by another systematic review of 62 cohort studies with 586,337 patients (Ravani et al. 2013). The risks of death from all causes, major cardiovascular events, and fatal infections associated with dialysis vascular access types are summarized in Table 12.1.

McGrogan et al. (2015) assessed outcomes of arteriovenous fistulas (AVF) in the elderly (anyone older than 60 years) and compared results of radiocephalic vs brachiocephalic AVF placements in a systematic review and meta-analysis. A total of 15 studies were included in the analysis of primary and secondary AVF patency rates. Pooled primary patency rates for radiocephalic and brachiocephalic AVFs were 49.7% and 58.5%, respectively. Pooled secondary AVF patency rates were 65.1% for radiocephalic and 72.7% for brachiocephalic AVFs. This meta-analysis confirmed that brachiocephalic AVFs have superior primary and secondary patency rates at 12 months compared with radiocephalic AVFs in the elderly.

The Fistula First Initiative has promoted AVFs as the vascular access of choice. Generally, snuff box and radio-cephalic are accepted and well described sites for AVFs, however, the forearm ulnar-basilic AVF is seldom used or recommended.

Table 12.1 Absolute risks of death from all causes, major cardiovascular events, and fatal infections associated with dialysis vascular access types

Vascular access comparison	Meta-analytic Relative Risk (RR)	Number of additional events per 1000 patients exposed per year
All-cause mortality		
Catheter vs. AV fistula	1.53	106 excess with catheter
Catheter vs. graft	1.38	91 excess with catheter
Graft vs. AV fistula	1.18	36 excess with graft
Major cardiovascular events		
Catheter vs. AV fistula	1.38	38 excess with catheter
Catheter vs. graft	1.26	28 excess with catheter
Gaft vs. AV fistula	1.07	7 excess with graft[a]
Fatal infections		
Catheter vs. AV fistula	2.12	28 excess with catheter
Catheter vs. graft	1.49	17 excess with catheter
Graft vs. AV fistula	1.36	9 excess with graft

According to meta-analysis by Ravani et al. (2013)
Note: [a]The 95% CI includes negative numbers, indicating that the superiority of graft versus fistula for cardiovascular events is uncertain (the 95% CI ranges between 5 fewer events and 21 in excess with grafts)

Al Shakarchi, Khawaja et al. (2016b) systematically reviewed the evidence base for the creation of the ulnar-basilic fistula. Eight studies were included in the review. Weighted pooled data revealed 1-year primary patency rate for ulnar-basilic AVFs of 53.0% with a secondary patency rate of 72.0%. The review showed that the ulnar-basilic AVF may be a viable alternative when a radio-cephalic AVF is not possible and dialysis is not required urgently. It has adequate 1-year primary and secondary patency rates and extremely low risk of haemodialysis access induced distal ischaemia.

12.2.1.2 Treatment of Thrombosed Dialysis Shunts

Should occluded AV fistulas and grafts be managed by surgery or endovascular intervention? Kuhan et al. (2013) carried out a systematic review and meta-analysis to answer this question. There were no randomized trials comparing surgery vs. endovascular therapy for native fistulas and vein grafts. Six randomized studies reporting on 573 occluded grafts were identified. Technical success, 30-day morbidity and primary patency at 30 days were similar between the two groups. There was no statistical difference between the two groups for 1-year primary patency. In conclusion, comparable results to surgery have been achieved with endovascular techniques for occluded prosthetic grafts for dialysis access. Long-term data comparing the two groups were lacking.

12.2.1.3 Preemptive Correction of Arteriovenous Access Stenosis

In a systematic review and meta-analysis including 14 trials (1,390 participants) benefits and harms of preemptive versus deferred correction of AV access stenosis were evaluated (Ravani et al. 2016a). In this paper and in an additional Cochrane review Ravani et al. (2016b) concluded that pre-emptive correction of a newly identified or known stenosis in a functional AV access does not improve access longevity. Although pre-emptive stenosis correction may be promising in fistulas, existing evidence is insufficient to guide clinical practice. While pre-emptive stenosis correction may reduce the risk of hospitalisation, this benefit is uncertain whereas there may be a substantial increase (i.e. 80%) in the use of access-related procedures and procedure-related adverse events (e.g. infection, mortality). The net effects of pre-emptive correction on harms and resource use are thus unclear.

12.2.2 Registry Data

Malas et al. (2015) performed a retrospective analysis of the cohort of patients in the US Renal Data System (USRDS) database who initiated dialysis between January 1, 2006, and December 31, 2010. In the total study cohort of 510,000 patients, 71,452 (14.0%) initiated hemodialysis (HD) with AVF, 17,562 (3.4%) initiated with arteriovenous graft (AVG), and 420,986 (82.5%) initiated with hemodialysis catheter (HC). Survival at 1 year was 78% in the HC group compared with 84% for the AVG group and 89% for the AVF group. Five-year survival in the HC group was 45% compared with 48% in the AVG group and 55% in the AVF group. Initiating HD with an AVF provided a significant mortality benefit compared with initiating dialysis with an AVG or HC. Despite this, most patients in the United States initiate HD with HC, and incident AVF use falls markedly short of the initial Kidney Disease Outcomes Quality Initiative target of 50% that was established more than 15 years ago.

The type of vascular access at the start of HD (incidence) between 2005 and 2009 was reported for a total of 13,044 patients from five countries in the ERA-EDTA (European Renal Association – European Dialysis and Transplant Association) – registry (Noordzij et al. 2014). The majority of patients started HD using a CVC. This percentage showed an increasing tendency over time, from 58% in 2005 to 68% in 2009. Conversely, the use of AVFs as the first vascular access at the start of HD decreased from 42% in 2005 to 32% in 2009. AVGs were used infrequently (<1%) as the first vascular access. The prevalence of vascular access types based on the vascular access type reported once a year in nine countries (n = 75,715) showed a similar trend. The percentage of patients with an AVF decreased from 66 to 62% over time. In contrast, the use of CVC in the prevalent group increased from 28% in 2005 to 32% in 2009. Use of AVGs remained stable over time at 5–6%. Reasons behind these trends were not given.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor (DPM) refers to 3442 patients in the United States and 8478 patients in19 other

nations. In the United States from August 2010 to August 2013, AVF use increased from 63 to 68%, while catheter use declined from 19 to 15%. Although AVF use did not differ greatly across age groups, AVG use was two-fold higher among black (26%) versus nonblack US patients (13%) in 2013. Across 20 countries in 2013, AVF use ranged from 49 to 92%, whereas catheter use ranged from 1 to 45% (Pisoni et al. 2015).

Using the USRDS database, Leake, Yuo et al. (2015b) identified incident HD patients in 2005 that started HD with a tunneled dialysis catheter (TDC) and survived at least 1 year. HD was initiated in 56,495 patients in 2005. Of those, 41,582 (74%) started with a TDC, 6368 (11%) with an AVF, and 2644 (5%) with an AVG. 10,966 (26.4%) patients of the TDC group died ≤ 1 year, and 16,461 (39.6%) never received a permanent access. A total of 6149 patients of the TDC group had an AVF (4524) or AVG (1625) procedure ≤3 months and had at least 1 year of follow-up available. In patients starting dialysis with a TDC, subsequent AVG placement was associated with earlier TDC removal along with fewer catheter days up to 6 months, compared with patients who underwent AVF placement. However, AVGs required more secondary procedures at all time points up to 1 year. The results suggest AVG placement may have an important role in decreasing TDC prevalence. In a further paper, Yuo et al. (2015) compared survival in patients with end-stage renal disease after creation of an AVF or AVG in patients starting HD with a TDC. The USRDS was used. A total of 138,245 patients were available for analysis who started HD with a TDC. In this group, 31,493 (22.8%) underwent AVF creation and 10,492 (7.6%) underwent AVG creation within 3 months of starting HD. After stratifying by age, in those younger than 65 years, AVF was superior to AVG (P = .031), but this was not evident in the elderly (65–79 years, P = .089; 80 years and older, P = .119). AVG and TDC appeared equivalent in patients younger than 65 years (P = .744), but AVG was associated with improved survival in the elderly (65–79 years and 80 years and older, both P < .001). After the 90-day mortality exclusion period, overall survival was short. For patients younger than 65 years, median survival was as follows: AVF, 3.02 years; AVG, 2.84 years; and TDC, 2.93 years. For patients between 65 and 80 years, median survival was as follows: AVF, 2.08 years; AVG, 2.03 years; and TDC, 1.23 years. For patients older than 80 years, median survival was as follows: AVF, 1.38 years; AVG, 1.58 years; and TDC, 0.83 years. In this retrospective review for patients who start HD through a TDC, placement of an AVF and AVG was associated with similar mortality hazard.

Hicks et al. (2015) analyzed the effects of age at hemodialysis initiation on mortality across different access types. The USRDS between the years 2006 and 2010 was used (507,791 patients ≥ 18 years). Increasing age was a significant predictor of overall mortality. Compared with patients with hemodialysis catheters (HCs), n = 418,932, overall risk-adjusted mortality was lowest in patients with AVFs (n = 71,316; adjusted hazard ratio [aHR] 0.63) followed by AVGs (n = 17,543; aHR, 0.83). AVF was superior to both HC and AVG for all age groups. However, there were no significant differences comparing adjusted mortality with AVG vs HC for patients aged 18–48 years or for patients >89 years, but AVG was superior to HC for patients 49–89 years of age. The mortality benefit of AVF was consistently superior

to that of AVG and HC for patients of all ages. The authors concluded that all patients 18–48 years should receive AVF for dialysis access whenever possible.

12.2.3 Clinical Studies

12.2.3.1 Choice of Vascular Access

A total of 1206 AVF, 689 (57%) radiocephalic AVF (RCAVF), 383 (32%) brachiocephalic AVF (BCAVF), and 134 (11%) brachiobasilic AVF (BBAVF), were analysed by Wilmink et al. (2016). Primary failure (PF) occurred in 23% of the 1206 AVF. PF was lower for BCAVF (17%) than RCAVF (26%) and BBAVF (26%). The median maturation time was 10.3 weeks. Cumulative patency, including PF, of RCAVF was significantly better than BCAVF and BBAVF. RCAVFs resulted in 3% more dialysis-person-years (py) per 100 operations for all patients and in 15% more dialysis-py in the over 80s. It could be concluded that RCAVFs have higher PF, but better survival than other AVF, and result in more dialysis time. Vascular access planning should allow for a maturation time of 10 weeks, for a 50% probability, and 16 weeks for a 75% probability, that an AVF can be used. The study suggested that the best strategy in access planning is to create an RCAVF, irrespective of age, 4 months before the anticipated dialysis start. In contrast, in a population of predominantly diabetic patients, Kim et al. (2015) reduced the placement of radiocephalic AVFs and moved away from the wrist and toward the elbow. They suggested that the radiocephalic AVF is not the best option for hemodialysis access in diabetic patients. In their study with 191 AVFs increasing brachiocephalic AVF creation and reducing reliance on radiocephalic AVFs resulted in a significant increase in primary functional patency at 1 year. This was achieved while maintaining the same high percentage of fistulas, a lower rate of central catheter infections, and the same low incidence of steal syndrome.

The AVF is the preferred hemodialysis access, but AVF-failure rate is high. Schinstock et al. (2011) examined in a retrospective cohort study (317 AVFs in 293 patients) AVF failure rates and predictors of such failure. After excluding the AVFs unused because of death, no hemodialysis initiation during follow-up, kidney transplantation, or indeterminate outcome, 49.0% (103 of 210) of the remaining AVFs were unsuitable for hemodialysis within a reasonable time. The 3-, 6-, 12-, and 18-month primary patency rates were 67%, 50%, 41%, and 30%, respectively, and 92%, 86%, 77%, and 73%, respectively, for secondary patency. The risk for reduced patency was increased by diabetes (HR, 1.54), but decreased when larger arteries were employed (HR, 0.83). In this study, artery size was the main predictor of AVF patency.

Lok et al. (2013) compared retrospectively 1012 AV fistulas with 128 grafts (first accesses). The majority of first accesses were placed in the forearm (59.5% of fistulas and 74.2% of grafts) compared with the upper arm (40.5% of fistulas and 25.8% of grafts). Primary failure was twice as high for fistulas as for grafts (39.7% and

18.8%, respectively). When primary failures were included in the analysis, the proportion of first accesses that survived during follow-up did not differ between fistulas and grafts: 350 of 1012 (35%) versus 39 of 128 (31%), respectively. However, when 426 primary failures were excluded from the analysis, fistulas appeared significantly more likely to survive than grafts: 350 of 610 (57%) versus 39 of 104 (37%). In conclusion, fistulas in this study did not demonstrate better cumulative patency than grafts unless primary failures were excluded; however, grafts required more interventions to maintain patency.

Competing issues contribute to the decision about which hemodialysis vascular access strategy to pursue. Synthetic vascular accesses (SVA) can be cannulated and used for hemodialysis much sooner than AVFs, greatly reducing the exposure to central venous catheter complications. Conversely, SVAs have higher failure/complication rates than those associated with AVFs. Therefore, Rosas and Feldman (2012) determined the cost-effectiveness of two different vascular access strategies among incident dialysis patients. In their model, the AVF1st strategy had a better average cost-utility than SVA1st as long as the AVF maturation rate was greater than 69%. Further, the AVF1st strategy became less costly than SVA1st only if the AVF maturation rate was greater than or equal to 82%. The study demonstrated that the current emphasis of placing AVFs in all dialysis patients may not be optimal. AVF1st strategy may be most appropriate only for a subset of hemodialysis patients whose risk of AVF maturation failure is relatively low.

Olsha et al. (2015) examined the outcome of 146 new accesses in 134 patients aged 80 years and older. There were 128 autogenous accesses (30 forearm, 91 upper arm, and seven transposed basilic veins) and 18 prosthetic accesses. Overall primary patency was 39% and 23% at 12 and 36 months, respectively, while the secondary patency rate was 92% and 77%, respectively. There was no significant difference in patency between the different types of access. According to this data, age should not disqualify these patients from the Fistula First Initiative. However, Cui et al. (2016) came to the opposite conclusion. They assumed that grafts are a first-line hemodialysis access option in select elderly patients. In their series of 138 fistulas and 44 grafts in elderly patients (≥75 years old) the primary failure rate was higher for the fistulas compared with the grafts, and more fistulas required one or more interventions before their successful use compared with grafts (31% vs 10%). In addition, the time to catheter-free dialysis was longer for fistulas than for grafts. However, the primary and secondary patency rates were comparable between the fistulas and grafts.

12.2.3.2 Alternative Vascular Accesses

Bourquelot et al. (2012) reported on 70 patients (72 accesses) who underwent transposition of the superficial femoral vein to create an autogenous arteriovenous hemodialysis access. Two patients had bilateral procedures. All patients had exhausted upper arm veins or had central vein obstructions. The femoral vein in these patients was mobilised, transposed in a straight subcutaneous tunnel and anastomosed

distally end-to-side to the superficial femoral artery. Thirteen patients (18%) experienced major complications necessitating fistula ligation (ischemic complications, five diabetic patients with peripheral arterial occlusive disease [one major amputation included]; lower leg compartment syndrome, one; acute venous hypertension, two; secondary major edema, two; high-output cardiac failure, one; bleeding, two). Finally, all the patent accesses (59/72) were utilized for dialysis after a mean interval of 2 ± 1 months resulting in an 82% success rate. According to life-table analysis, the primary patency rates at 1 and 9 years were 91% ± 4% and 45% ± 11%, respectively. Secondary patency rates at 2 and 9 years were 84% ± 5% and 56% ± 9%, respectively. Based on reasonable long-term patency and low rate of infection, the authors concluded that this method is a valuable alternative to arteriovenous grafts.

Ong et al. (2013) compared the outcomes of 209 patients receiving a first thigh graft with the outcomes of the first tunneled internal jugular catheter placed in hemodialysis patients during the study period (n = 472). The surgical technical failure rate of thigh grafts was 8.1%. The secondary thigh graft survival rates were 62% at 1 year, 54% at 2 years, and 38% at 5 years. Secondary survival was much worse for dialysis catheters than thigh grafts. One-year secondary survival rate was 31% for catheters versus 62% for thigh grafts. Infection-free survival was far worse for catheters than thigh grafts. The 1-year infection-free survival rate was 21% for catheters versus 79% for thigh grafts. According to this study, thigh grafts are a viable choice of vascular access in HD patients who have exhausted all options for a fistula or graft in both upper extremities.

The results of chest wall arteriovenous grafts (CWAVGs) based on the axillary artery and ipsilateral axillary vein and tunneled in the subcutaneous tissues of the chest were presented by Liechty et al. (2015). Sixty-seven grafts in 67 patients were reviewed, representing 0.56% of 1192 total dialysis access creations during the study period. Sixty interventions were performed postoperatively including 32 for thrombosis and 28 for venous stenosis. Six documented graft infections occurred (9%). The primary and secondary patency rates at 1 and 2 years were 69.5% and 36.9% and 81.6% and 57.6%, respectively. Twenty-three of the 67 patients died in the 2-year follow-up period (34%). The authors regarded CWAVGs as useful and appropriate for patients with difficult upper extremity access. The patency rates for this procedure were at least equivalent to other upper extremity grafts. Advantage could be the infection rate which was lower than that for femoral grafts or tunneled catheters, and there was no risk of steal syndrome.

12.2.3.3 Vascular Access in Paediatrics

Even though early transplantation is still the first-line therapy in paediatric patients with end-stage renal disease, up to 30% of these patients still require HD. Matoussevitch et al. (2015) reported on 31 patients, from 6 to 19 years, rated as unfit for transplantation for at least the next 6 months or who had already been on HD through a CVC. Thirty-one patients were provided with 32 AVFs; 26 received a

distal radiocephalic fistula, five a Gracz-type fistula and one a brachio-basilic fistula. All but two fistulae matured primarily, within an average time of 45 days until the first dialysis. The fistula 1-year primary and primary assisted patency rates were 78% and 94%, respectively. According to this study, the creation of a native vascular access is an effective and durable procedure in paediatric and adolescent patients.

Wartman et al. (2014) performed 101 AVFs in 93 patients, mean age 14 years (range, 3–19 years). At the time of surgery, 78% of patients had a previous CVC, and 24% had two or more catheters. Mean follow-up was 2.5 years. The 2-year and 4-year primary and secondary patency rates were 83% and 92%, and 65% and 83%, respectively. Increasing age was correlated with improved primary patency but had no effect on secondary patency. During the postoperative period, 75% of patients received a renal transplant. The data seems to confirm that the native AV fistula is the hemodialysis access type of choice in paediatric patients. It must here be emphasised, that the average age of this patient cohort was 14 years. In a further study of 111 HD patients from 13 European paediatric nephrology units (Hayes et al. 2012), the choice of vascular access depended on patient age, with patients with AVF/AVG having a median age of 16 years compared to 12 years for patients with CVCs. In total, CVCs were used in 60% patients, AVFs in 38% and two patients had an AVG. Overall, infective complications necessitating CVC change, occurred at a rate of 0.9 episodes/1000 catheter days. No infective complications were reported in patients with AVF/AVG access. Catheter malfunction (inadequate blood flow) was a more prevalent complication necessitating 22.4 thrombolytic interventions/1000 catheter days and 2.1 CVC changes/1000 catheter days. In this study CVCs remained the predominant choice of vascular access despite problems of malfunction and infection.

12.2.3.4 Prosthetic Arteriovenous Access

A variety of vascular grafts have been described for prosthetic arteriovenous access (Widmer and Windisch 2014). Current quality of evidence regarding postulated properties (Table 12.2) is low and the potential improvement of the results in comparison to standard prosthetic grafts is of minor significance.

Table 12.2 AVG types and their assumed properties

Access type	Assumed property
Synthetic graft (PTFE, Polyurethane)	Control
Grafts with altered geometry	Better patency, prevention of myointimal hyperplasia
Heparin-bonded grafts	Better patency
Early cannulation grafts	Reduced use of CVC
Biological prostheses	Lower rate of infection, superior patency?

According to Widmer and Windisch (2014)

Heparin-bonded polytetrafluoroethylene (hepPTFE) grafts

Allemang et al. (2014) compared the patency of AVGs for dialysis access with and without heparin bonding in a retrospective study (223 patients/265 prostheses, 23% of which were Heparin-PTFE). HepPTFE grafts failed to improve rates of primary, assisted primary, or secondary patency based on univariate analysis. The number of secondary interventions was similar in the two groups (1.1 interventions per person-year of follow-up PTFE versus 1.4 hepPTFE). This supports earlier results from Charlton-Ouw et al. (2012), who similarly saw no improvements in 1-year patency rates when using heparin-bonded AVGs. In their study with 138 upper extremity access procedures, including 64 brachiocephalic fistulae, 21 brachioaxillary heparin-bonded, and 21 brachioaxillary conventional AVGs, the 1-year cumulative patency rates for AVF, heparin-bonded AVG, and conventional AVGs were 83%, 44%, and 67%, respectively. Further experiences were reported by Zea et al. (2016). They performed 70 AVGs (32 hep PTFE and 38 nonhep PTFE). At 1 year, Kaplan-Meier survival curves showed that functional patency between hep PTFE and nonhep PTFE AVG were 60% and 75%, respectively. Primary and secondary patencies were not significantly different between groups; however, primary-assisted patency was at 1 year hep PTFE versus nonhep PTFE: 50% vs. 80%; P = 0.02). This study did not demonstrate a benefit to the routine use of hep PTFE for AVG creation especially given the higher cost of these grafts. Functional patency rates were not improved, and the rates of reintervention and thrombectomy were higher with hep PTFE AVGs.

Slightly better results with hepPTFE were seen in a randomized trial (Shemesh et al. 2015). In this study, 160 patients were randomized and followed up for a median of 23.5 months. Heparin-bonded grafts demonstrated a trend to improved patency, but the difference was not statistically significant. Primary patency was 35% and 14% for heparin-bonded grafts and 29% and 12% for standard ePTFE grafts at 6 and 12 months, respectively (P = .48). Assisted primary patency was 54%, 41%, and 27% for heparin-bonded grafts and 41%, 30%, and 23% for standard grafts at 12, 24, and 36 months, respectively (P = .12). However, there were significantly fewer thromboses in heparin-bonded grafts during the first 5 months (P = .020).

Davies et al. (2016) compared in a retrospective study the outcomes of hepPTFE grafts with standard wall PTFE (S-PTFE) arteriovenous grafts in 483 patients with ESRD. Mean time to access was 5.1 ± 1.8 weeks for hepPTFE and 6.9 ± 1.9 weeks for S-PTFE (P = .0001). The 2-year primary, assisted primary, and secondary patency rates were 20% ± 7% vs 18% ± 8%, 35% ± 8% vs 28% ± 7%, and 38% ± 6% vs 36% ± 7% for hepPTFE vs S-PTFE, respectively. Both groups underwent a similar number of secondary interventions. There were no significant differences in infection or pseudoaneurysm formation between both groups. Functional dialysis durations were equivalent. According to this data, hepPTFE grafts offer no distinct advantage over S-PTFE grafts for hemodialysis and should not be considered a preferential conduit for AVG.

Biological prostheses

In a prospective randomised study, Kennealey et al. (2011) compared 26 patients with a bovine carotid artery (BCA) graft (artegraft) with 27 patients with a

PTFE-prosthesis for permanent HD access. Although there was no significant difference in secondary patency rates, primary and assisted primary patency rates were significantly higher in BCA than in the ePTFE grafts (60.5% vs 10.1% and 60.5% vs 20.8% at 1 year, respectively). The most common complication was graft thrombosis which occurred 0.34 ± 0.09 times per patient year in the BCA group compared to 0.77 ± 0.16 times per patient year in the ePTFE group. The authors concluded that the BCA graft is an excellent option for patients on hemodialysis that are not suitable for native arteriovenous fistulas, as these grafts required fewer interventions than the ePTFE grafts to maintain patency.

Morosetti et al. (2011) conducted a small, randomised study, including 27 patients with 29 AVGs (Omniflow II-prostheses) and 30 patients with autogenous brachial-basilic AVF (BBAVF) in the upper arm. The rate of complications for patients who received BBAVF was similar to those who received AVG in the early postoperative period, whereas patients who received AVG showed a higher rate of adverse events over the long-term. Primary patency rates at 6, 12, and 24 months were 55%, 32%, and 21%, respectively, for AVG vs 86%, 61%, and 60%, respectively, for BBAVF. Secondary patency rates at 6, 12, and 24 months were 72%, 52%, and 34%, respectively, for AVG vs 86%, 76%, and 66%, respectively, for BBAVF. The results confirmed that native AVFs should be given preference over AVGs if possible. This is also the case when biological material is used as graft material.

Lawson et al. (2016) did two phase 2 trials to study the safety and efficacy of bioengineered human acellular vessels in 60 patients requiring haemodialysis. In 59 patients, the grafts were placed as a brachial-to-axillary straight graft, and in one patient the graft was placed in an axillary-to-axillary loop configuration. At 12 months, primary patency was 28% (95% CI 17–40), primary assisted patency was 38% (26–51), and secondary patency was 89% (74–93). Interventions to maintain or restore patency were done at a rate of 1.89 per patient-year. These first engineered, decellularised vascular prostheses had no clinical or ultrasound evidence of structural degeneration, or true aneurysm formation, over a mean follow-up of 16 months. Secondary patency of 97% at 6 months and 89% at 1 year was higher than that reported in multicentre studies of ePTFE. After implantation, the vessel repopulates and remodels with host cells and might have a resistance to infection only reported previously for native arteriovenous fistulas. Furthermore, the implant functioned as a suitable conduit for dialysis access and did not require a prolonged time for maturation.

Early cannulation grafts

Early cannulation AVG such as the GORE Acuseal, have “low bleed” properties permitting cannulation within 24 h of insertion. Thirty-seven patients treated with the GORE Acuseal were presented by Aitken et al. (2014). Thirty-six AVGs (97.3%) were successfully cannulated. Mean time to first cannulation was 30.4 ± 23.4 h (range: 2–192). Primary and secondary patency rates at 3, 6 and 12 months were 64.9%, 48.6%, 32.4% and 70.2%, 59.4%, 40.5% respectively. The systemic bacteremia rate was 0.2 per 1000 access days. Meanwhile the results of a prospective multicentre study have been published by Glickman et al. (2015). The GORE

Acuseal AVG was implanted in 138 patients. Three of the AVGs were never cannulated. The mean time to first cannulation of the remaining 135 grafts was 15 days (range, 0–116 days); the median time was 5 days. During the follow-up period, 80 of the 138 patients had a total of 220 graft revisions or interventions, primarily percutaneous transluminal angioplasty or thrombectomy. The majority of stenoses (62%) developed at the venous anastomosis. On Kaplan-Meier analysis, the cumulative graft patency rate at 1 year was 79%. The 1-year primary unassisted patency rate was 35%. Fifteen graft infections and 15 cases of steal syndrome required intervention. The study demonstrated that the early-cannulation AVG graft can be cannulated soon after implantation. The authors considered patency and complication rates comparable to those reported in the literature with standard PTFE grafts; however, a prospective randomised study remains to be done.

The FLIXENE is another early cannulation graft. Chiang et al. (2014) compared 45 FLIXENE grafts with 19 standard PTFE AVGs in a prospective observational study. Eighty-nine percent of FLIXENE grafts were used for dialysis, with 78% cannulated within 3 days. At 18 months, primary patency (FLIXENE 34% vs standard PTFE 24%), primary assisted patency (35% vs 36%) and secondary patency rate (51% vs 48%) were not statistically different; 20.2% of FLIXENE grafts were infected at 18 months requiring explantation compared with 40.3% of standard PTFE grafts. In this study FLIXENE could be cannulated for dialysis within 3 days with similar patency and complication rates as other prosthetic grafts. A total of 46 FLIXENE grafts were further tested in a prospective single-center nonrandomized study (Berard et al. 2015). Seven grafts were never cannulated during the study period. Of the remaining 39 grafts, 32 (82%) were successfully cannulated within the first week after implantation, including 16 (41%) on the first day. Primary assisted and secondary patency rates were 65% and 86%, respectively, at 6 months and 56% and 86%, respectively, at 1 year.

Al Shakarchi, Houston et al. (2015a) performed a systematic review on early cannulation grafts for haemodialysis. Fifteen studies were included and divided into the different types of graft. Flixene, Avflo, Rapidax and Acuseal grafts showed that early cannulation within 72 h was possible. All grafts showed similar patency and complication rates as previously published data on standard ePTFE grafts, but data did not allow specific graft recommendations.

Hemodialysis reliable outflow (HeRO) graft

In patients who have exhausted all upper arm options and may be central catheter dependent, an alternative has been proposed with the Hemodialysis Reliable Outflow (HeRO) graft. It comprises two elements, a graft and venous outflow component. The graft is anastomosed to the ipsilateral brachial artery and tunnelled subcutaneously. The venous outflow component is placed percutaneously into the right atrium through the subclavian or internal jugular vein and superior vena cava. This component is tunnelled subcutaneously towards the graft. Therefore, it bypasses central stenosis, primarily in the brachial, cephalic, and subclavian veins by positioning the tip of the outflow component beyond it in the right atrium. The two elements are subsequently attached to each other subcutaneously through a purpose designed

titanium connector. Al Shakarchi, Houston et al. (2015b) performed a literature review on eight articles published prior to December 31, 2014, dealing primarily with the use of the HeRO graft for dialysis. A total of 409 HeRO grafts had been reported. Mean 1-year primary and secondary patency rates were calculated to be 21.9% (9.6–37.2%) and 59.4% (39.4–78%) respectively. The pooled rate of steal syndrome from the six papers that reported its incidence was 6.3% (1–14.7%), and device related bacteraemia (per 1000 days) ranged between 0.13 and 0.7 in the six studies that reported it. The rate of interventions required to maintain HeRO patency ranged between 1.5 and three procedures per year. Although these results are poor compared with a native AVF or AVG, in the general dialysis population, the cohort of patients having a HeRO placed are highly selected complex patients who have had multiple failed AVFs or AVGs. The study confirmed that the number of bacteraemia episodes is significantly lower with the HeRO device than catheters. The primary patency while low can produce acceptable secondary patency rates following interventions.

Al Shakarchi, Inston et al. (2016a) conducted in addition a cost-consequence analysis to examine the intermediate-term effect of the HeRO graft compared with tunneled dialysis catheters (TDCs) on the costs and clinical consequences of managing patients with ESRD requiring long-term HD and presenting with compromised venous access in the National Health Service (NHS) in England. In the base case, a 100-patient cohort managed with the HeRO graft experienced 6 fewer failed devices, 53 fewer access-related infections, and 67 fewer device thromboses compared to patients managed with TDCs. Although the initial device and placement costs for the HeRO graft were greater than those for TDCs, net 1-year savings of £1200 per patient were estimated for individuals managed with the HeRO graft.

12.2.3.5 Endografts to Exclude Pseudoaneurysms

Open surgical revision is the standard of treatment for hemodialysis access pseudoaneurysm (PSA) repair. However, this approach results in interruption of dialysis patterns and may necessitate placement of a temporary CVC. Percutaneous covered stent, or endograft, placement is a viable and safe alternative to open surgical revision of PSAs that maintains uninterrupted patency and availability of the access. Kinning et al. (2013) reported on 24 patients in whom self-expanding covered endografts were placed percutaneously to exclude access PSAs. No procedural complications were observed. Primary assisted patency was 83% at 2 months and 50% at 1 year. Mean duration of patency was 17.6 months. Five patients required endograft explantation for infection. Shemesh et al. (2011) examined the outcome of endovascular management in 20 patients with access aneurysms. Functional patency at 12 months was 87%. These authors emphasized that endovascular management with stent grafts enables treatment of both the aneurysm and its accompanying draining vein stenosis and allows continued cannulation of the existing access and thus avoids the use of central catheters. Twenty-seven self-expanding stent grafts were used by Shah et al. (2012) to treat hemodialysis access (AV graft, n = 13; AV

fistula, n = 11) PSAs in 24 patients. The technical success rate was 100%. Balloon angioplasty of an outflow stenosis was performed in 56% of stent grafts. Treatment failure occurred in five (18.5%) stent grafts due to infection (n = 3) and thrombosis (n = 2). One hundred and eighty-day patency rate was 69.2%.

Not all reports are thus optimistic. Zink et al. (2013) placed 38 stent grafts, 9 were for pseudoaneurysms, 20 for stenosis, and 9 for a combination. The average length of follow-up was 218.6 days. Primary patency was 49%, with an assisted primary patency of 76%. Eleven patients (28.9%) presented with complications related to migration, fracture, erosion, or rupture. Once complication occurred, 10 of the 11 access sites had to be abandoned. The authors stressed that significant life-threatening complication can arise when fracture and migration of the stent grafts used for treating AV access occur. For this reason, primary surgical revision may still be the gold standard in the setting of pseudoaneurysm and complex anatomy; this is especially true if adequate sizing and landing zones for a stent graft cannot be assured.

12.2.3.6 Percutaneous Interventions on Failing Arteriovenous Fistulas and Grafts

Haskal et al. (2010) conducted a prospective, multicenter trial, randomly assigning 190 patients who were undergoing hemodialysis and who had a venous anastomotic stenosis in an AVG to undergo either balloon angioplasty alone or balloon angioplasty plus placement of the stent graft. In this study, percutaneous revision of venous anastomotic stenosis in patients with a prosthetic hemodialysis graft was improved with the use of a stent graft. At 6 months, the incidence of patency of the treatment area was significantly greater in the stent-graft group than in the balloon-angioplasty group (51% vs. 23%), as was the incidence of patency of the access circuit (38% vs. 20%). In addition, the incidence of freedom from subsequent interventions at 6 months was significantly greater in the stent-graft group than in the balloon-angioplasty group (32% vs. 16%).

Malka et al. (2016) determined the outcome of repeated percutaneous interventions on failing arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) for hemodialysis. Ninety-six second-time percutaneous interventions were performed on 52 AVFs and 44 AVGs in 91 patients. More than half of the total lesions (54%) were located in the venous outflow of the fistula or graft, whereas 43% of lesions in an AVG were located at the venous anastomosis. Angioplasty alone was performed in 82 procedures (85%), whereas uncovered stents were placed in 9 procedures (9%), and stent grafts were placed in 5 procedures (5%). Pharmacomechanical thrombectomy using the AngioJet device was performed in 32 patients with occluded fistulas or grafts. Pharmacomechanical thrombectomy was more common in AVGs (53%) compared with AVFs (17%).Technical success was achieved in 97% of all index procedures. In all access types, the Kaplan-Meier estimates of 1-year primary, primary assisted, and secondary patency rates were 32%, 86%, and 86%, respectively. In this study, the second percutaneous intervention on failing dialysis access was associated with excellent technical success but poor rates of primary

patency. However, acceptable secondary patency could be achieved with additional percutaneous interventions.

Agarwal et al. (2015) conducted a systematic review and meta-analysis with the aim to assess the safety and efficacy of percutaneous cutting balloon (PCB) angioplasty in comparison with conventional and high-pressure balloon angioplasty in the treatment of hemodialysis access site stenosis. Three studies with 1034 participants were included. The immediate procedural success rate was not significantly different in the PCB angioplasty and control arm respectively (87.2% vs. 83.7%). However, the 6-month target lesion patency was significantly higher in the PCB angioplasty arm (67.2% vs. 55.6%).

Khawaja et al. (2016) systematically assessed the reported efficacy and safety of Drug eluting balloon (DeB) angioplasty in percutaneous management of prosthetic and autologous HD access stenosis. Six studies reported on 254 interventions in 162 participants. Target lesions treated with DeBs were associated with a higher primary patency at 6 months as compared to non-DeBs. However, this body of evidence is small and clinically heterogeneous. A large multicentre RCT might help to clarify the role of DeBs in the percutaneous treatment of AV HD access stenosis.

12.2.3.7 Access Induced Ischemia (Steal Syndrome)

Aimaq and Katz (2013) presented their experiences with distal revascularisation and interval ligation (DRIL procedure) in 77 patients (81 interventions) with arterial steal syndrome after dialysis access surgery. On principle, the DRIL procedure involves ligation of the artery immediately distal to the origin of the AVF in conjunction with a reversed saphenous vein bypass. The latter is constructed from the artery proximal to the origin of the fistula to the artery distal to the site of ligation. Thirty-eight DRIL procedures were performed for ischemic rest pain (46.9%), 21 for digital ulceration (25.9%), 16 for neurological deficits (19.7%), and six for digital gangrene (7.4%). Complete symptom resolution was seen in 31 patients with ischemic rest pain (81.6%), 19 patients with digital ulcerations (90.5%), nine patients with neurological deficits (56.3%), and five patients with digital gangrene (83.3%). Fistula and brachial-brachial bypass survival 60 months after the DRIL procedure was 56% and 96.9%, respectively. The overall complication rate was 17.2%. The results demonstrate that the DRIL procedure is a very effective treatment for symptomatic steal syndrome. One hundred and thirty four DRILs were performed in 126 patients by Scali et al. (2013). The overall composite postoperative procedure complication rate was 27%, with the majority attributable to wound infection. Thirty-day mortality was 2% and mean follow-up was 14.8 ± 17.6 months. Symptoms fully resolved in 82% of patients, and 85% continued to use the index hemodialysis access for which the DRIL was performed at time of last follow-up. Cumulative incidences of loss of primary and primary-assisted patencies of the DRIL bypass were 5 ± 2% and 4 ± 2% at 1 year, and 22 ± 5% and 18 ± 5% at 5 years. The results of this study highlight the safety and efficacy of the DRIL procedure for management of access related hand ischemia.

Leake, Winger et al. (2015a) described experiences with a total of 201 patients that had 218 episodes of dialysis access-associated steal syndrome (DASS). Surgical procedures included ligation (73), distal revascularization with interval ligation (DRIL) (59), revision using distal inflow (RUDI) (21), banding (38), proximalization of arterial inflow (12), and distal radial artery ligation (13). Compared with ligation, DRIL had equal symptom resolution, no increase in complications, and fistula preservation. Compared with banding, DRIL resulted in superior fistula preservation and fewer complications. The conclusion was that DRIL should be considered the preferred procedure for management of DASS in patients with a functioning autologous fistula who can tolerate a major operation.

12.3 Conclusions for Clinical Practice

1. A wrist (radiocephalic) primary fistula, an elbow (brachiocephalic) primary fistula and a transposed brachial basilic vein fistula are the preferred hemodialysis vascular accesses.
2. Despite Fistula First Initiative recommendations, more than 80% of patients in the USA and more than two-thirds in Europe initiate hemodialysis with a tunnelled venous catheter.
3. Initiating HD with an AVF provides a significant mortality benefit compared with initiating dialysis with an AVG or HC.
4. In patients who have exhausted all upper arm options and may be central catheter dependent, the Hemodialysis Reliable Outflow (HeRO) graft offers an alternative vascular access. In comparison to tunnelled catheters, its use is cost-effective.
5. Percutaneous covered stent or endograft placement is a viable and safe alternative to open surgical revision of hemodialysis access pseudoaneurysms.
6. The distal revascularisation and interval-ligation (DRIL procedure) is the most frequently propagated intervention for access induced ischemia (steal syndrome).

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Chapter 13
The Diabetic Foot

13.1 Guidelines

13.1.1 Society for Vascular Surgery (SVS)

The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine developed a clinical practice guideline for the management of diabetic foot (Hingorani et al. 2016). Specific areas of focus included (1) prevention of diabetic foot ulceration, (2) off-loading, (3) diagnosis of osteomyelitis, (4) wound care, and (5) peripheral arterial disease.

1. *Prevention of diabetic foot ulceration*

- Recommendation 1: We recommend that patients with diabetes undergo annual interval foot inspections by physicians or advanced practice providers with training in foot care (Grade 1C).
- Recommendation 2: We recommend that foot examination include testing for peripheral neuropathy using the Semmes-Weinstein test (Grade 1B).
- Recommendation 3: We recommend education of the patients and their families about preventive foot care (Grade 1C).
- Recommendation 4:

  (a) We suggest against the routine use of specialized therapeutic footwear in average-risk diabetic patients (Grade 2C).
  (b) We recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities, or previous amputation (Grade 1B).

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- Recommendation 5: We suggest adequate glycemic control (hemoglobin A1c < 7% with strategies to minimize hypoglycemia) to reduce the incidence of diabetic foot ulcers (DFUs) and infections, with subsequent risk of amputation (Grade 2B).
- Recommendation 6: We recommend against prophylactic arterial revascularization to prevent diabetic foot ulcer (DFU) (Grade 1C).

2. *Off-loading DFUs*

- Recommendation 1: In patients with plantar DFU, we recommend offloading with a total contact cast (TCC) or irremovable fixed ankle walking boot (Grade 1B).
- Recommendation 2: In patients with DFU requiring frequent dressing changes, we suggest off-loading using a removable cast walker as an alternative to TCC and irremovable fixed ankle walking boot (Grade 2C). We suggest against using postoperative shoes or standard or customary footwear for off-loading plantar DFUs (Grade 2C).
- Recommendation 3: In patients with nonplantar wounds, we recommend using any modality that relieves pressure at the site of the ulcer, such as a surgical sandal or heel relief shoe (Grade 1C).
- Recommendation 4: In high-risk patients with healed DFU (including those with a prior history of DFU, partial foot amputation, or Charcot foot), we recommend wearing specific therapeutic footwear with pressure-relieving insoles to aid in prevention of new or recurrent foot ulcers (Grade 1C).

3. *Diagnosis of diabetic foot osteomyelitis (DFO)*

- Recommendation 1: In patients with a diabetic foot infection (DFI) with an open wound, we suggest doing a probe to bone (PTB) test to aid in diagnosis (Grade 2C).
- Recommendation 2: In all patients presenting with a new DFI, we suggest that serial plain radiographs of the affected foot be obtained to identify bone abnormalities (deformity, destruction) as well as soft tissue gas and radiopaque foreign bodies (Grade 2C).
- Recommendation 3: For those patients who require additional (ie, more sensitive or specific) imaging, particularly when soft tissue abscess is suspected or the diagnosis of osteomyelitis remains uncertain, we recommend using magnetic resonance imaging (MRI) as the study of choice. MRI is a valuable tool for diagnosis of osteomyelitis if the PTB test is inconclusive of if the plain film is not useful (Grade 1B).
- Recommendation 4: In patients with suspected DFO for whom MRI is contraindicated or unavailable, we suggest a leukocyte or antigranulocyte scan, preferably combined with a bone scan as the best alternative (Grade 2B).
- Recommendation 5: In patients at high risk for DFO, we recommend that the diagnosis is most definitively established by the combined findings on bone culture and histology (Grade 1C). When bone is débrided to treat osteomyelitis, we recommend sending a sample for culture and histology (Grade 1C).

- Recommendation 6: For patients not undergoing bone débridement, we suggest that clinicians consider obtaining a diagnostic bone biopsy when faced with diagnostic uncertainty, inadequate culture information, or failure of response to empirical treatment (Grade 2C).

4. Wound care for DFUs

- Recommendation 1: We recommend frequent evaluation at 1- to 4-week intervals with measurements of diabetic foot wounds to monitor reduction of wound size and healing progress (Grade 1C).
- Recommendation 1.1: We recommend evaluation for infection on initial presentation of all diabetic foot wounds, with initial sharp débridement of all infected diabetic ulcers, and urgent surgical intervention for foot infections involving abscess, gas, or necrotizing fasciitis (Grade 1B).
- Recommendation 1.2: We suggest that treatment of DFIs should follow the most current guidelines published by the Infectious Diseases Society of America (IDSA) (Ungraded).
- Recommendation 2: We recommend use of dressing products that maintain a moist wound bed, control exudate, and avoid maceration of surrounding intact skin for diabetic foot wounds (Grade 1B).
- Recommendation 3: We recommend sharp débridement of all devitalized tissue and surrounding callus material from diabetic foot ulcerations at 1- to 4-week intervals (Grade 1B).
- Recommendation 4: Considering lack of evidence for superiority of any given débridement technique, we suggest initial sharp débridement with subsequent choice of débridement method based on clinical context, availability of expertise and supplies, patient tolerance and preference, and cost-effectiveness (Grade 2C).
- Recommendation 5: For DFUs that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice. Re-evaluation of vascular status, infection control, and off-loading is recommended to ensure optimization before initiation of adjunctive wound therapy (Grade 1B).
- Recommendation 6: We suggest the use of negative pressure wound therapy for chronic diabetic foot wounds that do not demonstrate expected healing progression with standard or advanced wound dressings after 4–8 weeks of therapy (Grade 2B).
- Recommendation 7: We suggest consideration of the use of PDGF (becaplermin) for the treatment of DFUs that are recalcitrant to standard therapy (Grade 2B).
- Recommendation 8: We suggest consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of DFUs when recalcitrant to standard therapy (Grade 2B).

- Recommendation 9: We suggest consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when recalcitrant to standard therapy (Grade 2C).
- Recommendation 10: In patients with DFU who have adequate perfusion that fails to respond to 4–6 weeks of conservative management, we suggest hyperbaric oxygen therapy (Grade 2B).

5. *Peripheral arterial disease (PAD) and the DFU*

- Recommendation 1.1: We suggest that patients with diabetes have ankle-brachial index (ABI) measurements performed when they reach 50 years of age (Grade 2C).
- Recommendation 1.2: We suggest that patients with diabetes who have a prior history of DFU, prior abnormal vascular examination, prior intervention for peripheral vascular disease, or known atherosclerotic cardiovascular disease (eg, coronary, cerebral, or renal) have an annual vascular examination of the lower extremities and feet including ABI and toe pressures (Grade 2C).
- Recommendation 2: We recommend that patients with DFU have pedal perfusion assessed by ABI, ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure (TcPO2) annually (Grade 1B).
- Recommendation 3: In patients with DFU who have PAD, we recommend revascularization by either surgical bypass or endovascular therapy (Grade 1B).

Recommendation 3 (technical and implementation remarks)

- Prediction of patients most likely to require and to benefit from revascularization can be based on the Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIfI) lower extremity threatened limb classification.
- A combination of clinical judgment and careful interpretation of objective assessments of perfusion along with consideration of the wound and infection extent is required to select patients appropriately for revascularization.
- In functional patients with long-segment occlusive disease and a good autologous conduit, bypass is likely to be preferable.
- In the setting of tissue loss and diabetes, prosthetic bypass is inferior to bypass with vein conduit.
- The choice of intervention depends on the degree of ischemia, the extent of arterial disease, the extent of the wound, the presence or absence of infection, and the available expertise.

13.1.2 International Working Group on the Diabetic Foot (IWGDF)

Recommendations (Lipsky et al. 2016) are:
Classification/diagnosis

1. Diabetic foot infection must be diagnosed clinically, based on the presence of local or systemic signs or symptoms of inflammation (strength of recommendation strong; quality of evidence low).

2. Assess the severity of any diabetic foot infection using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification scheme (strength of recommendation strong; quality of evidence moderate).

Osteomyelitis

3. For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis, a negative test largely rules out the diagnosis, while in a high-risk patient, a positive test is largely diagnostic (strength of recommendation strong; quality of evidence high).
4. Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (strength of recommendation weak; quality of evidence moderate).
5. A definite diagnosis of bone infection usually requires positive results on microbiological (and, optimally, histological) examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (strength of recommendation strong; quality of evidence moderate).
6. A probable diagnosis of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, magnetic resonance imaging (MRI) or radionuclide scanning (strength of recommendation strong; quality of evidence weak).
7. Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (strength of recommendation strong; quality of evidence moderate).
8. Obtain plain X-rays of the foot in all cases of non-superficial diabetic foot infection (strength of recommendation strong; quality of evidence low).
9. Use MRI when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (strength of recommendation strong; quality of evidence moderate).
10. When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly single-photon emission computed tomography (CT) and CT (SPECT/CT) or fluorine-18-fluorodeoxyglucose positron emission tomography/CT scans (strength of recommendation weak; quality of evidence moderate).

Assessing severity

11. At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound and probe and assess the depth and extent of the infection to establish its severity (strength of recommendation strong; quality of evidence moderate).
12. At initial evaluation, assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (strength of recommendation strong; quality of evidence low).

Microbiological considerations

13. Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the causative microorganisms and their antibiotic sensitivity (strength of recommendation strong; quality of evidence high).

14. Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (strength of recommendation strong; quality of evidence low).
15. Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (strength of recommendation strong; quality of evidence low).

Surgical treatment

16. Consult a surgical specialist in selected cases of moderate, and all cases of severe, diabetic foot infection (strength of recommendation weak; quality of evidence low).
17. Perform urgent surgical interventions in cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (strength of recommendation strong; quality of evidence low).
18. Consider surgical intervention in cases of osteomyelitis accompanied by spreading soft tissue infection, destroyed soft tissue envelope, progressive bone destruction on X-ray or bone protruding through the ulcer (strength of recommendation strong; quality of evidence low).

Antimicrobial therapy

19. While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected wounds with antimicrobial therapy (strength of recommendation strong; quality of evidence low)
20. Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection and costs (strength of recommendation strong; quality of evidence moderate).
21. A course of antibiotic therapy of 1–2 weeks is usually adequate for most mild and moderate infections (strength of recommendation strong; quality of evidence high).
22. Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (strength of recommendation strong; quality of evidence low).
23. Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome (strength of recommendation strong; quality of evidence high).
24. For diabetic foot osteomyelitis, we recommend 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment if all infected bone is resected (strength of recommendation strong; quality of evidence moderate).
25. We suggest not using any adjunctive treatments for diabetic foot infection (strength of recommendation weak; quality of evidence low).
26. When treating a diabetic foot infection, assess for use of traditional remedies and previous antibiotic use and consider local bacterial pathogens and their susceptibility profile (strength of recommendation strong; quality of evidence low).

13.2 WIfI-Classification-System

The Society for Vascular Surgery has created a new classification of the threatened lower extremity. Risk stratification is based on three major factors that impact amputation risk and clinical management: Wound, Ischemia, and foot Infection (WIfI) (Mills et al. 2014). The target population for this system includes any patient with

- Ischemic rest pain, typically in the forefoot, with confirmatory, objective hemodynamic studies (Ankle-brachial index, ABI < 0.40; ankle pressure < 50 mm Hg; toe pressure < 30 mm Hg; Tissue-pO_2 [$TcPO_2$, transcutaneous oximetry] < 20 mm Hg)
- A diabetic foot ulcer
- Nonhealing lower limb or foot ulceration of at least 2 weeks duration
- Gangrene involving any portion of foot or the lower limb.

Since each of the three categories (wound, ischemia, and foot infection) has four grades of severity, the system produces a grid with 64 theoretically possible clinical combinations (WIfI classes). The implementation of this classification system is intended to permit more meaningful analysis of outcomes for various forms of therapy in this heterogeneous population.

An early validation of the WIfI classification system has been published by Cull et al. (2014). Data were prospectively obtained in139 patients with foot wounds who presented for lower extremity revascularization. The WIfI clinical stage was predictive of 1-year limb amputation (stage 1, 3%; stage 2, 10%; stage 3, 23%; stage 4, 40%) and wound nonhealing (stage 1, 8%; stage 2, 10%; stage 3, 23%; stage 4, 40%). The data justify the validation of the WIfI classification system in further trials.

Causey et al. (2016) undertook a retrospective analysis of prospectively gathered registry data of consecutive patients with limb-threatening conditions admitted to a fully integrated vascular/podiatry service over a 16-month period. Upon admission, limb risk was stratified using the WIfI system and patient risk was categorized using PIII classification (PREVENT III (PIII) critical limb ischemia (CLI) risk score (Schanzer et al. 2009)). There were 174 threatened limbs (143 hospitalized patients). PIII risk correlated with mortality whereas WIfI stage strongly predicted initial hospital duration of stay, and key mid-term limb outcomes. Surgical revascularization performed best in the limbs at greatest risk (WIfI stage 4), and autogenous vein bypass was the preferred conduit for open bypass. These data supported the use of WIfI and PIII as complementary staging tools in the management of chronic limb-threatening ischemia.

Measurement of toe pressure is an important part of the WIfI classification system and is usually performed on the first toe. However, measurement in diabetics is sometimes impossible due to painful ulceration or tissue loss. In a prospective study, Bhamidipaty et al. (2015) found that second toe systolic pressure measurements were interchangeable with those of the first toe within acceptable limits of 5–10 mmHg. Therefore, it seems reasonable to use the second toe pressure, when first toe pressure cannot be obtained.

Zhan et al. (2015) analyzed a total of 201 consecutive patients with threatened limbs. Ninety-three percent of patients had diabetes mellitus. These patients were

stratified into clinical stages 1–4 on the basis of the SVS WIfI classification. Among the 201 patients, 42 patients required major amputation. The classification system correlated with important clinical outcomes for limb salvage and wound healing. As the clinical stages progressed, the risk of major amputation increased, 1-year AFS declined, and wound healing time was prolonged. Overall, 90% of major amputations fell into the stage 4 group, and only 10% fell into the stage 3 group. One-year AFS rates were 100% (stage 1–2), 92% (stage 3), and 63% (stage 4), respectively.

13.3 Results

13.3.1 Revascularization

The guidelines of the Wound Healing Society (WHS) (Lavery et al. 2016) recommend that patients with ischemia should be considered for a revascularization procedure. Infrainguinal angioplasty and in situ bypass are associated with a significant improvement in ulcer healing (Level ll). Whether one of the two methods should be preferred to the other, is not stated. The International Working Group on the Diabetic Foot established a multidisciplinary working group to evaluate the effectiveness of revascularization of the ulcerated foot in patients with diabetes and PAD (Hinchliffe et al. 2016). There were no randomized controlled trials, but there were four nonrandomized studies with a control group. The major outcomes following endovascular or open bypass surgery were broadly similar among the studies. Following open surgery, the 1-year limb salvage rates were a median of 85%, and following endovascular revascularization, these rates were 78%. At 1-year follow-up, 60% or more of ulcers had healed following revascularization with either open bypass surgery or endovascular revascularization. There were insufficient data to recommend one method of revascularization over another.

Söderström et al. (2013) evaluated the benefit of infrapopliteal endovascular revascularization guided by an angiosome model of perfusion in the healing process of diabetic foot ulcers. A total of 250 consecutive legs with diabetic foot ulcers in 226 patients who had undergone infrapopliteal endovascular revascularization were evaluated. Direct flow to the foot ulcer based on the angiosome principle was achieved in 121 legs (48%) compared with 129 legs (52%) in which direct perfusion was not achieved. The ulcer healing rates were mean 48% at 6 months and 72% at 12 months for the direct group compared with 26 and 46% for the indirect group. The authors concluded that providing direct blood flow to the specific area of a diabetic foot ulcer has a favorable effect on ulcer healing and should be preferred to indirect revascularization. Fossaceca et al. (2013) also used the angiosome model to compare outcomes in patients treated by direct revascularization (DR) with patients treated with indirect revascularization (IR) technique. PTA was performed in 201 diabetic patients with below the knee disease. In 34 patients (16.9%), the treatment was performed via the IR technique. In this study, IR was similarly effective as compared to DR. Follow-up was 17.5 months. Major amputa-

Table 13.1 Open bypass procedures and endovascular procedures among diabetic foot ulcer patients in the United States

	Open bypass n = 92,029	Endovascular n= 108,124
Mean patient age (years)	68.6	68.6
Charges (US, $ 2012)	90,546	87,961
Female sex (%)	39.6	42.9
LOS (days)	12.0	9.4
Number of diagnoses	10.8	12.0
Number of procedures	4.1	5.8
Amputations (%) Major (%) Minor (%)	24.6 3.1 21.5	22.2 5.6 16.5
Any surgical complication (%)	14.4	5.8
Died during hospitalization (%)	1.7	1.6

Nationwide Inpatient Sample 2001–2010 (Adapted from Skrepnek et al. 2014). Mean values

tion rate was 9.6% in the DR group and 8.8% IR group, respectively. In both groups, there was a statistically significant increase of TcPO2 values at follow-up compared to baseline, without statistically significant differences in therapeutic efficacy.

Skrepnek et al. (2014) observed in the Nationwide Inpatient Sample a total of 2,497,363 inpatient DFU cases from 2001 to 2010, with 16.5% (n = 412,051) involving amputations (major = 34.8%, minor = 65.2%) and 8.5% (n = 211,534) involving a revascularization procedure (open only = 43.5%, EVT only = 51.1%, combination = 5.4%). From 2001 vs 2010, the volume of open procedures decreased 34.9%, and EVT volume increased 197.1%. Meanwhile, EVT has become the preferential treatment: 6893 open bypass only procedures were registered in 2010 as opposed to 14.926 endovascular interventions only. In addition, 1112 open bypasses with endovascular procedures combined were seen. Results of open bypass procedures and EVT are given in Table 13.1. Open procedures generally appeared to have a higher rate of overall surgical complications, similar to slightly greater inpatient mortality, charges, and a longer length of stay.

13.3.2 Prognosis

Prediction of wound healing and major amputation in patients with diabetic foot ulceration is clinically important to stratify risk and target interventions for limb salvage. In a systematic review, Brownrigg et al. (2016) found the measurement of skin perfusion pressures, toe pressures and TcPO2 to be more useful in predicting ulcer healing than ankle pressures or the ABI. Conversely, an ankle pressure of < 50 mmHg or an ABI < 0.5 was associated with a significant increase in the incidence of major amputation.

Dubský et al. (2013) examined factors associated with diabetic foot ulcer (DFU) recurrence in the prospective Eurodiale DFU study. During a 3-year follow-up period, a DFU had recurred in 42/73 patients (57.5%). Significant independent predictors for recurrence were plantar ulcer location [odds ratio (OR) 8.62]; presence of osteomyelitis (OR 5.17); HbA1c > 7.5% (OR 4.07), and CRP > 5 mg/l (OR 4.27). The influence of ulcer location on time to healing of diabetic foot ulcers was analyzed by multivariate Cox regression analysis for 1000 patients included in the Eurodiale study by Pickwell et al. (2013). Median time to healing is shown in Table 13.2. Time to ulcer healing increased progressively from toe to midfoot to heel, but did not differ between plantar and nonplantar ulcers. Other factors significantly influencing time to healing were the duration of diabetes, ulcer duration, the presence of heart failure and the presence of peripheral arterial disease.

Patients with DFU have a considerably worse prognosis than those with diabetes and no history of DFU. In a cohort study with 3.6 years follow up, Brownrigg et al. (2014) saw that DFU was associated with both cardiovascular disease (hazard ratio, 2.53) and all-cause mortality (hazard ratio, 3.98). In a further study, Martins-Mendes et al. (2014) also found that DFU occurrence has a major and independent impact on lower extremity amputation and death, even when adjusted for baseline complications. Thus the history of a DFU is a marker for poorer outcomes in patients with diabetes in this population.

Long-term data regarding patient and limb survival in patients with diabetic foot ulcers were reported by Morbach et al. (2012). Two hundred and fourty-seven patients with DFU and without previous major amputation consecutively presenting to a single diabetes center were included in this study. The mean follow-up period was 5.7 ± 4.4 years. Neuropathy and PAD were present at study initiation in 86.2% and 55.5% of the patients, respectively. Thirty-eight patients had a first major amputation during the follow-up period. The cumulative probabilities of a first major amputation were 8.7%, 12.5%, 15.9%, and 22.3% at years 1, 3, 5, and 10, respectively. The cumulative mortalities for the whole cohort at years 1, 3, 5, and 10 were 15.4%, 33.1%, 45.8%, and 70.4%, respectively. For patients with PAD at baseline, the corresponding numbers were 21.9%, 44.1%, 58.8%, and 81.0%, respectively. Significant predictors for death were age (HR per year, 1.08), male sex (HR 1.65), chronic renal insufficiency (HR 1.83), dialysis (HR 6.43), and PAD (HR 1.44).

Table 13.2 Time to healing of diabetic foot ulcers depending on ulcer location

Ulcer location	Median time to healing (days) [(95% confidence interval (CI)]
Toe	147 [135–159]
Midfoot	188 [158–218]
Heel	237 [205–269]
Plantar	172 [157–187]
Non-plantar	155 [138–172]

Adapted from Pickwell et al. (2013). Cox-regression-analysis of 1000 patients in the Eurodiale Consortium

13.3.3 Risk of Amputation

Malyar et al. (2016) determined the contemporary acute and long-term outcome of patients with PAD and diabetic foot syndrome (DFS) in Germany. Anonymized data of a large German health insurance (BARMER GEK, covering approximately eight million people, respective 10% of the entire German population) were analyzed. Patients were divided into three groups: Those with a main diagnosis of DFS (group 1), patients with PAD and a codiagnosis of diabetes mellitus (DM) (group 2), and those having PAD alone without DM or DFS (group 3). Among 40,335 analyzed patients, the distribution of DFS, PAD+DM, and of PAD alone was 17.3%, 21.5%, and 61.2%, respectively. The 1-, 2, 3-, and 4-year amputation-free survival was 89.8%, 88.5%, 87.4%, and 86.5% for PAD, 80.4%, 78.1%, 75.9%, and 74.4% for PAD+DM, and 55.8%, 52.2%, 48.9%, and 45.4% for DFS patients, respectively ($P < 0.001$ between the three different groups). The overall cumulative survival at 1-, 2-, 3-, and 4-year follow-up was 87.6%, 81.1%, 75.5%, and 70.0% for PAD, 83.2%, 75.0%, 67.6%, and 60.8% for PAD+DM, and 82.3%, 73.2%, 65.0%, and 57.4% for DFS patients, respectively ($P < 0.001$). Hence, DFS patients had the worst outcome regarding limb amputation and survival, followed by PAD+DM and PAD patients.

Lombardo et al. (2014) analyzed hospitalization for lower extremity amputations (LEAs) in persons with and without diabetes in Italy. During the period 2001–2010, a mean annual number of 11,639 individuals underwent a LEA, among them 58.6% had diabetes accounting for 60.7% of the total number of hospitalizations (mean annual number 13,581). The crude rate for LEAs in the year 2010 was 20.4 per 100,000 inhabitants: 247.2 for 100,000 persons with diabetes, and 8.6 for those without diabetes.

13.3.4 Local Therapy

The International Working Group of the Diabetic Foot (IWGDF) has updated a systematic review of the evidence supporting interventions to enhance the healing of chronic ulcers of the foot in diabetes (Game et al. 2016). They came to the following conclusions:

- The previous earlier positive reports from randomized studies of hyperbaric oxygen have now been countered by a large cohort study, which showed little evidence of improvement when used in the patient cohort that qualifies for reimbursement in the USA, which is different from those patients recruited into the RCTs. Consequently, the question of which patient group would most benefit from this type of intervention remains unanswered.
- Despite widespread use, there have been no further good studies on the use of negative pressure wound therapy (NPWT), and at present, the evidence to support its effectiveness or cost effectiveness in the healing of chronic ulcers of the foot in diabetes – as opposed to post-operative wounds – is not strong.

- Epidermal growth factor (EGF): there has been no advancement of knowledge on the effectiveness or cost effectiveness of this therapy.
- There have been no good quality studies, which advance our knowledge of the efficacy of any other growth factors, skin or skin substitutes or any other physical therapies.

The National Institute for Health and Care Excellence (NICE) (2015) recommends:

Do not offer the following to treat diabetic foot ulcers, unless as part of a clinical trial:

- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy

13.3.4.1 Wound Bed Preparation in the Treatment of Diabetic Ulcers

The Wound Healing Society (WHS) (Lavery et al. 2016) recommends:

- Initial debridement is required to remove the obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells. Wounds should be cleansed initially and at each dressing change using a neutral, nonirritating, nontoxic solution. Routine wound cleansing should be accomplished with a minimum of chemical and/or mechanical trauma.

Elraiyah, Domecq et al. (2016a) conducted a systematic review and meta-analysis to find the best available evidence for the effect of débridement on diabetic foot wound outcomes. Meta-analysis of three RCTs showed that autolytic débridement significantly increased the healing rate (relative risk [RR], 1.89). Meta-analysis of four studies (one RCT) showed that larval débridement reduced amputation (RR, 0.43) but did not increase complete healing (RR, 1.27). Surgical débridement was associated with shorter healing time compared with conventional wound care (one RCT). Insufficient evidence was found for comparisons between autolytic and larval débridement (one RCT), between ultrasound-guided and surgical débridement, and between hydrosurgical and surgical débridement. Hence, the choice of débridement method at the present time should be based on the available expertise, patient preferences, the clinical context and cost.

13.3.4.2 Dressing Products

The Wound Healing Society (WHS) (Lavery et al. 2016) recommends:

- Use a dressing that will maintain a moist wound-healing environment (Level III).

- Select a dressing that will manage the wound exudates and protect the peri-ulcer skin. (Level I)
- Select a dressing that is cost effective. (Level I)

There are three Cochrane reviews available for assessment. According to these, there is no research evidence to suggest that any type of hydrocolloid wound dressing is more effective in healing diabetic foot ulcers than other types of dressing or a topical cream containing plant extracts (Dumville et al. 2013a). In addition, there is no research evidence to suggest that alginate wound dressings are more effective in healing foot ulcers in people with diabetes than other types of dressing (Dumville et al. 2013b). And finally, there is also no research evidence to suggest that foam wound dressings are more effective in healing foot ulcers in people with diabetes than other types of dressing (Dumville et al. 2013c). Therefore, dressing cost and the wound management properties offered by each dressing type, e.g. exudate management dictate the choice of dressing.

13.3.4.3 Skin Substitutes

A Cochrane systematic review evaluated the effectiveness of skin substitutes on ulcer healing and limb salvage in the treatment of diabetic foot ulcers (Santema et al. 2016). Thirteen trials compared a skin substitute with standard care. The pooled results showed that skin substitutes can, in addition to standard care, increase the likelihood of achieving complete ulcer closure compared with standard care alone after 6–16 weeks. However, effectiveness on the long term, including lower limb salvage and recurrence, is currently lacking and cost-effectiveness is unclear.

13.3.4.4 Negative Pressure Wound Therapy

Zhang et al. (2014) conducted a meta-analysis to evaluate the effectiveness and safety of negative-pressure wound therapy (NPWT) for diabetic foot ulcers. The databases were derived from eight qualified studies that included a total of 669 patients. Overall, compared with the non-negative-pressure wound therapy-treated diabetic foot ulcers, negative pressure resulted in a significantly higher proportion of healed ulcers, more reduction of ulcer area, and shorter time to wound healing. NPWT patients also experienced significantly fewer major amputations, but the rate of minor amputations was not affected. The effects of NPWT compared with standard care or other adjuvant therapies in the healing of foot wounds in people with DM were also assessed in a Cochrane review (Dumville et al. 2013d). Five studies randomising 605 participants were included in this review. There was some evidence to suggest that NPWT is more effective in healing post-operative foot wounds and ulcers of the foot in people with DM compared with moist wound dressings. However, these findings were uncertain due to the possible risk of bias in the original studies.

13.3.4.5 Hyperbaric Oxygen Therapy

The Wound Healing Society (WHS) (Lavery et al. 2016) recommends: Hyperbaric oxygen therapy (HBOT) should be used to improve wound healing and reduce major amputation (Level I). Hyperbaric oxygen therapy may increase the amount of oxygen delivered to a wound in diabetic patients and thereby improve healing.

Stoekenbroek et al. (2014) performed a systematic review of randomized clinical trials (RCTs) to assess the additional value of HBOT in promoting the healing of diabetic foot ulcers and preventing amputations. Seven trials comprising 376 patients were included. Two trials were of good methodological quality. Pooling of data was deemed inappropriate because of heterogeneity. Two RCTs in patients with ischaemic ulcers found increased rates of complete healing at 1-year follow-up, but found no difference in amputation rates. A third trial in ischaemic ulcers found significantly lower major amputation rates in patients with HBOT, but did not report on wound healing. None of the RCTs in non-ischaemic ulcers reported differences in wound healing or amputation rates. The authors concluded that there is insufficient evidence to support the routine use of HBOT as an adjunct to standard wound care in diabetic patients with foot ulcers, considering the low quality of current evidence, the high costs of HBOT, and the burdensome nature of a full HBOT regimen.

Elraiyah, Tsapas et al. (2016b) also conducted a systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. Based on six RCTs, HBOT was associated with increased healing rate and reduced major amputation rate compared with conventional therapy. The quality of this evidence was considered low to moderate, potentially downgraded due to methodologic limitations of the included studies. In the meta-analysis of the six available observational studies the effect on amputation became imprecise and on the healing rate reversed. The authors concluded that the true effect of HBOT should be derived from RCTs because they provide higher-quality evidence (here, moderate).

Recently, a prospective, double-blind RCT has been performed to assess the efficacy of HBOT in reducing the need for major amputation and improving wound healing in patients with diabetes and chronic DFUs (Fedorko et al. 2016). One hundred and seven patients were randomly assigned and 103 were available for end point adjudication. Criteria for major amputation were met in 13 of 54 patients in the sham group and 11 of 49 in the HBOT group (odds ratio 0.91). Twelve (22%) patients in the sham group and 10 (20%) in the HBOT group were healed (0.90). All other indices of wound healing were also not statistically significantly different between groups. In this trial, HBOT did not offer an additional advantage to comprehensive wound care in reducing the indication for amputation or facilitating wound healing in patients with chronic DFUs.

13.3.4.6 Platelet-Rich Plasma

The Wound Healing Society (WHS) (Lavery et al. 2016) recommends: Platelet-rich plasma (Level l) and epidermal growth factor (Level II) have not demonstrated an increase in the proportion of wounds that heal and the healing rate of DFUs.

13.3.4.7 Off-Loading Methods for Diabetic Foot Ulcers

Increased plantar foot pressure is one of several key factors that lead to diabetic foot ulcers. Multiple methods have been proposed to relieve this pressure and thus enhance wound healing and potentially prevent relapse. Elraiyah, Prutsky et al. (2016c) performed a systematic review to evaluate the quality of the evidence supporting the existing off-loading methods. Nineteen interventional studies were identified, of which 13 were randomized controlled trials, including data from 1605 patients with diabetic foot ulcers using an off-loading method. The interventions described included total contact casting (TCC), instant total contact casting (iTCC) or irremovable cast walkers, removable cast walker (RCW), therapeutic shoes and insoles, felted foam, pneumatic walkers, and conventional dressing. The study demonstrated some advantages for TCC over RCW, therapeutic shoes, and conventional therapy. There was no advantage for iTCC over TCC. Irremovable casts were used in the studies in patients without ischemia. There was improved healing with half-shoe compared with conventional footwear. This study also showed that therapeutic shoes and insoles provided a clear benefit in preventing relapse in comparison with regular footwear. Data were sparse regarding other off-loading methods. In conclusion, benefits were demonstrated for use of TCC and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate was demonstrated with various therapeutic shoes and insoles in comparison with regular footwear.

13.3.5 Diabetic Foot Infection

Duhon et al. (2016) determined national trends in diabetic foot infection (DFI) incidence among hospitalized adults in the United States from 1996 to 2010. The data represented 1,059,552 DFI discharges. Overall, patients had a median age of 67 years and were predominately men (58%). Gangrene was the most common type of foot infection (38.9%), followed by foot cellulitis-abscess (20.7%), ulcer (17.7%), osteomyelitis (15%), and toe cellulitis-abscess (7.7%). Peripheral neuropathy (19.9%) and peripheral vascular disease (16.4%) were common in this population. DFI incidence decreased by 52% (2.3 DFIs/100 diabetes discharges in 1996 and 1.1 DFI/100 diabetes discharges in 2010). This dramatic decline in DFI incidence over 15 years might also be attributed to an increase in the diabetes discharges over the study period since the number of diabetes discharges nearly tripled. Overall, 21.6% of DFIs resulted in lower-extremity amputations (LEA). The proportion of patients experiencing LEA declined from 33.2% in 1996 to 17.1% in 2010. Peripheral vascular disease (odds ratio [OR], 2.89), peripheral neuropathy (OR, 2.62), male sex (OR, 1.67), and dialysis (OR, 1.28) were leading independent risk factors for DFI among diabetics, as determined by multivariable regression.

All infected diabetic foot wounds require treatment, which almost always includes antimicrobial therapy. A Cochrane review determined the effects and safety of systemic antibiotics in the treatment of DFIs compared with other systemic antibiotics, topical foot care or placebo (Selva Olid et al. 2015). Twenty studies were included in

this analysis. Most subjects were treated as inpatients with intravenous antibiotic therapy, at least initially. The initial antibiotic regimen is usually selected empirically, and it may be modified later depending on culture results and the patient's clinical response to the selected regimen. The findings of this review did not show that any specific systemic antibiotic agent or regimen is associated with better results over comparators in terms of clinical resolution of infection, or other end-points. Only one trial (at low risk of bias) identified a difference in the risk of clinical resolution of infection between two regimens. In this non-inferiority trial the proportion of participants whose infection resolved was significantly higher with ertapenem treatment (with added vancomycin if MRSA was isolated) than with tigecycline. In addition, participants treated with tigecycline experienced higher rates of adverse events.

Tone et al. (2015) conducted a randomized multicenter clinical study, the goal of which was to compare the effectiveness and tolerance of 6- versus 12-week antibiotic therapy in patients with diabetic foot osteomyelitis (DFO) treated nonsurgically using rifampicin or fluoroquinolone combinations as first-line therapy. Remission of osteomyelitis during the monitoring period was defined as complete and persistent (>4 weeks) healing of the wound (if present initially), absence of recurrent infection at the initial site or that of adjacent rays, and no need for surgical bone resection or amputation at the end of a follow-up period of at least 12 months after completion of antibiotic treatment. Fourty patients were included in the study. At the end of a mean posttreatment follow-up duration of 12 months, 26 patients (66%) were considered to be in remission, 12 (60%) from the 6-week group and 14 (70%) patients from the 12-week group. The study suggested that a 6-week duration of antibiotic therapy may be sufficient in patients with DFO treated without removal of the infected bone and is associated with better gastrointestinal tolerance in a setting of predominant use of rifampin combinations.

13.3.6 Nerve Decompression

Diabetic neuropathy may be due, in part, to compression of the nerves at sites of anatomic narrowing. Baltodano et al. (2013) systematically reviewed the current literature regarding the effect of neurolysis on pain relief, peripheral sensation recovery, and the incidence of ulcerations/amputations on diabetic patients with superimposed nerve compression of the lower extremities (LEs). Ten observational studies were considered relevant. A pooled number of 935 patients were included in the selected studies. Of these, 875 patients had diabetes and 1053 LEs underwent neurolysis for compressed nerves and were included in the meta-analysis. All the 1053 (100%) operated LEs had decompression of the tibial nerve at the tarsal tunnel and 1011 (96%) operated LEs had decompression of the common peroneal nerve at the fibular head and the deep peroneal nerve at the dorsum of the foot. The meta-analysis showed that neurolysis significantly improves pain, sensibility, and renders a low incidence of postoperative ulcerations/amputations. Pain relief after neurolysis occurred in 91% of the operated LEs, with worsening of symptoms in 5% and no improvement in 4%. Improvement on sensibility was less dramatic with a pooled significant improvement

on 2-point discrimination of 3.90 mm, occurring on 69% of the operated LEs. Postoperative ulceration/amputation incidence was significantly reduced compared to preoperative incidence (odds ratio = 0.066). According to this data neurolysis significantly improves outcomes for diabetic patients with compressed nerves of the LE. However, no randomized controlled trials have been published.

Nickerson and Rader (2014) treated a cohort of 42 patients with diabetic sensorimotor polyneuropathy, failed pharmacologic pain control, palpable pulses, and at least one positive Tinel's nerve percussion sign with unilateral multiple lower-leg external neurolyses for the indication of pain. All of the patients had healed at least one previous ipsilateral plantar diabetic foot ulceration (DFU). This group was evaluated a minimum of 12 months after operative nerve decompression and again 3 years later. The recurrence risk of ipsilateral DFU in that period was prospectively analyzed and compared with new ulcer occurrence in the contralateral intact, nonoperated control legs. Operated legs developed two ulcer recurrences (4.8%), and nine contralateral control legs developed ulcers (21.4%), requiring three amputations. Ulcer risk was 1.6% per patient per year in nerve decompression legs and 7% in nonoperated control legs. In this trial, adding operative nerve decompression at lower-leg fibro-osseous tunnels to standard postulcer treatment resulted in a significantly diminished rate of subsequent DFU in neuropathic high-risk feet.

Macaré van Maurik, van Hal et al. (2014) assessed the effect of lower extremity nerve decompression surgery for painful diabetic polyneuropathy on pain and sensibility in 42 patients with painful diabetic neuropathy. After randomization, the lower extremity nerves were decompressed at four sites in one limb. The contralateral limb was used as control (within-patient comparison). Visual analogue scale scores improved significantly from a mean of 6.1 preoperatively to 3.5 at 12 months postoperatively. The score was also significantly lower compared with the control leg score of 5.3 at 12 months. Overall, 73.7% of the patients improved their score on the visual analogue scale, of which 35.7% had a decrease of more than five points. These results suggest that surgical decompression of the nerves of the lower extremity can be added as a therapeutic option for patients with painful diabetic neuropathy who show signs of chronic nerve compression by means of a positive Tinel or other diagnostic criteria, when pain medication fails to reduce pain to an acceptable standard. However, decompression surgery did not influence health-related quality of life (Macaré van Maurik et al. 2015b). In addition, there was no evidence that surgical decompression of nerves of the lower extremity influences static balance within 1 year after surgery in patients with painful diabetic polyneuropathy (Macaré van Maurik et al. 2015a).

13.3.7 Tendon Lengthening and Fascia Release

Limited ankle joint dorsiflexion (i.e., equinus deformity) is associated with elevated plantar pressures, which subsequently increases the risk of plantar ulceration in people with diabetes. There is a threefold risk of equinus deformity in those with diabetes compared to those without. Shortening of the Achilles tendon can result in

plantarflexion at the ankle and increased plantar forefoot pressures during gait. Achilles tendon lengthening (ATL) and gastrocnemius recession (GR) procedures have been found to increase ankle joint dorsiflexion and ATL has been found to reduce plantar forefoot pressures. In addition, selective plantar fascia release (SPFR) has been proposed as an alternative procedure to ATL for the management of diabetic foot ulcers. Therefore, Dallimore and Kaminski (2015) reviewed systematically the literature investigating the effectiveness of ATL, GR and SPFR in healing and preventing diabetic foot ulcers. A total of 11 studies (614 participants) were included in the review, with a median sample size of 29 participants. There were two RCTs. The review found that ATL and GR appear to be effective surgical treatments for healing diabetic foot ulcers when an equinus deformity is present. There was no statistically significant difference between these procedures and the current gold standard treatment of TCC (total contact casting) for time to healing of the ulcer and the rate of ulcers healed. However, the rate of ulcer recurrence was found to be lower in participants who had undergone ATL or GR procedures compared to those treated with TCC alone. Conversely, surgery can expose patients to greater complications and adverse events and the long-term effectiveness and safety of these procedures remains unknown. The development of transfer ulcers, particularly under the heel, were the most common complications following ATL or GR procedures. As there was only one study investigating SPFR, this method could not be assessed conclusively. At present, ATL appears to be the procedure of choice as it is relatively quick and easy to perform.

13.4 Conclusions for Clinical Practice

1. Patients with diabetic foot and PAD may be treated with either endovascular intervention (ER) or open vascular reconstruction (OR); there are no evidence based recommendations showing that one is more advantageous than the other.
2. There is no research evidence to suggest that any type of wound dressing is more effective in healing diabetic foot ulcers than other types of dressing. Therefore, dressing cost and the wound management properties offered by each dressing type, e.g. exudate management dictate the choice of dressing.
3. There is some evidence to suggest that NPWT is more effective in healing postoperative foot wounds and ulcers of the foot in people with diabetes mellitus compared with moist wound dressings. However, these findings are uncertain due to the possible risk of bias in the original studies.
4. Patients with DFS have persistent high rates of limb amputation and of mortality. The 4-year amputation-free survival was 45.4% for DFS patients in a real-world setting.
5. Patients with DFU have a significantly worse prognosis than diabetic patients without a foot ulcer. DFU is an independent risk factor for amputation as well as mortality.
6. Surgical lower extremity nerve decompression improves pain and renders a lower incidence of postoperative ulcerations/amputations in patients with diabetic neuropathy.

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Chapter 14
Varicose Veins

14.1 Guideline Recommendations

14.1.1 NICE

The NICE guidelines recommend (NICE National Institute for Health and Care Excellence 2013):

In some people varicose veins are asymptomatic or cause only mild symptoms, but in others they cause pain, aching or itching and can have a significant effect on their quality of life. Varicose veins may become more severe over time and can lead to complications such as changes in skin pigmentation, bleeding or venous ulceration. It is not known which people will develop more severe disease but it is estimated that 3–6% of people who have varicose veins in their lifetime will develop venous ulcers.

Referral to a vascular service
Refer people to a vascular service if they have any of the following:

- Symptomatic primary or symptomatic recurrent varicose veins.
- Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency.
- Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence.
- A venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks).
- A healed venous leg ulcer.

Assessment
- Use duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux, and to plan treatment for people with suspected primary or recurrent varicose veins.

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Interventional treatment
For people with confirmed varicose veins and truncal reflux:

- Offer endothermal ablation and endovenous laser treatment of the long saphenous vein.
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy.
- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

If incompetent varicose tributaries are to be treated, consider treating them at the same time.

14.1.2 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)

Varicose veins of the lower limbs are dilated subcutaneous veins that are > 3 mm in diameter measured in the upright position (Gloviczki et al. 2011).

- *Duplex scanning*: we recommend that in patients with chronic venous disease, a complete history and detailed physical examination are complemented by duplex scanning of the deep and superficial veins. (Grade of recommendation 1/Level of Evidence: A)
- *Plethysmography*: we recommend that venous plethysmography be used for the noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C3-C6). (Grade 1/Level of Evidence: B)
- *Classification*: we recommend that the CEAP classification be used for patients with chronic venous disease. The basic CEAP classification is used for clinical practice, and the full CEAP classification system is used for clinical research. (Grade 1/Level of Evidence: A)
- *Outcome assessment*: We recommend that the revised Venous Clinical Severity Score is used for assessment of clinical outcome after therapy for varicose veins and more advanced chronic venous disease. (Grade 1/Level of Evidence: B). We recommend that a quality-of-life assessment is performed with a disease-specific instrument to evaluate patient-reported outcome and the severity of chronic venous disease. (Grade 1/Level of Evidence: B)
- *Compression therapy*: We suggest compression therapy using moderate pressure (20–30 mm Hg) for patients with symptomatic varicose veins. (Grade 2/Level of Evidence: C). We recommend compression as the primary therapeutic modality for healing venous ulcers. (Grade 1/Level of Evidence: B). We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation. (Grade 1/Level of Evidence: B).
- *Open venous surgery*: For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of

the knee. (Grade 2/Level of Evidence: B). To reduce hematoma formation, pain, and swelling, we recommend postoperative compression. The recommended period of compression in C2 patients is 1 week. (Grade 1/Level of Evidence: B). For treatment of small saphenous vein incompetence, we recommend high ligation of the vein at the knee crease, about 3–5 cm distal to the saphenopopliteal junction, with selective invagination stripping of the incompetent portion of the vein. (Grade 1/Level of Evidence: B). To decrease recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy. (Grade 1/Level of Evidence: A).

- *Endovenous thermal ablation*: Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for treatment of saphenous incompetence. (Grade 1/Level of Evidence: B). Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery. (Grade 1/Level of Evidence: B).
- *Sclerotherapy of varicose veins*: We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins. (Grade 1/Level of Evidence: B). For treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam. (Grade 1/Level of Evidence: B)
- *Treatment of perforating veins*: We recommend against selective treatment of incompetent perforating veins in patients with simple varicose veins (CEAP class C2). (Grade 1/Level of Evidence: B). We suggest treatment of "pathologic" perforating veins that includes those with an outward flow duration of ≥500 ms, with a diameter of ≥3.5 mm, located beneath a healed or open venous ulcer (CEAP class C5-C6). (Grade 2/Level of Evidence: B)

14.1.3 European Society for Vascular Surgery (ESVS)

The clinical practice guidelines recommend among others (Wittens et al. 2015):

- *Recommendation 1*: Use of the Clinical Etiological Anatomical Pathophysiological (CEAP) classification is recommended as a standardized, descriptive classification tool to assess disease severity in patients with chronic venous disease for research and audit. (Class I/Level of Evidence: B)
- *Recommendation 4*: Disease severity and burden of disease should be reliably assessed by generic tools in the form of the physical component of the SF-36 and the EuroQol-5D, respectively. (Class IIa/Level of Evidence: B)
- *Recommendation 9* (Duplex ultrasound examination): To define venous incompetence the following cut off values are recommended: retrograde flow lasting more than 0.5 s in the superficial venous system, the deep femoral vein, and the calf veins, more than 1 s in the common femoral vein, the femoral vein, and the popliteal vein, and more than 0.35 s in perforating veins. (Class I/Level of Evidence: B)

- *Recommendation 11*: Duplex ultrasound is recommended as the primary diagnostic tool of choice in suspected chronic venous disease, to reliably evaluate the specific venous anatomy and to identify the source and pattern of reflux. (Class I/Level of Evidence: A)
- *Recommendation 14*: Plethysmography may be considered for the assessment of quantitative parameters related to venous function (Class IIb/Level of Evidence: C)
- *Recommendation 16*: Phlebography may be considered in cases where other diagnostic tools are inconclusive (mainly in the diagnosis of abdominal/pelvic vein diseases). (Class IIb/Level of Evidence: B)
- *Recommendation 23*: Elastic stockings are recommended as an effective treatment modality for symptoms and signs of chronic venous disease. (Class I/Level of Evidence: B)
- *Recommendation 39*: Foam sclerotherapy is recommended as a second choice treatment of varicose veins (C2) and for more advanced stages of chronic venous disease (C3-C6) in patients with saphenous vein incompetence, not eligible for surgery or endovenous ablation. (Class I/Level of Evidence: A)
- *Recommendation 40*: Foam sclerotherapy should be considered as primary treatment in patients with recurrent varicose veins, and in elderly and frail patients with venous ulcers. (Class IIa/Level of Evidence: B)
- *Recommendation 41*: Liquid sclerotherapy should be considered for treating telangiectasias and reticular veins (C1). (Class IIa/Level of Evidence: B)
- *Recommendation 42*: Transcutaneous laser may be indicated for treatment of telangiectasias, only when sclerotherapy is not applicable. (Class IIb/Level of Evidence: C)
- *Recommendation 43*: For the treatment of great saphenous vein reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques are recommended in preference to surgery. (Class I/Level of Evidence: A)
- *Recommendation 44*: For the treatment of great saphenous vein reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques are recommended in preference to foam sclerotherapy. (Class I/Level of Evidence: A)
- *Recommendation 45*: For the treatment of small saphenous vein reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques should be considered. Access to the small saphenous vein should be gained no lower than mid-calf. (Class IIa/Level of Evidence: B)
- *Recommendation 46*: For non-complicated varicose veins (C2, C3), surgical treatment is recommended instead of conservative management, to improve symptoms, cosmetics, and quality of life. (Class I/Level of Evidence: B)
- *Recommendation 47*: In cases in which surgical treatment of the refluxing saphenous vein is performed, high ligation and stripping is recommended instead of high ligation only. (Class I/Level of Evidence: A)
- *Recommendation 48*: Surgical stripping of the [great] saphenous vein without high ligation leaving a 2 cm stump may be considered. (Class IIb/Level of Evidence: B)

- *Recommendation 49*: If high ligation is performed, oversewing the great saphenous vein stump, interposition of a polytetrafluoroethylene patch, or closure of the cribriform fascia may be considered, in order to reduce the effect of neovascularization at the saphenofemoral junction. (Class IIb/Level of Evidence: B)
- *Recommendation 51:* When performing endovenous thermal ablation of a refluxing saphenous trunk, adding concomitant phlebectomies should be considered. (Class IIa/Level of Evidence: B)
- *Recommendation 52*: To treat tributary varicose veins, ambulatory phlebectomy should be considered. (Class IIa/Level of Evidence: C)

14.1.4 European Guidelines for Sclerotherapy

This guideline was drafted on behalf of 23 European Phlebological Societies (Rabe et al. 2014).

Indications
We recommend sclerotherapy for all types of veins, in particular:

- Incompetent saphenous veins (GRADE 1A)
- Tributary varicose veins (GRADE 1B)
- Incompetent perforating veins (GRADE 1B)
- Reticular varicose veins (GRADE 1A)
- Telangiectasias (spider veins) (GRADE 1A)
- Residual and recurrent varicose veins after previous interventions (GRADE 1B)
- Varicose veins of pelvic origin (GRADE 1B)
- Varicose veins (refluxing veins) in proximity of leg ulcers (GRADE 1B)
- Venous malformations (GRADE 1B).

We recommend liquid sclerotherapy as the method of choice for ablation of telangiectasias and reticular varicose veins (C1) (GRADE 1A). Foam sclerotherapy of C1 varicose veins is an alternative method (GRADE 2B).

We recommend foam sclerotherapy over liquid sclerotherapy for the treatment of saphenous veins (GRADE 1A), venous malformations (GRADE 2B) and recurrent varices after previous treatment, accessory saphenous varices, nonsaphenous varices and incompetent perforating veins (GRADE 1C).

Contraindications
Absolute contraindications:

- Known allergy to the sclerosant
- Acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE)
- Local infection in the area of sclerotherapy or severe generalized infection
- Long-lasting immobility and confinement to bed
- For foam sclerotherapy in addition: Known symptomatic right-to-left shunt (e.g. symptomatic patent foramen ovale).

Relative contraindications (individual benefit–risk assessment mandatory):

- Pregnancy
- Breast feeding (interrupt breast feeding for 2–3 days)
- Severe peripheral arterial occlusive disease
- Poor general health
- Strong predisposition to allergies
- High thromboembolic risk (e.g. history of thromboembolic events, known severe thrombophilia, hypercoagulable state and active cancer)
- Acute superficial venous thrombosis
- For foam sclerotherapy in addition: Neurological disturbances, including migraine, following previous foam sclerotherapy.

14.2 Results

14.2.1 Sclerotherapy

Systematic review
Jia et al. (2007) reviewed the safety and efficacy of foam sclerotherapy. Sixty-nine studies were included. The median rates of serious adverse events, including pulmonary embolism and deep vein thrombosis, were less than 1%. The median rate of visual disturbance was 1.4%, headache 4.2%, thrombophlebitis 4.7%, matting/skin staining/pigmentation 17.8% and pain at the site of injection 25.6%. The median rate of complete occlusion of treated veins was 87.0% and for recurrence or development of new veins it was 8.1%. Meta-analysis for complete occlusion suggested that foam sclerotherapy is less effective than surgery (relative risk (RR) 0.86) but more effective than liquid sclerotherapy (RR 1.39), although there was substantial heterogeneity between studies. Foam sclerotherapy appeared to be efficacious for both main trunk and minor vein disease. Foam sclerotherapy is conducted as an outpatient procedure, does not require general anaesthesia and, compared with surgery, results in an earlier return to normal activities. However, several treatment sessions may be required.

Studies
The Board of the French Society of Phlebology sponsored a prospective multicenter registry in 22 phlebology clinics to report their activity and complications (Guex et al. 2005). During a median of 8 (±3.1) weeks, 12.173 sessions of sclerotherapy were carried out, 5.434 with liquid sclerosants, 6.395 with foam, and 344 using both. Foam sclerosants were less frequently used than liquid for treatment of reticular and spider veins (2.293 vs 3.631). But foam was used significantly more in the treatment of great saphenous veins (1.533 vs 261) and small saphenous veins (492 vs 109). Ultrasound guidance was used in 4.088 sessions (33.9%). Injections of saphenous veins represented 17% of sclerotherapy sessions in this registry. Forty-nine incidents

or accidents were reported (0.4%). Visual disturbances were the most frequently recorded adverse events. They were observed either with liquid (n = 4) or with foam (n = 16). This complication occurred almost always when air was injected (19 of 20 times). All cases spontaneously regressed, without long-term effects. In addition, one femoral vein thrombosis and one case of distal muscular vein thrombosis were noted. Pulmonary emboli, skin necrosis, muscular necrosis, or arterial injection were not seen. The results demonstrate that sclerotherapy is a very safe procedure, and that the risks of complications are extremely low.

Long-term incidence of adverse events with polidocanol was registered in the French Polidocanol Study (Guex et al. 2010). Between April 2004 and April 2008, 1.605 patients (6.444 treatment sessions) who had received at least one polidocanol injection were surveyed. A total of 3.357 patient years were covered. Most of the sessions were performed with sclerosants in foamed formulation (n = 4.403); the rest (n = 2.041) was performed with liquid sclerosants. Thirty-seven patients (total of 51 sessions) showed an adverse event that could be attributed to a treatment session with polidocanol. The global rate of incidence of adverse events related to polidocanol was 0.8% (per session) and 0.02 per patient year. The five reactions observed after injection with polidocanol liquid were one cramp, two inflammatory reactions, one pigmentation, and one visual disturbance. The total rate of adverse events with liquid polidocanol was 0.25%. Most common adverse reactions directly related to polidocanol foam were 13 visual disturbances. Only one such event could be seen after treatment with the liquid. There were seven cases of headaches (including migraines), and eight muscular vein thromboses with polidocanol foam. The total incidence of adverse events with foamed polidocanol was 1.07%. These results demonstrate that sclerotherapy with polidocanol is safe, especially in the long term. The authors assumed that ultrasound-guided foam sclerotherapy (UGFS) is a reference method in the treatment of incompetent saphenous trunks. The use of liquid, with an incidence of side effects lower than 0.4%, perfectly fits for the treatment of benign lesions such as small varices, reticular veins, or telangiectasias, whereas foamed polidocanol injected under ultrasound guidance used in the treatment of large varicose veins presents fewer side effects than surgery, with which it competes.

Between April 2004 and May 2007, 351 patients (479 limbs) were treated with UGFS by Darvall et al. (2014). The median volume of foam injected was 10 (range 2–16) ml. One hundred legs (20.9%) had ‘tidy up’ injections at 4 weeks. After a minimum of 5 years, attempts were made to contact all patients, and a follow-up appointment was sent along with a questionnaire booklet. This included both quality-of-life instruments, a questionnaire regarding fulfilment of expectations since UGFS, and some questions regarding overall satisfaction with treatment. A total of 285 patients (391 limbs) attended for review, giving an 81.2% response rate, at a median of 71 months after treatment. The majority of patients were highly satisfied with their treatment, and 82.0% gave a score of between 8 and 10 (highly satisfied); only 3.3% were dissatisfied. Some 91.0% of patients would recommend the treatment to others. The estimated cumulative proportion of patients requiring retreatment at 5 years was 15.3%. The results emphasize the cost-effectiveness of UGFS.

King et al. (2015) determined in a multicenter study if a single administration of ≤15 mL of pharmaceutical-grade polidocanol endovenous microfoam (PEM, now approved in the United States as Varithena [polidocanol injectable foam]) could alleviate symptoms and improve appearance of varicose veins in a typical population of patients with moderate to very severe symptoms of superficial venous incompetence and visible varicosities of the great saphenous vein (GSV) system. Two hundred seventy-nine patients were treated with either placebo (n = 56) or PEM 0.125% (n = 57), 0.5% (n = 51), 1% (n = 52), or 2% (n = 63). At Week 8, VVSymQ (Varicose Veins Symptoms Questionnaire) scores for the pooled PEM group (0.5% + 1% + 2%; $p < .0001$) and individual dose concentrations ($p < .001$) were significantly superior to placebo. The study demonstrated the benefit of treatment with PEM in the improvement of symptoms and appearance of varicose veins in patients with an incompetent GSV and/or accessory saphenous veins and visible varicosities. Significant improvements in disease-specific quality of life also were demonstrated. There was a low rate of deep venous thrombi, no pulmonary emboli, and no cerebrovascular or neurological events. This ultrasound-guided technique requires no tumescent anesthesia. Patients are ambulatory immediately after the procedure. Efficacy can be achieved in a single treatment. However, the recommendation is to limit the amount of PEM to 15 mL per session. Therefore, patients with more extensive disease might need more than one treatment.

Shadid et al. (2012) compared in a multicentre randomized controlled non-inferiority trial the effectiveness and costs of ultrasound-guided foam sclerotherapy (UGFS) and surgery for treatment of the incompetent great saphenous vein (GSV). Two hundred thirty patients were treated by UGFS and 200 underwent GSV stripping. The 2-year probability of recurrence was similar in the UGFS and surgery groups: 11.3% and 9.0%. At 2 years, reflux irrespective of venous symptoms was significantly more frequent in the UGFS group (35.0%) than in the surgery group (21.0%). Mean (s. d.) hospital costs per patient over 2 years were €774(344) per patient for UGFS and €1824 (141) for stripping. The study supports the broader use of UGFS due to the non-inferiority concerning recurrent clinical symptoms and its cost-effectiveness.

14.2.2 Endovenous Thermal Ablation

14.2.2.1 Meta-analyses and Systematic Reviews

For their guidelines, the Society for Vascular Surgery (SVS) partnered with the American Venous Forum (AVF) commissioned Murad et al. (2011) to conduct a systematic review and meta-analysis to summarize the best-available evidence about the benefits and harms of the different treatments of varicose veins. Thirty-nine eligible studies (30 were randomized trials) enrolling 8285 participants were found. Surgery appeared to have low- to moderate-quality evidence demonstrating less recurrence and better long-term results. Compared with surgery, however, liquid or foam sclerotherapy and endoluminal thermal ablation therapies (laser and

Table 14.1 Commonly reported adverse events with surgery, liquid sclerotherapy, laser ablation, radiofrequency ablation, and foam therapy for varicose veins

Surgery
Wound infection 3–6%/Sural or saphenous nerve injury, 10–23%/Hematoma, 31%/superficial phlebitis, 0–12%
Sclerotherapy
Skin staining or necrosis, 3%/Superficial phlebitis, 22–27%
Laser ablation
Purpura/bruising, 11–23%/Erythema, 33%/Hyperpigmentation, 57%/Hypopigmentation, 2%/Blistering/sloughing, 7%/Scaring, 13%/Telangiectatic matting, 28%/Edema, 15%/Paresthesia, 1–2%/Superficial phlebitis 6%
Radiofrequency ablation
Saphenous nerve paresthesia, 13%/Superficial phlebitis, 0–20%/Hematoma, 7%/Thermal skin injury, 7%/Paresthesia, <1%/Leg edema, <1%
Foam therapy
Contusion, bruising, hematoma, 61%/Skin pigmentation, 51%/Headache, 11%

Meta-analysis from Murad et al. 2011

radiofrequency) were associated with faster return to work, shorter duration of disability, and less pain. The evidence on quality of life was sparse and inconclusive. Data on outcomes of DVT and PE were sparse and poorly reported. In conclusion, very low quality evidence suggested that the available treatments for varicose veins (surgery, sclerotherapy, foam therapy, laser endoluminal ablation and radiofrequency endoluminal ablation) appear to be safe with rare side effects. Surgery is the only treatment with long-term effectiveness data. Table 14.1 summarizes the reported frequency of local complications associated with surgery, liquid sclerotherapy, laser ablation, radiofrequency ablation, and foam therapy.

In addition, a Cochrane review (Nesbitt et al. 2014) determined whether endovenous ablation (radiofrequency and laser) and foam sclerotherapy have any advantages or disadvantages in comparison with open surgical saphenofemoral ligation and stripping of great saphenous vein varices. All randomized controlled trials (RCTs) of ultrasound-guided foam sclerotherapy (UGFS), radiofrequency ablation (RFA), endovenous laser therapy (EVLT) and open surgery or high ligation and stripping (HL/S) were considered for inclusion (last search January 2014). Thirteen studies with a combined total of 3081 randomized patients were included in this analysis. Clinical trial evidence suggested that UGFS, EVLT and RFA are at least as effective as surgery in the treatment of great saphenous varicose veins. Due to large incompatibilities between trials and different time point measurements for outcomes, the evidence is lacking in robustness.

14.2.2.2 Venous Leg Ulcers

Venous leg ulcers represent the worst extreme within the spectrum of chronic venous disease. Samuel et al. (2013a) determined the effects of superficial endovenous thermal ablation on the healing, recurrence and quality of life of people with

active or healed venous ulcers. This Cochrane review identified no eligible RCTs. There is an absence of evidence regarding the effects of superficial endovenous thermal ablation on ulcer healing, recurrence or quality of life of people with venous leg ulcer disease. Adequately-powered, high quality RCTs comparing endovenous thermal ablative interventions with compression therapy are urgently required to explore this treatment strategy. There is evidence from two systematic reviews and meta-analyses that healing outcomes (including time to healing) are better when patients with leg ulcers receive compression compared with no compression (O'Meara et al. (2012); Mauck et al. (2014a)).

Mauck et al. (2014b) also summarized the evidence regarding the efficacy of surgical interventions compared with conservative management alone (compression) on ulcer healing and recurrence in patients with lower extremity ulceration due to venous disease. Seven studies compared open surgical procedures on the venous system (with or without compression) with compression alone on ulcer healing outcomes, representing 572 limbs in the surgical group and 571 limbs in the compression group. The pooled risk ratio (RR) was 1.06, demonstrating that ulcer healing outcomes are only slightly better in the surgery group. There was no difference in ulcer healing outcomes when only RCTs were included. Surgical intervention resulted in less ulcer recurrence. However, when only RCTs were included, there was a trend toward surgical intervention resulting in less ulcer recurrence, but this was no longer statistically significant. The current evidence does not definitively support the superiority of open or endovascular surgical interventions compared with compression alone with respect to ulcer healing and ulcer recurrence outcomes in patients with lower extremity venous ulcers.

14.2.2.3 Randomized Studies with Endovenous Laser Therapy

EVLT vs. open surgery

Patients with symptomatic varicose veins due to GSV insufficiency were randomized to HL/S (100 limbs) or EVLT (104 limbs) by Christenson et al. (2010). Major complications, such as deep vein thrombosis or wound infection were not observed in either group. HL/S limbs had significantly more postoperative hematomas than EVLT limbs, and EVLT patients reported more bruising. At 1 year follow-up, two GSVs in the EVLT group reopened and three partially reopened. No open GSVs occurred in HL/S limbs. Ninety-eight percent of the limbs in both groups were free of symptoms. Improvement in quality of life was similar after HL/S and EVLT. At 2 years after treatment, however, two GSVs were completely reopened and five were partially reopened after EVLT, which was significantly higher than after HL/S. Three of these patients required a reintervention due to recurrent symptoms.

Rass et al. (2015) compared the long-term clinical efficacy of EVLT with (HL/S) as standard treatment for great saphenous vein (GSV) incompetence in a RCT. Two hundred and eighty-one legs (81% of the study population) were evaluated with a median follow-up of 60.4 (EVLT) and 60.7 months (HL/S). Overall, recurrent varicose veins after surgery (REVAS) were similarly observed in both groups: 45%

(EVLT) and 54% (HL/S). Patients of the EVLT group showed significantly more clinical recurrences in the operated region (REVAS same site: 18% vs. 5%). In contrast, more different site recurrences were observed in the HL/S group: 50% vs. 31%. Duplex detected saphenofemoral refluxes occurred more frequently after EVLT: 28% vs. 5%. Both treatments improved disease severity and quality of life without any difference. In terms of same site clinical recurrence and saphenofemoral refluxes, HL/S was superior to EVLT 5 years after treatment.

The clinical effectiveness and recurrence rates from another randomized trial of EVLT and surgery for varicose veins were reported by Carradice et al. (2011). In this trial, including 280 patients, initial technical success was greater following EVLT: 99.3 versus 92.4%. Surgical failures related mainly to an inability to strip the above-knee GSV. The clinical recurrence rate at 1 year was lower after EVLT: 4.0 versus 20.4%. Twelve of 23 surgical recurrences were related to an incompetent below-knee GSV and 10 to neovascularization. Out of five recurrences after EVLT, two were related to neoreflux in the groin tributaries and one to recanalization. Clinical recurrence was associated with worse Aberdeen Varicose Vein Questionnaire (AVVQ) scores.

In addition, this group (Samuel et al. 2013b) compared the gold standard of conventional surgery and endovenous laser ablation in the management of small saphenous vein (SSV) incompetence. Patients with unilateral, primary saphenopopliteal junction incompetence and SSV reflux were randomized equally into parallel groups receiving either surgery (n = 53) or EVLT (n = 53). The primary outcome of abolition of SSV reflux on duplex ultrasound (DUS) at 6 weeks was significantly higher for 51 (96.2%) patients in the EVLT group than 38 (71.7%) patients in the surgery group. Postoperative pain was significantly lower after EVLT, allowing an earlier return to work and normal function. Minor complication rates were relatively low in both groups; however, sensory disturbance (predominantly in the sural nerve distribution) was significantly higher in the surgical group at 6-week follow-up – 26.4% compared with 7.5% in the EVLT group. Clinical recurrence over the 1-year follow-up period was 16.9% (surgical) versus 9.4% (EVLT group). Both groups demonstrated similar improvements in Venous Clinical Severity Score and quality of life over the study period. In summary, this RCT suggested equivalent improvements in clinical severity and at least noninferiority of EVLT compared with conventional surgery in the treatment of SSV incompetence. Meanwhile, the 2-year follow-up results of this trial have been reported (Nandhra et al. 2015). EVLT remained superior to surgery in eradicating axial reflux in 36 patients (81.2%) compared with 29 (65.9%) in the surgery group. There was no significant difference in clinical recurrence (EVLT: seven of 44 [16%] vs surgery: 10 of 44 [23%]), sensory disturbance (EVLT: one [2.4%] vs surgery three [6.8%]) or any quality of life domain. The study did not appear to suggest that the improved abolition of reflux after EVLT compared with surgery was associated with superior outcomes than those seen after surgery by this time point, because equal effect was shown in both groups. EVLT was therefore superior in the short-term and not inferior by 2 years.

Rasmussen et al. (2013) published results of the first RCT with a 5-year follow-up comparing endovenous laser ablation with high ligation and pin-stripping in

patients with great saphenous vein incompetence. A total of 121 consecutive patients (137 legs) were randomized to surgery or EVLT. In the EVLT and stripping group, nine (17.9%) and four (10.1%) of GSVs had open refluxing segments of 5 cm or more (ns). Clinical recurrence was recorded in 46.6% (EVLT) and 54.6% (HL/S), whereas reoperations were performed in 38.6% and 37.7%. Venous Clinical Severity Score and Aberdeen Varicose Vein Symptoms Severity Score improved in both groups. In conclusion, the 5-year follow-up results of this RCT did not show any significant difference between the two groups in primary or secondary end points.

Five-year follow-up results of a RCT comparing saphenofemoral ligation and stripping (SFL/S) of the great saphenous vein with EVLT also have been presented by Gauw et al. (2016). One-hundred thirty legs of 121 patients with GSV insufficiency were randomized to undergo SFL/S (n = 68) or EVLT (n = 62). At the 5-year follow-up, a significantly higher varicose vein recurrence rate originated at the SFJ region after EVLT (33%) compared with SFL/S (17%). The incidence of recurrence detected by DUS at 5 years was 49% after the EVLT procedure vs 23% after the SFL/S procedure. After 5 years of follow-up, 80% of patients in the SFL/S group did not undergo a secondary procedure compared with 70% of patients in the EVLT group. There were no differences in the relief of venous symptoms, CEAP staging, or general QoL between the groups.

High ligation and stripping (HL/S) was compared to EVLT for the therapy of great saphenous varicose veins by Flessenkämper et al. (2016). A total of 449 patients were randomized into three different treatment groups: HL/S group (n = 159), EVLT group (n = 142) or a combination of EVLT with high ligation (high ligation/EVLT group, n = 148). Follow-up rates were at 2 years 74%, 4 years 39%, 5 years 36% and 6 years 31%. Most reflux into the great saphenous vein appeared in the EVLT group (after 6 years: HLS vs EVLT $p = 0.0102$; high ligation/EVLT vs. EVLT $p < 0.0002$). However, clinical recurrence appeared with the same frequency in all three treatment groups during up to 6 years follow-up.

EVLT, UGFS and conventional surgery

A total of 240 consecutive patients with primary symptomatic great saphenous vein reflux were randomized by Biemans et al. (2013) to EVLT, UGFS, or conventional surgery (CS), consisting of high ligation and short stripping. After 1 year, the anatomic success rate defined as obliteration or absence of the treated vein on ultrasound examination was highest after EVLT (88.5%), followed by CS (88.2%) and UGFS (72.2%). The complication rate was low and comparable between treatment groups. All groups showed significant improvement of EuroQol 5 and Chronic Venous Insufficiency Quality-of-Life Questionnaire scores after therapy; 84.3% of all treated patients showed an improvement of the "C" of the CEAP classification. In this study, EVLT was as effective as CS and superior to UGFS according to occlusion on ultrasound duplex. Now, the long-term outcomes of this study have been published (van der Velden et al. 2015). In total, 193 (86.2%) of 224 treated legs (170 patients) were evaluated. At 5 years after intervention, the treated GSV was completely obliterated or absent in 85% of legs in the CS group, 77% in the EVLT group, and 23% in the UGFS group. Patients treated with conventional surgery or

EVLT were four times more likely to have persisting obliteration of the above-knee GSV than patients in the UGFS group at 5 years. At 5 years in the CS and EVLT groups, the estimated cumulative proportion of legs without above-knee GSV reflux was 85% and 82%, compared with 41% in the UGFS group. Patients treated with conventional surgery or EVLT were three times more likely to have absence of above-knee GSV reflux than patients in the UGFS group after 5 years of follow-up. At 5 years, 44% of legs in the CS group, 11% in the EVLT group and 3% in the UGFS group had developed some degree of neovascularization. During the 5-year follow-up, 32% of legs treated initially with UGFS required one or more reinterventions of the GSV above the knee. Conversely, only 10% of limbs in the CS and EVLT groups had one or more reinterventions over time. In conclusion, EVLT and conventional surgery were more effective than UGFS in obliterating the GSV 5 years after intervention. UGFS was associated with substantial rates of GSV reflux and inferior Chronic Venous Insufficiency quality-of-life Questionnaire (CIVIQ) scores compared with EVLT and conventional surgery.

The Comparison of Laser, Surgery, and Foam Sclerotherapy (CLASS) trial is the largest multicentre trial to have compared surgery with the two most commonly performed newer treatment options, namely foam sclerotherapy and thermal ablation by EVLT for treatment of varicose veins (Brittenden et al. 2014). Seven hundred eighty-five patients were included in the trial. The frequency of procedural complications was similar in the foam group (6%) and the surgery group (7%) but was lower in the laser group (1%) than in the surgery group. At 6 months, the mean disease-specific quality of life was slightly worse after treatment with foam than after surgery but was similar in the laser and surgery groups. Measures of clinical success were similar among the groups, but successful ablation of the main trunks of the saphenous vein was less common in the foam group than in the surgery group. In conclusion, all treatments had similar clinical efficacy, but complications were less frequent after laser treatment and ablation rates were lower after foam treatment.

Furthermore, participants of the CLASS trial were followed up 6 weeks after treatment and asked to complete the Behavioural Recovery After treatment for Varicose Veins (BRAVVO) questionnaire (Cotton et al. 2016). This is a 15-item instrument that covers eight activity behaviours (tasks or actions an individual is capable of doing in an idealized situation) and seven participation behaviours (what the individual does in an everyday, real-world situation) that were identified to be important from the patient's perspective. Both UGFS and EVLT resulted in a more rapid recovery compared with surgery for 13 of the 15 behaviours. UGFS was superior to EVLT in terms of return to full time work, looking after children and walking (both short and long distances).

In addition, clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins have been evaluated based on the results of the CLASS trial in a HTA report (Brittenden et al. 2015). According to this analysis, the CLASS trial has shown that EVLT (performed under a local anaesthetic, in a predominantly clinic-based setting) has the highest probability of being cost-effective at accepted thresholds of willingness to pay per QALY. For

patients in whom thermal ablation may be unsuitable or declined, the results from the CLASS trial suggest that surgery rather than foam sclerotherapy should be considered. In a two-way comparison between foam and surgery, surgery was found to have the greatest probability of being cost-effective at 5 years, although a great deal of uncertainty surrounds this finding owing to the significantly higher cost of surgery and lack of long-term recurrence rate data for both interventions. Therefore, these early results cannot be used to determine definitive recommendations for the treatment of varicose veins because late recurrence rates and the need for further treatment also need to be considered. This underlines the importance of the 5-year follow-up of patients in the CLASS study.

14.2.2.4 Studies with Endovenous Radiofrequency Ablation

EVLT (n = 64) and radiofrequency ablation (RFA) (n = 67) were compared in a randomized clinical trial in patients with primary great saphenous vein reflux (Shepherd et al. 2010). The primary outcome measure was postprocedural pain after 3 days, secondary outcome measures were quality of life at 6 weeks. In this trial, RFA using VNUS ClosureFAST was associated with less postprocedural pain than EVLT. However, clinical and quality-of-life improvements were similar after 6 weeks for the two treatments. Gale et al. (2010) randomized patients with symptomatic primary venous insufficiency due to GSV incompetence to RFA or EVLT. RFA was performed with the ClosurePlus system. The study enrolled 118 patients (141 limbs). More bruising occurred in the EVLT group at 1 week, but at 1 month, there was no difference in bruising between groups. EVLT was associated with greater discomfort in the perioperative period but provided a more secure closure over the long-term than RFA. At 1 year, DUS imaging showed evidence of recanalization with reflux in 11 RFA and 2 EVLT patients. Nordon et al. (2011) compared the RFA and EVLT strategies in a prospective double-blind clinical trial. A total of 159 patients with primary unilateral GSV reflux were randomized to RFA (79 patients) or EVLT (80 patients). At 3 months, occlusion was 97% for RFA and 96% for EVLT. Median percentage above-knee bruise area was greater after EVLT (3.85%) than after RFA (0.6%). Postoperative pain assessed at each of the first 7 postoperative days was less after RFA. Changes in QoL at 3 months were similar in both groups. EVLT and RFA were also compared in the treatment of 120 patients with great saphenous vein diameters of 10 mm or more (Mese et al. 2015). Patients were assessed on the second day, the first week, and the first, third, and sixth months. No major complication was observed in any patient. There was no statistically significant difference between the groups in terms of pain during the procedure or postoperatively. Recanalization developed during monitoring in 3 patients in the RFA group (5%) and no patient in the EVLA group.

A randomized clinical trial comparing EVLT, RFA, foam sclerotherapy and surgical stripping for great saphenous varicose veins was performed by Rasmussen et al. (2011). Five hundred consecutive patients (580 legs) were included in this trial. At 1 year, 5.8%, 4.8%, 16.3% and 4.8% of the GSVs were patent and refluxing in the laser, radiofrequency, foam and stripping groups respectively. The technical

failure rate was highest after foam sclerotherapy, but both RFA and foam were associated with a faster recovery and less postoperative pain than EVLT and stripping. The mean postintervention pain scores (scale 0–10) were 2.58, 1.21, 1.60 and 2.25 respectively. The median time to return to normal function was 2, 1, 1 and 4 days respectively ($P < 0.001$).

Controlled trials comparing RFA and surgical stripping are rare. Subramonia and Lees (Subramonia and Lees 2010) randomized 93 consecutive patients with symptomatic varicose veins due to isolated GSV incompetence. Forty-seven patients had RFA and 41 had conventional surgery; five were not treated. Postoperative pain and analgesic requirements were considerably less following RFA. Pain scores beyond the first week similarly favoured RFA. After a conventional operation, 15 of 41 patients returned to normal activities within a week, whereas after RFA 35 of 47 patients returned to usual activities within 5 days. Patient satisfaction was significantly better after RFA. However, the significance of this study is limited in the absence of mid-term and long-term results.

In addition, a non-randomized prospective, multicentre, cohort study was designed to evaluate the long-term effects of RFA of the GSV using a catheter with an integrated heating element, the ClosureFast™ procedure (Proebstle et al. 2015a). Unselected, consecutively screened patients presenting with signs and symptoms of lower-limb venous disease in the GSV with confirmed reflux and eligible for endovascular treatment, were candidates for the study. Two hundred ninety-five legs were treated. Technical success was achieved in all legs. Using Kaplan–Meier estimates, the GSV occlusion rate was 91.9% at 5 years and the reflux-free GSV was 94.9%. According to the Venous Clinical Severity Score (VCSS) assessment, 92·4 per cent of the treated limbs were pain-free at the 5-year follow-up visit. In consequence, RFA is an effective and durable treatment for great saphenous varicose veins.

14.2.2.5 Clinical Effectiveness and Cost-effectiveness of Minimally Invasive Techniques

Clinical effectiveness and cost-effectiveness of new minimally invasive techniques compared with other techniques, including traditional surgical techniques, liquid sclerotherapy (LS) and conservative management, in the management of varicose veins were evaluated by Carroll et al. (2013). The economic analysis was undertaken from a UK NHS perspective. This literature search identified 34 RCTs (54 papers) for the clinical effectiveness review. The main results were:

- The minimally invasive techniques reported clinical outcomes similar to surgery. Rates of recurrence were slightly lower for EVLT, RFA and foam sclerotherapy (FS), especially for longer follow-up periods.
- VCSS was lower for EVLT and FS than for stripping, but slightly higher for RFA; short-term pain was less for FS and RFA but higher for EVLT.
- Higher quality-of-life scores were reported for all evaluated interventions than for stripping.

- Differences between treatments were negligible in terms of clinical outcomes, but marginally favour the novel treatments relative to stripping. So the treatment with the lowest cost appears to be most cost-effective.
- FS costs £530 less than stripping, and is marginally more effective, with a probability of being the most cost-effective treatment above 90% for willingness-to-pay thresholds in the range £20,000–50,000.
- Endovenous laser ablation and RFA both cost more than surgery, and with very little difference in QALYs they cannot be considered cost-effective at the usual threshold of £20,000–30,000.

A further economic analysis was constructed by Marsden et al. (2015) to compare the cost-effectiveness of surgery, endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), and compression stockings (CS) for symptomatic varicose veins. The analysis was based on a Markov decision model. The model had a 5-year time horizon, and took the perspective of the UK National Health Service. The most important finding of this study was that all interventional treatments (surgery, ETA, and UGFS) for varicose veins are cost-effective compared with compression therapy. The study also found that ETA is cost-effective compared with surgery and UGFS. ETA produced the greatest QALY gain, and was therefore the most clinically effective treatment, yet it came at an additional cost compared to UGFS, of £151 (note that this includes the downstream costs of top-up treatments and clinical recurrence, as well as the cost of the initial procedure). Using the mean costs and QALYs generated by the probabilistic sensitivity analysis, the incremental cost-effectiveness ratio (ICER) of the ETA to FS was £3161. This is below the NICE threshold of £20,000 per QALY gained, and therefore ETA was found to be the cost-effective strategy. When ETA is not deemed suitable for a patient, UGFS is likely to be the optimal strategy. Surgery represents the optimal choice if neither ETA nor UGFS is thought suitable.

The former network meta-analysis (NMA) presented by Carroll et al. (2013) found FS to be cost-effective compared with surgery, EVLT, and RFA. This study differed from the model presented by Marsden et al. (2015), as the analysis focused on technical (as opposed to clinical) recurrence, which included outcomes such as reflux, recanalization and incomplete obliteration of the vein, all analyzed together in a NMA. Using this method, little clinical difference was found between the strategies, and the model was therefore largely driven by the cost of the treatments. FS was the cheapest treatment; therefore, this was the cost-effective option in the base case. In contrast, Marsden et al. (2015) raised concerns about the use of technical recurrence as a key clinical outcome (as, for example, recurrent reflux may not lead to recurrent symptoms), and about the cost figures used. Specifically, it was not agreed that EVLT and RFA would be more costly than surgery.

Shepherd et al. (2015), finally, compared clinical outcomes and cost-effectiveness of EVLT with RFA in the setting of a randomized clinical trial. A total of 131 patients were randomized, of which 110 attended 6-month follow-up (EVLT n = 54; RFA n = 56). Improvements in quality of life and VCSS achieved at 6 weeks were maintained at 6 months, with no significant difference detected between treatment groups. There were no differences in treatment failure rates. There were small dif-

ferences in favor of EVLT in terms of costs and 6-month HRQOL but these were not statistically significant. However, RFA was associated with less pain at up to 10 days. Based on the data from this study, EVLT is more likely to be cost-effective than RFA at 6 months. Nevertheless, absolute differences in costs and HRQOL are small and so there is a strong case for leaving the choice to clinician and patient preference.

14.2.3 Further Minimally Invasive Techniques

Endovascular thermal ablation (EVTA) is a successful treatment modality, but it requires the use of perivenous tumescent anesthesia and can still cause a variety of side effects like postoperative pain, bruising, and sensory nerve damage. The following minimally invasive techniques are propagated with the objective to achieve a safer and easier method of varicose vein ablation that has fewer side effects. Long-term effectiveness has not been proven so far.

14.2.3.1 Steam Ablation

The newest method of endovenous thermal ablation is pulsated steam, which works by heating the vein with steam at 120 °C. The procedure is very similar to EVLT. Van den Bos et al. (2011) assessed the effectiveness of steam ablation of varicose veins in sheep and in humans. In a pilot study, steam ablation was performed under local tumescent anesthesia in an outpatient setting and was effective in 19 of 20 patients up to 6 months of follow-up. The first phase II study of steam ablation technology for treating superficial venous insufficiency was performed by Milleret et al. (2013). A total of 75 patients (88 limbs) were treated in this multicenter trial, 92% had saphenofemoral incompetence. Successful venous obliteration, with little pain and minimal adverse events, was obtained at 6 months in 96% of treated veins. Van den Bos et al. (2014) compared endovenous laser ablation and endovenous steam ablation (EVSA) for great saphenous varicose veins in a non-inferiority study. A total of 227 legs were treated. At 1 year, the treatment success rate after high-dose EVSA was not inferior to that of EVLT: 92% vs 96%, respectively. Patients treated with EVSA reported less postprocedural pain, fewer days of analgesia use, were more satisfied with therapy, and had a shorter convalescence. Complication rates were comparable.

14.2.3.2 Mechano-chemical Ablation

Mechano-chemical endovenous ablation using the ClariVein® system uses a micropuncture technique and a 4-Fr sheath to allow a catheter to be placed 1.5 cm from the saphenofemoral junction. Unlike EVLT or RFA, no tumescence is required. The

technique depends on a wire rotating at 3500 r/min causing endothelial damage whilst liquid sclerosant (1.5% sodium tetradecyl sulphate) is infused (Vun et al. 2015). Fifty-one great saphenous veins and six short saphenous veins were treated by Vun et al. (Vun et al. 2015) and followed up with duplex for 10 months. No major complications or deep vein thrombosis were reported. Technical success rate was 91%. Comparison with 50 RFA and 40 EVLT showed procedure times were significantly less for ClariVein(®) (23.0 ± 8.3 min) than for either RFA (37.9 ± 8.3 min) or EVLT (44.1 ± 11.4 min). Median pain scores were significantly lower for ClariVein(®) than RFA and EVLT. Experiences with the ClariVein® treatment for varicose veins in 300 patients (371 legs) were reported by Tang et al. (2017), too. Three hundred ninety-three procedures were completed successfully under local anaesthetic. Complete occlusion of the treated vein was initially achieved in all the patients, but at 8 weeks' follow-up, there was only partial obliteration in 13/393 (3.3%) veins. Procedures were well tolerated with a mean pain score of 0.8 (0–10). No significant complications were seen. Safety of the procedure and technical effectiveness were analyzed also by Deijen et al. (2016). They performed mechano-chemical endovenous ablation in 570 incompetent veins (449 patients). Four hundred fifty-seven veins (90%) were occluded at a follow-up of 6 to 12 weeks.

A 2-year analysis on the efficacy of mechano-chemical ablation in patients with symptomatic C2 or more advanced chronic venous disease has been published by Kim et al. (2017). Of the initial 126 patients, there were 65 patients with 24 months' follow-up. Closure rates were 100% at 1 week, 95% at 12 months, and 92% at 24 months. There was significant improvement in CEAP and venous clinical severity score for all time intervals.

In the multicentre Venefit™ versus ClariVein® for varicose veins trial, 119 patients were randomised to receive mechanochemical ablation (ClariVein®) or radiofrequency ablation (Bootun et al. 2016). Maximum pain score was significantly lower in the mechanochemical ablation group compared to the radiofrequency ablation group. Average pain score was also significantly lower in the mechanochemical ablation group. Sixty-six percent attended follow-up at 1 month, and the complete or proximal occlusion rates were 92% for both groups. At 1 month, the clinical and quality of life scores for both groups had similar improvements. Final results of this trial were published by Lane et al. (2017). Pain secondary to truncal ablation was less painful with mechanochemical ablation than RFA with similar short-term technical, quality of life and safety outcomes.

Lam et al. (2016) conducted a study to identify the ideal polidocanol dosage and form for ClariVein® mechano-chemical ablation in order to occlude the great saphenous vein. Patients with incompetent truncal veins were randomized to 3 groups: group 1 consisted of mechano-chemical ablation +2% polidocanol liquid, group 2: mechano-chemical ablation +3% polidocanol liquid and group 3: mechano-chemical ablation +1% polidocanol foam. At 6 weeks post-treatment duplex ultrasound showed that 25 out of 25 = 100%, 27 out of 28 = 96.4% and 13 out of 23 = 56.5% veins were occluded in group 1,2, and 3, respectively. As consequence, mechano-

chemical ablation using ClariVein® combined with 1% polidocanol microfoam should not be considered as a treatment option of incompetent truncal veins.

14.2.3.3 Cyanoacrylate-Embolization

The advantages of Cyanoacrylate-Embolization (CAE) for the treatment of incompetent truncal veins are, first, because CAE does not require the use of tumescent anesthesia, the patient avoids its associated burden; and second, CAE may also allow elimination of postprocedure compression stockings, for which compliance is known to be poor.

In a prospective multicenter cohort study, incompetent GSVs received endovenous embolization with a unique endovenous cyanoacrylate adhesive implant. Neither tumescent anesthesia nor postinterventional compression stockings were used. In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, 70 GSVs were treated. Cumulative 12-month survival free from recanalization was 92.9%. Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days. Pain without a phlebitic reaction was observed in five patients (8.6%) for a median duration of 1 day. No serious adverse event occurred. Paresthesia was not observed (Proebstle et al. 2015b).

The prospective, multicenter randomized VeClose trial compared CAE with RFA for the treatment of the incompetent GSV (Morrison et al. 2015). Two hundred twenty-two subjects were randomly assigned to either CAE or RFA. Most (87%) subjects had CEAP clinical class 2 and 3 venous disease. At month 1, patency of the treated vein segment on duplex ultrasound was identified in 15 GSVs treated with RFA and 0 GSVs treated with CAE, with closure rates of 86% and 100%, respectively. The study showed that occlusion of the target vein at 3 months by CAE was at least as effective as RFA. Three-month probability of complete closure of the target GSV with CAE in this study was 99%. Adverse events were similar between groups. Pain experienced during the procedure was mild and similar between treatment groups. At day 3, less ecchymosis in the treated region was present after CAE compared with RFA. The rate of postoperative phlebitis was slightly higher for CAE but not statistically significant compared with RFA.

Early results of a retrospective study of the use of N-butyl cyanoacrylate (VariClose®)-based non-tumescent endovenous ablation for the treatment of patients with varicose veins were reported by Yasim et al. (2016). A percutaneous entry was made under local anesthesia to the great saphenous vein in 169 patients and to the small saphenous vein in 11 patients. The mean follow-up time was 5.5 months. Recanalization was not observed in any of the patients during follow-up. Bozkurt and Yılmaz (2016) compared prospectively CAE and EVLT in 310 patients with varicose veins. Primary endpoint of this study was complete occlusion of the great saphenous vein. Operative time was shorter, and periprocedural pain was less in cyanoacrylate ablation group compared to the endovenous laser ablation group. Ecchymosis at the

third day was also significantly less in CAE. Temporary or permanent paresthesia developed in seven patients in EVLT group and none in CAE group. One, three, and 12 months closure rates were 87.1, 91.7, and 92.2% for EVLT and 96.7, 96.6, and 95.8% for CAE groups. The study demonstrated efficacy and safety of CAE for treatment of venous insufficiency. Results of a further safety and efficacy study were presented by Chan et al. (2017). Fifty-seven legs in 29 patients with primary varicose veins and great saphenous vein (GSV) reflux were treated with CAE. All the patients were discharged the same day of operation. Median time to return to work was 1 day. With median follow-up period of 9 months (range 1–13 months), no clinical recurrence of varicosity was observed.

14.2.4 Compression Stockings as Initial Treatment Option for Varicose Veins

Shingler et al. (2013) assessed the effectiveness of compression stockings for the only and initial treatment of varicose veins in patients without healed or active venous ulceration. Randomized controlled trials (RCTs) were included in this Cochrane review if they involved participants diagnosed with primary trunk varicose veins without healed or active venous ulceration. Seven studies involving 356 participants were found. Different levels of pressure were exerted by the stockings in the studies, ranging from 10 to 50 mmHg. One study assessed compression hosiery versus no compression hosiery. The symptoms subjectively improved with the wearing of stockings across trials that assessed this outcome, but these assessments were not made by comparing one randomised arm of a trial with a control arm and are therefore subject to bias. There is insufficient, high quality evidence to determine whether or not compression stockings are effective as the sole and initial treatment of varicose veins in people without healed or active venous ulceration, or whether any type of stocking is superior to any other type.

In the meantime, compression therapy and surgery of varicose veins have been compared in a RCT (Sell et al. 2014). The inclusion criteria for patients were significant superficial truncal venous reflux verified with DUS and clinical class (CEAP) C2–C3 disease. One hundred thirty-three patients were randomized to receive surgery or conservative treatment with compression stockings. At 2 years, 70/76 patients in the surgery group and 11/77 patients in the compression group had been operated on. VCSS-S decreased from 4.6 to 3.5 in the compression group and from 4.8 to 0.6 in the surgery group. Patients who underwent surgery showed significant improvement in the measures of clinical severity of the disease as well as in disease-specific quality of life compared with those patients who were under compression therapy only. In addition, after the study follow-up ended, almost all patients in the compression therapy group sought treatment for the superficial venous reflux. Patients with varicose veins with C2–C3 clinical class benefit from surgical elimination of superficial venous reflux when compared with compression stockings only.

14.3 Conclusions for Clinical Practice

1. All interventional treatments (surgery, endovenous thermal ablation, and ultrasound-guided foam sclerotherapy) for varicose veins are cost-effective compared with compression therapy.
2. For the treatment of great saphenous vein reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques are recommended in preference to surgery.
3. For the treatment of great saphenous vein reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques are recommended in preference to foam sclerotherapy.
4. Foam sclerotherapy is recommended as a second choice treatment of varicose veins and for more advanced stages of chronic venous disease in patients with saphenous vein incompetence, not eligible for surgery or endovenous ablation.
5. The significance of mechano-chemical endovenous ablation and cyanoacrylate-embolization cannot be conclusively evaluated as long as long-term follow-up data are missing.

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