Evidence-based Therapy in Vascular Surgery

E. Sebastian Debus
Reinhart T. Grundmann

Second Edition

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Preface

The topic of the second edition of this book is vascular and endovascular surgery and vascular medicine. Thereby, all prevalent arterial vascular diseases are discussed, from extracranial carotid artery stenosis to peripheral arterial occlusive disease and the diabetic foot. Furthermore, evidence-based therapy for hemodialysis access, varicose veins, deep vein thrombosis, and venous leg ulcer is presented. This is not a textbook that describes surgical techniques. Instead its intention is to advise the reader on which surgical or endovascular procedure is currently the best justified (indication) in specific situations and what the expected results should be from a quality assurance perspective. This starts with the presentation of guideline recommendations from the most recognized professional societies, which are not necessarily the same in all countries. The second focus of this book is 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 nonrandomized clinical studies, large cohort studies, and registries are explained.

In terms of structure and objectives, nothing has changed in this issue since the conception of the first edition except for the extension of the number of chapters and a new chapter on perioperative management. Nevertheless, it is much more than just a re-edition—in fact we are presenting the reader with a completely new book. The reason for this is another objective of this series, the timeliness. Based on a comprehensive, systematic literature search in PubMed, all the important publications of the last 5 years are presented here. This not only provides the reader with the evidence, but also the latest state of knowledge or discussion. In order not to go too far, it was necessary to delete many publications from previous years, which may still be of value, so that each new edition of this series is more of a supplement than a replacement for the previous edition.

The book is aimed at a broad readership, including residents and junior doctors, as well as experienced practitioners looking to stay informed about the latest developments in our field—which can also have practical and possibly justiciable

consequences, especially in the case of guideline recommendations or in medical malpractice criticism.

In conclusion, we thank all employees of Springer Nature, who participated in this project for their kind assistance, and especially Ms. Mahalakshmi and Ms. Morton for their collaboration and coordination of this book project.

Hamburg, Germany — E. Sebastian Debus
Burghausen, Germany — Reinhart T. Grundmann

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Chapter 1
Extracranial Carotid Stenosis

1.1 Guidelines

1.1.1 Guideline of the European Society for Vascular Surgery (ESVS) [1]

1.1.1.1 Unchanged Recommendations

- No. 19: For average surgical risk patients with an asymptomatic 60–99% stenosis, carotid endarterectomy should be considered in the presence of one or more imaging or clinical characteristics that may be associated with an increased risk of late stroke, provided 30 day stroke/death rates are ≤3% and patient life expectancy exceeds 5 years. (Class IIa/Level B).
- No. 20: For average surgical risk patients with an asymptomatic 60–99% stenosis in the presence of one or more imaging or clinical characteristics that may be associated with an increased risk of late stroke, carotid stenting may be an alternative to carotid endarterectomy, provided 30 day stroke/death rates are ≤3% and patient life expectancy exceeds 5 years. (Class IIb/Level B).
- No. 40: For patients reporting carotid territory symptoms within the preceding 6 months and who have a 70–99% carotid stenosis, carotid endarterectomy is recommended provided the 30 day risk of death/stroke rate is <6%. (Class I/Level A).
- No.41: For patients reporting carotid territory symptoms within the preceding 6 months and who have a 50–69% carotid stenosis, carotid endarterectomy should be considered provided the documented 30 day risk of death/stroke rate is <6%. (Class IIa/Level A).
- No. 42: For patients aged ≥70 years who have experienced a carotid territory transient ischaemic attack or ischaemic stroke within the preceding 6 months in association with a 50–99% carotid stenosis, it is recommended that they should

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be treated by carotid endarterectomy, rather than carotid stenting. (Class I/Level A).

- No. 43: For patients aged <70 years who have experienced a carotid territory transient ischaemic attack or ischaemic stroke within the preceding 6 months in association with a 50–99% carotid stenosis, carotid artery stenting may be considered an alternative to endarterectomy, provided the documented 30 day risk of death/stroke is <6%. (Class IIb/Level A).
- N0. 44: For symptomatic patients with a 50–99% stenosis in whom a carotid intervention is considered appropriate, it is recommended that this be performed as soon as possible, preferably within 14 days of symptom onset. (Class I/Level A).
- No. 45: For patients who are undergoing revascularisation within the first 14 days after onset of symptoms, it is recommended that they should undergo carotid endarterectomy, rather than carotid stenting. (Class I/Level A).
- No. 46: For patients with 50–99% stenoses who experience a disabling stroke (modified Rankin score ≥ 3), or whose area of infarction exceeds one third of the ipsilateral middle cerebral artery territory, or who have altered consciousness/drowsiness, it is recommended to defer carotid interventions to minimise the risks of post-operative parenchymal haemorrhage. (Class I/Level C).
- No. 47: For patients with 50–99% stenoses who present with stroke in evolution or crescendo transient ischaemic attacks, urgent carotid endarterectomy should be considered, preferably within 24 h. (Class IIa/Level C).

1.1.1.2 New Class I Recommendations Are Among Others

- No. 23: For symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting following a transient ischaemic attack or minor ischaemic stroke, short term aspirin plus clopidogrel for 21 days followed by clopidogrel monotherapy, or long term aspirin plus dipyridamole modified release is recommended.
- No. 24: For recently symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole monotherapy or ticagrelor monotherapy is recommended.
- No. 25: For recently symptomatic carotid stenosis patients in whom carotid endarterectomy is being considered, it is recommended that neurologists/stroke physicians and vascular surgeons develop local protocols to specify preferred antiplatelet regimens (combination therapy vs. monotherapy), so as not to delay urgent carotid surgery.
- No. 58: For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus within the carotid artery, therapeutic anticoagulation is recommended.
- No. 63: For patients with a transient ischaemic attack or minor ischaemic stroke in the presence of newly diagnosed or known atrial fibrillation and an ipsilateral

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50–99% carotid stenosis, comprehensive neurovascular work up with multidisciplinary team review is recommended to determine whether urgent carotid revascularisation or anticoagulation alone is indicated.

- No. 64: For patients who have been started on anticoagulation (on the basis that cardiac embolism was considered the most likely cause of their transient ischaemic attack or stroke) but who then report recurrent event(s) in the territory ipsilateral to a 50–99% carotid stenosis whilst on therapeutic levels of anticoagulation, carotid endarterectomy or carotid artery stenting is recommended.
- No. 66: For patients undergoing carotid endarterectomy, it is recommended that the operation be performed by trained vascular surgeons, rather than by surgeons from other specialties.
- No. 91: For patients experiencing a peri-operative stroke, it is recommended to differentiate between an intra-operative and a post-operative stroke.
- No. 92: For patients who develop an ipsilateral neurological deficit after flow is restored following carotid clamp release when carotid endarterectomy is performed under locoregional anaesthesia, immediate re-exploration of the carotid artery is recommended.
- No. 93: For patients who develop an ipsilateral or contralateral stroke at any time period following carotid endarterectomy or carotid artery stenting, urgent diagnostic neurovascular imaging of both carotid arteries and the brain is recommended.

1.1.1.3 New Class IIa Recommendations

- No. 49: For patients with acute ischaemic stroke due to a symptomatic 50–99% carotid stenosis who have received intravenous thrombolysis, delaying carotid endarterectomy or carotid stenting by 6 days following completion of thrombolysis should be considered.
- No. 54: For recently symptomatic patients with 50–99% stenoses and contralateral carotid occlusion or previous cervical radiation therapy, the choice of carotid endarterectomy or carotid artery stenting should be considered on an individual basis.
- No. 62: For patients with confirmed ocular ischaemia syndrome and a 50–99% ipsilateral carotid stenosis, carotid endarterectomy or carotid stenting should be considered to prevent further ischaemia induced retinal neovascularisation.
- No. 77: For patients undergoing carotid endarterectomy, intra-operative completion imaging with angiography, duplex ultrasound or angioscopy should be considered in order to reduce the risk of peri-operative stroke.
- No. 82: For patients selected to undergo carotid artery stenting, transradial or transcarotid artery revascularisation should be considered as an alternative to transfemoral carotid artery stenting, especially where transfemoral access may confer a higher risk of complications.

- No. 83: For patients undergoing carotid artery stenting, decisions regarding stent design (open cell, closed cell) should be considered at the discretion of the operator.
- No. 85: For patients undergoing carotid artery stenting, when pre-dilatation is planned, balloon diameters <5 mm should be considered in order to reduce the risk of peri-procedural stroke or transient ischaemic attack.
- No. 88: For patients undergoing carotid artery stenting, decisions regarding choice of cerebral protection (filter, proximal flow reversal) should be considered at the discretion of the operator.

1.1.1.4 New Class IIb Recommendations

- No. 51: For a patient with acute ischaemic stroke undergoing intracranial mechanical thrombectomy with a tandem 50–99% carotid stenosis and a small area of ipsilateral infarction, synchronous carotid stenting may be considered in the presence of poor antegrade internal carotid artery flow or poor collateralisation via the circle of Willis after mechanical thrombectomy.
- No. 57: For patients with carotid near occlusion and distal vessel collapse with recurrent carotid territory symptoms (despite best medical therapy), carotid endarterectomy or carotid artery stenting may be considered only after multidisciplinary team review.
- No. 59: For patients presenting with recent carotid territory symptoms and free floating thrombus who develop recurrent symptoms whilst receiving anticoagulation therapy, surgical or endovascular removal of the thrombus may be considered.
- No. 61: For symptomatic patients with a carotid web [=shelf-like protrusions of intimal fibrous tissue arising at the posterior wall of the carotid bulb/focal intimal variant of fibromuscular dysplasia] in whom no other cause for stroke can be identified after detailed neurovascular work up, carotid endarterectomy or carotid artery stenting may be considered to prevent recurrent stroke.
- No. 90: For patients undergoing transfemoral carotid stenting, at least twelve carotid stent procedures per year (per operator) may be considered an appropriate operator volume threshold to maintain optimal outcomes.
- No. 101: In selected high risk for surgery patients or emergency patients with suspected prosthetic patch infection, insertion of a covered stent may be considered, as part of the three stage EndoVAC technique.

1.1.1.5 Class III: Non-recommendations

- No. 60: For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus, intravenous thrombolysis is *not* recommended.

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- No. 86: For patients undergoing carotid artery stenting, post-dilation is *not* recommended when the residual stenosis is <30%, in order to reduce haemodynamic instability.
- No. 128: For patients presenting with a vertebrobasilar territory transient ischaemic attack or stroke and a 50–99% vertebral artery stenosis, routine stenting is *not* recommended.

1.1.2 European Stroke Organisation Guideline on Endarterectomy and Stenting for Carotid Artery Stenosis [2]

- In patients with ≥60% asymptomatic carotid artery stenosis considered to be at increased risk of stroke on best medical therapy alone, we recommend carotid endarterectomy. Quality of evidence: Moderate; Strength of recommendation: Strong for carotid endarterectomy. (This recommendation is independent of sex and stenosis severity).
- In patients with asymptomatic carotid stenosis in whom revascularisation is considered to be appropriate, we suggest endarterectomy as the current treatment of choice. Quality of evidence: Moderate; Strength of recommendation: Weak for carotid endarterectomy.
- In patients with severe (70–99%) symptomatic carotid artery stenosis, we recommend carotid endarterectomy. Quality of evidence: High; Strength of recommendation: Strong for carotid endarterectomy.
- In patients with moderate (50–69%) symptomatic carotid artery stenosis, we suggest carotid endarterectomy. Quality of evidence: Low; Strength of recommendation: Weak for carotid endarterectomy.
- In patients with symptomatic carotid artery stenosis requiring revascularisation, we recommend endarterectomy as the treatment of choice. Quality of evidence: Moderate; Strength of recommendation: Strong for carotid endarterectomy.
- In patients with symptomatic carotid stenosis <70 years old requiring revascularisation, we suggest that stenting may be considered as an alternative to endarterectomy. Quality of evidence: Low; Strength of recommendation: Weak for carotid stenting.

1.1.3 *Society for Vascular Surgery Clinical Practice Guidelines for Management of Extracranial Cerebrovascular Disease [3]*

- For low surgical risk patients with asymptomatic carotid bifurcation atherosclerosis and stenosis of >70% (documented by validated duplex ultrasound or CTA/angiography), we recommend CEA with best medical therapy instead of maximal medical therapy alone for the long-term prevention of stroke and death. Level of recommendation: grade 1 (strong); quality of evidence: B (moderate).
- We recommend CEA over TF (transfemoral)-carotid artery stenting (CAS) in low- and standard-risk patients with >50% symptomatic carotid artery stenosis. Level of recommendation: grade 1 (strong); quality of evidence: A (high).
- In patients with recent stable stroke (modified Rankin scale score 0–2), we recommend carotid revascularization for symptomatic patients with >50% stenosis to be performed as soon as the patient is neurologically stable after 48 h but definitely before 14 days after the onset of symptoms. Level of recommendation: grade 1 (strong); quality of evidence: B (moderate).
- In patients undergoing revascularization within the first 14 days after the onset of symptoms, we recommend CEA rather than carotid stenting. Level of recommendation: grade 1 (strong); quality of evidence: B (moderate).
- We recommend against revascularization, regardless of the extent of stenosis for patients who experienced a disabling stroke, have a modified Rankin scale score of ≥3, whose area of infarction is >30% of the ipsilateral middle cerebral artery territory, or who have altered consciousness to minimize the risk of postoperative parenchymal hemorrhage. These patients can be reevaluated for revascularization later if their neurologic recovery is satisfactory. Level of recommendation: grade 1 (strong); quality of evidence: C (low).
- We recommend against routine screening for clinically asymptomatic carotid artery stenosis in individuals without cerebrovascular symptoms or significant risk factors for carotid artery disease. Level of recommendation: grade 1 (strong); quality of evidence: B (moderate).
- In selected asymptomatic patients who are at an increased risk of carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis, especially if patients are willing to consider carotid intervention if significant stenosis is discovered. Level of recommendation: grade 2 (weak); quality of evidence: B (moderate).
- In asymptomatic patients who are undergoing screening for carotid artery stenosis, we recommend duplex ultrasound performed in an accredited vascular laboratory as the imaging modality of choice instead of CTA, MRA, or other imaging modalities. Level of recommendation: grade 1 (strong); quality of evidence: B (moderate).
- For patients with symptomatic carotid stenosis of 50% to 99%, who require both CEA and CABG, we suggest CEA before, or concomitant with, CABG to potentially reduce the risk of stroke and stroke/death. The sequencing of the interven-

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tion depends on the clinical presentation and institutional experience. Level of recommendation: grade 2 (weak); quality of evidence: C (low).
- In patients with severe (70%–99%) bilateral asymptomatic carotid stenosis or severe asymptomatic stenosis and contralateral occlusion, we suggest CEA before, or concomitant with, CABG. Level of recommendation: grade 2 (weak); quality of evidence: C (low).
- In patients requiring carotid intervention, staged or synchronous with coronary intervention, we suggest that the decision between CEA and CAS be determined by the timing of procedure, the need for anticoagulation or antiplatelet therapy, patient anatomy, and patient characteristics. Level of recommendation: grade 2 (weak); quality of evidence: B (moderate).

1.2 Results

1.2.1 Randomised Trials

1.2.1.1 Carotid Endarterectomy or Stenting or Best Medical Treatment

SPACE-2 is the first randomised controlled trial to present data directly comparing CEA plus BMT, CAS plus BMT, and BMT alone as treatment modalities for asymptomatic carotid stenosis [4]. 513 patients across SPACE-2, SPACE-2a, and SPACE-2b were recruited and surveyed between July 9, 2009, and Dec 12, 2019, of whom 203 (40%) were allocated to CEA plus BMT, 197 (38%) to CAS plus BMT, and 113 (22%) to BMT alone. Median follow-up was 59·9 months. A risk reduction with adequate BMT, known from registry data, was also shown in SPACE-2. Superiority of CEA plus BMT or CAS plus BMT over BMT alone could not be shown in the 5-year follow-up period, although CEA showed a stable postprocedural period. Because of the small sample size, results should be interpreted with caution.

1.2.1.2 CEA and CAS in Asymptomatic Carotid Stenosis

The ACST-2 Trial [5] is a randomised multicentre trial in which a total of 3625 patients with asymptomatic carotid stenosis were assigned to either CEA (n = 1814) or CAS (n = 1811), with good medical treatment and a median follow-up of 5 years. Overall, 1% of patients developed a disabling stroke periprocedurally (15 in CAS and 18 in CEA) and 2% developed a non-disabling stroke (48 in CAS and 29 in CEA). In each group, the rate of fatal or disabling non-procedural stroke Kaplan-Meier estimated was 2.5% at 5 years, and 5.3% versus 4.5% for CAS vs CEA for stroke of any type. The conclusion was that severe complications are similarly rare with competent CAS and CEA and that the long-term outcomes of both carotid procedures are comparable in terms of fatal or disabling stroke.

1.2.1.3 Long-Term Outcome Following CEA and CAS in Symptomatic Patients

For a comparison of long-term outcome after CEA and CAS in patients with symptomatic carotid stenosis, Brott et al. [6] pooled data from 4 randomised trials (EVA-3S, SPACE, ICSS and CREST). 4754 patients were followed up for a maximum of 12.4 years. The median length of follow-up for each trial ranged from 2.0 to 6.9 years. Pooled analysis showed that long-term outcomes after CAS and CEA were remarkably similar, with an annual rate of ipsilateral stroke per person-year of 0.60% for CEA and 0.64% for CAS. Consequently, patients who experienced no adverse events in the periprocedural period received qualitatively similar care with CAS and CEA. Nonetheless, the peri- and post- procedural risks combined favoured CEA, with treatment differences at 1, 3, 5, 7 and 9 years all ranging between 2.8% (95% CI: 1.1% to 4.4%) and 4.1% (95% CI: 2.0 to 6.3%). The authors concluded that although long-term outcome (periprocedural and postprocedural risks combined) continued to favour CEA, the similarity in post-procedural outcomes suggests that improvements in the periprocedural safety of CAS may provide similar outcomes of both procedures in the future.

1.2.2 Meta-Analyses Open Procedure and CAS

1.2.2.1 Cochrane Reviews: CEA and CAS in Symptomatic and Asymptomatic Carotid Stenosis

A Cochrane Review [7], based on pooled data from three randomised trials with 6092 patients, came to the following conclusions regarding the balance of benefit vs. risk of CEA versus best possible drug treatment in patients with recent TIA or non-disabling stroke:

- Surgery increased the 5-year risk of any stroke or surgical death in participants with stenosis <30% (risk ratio 1.25; 1746 participants, high-quality evidence).
- Surgery reduced the 5-year risk of any stroke or operative death in participants with stenosis 30% to 49% (risk ratio 0.97; 1429 participants, high-quality evidence).
- Surgical intervention was of benefit in participants with stenosis 50% to 69% (risk ratio 0.77; 1549 participants, moderate-quality evidence).
- Surgical intervention was of high benefit in participants with 70% to 99% stenosis without near-occlusion (risk ratio 0.53; 1095 participants, moderate-quality evidence).
- Surgery reduced the 5-year risk of any stroke or operative death in participants with a near-occlusion (risk ratio 0.95; 271 participants, moderate-quality evidence).

A second Cochrane Review [8] looked at the comparison of CAS and CEA in asymptomatic and symptomatic patients with carotid stenosis based on 22 trials (9753 participants). This analysis also included studies comparing CAS with medical therapy alone. According to the results, stenting is associated with a higher risk of periprocedural stroke or death than CEA in patients with symptomatic carotid stenosis. The additional risk is mainly due to an increase in minor non-disabling strokes in patients older than 70 years. Beyond the periprocedural period, CAS is as effective as CEA in preventing recurrent stroke. The combination (safety of the procedure and long-term effectiveness) still favours endarterectomy. In patients with asymptomatic carotid stenosis, there may be a small increase in risk of periprocedural stroke or death with stenting compared with endarterectomy. However, the confidence intervals of treatment effects are wide and additional data from randomised trials are needed in patients with asymptomatic stenosis.

1.2.2.2 Redo Stenting or CEA for In-Stent Stenosis After CAS

Guo et al. [9], in a meta-analysis based on 11 studies with 1057 patients undergoing revascularisation for in-stent stenosis, found redo stenting (rCAS) in 894 cases and CEA in 163 patients. Overall, there were no significant differences between the two approaches in terms of short- and mid-term stroke rates, death and other perioperative complications. However, in most patients, rCAS is preferred to CEA as the less invasive procedure for in-stent stenosis, depending on the experience of the local team.

1.2.2.3 Tandem Carotid Artery Lesions

Tandem lesions, defined as stenoses in the common carotid artery (CCA) or innominate artery combined with stenoses in the ipsilateral internal carotid artery (ICA) or carotid bifurcation, can be treated with a hybrid approach (CEA of the internal carotid artery/bifurcation and balloon angioplasty/stenting of the proximal lesion via the same cervical incision). Qi et al. [10] performed a meta-analysis based on 15 studies and 275 patients. They reported a technical success rate of 99.8% and pooled perioperative complications rates of death 1.5%, stroke 2.6%, stroke/death 3.3% and myocardial infarction 3.2%. Overall primary patency rates were 99.2% and 88.2% at 1 and 2 years, respectively. Reintervention rates accounted for 6.6% and pooled overall survival rates were 89.9%, 83.7% and 75.9% at 1, 3 and 5 years, respectively. Operations in which CEA was performed first had a significantly greater risk of perioperative stroke compared with those in which proximal intervention had been performed first (5.7% vs. 0.0%; $p = 0.01$). The authors considered the hybrid approach a reasonable option for tandem lesions, with a high technical success rate. Stenting should be performed before CEA and dual antiplatelet therapy should be given perioperatively.

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1.2.2.4 CEA or CAS for Contralateral Carotid Occlusion

Contralateral carotid occlusion is considered a risk factor in CEA. The extent to which CAS is equivalent to CEA in this situation was investigated by Sun et al. [11] in a meta-analysis (6 retrospective studies/6953 patients). There were no significant differences with regard to perioperative stroke, but CEA was associated with a reduced risk of death compared with CAS (odds ratio: 0.45; 95% CI: 0.29–0.70; $P < 0.001$). There was no difference between CEA and CAS in the risk of perioperative myocardial infarction and major adverse cardiovascular events. The reduced risk of death was mainly found in the subgroups patients <70 years, proportion of men ≥70%, proportion of coronary disease <40%, proportion of hypertension ≥80%, proportion of diabetes mellitus ≥30% and proportion of smokers ≥40%. The authors considered these factors to be indicative of severe atherosclerosis, with possible plaque formation, and subsequently plaque detachment in CAS.

1.2.2.5 Synchronous CEA and Coronary Artery Bypass Graft vs. Staged CAS

In a meta-analysis, Giannopoulos et al. [12] compared synchronous CEA and coronary artery bypass graft (CABG) vs. staged CAS and CABG for patients with concomitant coronary artery disease (CAD) and carotid artery stenosis in terms of perioperative (30-day) outcomes. They found 5 studies with 16,712 patients. Coronary bypasses were performed synchronously with CEA (same operating room, same day) or after CAS, either during the same hospital stay or up to 2 months after. There were no significant differences in perioperative stroke, TIA and myocardial infarction between the two groups, but patients with simultaneous CEA and CABG had a significantly higher risk for perioperative mortality (4% vs. 2%). The extent to which the different results were due to patient selection could not be clarified given the retrospective nature of the study, so that ultimately the question of whether a staged approach with preference for CAS has advantages must remain open without further studies.

1.2.2.6 Carotid Interventions Following Thrombolysis

Thrombolytic therapy (TT) is recommended in patients with a suspected acute ischaemic stroke. Approximately 10% to 20% of patients thrombolysed for acute stroke have an underlying 50% to 90% stenosis of the ipsilateral internal carotid artery and thus may become candidates for CEA or CAS. Kakkos et al. [13] evaluated the safety of CAS and CEA after TT. The question is when the procedure is most appropriate, given the increased risk of bleeding. In a meta-analysis of 25 studies (n = 147,810 patients), 2076 patients underwent CEA and 481 CAS following TT. Patients with CEA after thrombolysis had a significantly higher risk of intracerebral haematomas and local haematomas compared to patients with CEA without

prior thrombolysis. The periprocedural risk was also significantly higher for CAS. In the meta-regression analysis, the risk of perioperative death/stroke was 13% if CEA was performed 3 days after thrombolysis and 10.6% when performed after 4 days and up to 6% after 6 to 7 days. The message was that it may be safer to defer CEA for 67 days after TT.

1.2.2.7 Near Infrared Spectroscopy in Carotid Endarterectomy

Near infrared spectroscopy (NIRS) is a cost-effective method to continuously measure cerebral oxygenation non-invasively. NIRS quantifies the level of oxygenated haemoglobin based on its absorption of light in the infrared spectrum. In a systematic review (67 articles), Khan et al. [14] explored the extent to which NIRS is able to detect intraoperative ischaemic events. They concluded that NIRS has low sensitivity and high specificity to identify intraoperative ischaemia compared with awake monitoring. The bias risk of the reports was unclear. The NIRS signal dropped consistently after artery clamping in most studies and recovered to baseline values after de-clamping, with larger drops observed for ischaemic events. Without further studies, the authors did not want to make a final assessment of the value of the procedure, partly because studies suggest that the external carotid artery contributes to 15% to about 20% of the signals. They only concluded that cerebral monitoring using near infrared spectroscopy during carotid endarterectomy demonstrates reliable decreases across carotid clamping that may be useful in identifying patients with ischaemic events.

1.2.2.8 CEA Closure Techniques

A network meta-analysis by Lazarides et al. [15] on carotid artery closure techniques following carotid endarterectomy included 23 randomised trials with 4440 patients, representing seven different techniques: primary carotid closure, n = 753; eversion endarterectomy, n = 431; vein patch closure, n = 973; PTFE patch, n = 948; Dacron patch, n = 828; bovine pericardium patch, n = 249; and polyurethane patch, n = 258). Network meta-analysis showed a reduced combined stroke/death rate at 30 days for eversion endarterectomy compared with all other methods of arterial closure, except for PTFE and bovine pericardium. In addition, eversion endarterectomy was associated with the lowest restenosis rate compared with all other methods. Eversion endarterectomy was significantly superior to Dacron patches with regard of late restenosis. Rare catastrophic complications of vein patch blow out or synthetic patch infection were reported in 0.2% of the total (n = 9/4400), so no comparisons could be made. Eversion endarterectomy and patching with bovine pericardium or PTFE thus appear to be the best procedures for carotid closure.

1.2.2.9 Cost-Effectiveness of CEA and Stenting

Sridharan et al. [16] compared the cost-effectiveness of CEA with that of transfemoral carotid artery stenting (TFCAS) and transcarotid arterial revascularisation (TCAR) for carotid stenosis from a cost-utility standpoint in the United States healthcare system. Data from CREST (Carotid Revascularisation Endarterectomy vs. Stenting Trial), the Vascular Quality Initiative Surveillance Project, and local cost data were included in the analysis. A Markov state-transition model was developed to estimate lifetime costs in $US and effectiveness in QUALYs (quality-adjusted life years) for both asymptomatic and symptomatic patients. In the base-case scenario, the cost per QUALY gained was $160,642 for TCAR compared with CEA. TFCAS was less effective than the other strategies and more expensive, largely due to a greater periprocedural stroke risk. If the risk of stroke with TCAR was <0.9% (base-case risk, 1.4%), TCAR was economically favorable compared with CEA at its current procedural cost. In a probabilistic sensitivity analysis, varying all parameters simultaneously over distributions, CEA was favored in 80% of model iterations at $100,000/QALY, with TCAR favored in 19%. In conclusion, at current cost and outcomes, TCAR does not meet a traditional cost-effectiveness threshold to replace CEA as the primary treatment modality for carotid stenosis. TFCAS is the least cost-effective strategy for carotid revascularisation.

1.2.3 Registry Data

1.2.3.1 Prognosis for Asymptomatic Patients Without Surgical Intervention

Chang et al. [17] reported on a retrospective cohort study of 3737 adults with severe (70–99%) asymptomatic carotid stenosis diagnosed between 2008 and 2012. Patients had no previous ipsilateral neurological event or carotid intervention in the last 6 months. Follow-up extended to 2019. The mean annual stroke rate in this population was 0.9%; Kaplan-Meier estimated ipsilateral stroke rate at 5 years was 4.7% (95% CI 3.9%–5.7%). The non-adjusted all-cause mortality was 51.4%, with a mean annual mortality rate of 13.6%. The authors concluded that the number of patients at high risk of stroke in asymptomatic carotid stenosis is likely to be much smaller than current standards suggest.

1.2.3.2 CAS and CEA vs. Medical Therapy

Keyhani et al. [18] conducted a retrospective cohort study based on data from 219,979 Veterans >65 years who received carotid imaging for asymptomatic carotid stenosis in 2005–2009 and were enrolled in the US Veterans Health Administration database. They constructed two comparable groups of patients who either received

medical treatment (n = 2509) or were stented (CAS n = 551) and followed them for 5 years. The observed rate of stroke/death (perioperative complications) at 30 days was 2.2% in the CAS arm. The 5-year risk of fatal and non-fatal stroke was similar for both groups (CAS 6.9%, medical therapy 7.1%). The message was that no differences in the treatment of asymptomatic carotid stenosis were found between medical therapy and CAS in this study of older men.

The same group also used the US Veterans Health Administration database to investigate whether early CEA is superior to initial medical therapy in patients with asymptomatic carotid stenosis [19]. 2712 patients (98.8% men, mean age 73.6 years) received CEA, and 2509 patients (98.8% men, mean age 73.6 years) received initial medical therapy within 1 year after the index carotid imaging. The observed rate of stroke/death (perioperative complications) within 30 days in the CEA cohort was 2.5%. The 5-year risk of fatal and non-fatal stroke was lower in patients randomised to CEA (5.6%) compared to patients randomised to initial medical treatment (7.8%). When the risk of non-stroke-related mortality was included in the analysis, there were no significant differences in mortality risk between the two cohorts. In this study, the absolute reduction in the risk of fatal and non-fatal stroke associated with early CEA was less than half that reported in studies initiated 20 years ago. The data from this study suggest that, given the existing baseline perioperative risk for CEA, initial medical treatment may be an equally acceptable treatment strategy for asymptomatic carotid stenosis.

1.2.3.3 CEA and CAS Results

Krawisz et al. [20] found 4624 (7.9%) patients with contralateral carotid occlusion among 58,423 patients who underwent carotid revascularisation. Of those, 68.9% (n = 3185) underwent CAS and 31.1% (1439) underwent CEA. Unadjusted composite outcome rates (in-hospital death/stroke/myocardial infarction) were lower after CAS than after CEA (2.1% vs. 3.6%). Following adjustment, contralateral carotid occlusion was associated with a 71% increase in the odds of an adverse outcome after CEA compared with no increase after CAS. This means that only with CEA, but not with CAS, contralateral carotid occlusion increased the risk of intervention.

Perioperative outcome and readmission rates in a total of 378,354 CEA and 57,273 CAS patients were determined over a 6-year period (2010 to 2015) by Cole et al. [21] using the USA Nationwide Readmissions Database. CEA volume decreased by an average of 2669 procedures per year ($p = 0.001$) with stable CAS volume. After matching (CEA n = 24,411/CAS n = 24,403), CEA patients had a higher rate of periprocedural stroke than CAS patients, driven by a higher risk of stroke in symptomatic patients (8.1% vs. 5.6%; $p < 0.001$), but a lower rate of overall inpatient mortality (0.8% vs. 1.4%; $p < 0.001$) (Table 1.1). CEA patients were less likely to be readmitted within 30 days (7.2% vs. 8.0%; $p = 0.018$). The same was true for the readmission rate after 90 days (12.3% vs. 14.1%; $p < 0.001$). Mean hospital costs were lower for CEA at $14,433 vs $19,172 with CAS ($p < 0.001$). The

Table 1.1 Perioperative outcome and readmission rates in CEA and CAS patients. Data from the Nationwide Readmissions Database. Propensity score matched comparison (according to Cole et al. [21])

Parameter	CAS (n = 24,403)	CEA (n = 24,411)	P
Periprocedural			
– Stroke	454 (1.9%)	635 (2.6%)	< 0.001
– Myocardial infarction	324 (1.3%)	374 (1.5%)	0.062
– Peripheral vascular complication	114 (0.5%)	18 (0.07%)	< 0.001
– Respiratory complication	1013 (4.2%)	1187 (4.9%)	< 0.001
– Haematoma or bleeding	1014 (4.2%)	1553 (6.4%)	< 0.001
On discharge			
– Death	342 (1.4%)	192 (0.8%)	< 0.001
– Costs (USD)	19,172	14,433	< 0.001
– Re-admission after 30 days	1946 (8.0%)	1763 (7.2%)	0.002
– Re-admission after 90 days	3439 (14.1%)	3009 (12.3%)	<0.001

authors emphasised that since the CREST trial was published, which showed nearly twice the risk of stroke in CAS patients compared with CEA patients, the results of CAS have improved significantly. Nevertheless, CEA was associated with lower procedure cost and readmission rate.

Hammar et al. [22] identified 7653 patients (mean age 72 ± 8 years, 67% men) who underwent primary CEA or CAS for symptomatic carotid stenosis in the Swedish Swedvasc registry from 2008 to 2017. Peri-operative stroke or death occurred in 275 patients (64 deaths, 211 strokes), corresponding to 3.6% of the cohort. The mean follow-up time was reported as 4.21 ± 2.55 years. In this cohort, the incidence rate of any stroke was 1.9% per year after the perioperative period. 1485 (19.6%) patients died during the follow up period, corresponding to a mortality rate of 4.6%/year. Patients treated with CAS had an increased risk of ipsilateral ischaemic stroke compared with those operated by CEA (adjusted HR 3.20, 95% CI 2.03–5.03). Patients older than 80 years had an increased risk of ipsilateral ischaemic stroke compared with patients aged 65–79 years (HR 1.94, 95% CI 1.43–2.65). Stroke of any type was observed in 7.7% of patients. The authors concluded that low incidence of late ipsilateral ischaemic stroke is obtainable after CEA for symptomatic carotid stenosis. Only age above 80 years and CAS compared with CEA were associated with increased risk of ipsilateral ischaemic stroke.

1.2.4 Transcervical Carotid Artery Revascularization (TCAR)

1.2.4.1 Meta-Analyses of Outcome After TCAR

A systematic review and meta-analysis of prospective and retrospective studies reporting the outcomes of patients who had undergone transcervical carotid artery revascularization (TCAR) for carotid artery was performed by Sagris et al. [23]

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Table 1.2 Outcome after Transcervical Carotid Artery Revascularization (TCAR) (according to Sagris et al. [23]). Meta-analysis based on 45 studies with 14,588 patients

Parameter	Studies included (n)	Events/patients total, n (%)
30-day mortality	44	75/14,427 (0.5)
30-day stroke (total)	41	179/13,744 (1.3)
– Symptomatic patients only	10	61/3830 (1.6)
30-day TIA (total)	30	97/12,667 (0.8)
– Symptomatic patients only	5	15/1953 (0.8)
30-day myocardial infarction (total)	34	65/14,173 (0.6)
– Symptomatic patients only	9	10/3674 (0.3)
Technical success	30	1195/1223 (99.0)
Access site complications	30	288/9305 (2.0)
Cranial nerve injury	21	33/8994 (0.36)
Haemodynamic instability	6	1306/5183 (21.0)
Bleeding	20	278/8726 (2.0)

based on 45 studies with 14,588 patients, published by May 2020 (Table 1.2). The technical success rate was 99%. Cranial nerve injuries were very rare (33 in 8994 patients), bleeding complications were reported at 2%. The overall periprocedural all-cause mortality and stroke rate was 0.5% and 1.3%, respectively, and the TIA rate was 0.8%. In-stent restenosis was observed in 4 of 260 patients (1.5%; 7 studies), and early (30-day) reocclusion or acute thrombosis of the target lesion occurred in 12 of 1243 patients (~1%; 11 studies). The results provided significant evidence that TCAR is a very promising and safe carotid revascularization approach with favorable technical success rates associated with low periprocedural stroke and CN injury rates. However, the data did not allow a direct comparison with CAS and CEA; these were predominantly single-arm studies.

Another meta-analysis [24] included 18 studies, published up to September 2020, with 4852 patients. The authors reported a pooled 30-day mortality rate of 0.7%, a 30-day stroke rate of 1.4% and a stroke/TIA rate of 2%. The pooled technical success rate was 97.6%. Cranial nerve injuries (10 studies) were observed in 1.2% and the early myocardial infarction rate was 0.4%. The rate of haematoma/bleeding was 3.4% (one third of these cases required drainage or intervention). Within a follow-up of 3–40 months, the restenosis rate was 4% (9 studies) and the stroke/death rate was 4.5% (5 studies). The authors reported a higher risk of early stroke/TIA for symptomatic patients than for asymptomatic patients (2.5% vs. 1.2%).

Both meta-analyses describe TCAR as a promising procedure with low rates of early death, stroke and other complications. Long-term results remain to be seen.

1.2.4.2 TCAR-Study Results

Columbo et al. [25] tested the hypothesis that TCAR may be particularly valuable in patients with challenging anatomy, such as a high carotid artery bifurcation or a carotid lesion close to the skull base, that would make traditional carotid endarterectomy (CEA) technically difficult. For these patients, TCAR provides a therapeutic alternative that may be associated with a lower risk profile than CEA. Patients captured by the Vascular Quality Initiative (VQI) database who underwent TCAR or CEA from January 2015 were analyzed. 7664 patients (8.9%) underwent TCAR and 78,363 patients (91.1%) underwent CEA. The use of TCAR out of the total carotid revascularization procedures increased from 90 of 12,276 procedures (0.7%) in 2015 to 2718 of 15,956 procedures (17.0%) in 2019, a 24-fold increase over 5 years. Overall, the crude rate of MACE (Major Adverse Cardiovascular Events = composite stroke, myocardial infarction, death) was similar for TCAR (2.3%) and CEA (2.4%). However, over time, the rate of MACE decreased for CEA (from 2.5% to 1.9%); this was also the case with TCAR, but not significantly (from 3.1% to 2.2%). Centres that included TCAR in their treatment spectrum showed a 10% decrease in the likelihood of MACE at 12 months after TCAR adoption compared to centres that continued to perform CEA only. The study demonstrated that availability of TCAR at a hospital was associated with a decrease in the likelihood of perioperative MACE after carotid revascularization.

In a retrospective analysis of VQI data, Mehta et al. [26] investigated whether 80-year-old patients would benefit from TCAR. Among 33,115 patients who underwent either CEA, TFCAS or TCAR for carotid artery stenosis, 21% were at least 80 years old. Across all, 80-year-old patients had higher death/stroke rates compared to younger patients. Among octogenarians, the adjusted hazards of TCARs relative to CEAs was similar for both 30-day stroke/death (hazard ratio [HR], 1.12; 95% confidence interval [CI], 0.59–2.13) and 1-year stroke/death (HR, 1.28; 95% CI, 0.85–1.94), whereas transfemoral carotid artery stenting had higher hazards of both 30-day stroke/death (HR, 1.78; 95% CI, 1.10–2.89) and 1-year stroke/death (HR, 1.85; 95% CI, 1.35–2.54). The authors concluded that TCARs may serve as a promising less invasive treatment for carotid disease in older patients who are deemed high anatomic, surgical, or clinical risk for CEAs.

1.3 Conclusions for Clinical Practice

1. CEA is the method of choice for the treatment of asymptomatic and symptomatic carotid stenosis. Nevertheless, the postprocedural outcomes after CEA and CAS suggest that improvements in the periprocedural safety of CAS may provide similar outcomes of both procedures in the future.

2. All patients should take acetylsalicylic acid (ASA, 100 mg) before and after CEA, continuous treatment with ASA should not be interrupted. All patients should take a statin before and after CEA, continuous therapy with statins should not be interrupted. Dual antiplatelet therapy with ASA (100 mg) and clopidogrel (75 mg) should precede CAS. Dual antiplatelet therapy should be maintained for at least 1 month.
3. CEA should be performed as early as possible (within 3–14 days) after the index event.
4. The choice of surgical procedure (eversion CEA, conventional CEA with patchplasty) should be made depending on the personal experience of the operating surgeon and the lesion's anatomy.
5. Patchplasty should always be used for conventional CEA. There is insufficient evidence for the routine (obligatory) insertion of a shunt during surgical carotid reconstruction. Intraoperative neuromonitoring should be considered for CEA under general anaesthesia.
6. Transcarotid arterial revascularisation (TCAR) is a promising procedure with low rates of early death, stroke and other complications. Long-term results remain to be seen. However, the data do not yet allow a direct comparison with CAS and CEA; the reports are predominantly single-arm studies.

1.4 Perioperative Management

1.4.1 Imaging Strategies in Carotid Artery Disease

1.4.1.1 European Society for Vascular Surgery (ESVS) [1]

Recommendation 1: For patients undergoing evaluation of the extent and severity of extracranial carotid stenoses, duplex ultrasound, computed tomographic angiography and/or magnetic resonance angiography are recommended. (Class I; Level B).

Recommendation 2: For patients where carotid endarterectomy is being considered, it is recommended that duplex ultrasound stenosis estimation be corroborated by computed tomographic angiography or magnetic resonance angiography, or by a repeat duplex ultrasound performed by a second operator. (Class I; Level B).

Recommendation 3: For a patient where carotid artery stenting is being considered, it is recommended that any duplex ultrasound study be followed by computed tomographic angiography or magnetic resonance angiography, which will provide additional information on the aortic arch, as well as the extra- and intracranial circulation. (Class I; Level B).

1.4.2 Anaesthesia

1.4.2.1 European Society for Vascular Surgery (ESVS) [1]

Recommendation 65: In patients undergoing carotid endarterectomy, decisions regarding choice of anaesthesia (locoregional, general) should be considered at the discretion of the surgeon/anaesthetist performing the procedure, taking account of local experience, patient preference, and preferred antiplatelet strategy. (Class IIA/ Level B).

1.4.2.2 Studies

Harky et al. [27] published a meta-analysis comparing general (GA) and local anaesthesia (LA) for CEA. 31 studies (including 6 randomised controlled trials (RCT)) with a total of 152,376 patients were analysed. LA was associated with shorter operative time (mean difference − 9.15 min; p = 0.005), less strokes (OR = 0.76; 95% CI = 0.59–0.92; p = 0.006), cardiac complications (OR = 0.59; 95% CI = 0.47–0.73; p < 0.00001) and lower in-hospital mortality (OR = 0.72; 95% CI = 0.59–0.9; p = 0.003). Transient neurological deficits occurred with similar frequency in both groups. In a subgroup analysis, only the randomised controlled trials were assessed. The number of patients included there was relatively small (total n = 3956). There was no significant difference between LA and general anaesthesia for CEA. In summary, this meta-analysis showed a slight superiority of LA over general anaesthesia when evaluating the non-randomised (larger) data set, while the randomised trials did not show any differences. Anaesthetic choice in CEA therefore depends on the experience of the anaesthetist and surgeon and on the patient's preferences.

1.4.3 Perioperative Antibiotic Prophylaxis

1.4.3.1 Guidelines American Society of Health-System Pharmacists (ASHP) [28]

- Patients undergoing brachiocephalic procedures (e.g., CEA, brachial artery repair) without implantation of prosthetic graft material do not appear to benefit from routine antimicrobial prophylaxis.

1.4.3.2 The Steering Committee of the French Society of Anaesthesia and Resuscitation [29]

- Arterial endoprosthesis, Carotid surgery with patch: perioperative antibiotic prophylaxis with 2 g cefazolin or cefamandole or cefuroxime 1.5 g slow i.v.; Single dose (if duration >2 h, reinject 0.75 g).
- Carotid procedures without patch: No antibiotic prophylaxis.
- Angiography, Angioplasty: No antibiotic prophylaxis.
- Stent (excluding intra-coronary): Cefazolin 2 g i.v. slow; Single dose (if duration >4 h, reinject 1 g).

1.4.4 Beta-Blocker Perioperative

1.4.4.1 European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA)- Guideline [30]

In this guideline, CEA and CAS are designated as low perioperative risk procedures in patients with asymptomatic carotid stenosis; in patients with symptomatic carotid stenosis, CEA and CAS are assigned to the moderate perioperative risk category. For these categories, the following recommendations apply with regard to the management of perioperative medication with beta-blockers:

- Perioperative continuation of beta-blockers is recommended in patients currently receiving this medication.
- Preoperative initiation of beta-blockers may be considered in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status ≥3 [this does not include CAS and CEA].
- Preoperative initiation of beta-blockers may be considered in patients who have known ischaemic heart disease or myocardial ischaemia.
- Preoperative initiation of treatment with beta-blockers is *not* recommended in patients scheduled for low-risk surgery [this would generally be CEA and CAS in asymptomatic carotid stenosis].

1.4.5 Blood Pressure Management After Carotid Intervention

1.4.5.1 ESVS-Guideline [1]

- Recommendation 38: For patients presenting with a transient ischaemic attack or minor ischaemic stroke with hypertension, antihypertensive treatment is recommended. (Recommendation class I, evidence level A).
- Recommendation 39: For symptomatic carotid stenosis patients awaiting endarterectomy or stenting, caution should be considered when rapidly lowering blood

pressure in the early time period after onset of symptoms, but uncontrolled hypertension (>180/90 mmHg) should be treated. (Recommendation class IIa, evidence level C).

- Recommendation 94: For patients with post-carotid hypotension, administration of intravenous crystalloids and volume expanders should be considered as first line treatment. If this fails to improve blood pressure, titrated intravenous vasopressors should be considered to maintain systolic blood pressure > 90 mmHg. (Recommendation class IIa, evidence level C).
- Recommendation 95: For patients undergoing carotid interventions, regular blood pressure monitoring is recommended for the first 3–6 h after carotid endarterectomy, as well as in carotid stent patients who develop haemodynamic instability during the procedure. (Recommendation class I, evidence level C).
- Recommendation 96: For carotid stenting patients who develop haemodynamic instability during the procedure, regular blood pressure monitoring is recommended for the first 24 h after carotid revascularisation. (Recommendation class I, evidence level C).
- Recommendation 97: In centres performing carotid interventions, it is recommended that they have written criteria for treating post-procedural hypertension. (Recommendation class I, evidence level C).

1.4.5.2 Studies

A review by Vanpeteghem et al. [31] is available on perioperative haemodynamic management in carotid surgery. According to this, severe postoperative hypertension is defined by a systolic blood pressure of at least 180 mmHg. In these cases, invasive blood pressure monitoring is recommended with the aim of keeping the systolic blood pressure below 160 mmHg. The antihypertensive agents commonly used in carotid surgery are listed in Table 1.3.

Table 1.3 Commonly used antihypertensives agents in carotid artery surgery (according to Vanpeteghem et al. [31])

Drug	Mechanism of action	Recommended intravenous dose
Esmolol	Selective β_1-antagonist	– Loading dose 0.5–1 mg/kg – Continuous infusion: 25–300 µg/kg/min
Labetolol	Selective α_1–antagonist, non-selective β-antagonist	– Loading dose 20 mg – Continuous infusion: 0.5–2 mg/min
Nicardipine	Calcium channel blocker	– 2–4 mg/min until desired effect – Maintenance 3–30 mg/h
Clonidine	α_2-agonist	– Loading dose 2–4 µg/kg – Continuous. Infusion: 1–4 µg/kg/h
Sodium-nitroprusside	NO-release	– Continuous infusion: 0.25–2 µg/kg/min
Nitroglycerine	NO-release	– Continuous infusion: 0.25–2 µg/kg/min

The extent to which low-dose dexmedetomidine can contribute to hemodynamic stability during the emergence and the recovery phases of general anesthesia in patients undergoing carotid endarterectomy was evaluated by Tsujikawa and Ikeshita [32] in a double-blind randomised placebo-controlled trial. Dexmedetomidine is a highly selective α2-adrenoceptor agonist that is significantly more specific than clonidine. Dexmedetomidine decreases the release of noradrenaline. In this study, patients in the therapy group received dexmedetomidine intraoperatively and in the first 3 h after surgery, which resulted in significantly less use of nicardipine for blood pressure regulation compared to the control group. The use of dexmedetomidine facilitates blood pressure management in the immediate postoperative period after CEA under general anaesthesia.

1.4.5.3 Hyperperfusion Syndrome

Cerebral hyperperfusion syndrome (CHS) is a preventable cause of perioperative stroke after CEA [33]. It typically develops in the first postoperative week, with a peak on day 6 after CEA and after 12 h in CAS. Cerebral hyperperfusion is defined as an increase in blood flow velocity in the middle cerebral artery >100% compared to the preoperative baseline [31]. Bouri et al. [33] proposed the following definition for CHS:

1. Occurrence within 30 days after CEA.
2. Evidence of hyperperfusion (on transcranial Doppler [TCD], single photon emission computed tomography [SPECT] or CT/MR perfusion imaging), or systolic blood pressure > 180 mmHg.
3. Clinical features such as new headache, seizure, hemiparesis, Glasgow Coma Scale (GCS) < 15 or radiological features such as cerebral oedema or intracerebral haemorrhage: and
4. No evidence of new cerebral ischaemia, postoperative carotid occlusion and metabolic or pharmacologic cause.

Therapy consists of lowering the blood pressure to systolic <140 mmHg or higher when symptoms disappear. Patients should be admitted to a monitoring unit. Another consequence is that patients be not discharged with severe hypertension or a systolic blood pressure that is rising.

1.4.6 Perioperative Management of Patients with Anticoagulants

1.4.6.1 European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA)- Guideline [30]

Patients treated with oral anticoagulant therapy using vitamin K antagonists (VKAs) are subject to an increased risk of peri-and post-procedural bleeding. If the international normalized ratio (INR) is ≤1.5, surgery can be performed safely; however, in

anticoagulated patients with a high risk of thrombo-embolism—for example, patients with:

- Atrial fibrillation with a CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age ≥ 75 (Doubled), Diabetes, Stroke (Doubled)—Vascular disease, Age 65–74 and Sex category (Female) score of ≥4] or
- mechanical prosthetic heart valves, newly inserted biological prosthetic heart valves, or
- mitral valvular repair (within the past 3 months) or
- recent venous thrombo-embolism (within 3 months) or
- thrombophilia,

  discontinuation of VKAs is hazardous and these patients will need bridging therapy with unfractionated heparin (UFH) or therapeutic-dose LMWH. In general, there is better evidence for the efficacy and safety of LMWH compared to UFH. LMWH is usually administered subcutaneously and weight-adjusted, once or twice daily, without laboratory monitoring. Therapeutic doses (LMWH twice daily) are recommended for patients at high risk of thromboembolism (TE), and prophylactic once-daily doses in low-risk patients. The last dose of LMWH should be administered no later than 12 h before the procedure. Further dose adjustment is necessary in patients with moderate- to-high kidney function impairment. It is recommended that VKA treatment be stopped 3–5 days before surgery (depending on the type of VKA), with daily INR measurements, until <1.5 is reached, and that LMWH or UFH be started 1 day after discontinuation of VKA—or later, as soon as the INR is <2.0.

  VKA treatment should be resumed on day 1 or 2 after surgery—depending on adequate haemostasis—with the preoperative maintenance dose plus a boosting dose of 50% for two consecutive days; the maintenance dose should be administrated thereafter. LMWH or UFH should be continued until the INR returns to therapeutic levels.
- In patients treated with the direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban or edoxaban, bridging is unnecessary in most cases due to their short biological half-lives. An exception to this rule is the patient with high thromboembolic risk, whose surgical intervention is delayed for several days. The overall recommendation is to stop DOACs for 2–3 times their respective biological half-lives prior to surgery in surgical interventions with ‘normal’ bleeding risk, and 4–5 times the biological half-lives before surgery in surgical interventions with high bleeding risk.

  Because of the fast ‘on’-effect of DOACs (in comparison with VKAs), resumption of treatment after surgery should be delayed for 1–2 (in some cases 3–5) days, until post-surgical bleeding tendency is diminished.

1.4.7 Intraoperative Heparin and Reversal

Guideline recommendations on intraoperative anticoagulation are lacking, but in the European Carotid Surgery Trial [34], the only surgical technique associated with a significant increase in stroke/death was that in which no intraoperative anticoagulation was given. Consequently, most surgeons routinely give intravenous unfractionated heparin before clamping the artery, but there is no consensus on dosage. Some titrate the dosage based on the activated coagulation time (ACT), others use a standard dose of 3000 to 5000 I.U. Evidence to favour either method is not available [35].

The question is whether heparin should be reversed with protamine at the end of the procedure. The ESVS guidelines [1] recommend:

- Recommendation 69: For patients undergoing carotid endarterectomy, protamine reversal of heparin should be considered. (Recommendation class IIa, evidence level B).

  The reduced risk of bleeding after protamine administration must be considered against a possible increased rate of thrombotic complications. A meta-analysis of 12 observational studies with 10,621 patients is available [36]. According to this analysis, surgeons should consider the use of protamine routinely in CEA to reduce the risk of bleeding. Protamine did not lead to an increased rate of thrombotic complications, including stroke, myocardial infarction or death.

  The results of this meta-analysis were confirmed by a review of a prospective national registry (Society for Vascular Surgery Vascular Quality Initiative) of 72,787 patients undergoing elective asymptomatic CEA by 1879 surgeons from 316 centres in the USA and Canada from 2012 to 2018 [37]. 69% of patients received protamine, while 31% did not, with protamine administration increasing over time, to a final 73% of patients. This study documented the safety and efficacy of using protamine sulphate to reverse intra-operative heparin at the time of carotid endarterectomy (CEA) using a large national analysis. The work demonstrated a 50% reduction in reoperation for bleeding events with no attendant increased risk of stroke, myocardial infarction or death in patients who received protamine. Furthermore, this analysis highlighted the precarious nature of operative re-exploration for bleeding in patients who did not receive protamine with substantially increased rates of thrombotic complications. Based on this analysis, surgeons should strongly consider using protamine at the time of CEA to optimise surgical outcomes. The authors identified heparin reversal with protamine as a quality indicator in CEA.

1.4.8 Prevention of Venous Thromboembolism

There are no clear guideline recommendations on perioperative prevention of venous thromboembolism with CEA, perhaps due to the rarity of the events. In an analysis of the National Surgical Quality Improvement Program (NSQIP) database (45,548 vascular procedures, including 20,785 CEA), the incidence of venous thromboembolism (VTE) after CEA was the lowest of all vascular procedures at 0.2% [38]. The authors explained the low rate of VTE after CEA by the fact that these patients are able to ambulate early after their operation, in contrast to other vascular procedures, highlighting the importance of early ambulation for reduction of VTE risk. Other factors that contribute to the low incidence of VTE after CEA could be the relatively short duration of surgery and the aggressive antiplatelet strategies. Accordingly, the authors did not comment on the need for VTE prophylaxis in CEA and referred to the recommendations of the American College of Chest Physicians on VTE prophylaxis in non-orthopaedic surgical patients [39]. There, the risk of VTE for CEA is also given as only 0.2% and it is stated:

- Among patients with a very low risk of symptomatic VTE (0.5%), there is moderate-quality evidence that the harms of pharmacologic prophylaxis with low-dose unfractionated heparin or low-molecular-weight heparin (LMWH) outweigh the benefits. Compared with no prophylaxis, one can expect zero to three fewer nonfatal VTE events and four to 10 more nonfatal major bleeding complications per 1000 patients treated with unfractionated heparin. Trade-offs are similar for LMWH and no prophylaxis.
- For patients at very low risk for VTE (< 0.5%) we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation.

  Consequently, according to this guideline, prevention of VTE is not necessary in CEA.

1.4.9 Antiplatelet Therapy with CEA/CAS

1.4.9.1 European Society for Vascular Surgery (ESVS) [1]

- Recommendation 9: For patients with >50% asymptomatic carotid stenosis, lower dose aspirin (75–325 mg daily) should be considered, mainly for the prevention of late myocardial infarction and other cardiovascular events. (Class IIA; Level C).
- Recommendation 10: For patients with >50% asymptomatic carotid stenosis who are intolerant or allergic to aspirin, clopidogrel 75 mg daily should be considered. If intolerant or allergic to both aspirin and clopidogrel, dipyridamole monotherapy (200 mg twice daily) should be considered. (Class IIA; Level C).

- Recommendation 11: For patients with asymptomatic carotid stenosis who are undergoing CEA, lower-dose aspirin (75–325 mg daily) rather than higher-dose aspirin (> 325 mg daily) is recommended. (Class I; Level B).
- Recommendation 12: For patients with asymptomatic carotid stenosis undergoing carotid stenting, combination antiplatelet therapy with aspirin (75–325 mg daily) and clopidogrel (75 mg daily) is recommended. Clopidogrel (75 mg daily) should be started at least 3 days before stenting or as a single 300 mg loading dose given in urgent cases. Aspirin and clopidogrel should be continued for at least 4 weeks after stenting and then antiplatelet monotherapy should be continued indefinitely. (Class I; Level B).
- Recommendation 26: For recently symptomatic carotid stenosis patients scheduled to undergo carotid endarterectomy, it is recommended that all be prescribed antiplatelet therapy throughout the peri-operative period and in the long term. (Class I; Level A).
- Recommendation 27: For recently symptomatic patients with a 50–99% carotid stenosis who are to undergo carotid endarterectomy, peri-operative combination antiplatelet therapy should be considered, and should be started after imaging has excluded intracranial haemorrhage. (Class IIA; Level C).
- Recommendation 28: In recently symptomatic patients with a 50–99% carotid stenosis who are to undergo carotid endarterectomy where antiplatelet monotherapy is preferred to combination therapy, aspirin (300–325 mg daily for 14 days, followed by 75–162 mg daily) should be considered. (Class IIA; Level B).
- Recommendation 29: For recently symptomatic patients undergoing carotid endarterectomy on aspirin monotherapy, lower dose aspirin (75–325 mg daily) rather than higher dose (>325 mg daily) is recommended. (Class I; Level B).
- Recommendation 30: For recently symptomatic carotid stenosis patients undergoing carotid endarterectomy who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole modified release monotherapy (200 mg twice daily) is recommended. (Class I; Level C).
- Recommendation 31: For recently symptomatic patients undergoing carotid stenting, combination antiplatelet therapy with aspirin (75–325 mg daily) and clopidogrel is recommended. Clopidogrel (75 mg daily) should be started at least 3 days prior to stenting or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least 4 weeks after stenting and then long term antiplatelet monotherapy (preferably clopidogrel 75 mg daily) should be continued indefinitely. (Class I; Level C).
- Recommendation 32: For patients who have undergone carotid endarterectomy or carotid stenting, long term aspirin + clopidogrel therapy is ***not*** recommended unless required for cardiac or other vascular disease indications. (Class III; Level A).

1.4.10 Patients with Atrial Fibrillation: Combination Therapy with Oral Anticoagulants and Antiplatelets

1.4.10.1 Studies

In an analysis of the National Inpatient Sample (NIS) from 2005 to 2009 (n = 672,074 patients), 8.8% of patients who underwent CEA or CAS had atrial fibrillation (AF). Atrial fibrillation was associated with an increased rate of postoperative stroke in patients undergoing CEA but not in patients undergoing CAS [40]. The relative risk of the composite end point of postoperative stroke, cardiac complications, and mortality was increased in patients with atrial fibrillation undergoing CAS (OR, 1.43; 95% CI, 1.18–1.74) and in those undergoing CEA (OR, 3.18; 95% CI, 2.89–3.49). After adjustment for potential confounders, the odds of the composite end point of postoperative stroke, cardiac complications, and mortality in atrial fibrillation patients were significantly higher among patients who underwent CEA (compared with those who underwent CAS). An opposite relationship was seen in patients without atrial fibrillation, in whom the composite end point was significantly lower in patients undergoing CEA. This analysis suggests that almost 10% of CAS and CEA is performed in patients with atrial fibrillation in general practice, and higher rates of adverse events are observed among these patients, particularly those undergoing CEA.

1.4.10.2 Guidelines

The question of the extent to which patients with atrial fibrillation who underwent CEA or CAS should receive a comedication of antiplatelet therapy and anticoagulants is not definitively answered in the ESVS guideline. The **2016 European Society of Cardiology (ESC) guidelines** for the management of atrial fibrillation [41] recommend:

- After TIA or stroke, combination therapy of oral anticoagulation and an antiplatelet is ***not*** recommended. (harm; recommendation grade III/evidence level B).
- This means that patients with atrial fibrillation should receive long-term monotherapy with oral anticoagulants. There is no indication for additional antiplatelet therapy in patients with atrial fibrillation who underwent CEA.

  As far as patients with atrial fibrillation who underwent CAS are concerned, the ESC guideline leaves this question unanswered. However, analogous to coronary stent implantation in patients with atrial fibrillation, it has been common practice up to now to administer antiplatelets (monotherapy with either ASA, 75–325 mg daily, or clopidogrel, 75 mg daily, or a combination of both drugs) for 4 weeks in addition to concomitant anticoagulation for reasons of fear of early thrombotic occlusion. Whether this therapy should be continued for longer is unclear.

For the coronary stent, the **ESC guidelines** [41] recommend:

- After elective coronary stenting for stable coronary artery disease in atrial fibrillation (AF) patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events. (Recommendation class IIa/evidence level B).
- After an ACS (acute coronary syndrome) with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events. (Recommendation class IIa/evidence level C).
- The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding. (Recommendation class IIa/evidence level B).
- Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients. (Recommendation class IIb/evidence level C).

1.4.11 Lipid-Lowering Therapy (Statins)

1.4.11.1 European Society for Vascular Surgery (ESVS) [1]

- Recommendation 13: For patients with asymptomatic carotid stenosis, lipid lowering therapy with statins (with or without ezetimibe) is recommended for the long-term prevention of stroke, myocardial infarction, and other cardiovascular events. (Class I; Level B).
- Recommendation 34: For patients with a symptomatic carotid stenosis, statin therapy is recommended for the long term prevention of stroke, myocardial infarction and other cardiovascular events. (Class I; Level B).
- Recommendation 35: For symptomatic carotid stenosis patients who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe (10 mg daily) is recommended. (Class I; Level B).
- Recommendation 36: For symptomatic carotid stenosis patients who are intolerant of, or not achieving target low density lipoprotein levels on statins, with or without ezetimibe, additional or alternative treatment with PCSK9 inhibitors should be considered. (Class IIA; Level B).
- Recommendation 37: For patients scheduled to undergo endarterectomy or stenting, it is recommended to commence statin therapy pre-operatively. (Class I; Level A).

1.4.11.2 European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA)- Guideline [30]

- Peri-operative continuation of statins is recommended, favouring statins with a long half-life or extended-release formulation.
- Preoperative initiation of statin treatment should be considered in patients undergoing vascular surgery, ideally at least 2 weeks prior to surgery.

1.4.12 Diabetes Mellitus

1.4.12.1 European Society for Vascular Surgery (ESVS) [1]

- No. 16: For diabetic patients with asymptomatic carotid stenoses, optimal glycaemic control is recommended. (Class I; Level B).

1.4.12.2 Studies

The importance of well controlled diabetes in patients with CEA was highlighted by Parr et al. [42] based on 614,190 patients from the 2006–2013 National Inpatient Sample. Patients with uncontrolled diabetes had significantly higher rates of stroke (3.27% vs. 0.93%), myocardial infarction (3.35% vs. 1.10%) and higher hospital mortality (1.43% vs. 0.25%) than patients with well-controlled diabetes. In patients without diabetes, the comparative figures were 0.94% (stroke), 0.87% (myocardial infarction) and 0.27% (hospital mortality). In addition to the less favourable outcome, higher treatment cost and a longer hospital stay were also observed in patients with uncontrolled diabetes. This finding highlights the importance of considering the state of control of a patient's disease rather than just whether they carry a diagnosis of diabetes when weighing the benefits and costs of CEA.

1.4.13 Wound Drainage After CEA

1.4.13.1 European Society for Vascular Surgery (ESVS) [1]

- No. 79: For patients undergoing carotid endarterectomy, selective wound drainage should be considered. (Class IIA; Level B).

1.4.13.2 Studies

The rationale behind the use of drains is to prevent fluid collections, which in the neck might cause respiratory complications or become secondarily infected. In the only (small) randomised study with a total of 70 patients with CEA and 106 groin

dissections, in which the volume of fluid was accurately measured postoperatively, the placement of a drain failed to significantly decrease the risk of haematoma requiring surgical evacuation or amount of fluid collections [43]. Most haematomas were small, with or without drainage. Wound complications were not significantly affected by drainage and were not related to the presence of fluid collections. If significant fluid collections occurred, they could not be prevented by drainage. The study argued against the routine placement of a drain after CEA.

Recently, Smolock et al. [44] analysed data from 47,752 patients in the Vascular Quality Initiative (VQI) registry who underwent CEA between 2011 and 2015. Drains were placed in 19,425 patients and no drains were placed in 28,327. Patients with drain placement were more likely to be taking a preoperative $P2Y_{12}$ ($p > 0.001$), to have prior CEA or carotid artery stenting ($P < .001$), to use dextran ($P < .001$), and to have a concomitant procedure or coronary artery bypass graft ($P < .001$) and less likely to use protamine ($P < .001$) compared with those without drain placement. Drain placement did not prevent return to the OR for bleeding ($P < .22$). Re-exploration of the carotid artery after closure in the OR ($P < .001$), preoperative P2Y12 antagonist use ($P < .001$), and no protamine use ($P < .001$) were predictors for return to the OR for bleeding among those with drain placement. Of patients requiring return to the OR for bleeding, drain placement did not influence 30-day stroke ($P = .82$), 30-day mortality ($P = .43$), or 30-day combined stroke/mortality ($P = .42$) compared with those without drain placement. Drain placement did not influence postoperative wound infection ($P < .3$). Hospital length of stay was increased in patients with drain placement ($P < .001$). In conclusion, drain placement after CEA did not reduce return to the OR for bleeding, nor did it reduce perioperative stroke or death, but drain placement was associated with increased length of stay.

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Chapter 2
Thoracic-Outlet-Syndrome



2.1 Guidelines

2.1.1 Society for Vascular Surgery

There are no guidelines for thoracic outlet syndrome (TOS); only the Society for Vascular Surgery has defined reporting standards [1, 2]. They focus on the description of findings, diagnosis, treatment and presentation of results, including follow-up. These excellent explanations are very comprehensive and can therefore not be referred to in detail here. In the following, we will limit ourselves to the classification and anatomy, and reporting standards.

2.1.1.1 Classification

- TOS is commonly referred to as one clinical entity. However, there are three distinct types of TOS, depending on the principal anatomic structures involved and the clinical syndromes that result. Diagnosis, treatment, and outcomes vary, and these must be reported as separate entities.
- Neurogenic TOS (NTOS): Neurogenic symptoms are most common, caused by brachial plexus compression or irritation at the scalene triangle or pectoralis minor space. Patients have symptoms caused by compression and irritation of the brachial plexus.
- Venous TOS (VTOS): Venous symptoms are caused by subclavian vein compression at the costoclavicular junction or occasionally the pectoralis minor space and present as acute or chronic upper extremity deep venous thrombosis (Paget-Schroetter syndrome, effort thrombosis) or positional swelling (McCleery syndrome). Patients have signs and symptoms caused by intermittent compres-

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sion or partial or complete thrombosis of the subclavian vein at the costoclavicular junction.
- Arterial TOS (ATOS): ATOS occurs when the subclavian artery is compressed at the scalene triangle, often by an anomalous bone structure, and presents as either symptomatic ischemia with the arm elevated or fixed arterial damage (stenosis, occlusion, or aneurysmal degeneration resulting in upper extremity ischemia, commonly due to embolization). Note that to diagnose ATOS, the limb must be objectively ischemic with stress maneuvers; pulse obliteration and asymptomatic hemodynamic or anatomic changes with provocative maneuvers in the absence of such changes do not meet the definition of ATOS.

2.1.1.2 Reporting Standards: Treatment

NTOS

- Ergonomic modifications at work and home or workplace.
- Physical therapy.
- Any other therapy attempted (massage, chiropractic) and results thereof.
- Medications.
- Therapeutic muscular, perineural, epidural or other injections (steroids, botulinum toxin).
- Operative decompression of the thoracic outlet, potentially including brachial plexus neurolysis.
  - Surgical approach and structures removed or altered, with precise attention paid to terminology [as described in this guideline] (including extent of rib resection, anomalous anatomy observed, pectoralis minor tenotomy, neurolysis, and any wrapping or other treatment of the nerves).
  - Pleural entry, use of chest drainage.
  - Intraoperative complications.
  - Postoperative pain control methods used.
  - Length of hospital stay.
  - Any postoperative complications or readmissions within 30 days.

VTOS

- Axillosubclavian venous thrombolysis.
  - Duration of symptoms in days and classification as before.
  - Successful or unsuccessful wire passage.
  - Technique: conventional (infusion during 6 to 48 h) or pharmacomechanical (immediate mechanically assisted thrombus removal).
  - Any adjunctive measures used (e.g., balloon venoplasty; note that stenting is contraindicated in this situation).

  - Results of thrombolysis.
  - Any complications.

- Operative thoracic outlet decompression or venous intervention.

  - Duration of symptoms in days and classification as before.
  - Whether the patient has received thrombolysis before surgery and results thereof. If so, interval in days between the cessation of thrombolysis and surgery.
  - Status of the subclavian vein at the time of operation.
  - Surgical approach and structures removed.
  - Presence or absence of occult anterior first rib fracture or osteophytic degeneration.
  - Use of external axillary-subclavian venolysis and status of vein thereafter.
  - Whether any adjunctive procedures were performed.

    Intraoperative venography.
    Endovenous intervention.
    Surgical repair of the subclavian vein, including details of repair and material used.
    Other reconstruction (jugular turndown, arteriovenous fistula creation).

  - Pleural entry, use of chest drainage.
  - Intraoperative complications.
  - Postoperative pain control and methods used.
  - Length of hospital stay.
  - All postoperative complications or readmissions within 30 days.
  - Postoperative anticoagulation or antiplatelet therapy, with duration.

ATOS

Description of treatment should be categorized into the three goals of treatment for patients with ATOS:

1. repair/replacement of the damaged subclavian artery (local disease);
2. correction of the original inciting cause at the thoracic outlet (cause); and
3. correction of any distal embolic or other problems (distal disease).

As many details as possible should be documented:

- Catheter-directed thrombolysis.

  - Any endovascular intervention done at this time should be recorded.
  - Any complications should be recorded.
  - Status of arm and hand at cessation of lysis should be recorded.

- Operative management.

- Whether the patient has received thrombolysis before surgery. If so, interval (in days) between cessation of thrombolysis and surgery.
- Status of the artery at the time of operation (at scalene triangle and in arm).
- Surgical approach and structures removed.
- Whether any adjunctive procedures were performed.

  Endoluminal intervention.
  Arterial repair, replacement, or bypass.
  [For either, conduit or material used]
  Distal embolectomy.
  Fasciotomy.

- Completion arteriography or duplex ultrasound.
- Neurological status before and after surgery.
- Pleural entry, use of chest drainage.
- Intraoperative complications.
- Postoperative pain control methods used.
- Length of hospital stay.
- All postoperative complications or readmissions within 30 days.

2.1.2 American College of Radiology Appropriateness Criteria

The American College of Radiology has published criteria for appropriate imaging in NTOS, VTOS and ATOS [3].

- Radiography of the chest and either MRI without and with IV contrast of the chest or MRI without IV contrast of the chest are usually appropriate for the initial and follow-up imaging after surgery or intervention for patients with NTOS.
- Radiography of the chest and US duplex Doppler of the subclavian artery and vein, CT with IV contrast of the chest, or catheter venography of the upper extremity are usually appropriate for the initial and follow-up imaging after surgery or intervention for patients with VTOS.
- Radiography of the chest and CTA with IV contrast of the chest, MRA without and with IV contrast of the chest, US duplex Doppler of the subclavian artery and vein, or arteriography of the upper extremity are usually appropriate for the initial and follow-up imaging after surgery or intervention for patients with ATOS.

2.2 Results

2.2.1 Meta-Analyses/Systematic Reviews

2.2.1.1 Surgical Procedures for NTOS

In a systematic review, Yin et al. [4] compared the treatment outcomes of three alternative surgical procedures for NTOS: transaxillary first rib excision, 17 studies/ supraclavicular first rib excision with scalenectomy, 9 studies/and supraclavicular release leaving the first rib intact, 14 studies. In this analysis, supraclavicular relase had the highest point estimates of success rate and complete relief rate (85% and 61%, respectively), followed by supraclavicular first rib excision (77% and 57%, respectively) and transaxillary first rib excision (76% and 53%, respectively). The probabilities of complete relief rate of 50% or greater were 67%, 71%, and 69% for transaxillary first rib excision, supraclavicular first rib excision, and supraclavicular release, respectively. Sensitivity analyses showed similar results. The complication rates for transaxillary first rib excision, supraclavicular first rib excision, and supraclavicular release were, respectively, 22.5%, 25.9%, and 12.6%. These findings suggest that resection of the first rib is not necessary for surgical treatment of patients with neurogenic TOS.

In a second meta-analysis, Blondin et al. [5] came to a similar conclusion: rib-sparing scalenectomy (RSS) is an effective option for the treatment of NTOS, RSS is sufficient for treating NTOS without the added morbidity of first rib resection.

2.2.1.2 Procedures for Paget-Schrötter Syndrome (VTOS)

For a meta-analysis on the treatment of Paget-Schrötter syndrome, Karaolanis et al. [6] found 25 studies with 1511 patients. Thrombolysis was performed in 1177 (77.9%) patients, anticoagulation in 658 (43.5%) and decompression of the thoracic outlet in 1293 (85.6%). The complete thrombus resolution was estimated at 78.1% after thrombolysis, and the respective pooled proportion for partial resolution of thrombus was 23.7%. Despite thrombolytic therapy, additional balloon angioplasty was performed in 212 patients for residual stenosis, although only 36 stents were implanted. After anticoagulation, complete thrombus resolution was seen in 40.7% and partial resolution in 29.1%. During follow-up, 51.75% of patients with any initial treatment modality had no remaining thrombus and 84.7% of these patients were free of symptoms. A subgroup meta-analysis with 20 studies and 1309 patients, showed significantly improved vein patency and symptom resolution in patients who had first rib resection with or without venoplasty, compared with those who had only thrombolysis. The data suggest that resection of the first rib after thrombolysis is the treatment of choice in the majority of patients with Paget-Schrötter syndrome.

2.2.2 Studies

2.2.2.1 TOS: Incidence/Registry Data

Based on a prospectively maintained database of an academic TOS centre with 526 admitted patients in 47 months, Illig et al. [7] reported the ratio of NTOS, VTOS and ATOS in the admission diagnoses as 82%, 16% and 2%, respectively. NTOS was also the TOS most commonly treated surgically (73%, 25%, 3%). They estimated the annual incidence of NTOS to be approximately 3 cases/100,000 population, and that of VTOS to be 1/100,000. Although TOS is considered a rare disease, the incidence according to this calculation was not lower than that of amyotrophic lateral sclerosis, for example.

George et al. [8] analysed 3547 TOS operations recorded in the National Inpatient Sample for the years 2010 to 2015 (89.2% NTOS, 9.9% VTOS and 0.9% ATOS). They estimated that a total of 18,210 TOS surgeries were performed in the US during this time, with an upward trend. Higher volume centres (≥10 cases/year) represented 5.2% of hospitals, but 37% of cases, and achieved significantly lower overall major complication rates, but no difference in neurologic complications. Overall mortality was less than 0.6% and was highest after procedures for VTOS (4.2%), followed by 0.2% for NTOS and 0% for ATOS. Neurological complications occurred in 0.34% of cases, brachial plexus injuries in 0.11%, iatrogenic pneumothorax in 3.3% and vascular complications in 8.7% in VTOS, 9.7% in ATOS and only 2.1% in NTOS. Higher volume centers delivered higher value care: less or similar operative morbidity with lower total hospital charges.

In a retrospective analysis of the National Surgical Quality Improvement Program database from 2005 to 2014, Jubbal et al. [9] found 1853 patients with TOS. The purpose of this study was to identify the most common techniques used to treat TOS and compare complication rates. The most common procedures were first rib resection (64%), followed by anterior scalenectomy with cervical rib resection (32.9%), brachial plexus decompression (27.2%) and anterior scalenectomy without cervical rib resection (8.9%). The authors reviewed complication rates and concluded that surgical treatment of TOS most commonly involves first rib resection, which is not associated with an increased risk of medical or surgical complications. Factors that demonstrated association with medical complications included female gender, ASA classification of 3 or greater, and prolonged operative time. No factors demonstrated statistically significant association with surgical complications.

2.2.2.2 VTOS: Outcome

The outcome in 36 patients with chronic VTOS was presented by Pesser et al. [10]. VTOS was considered chronic when symptoms and venous stenosis or occlusion were present for >3 months after the initial primary upper extremity deep vein thrombosis event. Treatment algorithm consisted of transaxillary first rib resection

for thoracic outlet decompression, external venolysis, and intraoperative venography, followed by percutaneous low-pressure diagnostic balloon inflation, in a single setting. Chronic occlusions that could not be recanalized with a guidewire were excluded. At a mean follow-up of 24 months, 83% of patients were free of symptoms. The functional outcome measures and quality of life had all improved significantly ($P < .01$). A return to daily activities was achieved by 93% of the patients. The treatment of patients with chronic venous thoracic outlet syndrome using a same admission treatment algorithm consisting of transaxillary thoracic outlet decompression, external venolysis, and percutaneous transluminal angioplasty is effective and leads to significant improvement in functional outcome and physical quality of life.

Another case series on patients with VTOS included 15 patients each with supraclavicular and 15 patients with infraclavicular decompression [11]. Infraclavicular thoracic outlet decompression was associated with fewer patients with postoperative symptoms, 0 of 15 (0%) versus 8 of 15 (53.3%), ($P = 0.0022$), and infraclavicular thoracic outlet decompression demonstrated improved patency, 15 of 15 (100%) versus 8 of 15 (53.3%), ($P = 0.028$) at a mean combined follow-up of 8.47 ± 10.8 months.

The supraclavicular approach was also compared with the infraclavicular approach in patients with VTOS by Dua et al. [12]. 109 rib resections were performed, 54 via a supraclavicular and 55 via an infraclavicular approach. There was a significant decrease in the number of complications in the infraclavicular cohort compared with the supraclavicular group, but the long-term outcomes in terms of venous patency and quality of life did not differ between the two groups. Dua et al. [13] also reported long-term functional outcomes in 170 patients with 188 rib resections for all forms of TOS (102 NTOS, 82 VTOS, 4 ATOS) with a mean follow-up time of 5.3 years. 167 (88.9%) patients returned to baseline activities postoperatively, this included active athletes, and 96% of patients stated they were satisfied and would undergo the procedure again.

Silverberg et al. [14] chose a different approach. They reported the long-term results in 18 patients with Paget-Schrötter syndrome who were treated exclusively with anticoagulation and catheter-directed thrombolysis (up to 72 h) without surgical management. Patients excluded were those with a clinical presentation exceeding 14 days from the development of symptoms to hospital admission and patients with an existing contraindication to thrombolysis. After thrombolysis, the treated veins were found to be patent on venography in 16 of 18 patients. Two patients had occluded subclavian/axillary veins. All patients with successful catheter-based thrombolysis were found to have focal stenotic lesions in the subclavian vein; PTA was performed in only 4 patients with high-grade stenosis >80%. After thrombolysis, patients were anticoagulated for a mean of 26 months. Mean time from the index event to the follow-up clinic visit was 109 (37–176) months. 17 patients (94%) had a Villalta score of 0–3, equivalent to non-existent post-thrombotic syndrome. 14 patients (78%) were completely asymptomatic. None of the patients suffered from impaired quality of life. The study demonstrates that patients with Paget-Schroetter syndrome treated with catheter-directed thrombolysis and

anticoagulation, but no rib resection did not develop post-thrombotic syndrome and did not suffer from an impaired quality of life.

2.2.2.3 NTOS: Outcome

Balderman et al. [15] assessed the results of physical therapy management and surgical treatment in a prospective observational cohort of patients with neurogenic thoracic outlet syndrome (NTOS) using patient-reported outcomes measures. During a median follow-up >12 months of 130 patients with NTOS, 40 (31%) obtained symptom improvement with physical therapy alone and 90 (69%) underwent surgery. Surgery for NTOS consisted of supraclavicular decompression (with complete anterior and middle scalenectomy, first rib resection, and brachial plexus neurolysis) or subcoracoid decompression (pectoralis minor tenotomy), or both. Patients rated the outcome after surgery as excellent in 27%, good in 36%, fair in 26% and poor in 12%. Despite substantial pretreatment disability, surgery for NTOS can be effective when physical therapy is insufficient, with substantial symptom improvement in approximately 90% of patients. These outcomes were reflected by changes in Disability of the Arm, Shoulder, and Hand scores, but no specific factors predicted which patients will benefit from physical therapy alone or will require surgery.

The first single centre prospective cohort study to describe the implementation of a multidisciplinary diagnostic care pathway for patients with NTOS based on the SVS reporting standards was published by Pesser et al. [16]. NTOS was diagnosed in 476 of 856 (55.6%) referred patients. Dedicated physiotherapy as the primary treatment was successful in 186 patients (39.1%). Surgical treatment was performed in 290 (60.9%) patients, of whom 274 were included in the follow up (mean follow-up 16.9 ± 9.2 months). Surgical treatment consisted of thoracic outlet decompression, which included a complete resection of the first rib, partial anterior and medial scalenectomy and a thorough neurolysis of the branches of the lower brachial plexus. At follow-up, surgical outcome was considered excellent in 83 patients (30.3%), good in 114 (41.6%), fair in 43 (15.7%) and poor (recurrent or persistent NTOS) in 34 (12.4%). The results suggest a prominent role for multidisciplinary care pathways in NTOS diagnostics, underline the role of dedicated physiotherapy as the primary treatment, and show good to excellent short term treatment outcomes in the majority of the surgically treated NTOS patients following previous unsuccessful physiotherapy.

Johansen [17] questioned the indication for first rib resection in NTOS. He reported on a retrospective series of 504 thoracic outlet decompression procedures in 442 patients with scalene block-proved neurogenic thoracic outlet syndrome. Patients underwent anterior, middle and minimus scalenectomy and brachial plexus neurolysis via a supraclavicular incision, combined with pectoralis minor tenotomy through a small vertical infraclavicular incision. No first ribs were excised, and all procedures were performed by a single surgeon. All patients had a positive preoperative response to scalenus blockade using local anaesthetic. The average operative

time was 1.15 h, and the average length of stay was 1.05 days. Major complications (intraoperative arterial injury, wound haematoma requiring reoperation, and chylothorax) were seen in 7 patients (1.4%). All but two patients (99.6%) had symptomatic improvement, with 90.9% experiencing ≥50% improvement in preoperative symptoms and function. These results make it questionable whether the first rib should actually be resected in NTOS.

Ruopsa et al. [18] also pointed out that rib resection was probably unnecessary in most of their patients with NTOS. They reported long-term outcomes in 94 patients with NTOS and scalenectomy with a mean follow-up of 12.9 years. 82% of women and 57% of men reported that aid from surgery had been excellent or good. 69% reported that surgery helped considerably for at least a mean of 9.9 years. The weak point of this study is the fact that of 210 patients operated on, only 94 (47%) ultimately accepted the invitation for a follow-up examination.

The learning curve for supraclavicular thoracic outlet decompression with first and/or cervical rib resection of a single surgeon was reported by Panda et al. [19]. Indication was an NTOS. The mean operative time was 201.5 (SD 56.7) minutes for 114 patients. A plateau was reached after 45 to 55 operations. The operative times before and after the first 51 operations (first and second collectives) were 231.1 (213.6–248.6) vs. 178.3 (168.4–188.3) minutes ($p < 0.001$). There were no significant differences between the two groups regarding the length of postoperative stay, duration of closed-suction drainage, and frequency of complications. At follow-up after a mean of 90 days, patients in both the early and late cohorts reported a significant improvement in their symptoms (74% vs. 73%). Certain preoperative considerations (ASA classification and failed preoperative botulinum injection) were associated with minimal improvement in postoperative symptoms.

Goeteyn et al. [20] highlighted the controversial surgical treatment of NTOS and conducted the first (small) randomised trial to objectify the effect of thoracic outlet decompression (TOD). Patients with a diagnosis of NTOS refractory to conservative therapy were randomised to one of two intervention arms, receiving either a transaxillary thoracic outlet decompression (complete resection of the first rib and partial scalenus resection) ($n = 25$) or continued conservative treatment ($n = 25$). After 3 months, the conservative treated group was also offered a transaxillary thoracic outlet decompression. The primary outcome was change in the Disability of the Arm, Shoulder and Hand (DASH) questionnaire score. At 3 months, there was a statistically significant difference in DASH scores (transaxillary decompression mean 45.15, conservative treatment 64.92; $p < 0.001$). All patients in the conservative treatment group applied for surgery 3 months after randomisation. After surgery of the conservative treatment group, there was no statistically significant difference between the groups for all primary and secondary outcome measures. The conclusion was that surgical thoracic outlet decompression is effective in improving symptoms in patients with NTOS who do not respond to conservative treatment.

In addition, Goeteyn et al. [21] reported the results of redo thoracic outlet decompression surgery through the supraclavicular approach for persistent or recurrent NTOS. Recurrent NTOS was assumed to occur when symptoms reappeared after an initial successful period following a first thoracic outlet decompression. The redo

procedure consisted of complete (cartilage-cartilage) resection of the first rib, any bony and fibrous anomalies, complete anterior and middle scalenectomy, and complete neurolysis of the brachial plexus (complete anatomical decompression of the brachial plexus). In total, 45 patients had redo surgery. Postoperative complications were seen in eight patients (18.18%). One patient had postoperative complications with permanent impairment (Horner syndrome). Seven patients had postoperative complications with full recovery (three patients had a chylous leakage that was treated with a median-chain triglycerides diet for 6 weeks, three patients had transient phrenic nerve palsy with full recovery <6 weeks, and one patient had a discrete Horner syndrome that resolved in 6 weeks). The median time of follow-up was 19.50 months (interquartile range, 14.00 months). Postoperatively, there was a significant decrease in the DASH score. Patients with first rib remnants showed a significant better response compared with patients without first rib remnants.

2.2.2.4 ATOS: Outcome

ATOS is the least common presentation of TOS, accounting for 1% to 2% of cases. Pantoja et al. [22] saw only 51 cases with ATOS among 2200 patients with TOS between January 1986 and March 2021. Subclavian artery pathology included 16 aneurysms (31%), 15 stenoses (29%), and 19 occlusions (37%). Transaxillary decompression was performed in 50 patients, including 50 first rib resections and 23 transaxillary cervical rib resections. Among the 51 decompression cases, approximately 41% (21 cases) required arterial reconstruction: 13 open surgical reconstructions (11 bypass grafts, 2 primary aneurysm repairs) and 8 stentgraft repairs. Comparing two time periods (1986–2003 vs 2003–2021), thrombolysis (5 vs 10) and stentgraft repairs (0 vs 8) increased, whereas open subclavian artery repair (11 vs 2) decreased. Return-to-work rates (74% vs 96%) and good-excellent Derkash scores (81% vs 96%) were comparable. The study described the evolving role of endovascular management of ATOS over the past two decades and documented the expanded role of vascular surgeons in the endovascular management of ATOS at a single institution. Compared with open repair, stent graft repair of the subclavian artery may be associated with shorter operative times, less blood loss, but decreased patency, without changes in long-term functional outcomes.

2.2.2.5 Transaxillary Access

Stilo et al. [23] reported a single surgeon's technique and experience with first rib resection through transaxillary approach, video-assisted in recent years, in 103 patients with TOS (NTOS 58.2%, VTOS 31.1%, ATOS 7.76%). Thirteen (12.6%) patients had cervical rib and sixteen cases (15.5%) had bilateral TOS. The technical success rate was 100%. Three patients (2.9%) presented with hand ischemia and needed an arm vein bypass after rib resection. One (0.9%) intraoperative arterial injury was reported, and nerve injury rate was 1.8%. At 30-day re-intervention rate

was 0.9%: one patient experienced hemothorax solved by thoracoscopic drainage. Restrict pneumothorax was reported in 42 patients (40.8%) treated with pleural drainage. At mean follow-up of 93 ± 9 months partial symptoms recurrence was present in 6 patients (5.8%). The authors advocated the transaxillary approach with resection of the first rib as a safe standard procedure for TOS.

Experience with a modification of the transaxillary first and cervical rib resection technique was described by Moridzadeh et al. [24]. Instead of transecting the ribs en bloc, this approach relied on dividing the junction at the first and cervical ribs and then removing the individual segments. The separated segments of the first rib could then be individually distracted, allowing for improved mobilization, retraction, dissection, and removal of the individual segments. All cases were performed with the assistance of high-definition video endoscopy. 38 patients had undergone complete transaxillary resection of 40 fully formed cervical ribs (10 class 3 and 30 class 4). Of these 38 patients, 74% were women. The presentations had been neurogenic (65%), arterial (31%), and venous (5%). The duration of surgery averaged 141 min, blood loss was 65 mL, and length of stay was 2.1 days. None of the patients had experienced brachial plexus, phrenic, or long thoracic nerve injury. The average follow-up period was 65 months. The final mean postoperative SPS and QuickDASH scores were lower than the scores at presentation (SPS score, 6.4 vs 1.2; $P < .001$; QuickDASH score, 50 vs 17; $P < .001$). Transaxillary resection of fully formed cervical ribs should be considered a safe and effective operation.

2.2.2.6 Robotic Surgery

Martinez et al. [25] presented a retrospective review and analysis of data collected from a 16-year experience of a single surgeon using a robotic surgical system and technique for TOS surgery. 412 transaxillary decompression procedures using the robotic da Vinci Surgical System were performed in 306 patients for first rib resection and cervical band removal. In 204 (49%) procedures, the transaxillary approach was used alone, and in 174 (41%) operations an open supraclavicular approach preceded the robotic transaxillary approach (for cervical rib excision (n = 48) and anterior scalenectomy). In 126 of 412 (31%) operations, the supraclavicular approach was for total anterior scalenectomy in patients who had predominantly had cervical C5, C6, and C7 upper plexus syndrome. None of the patients died, and no patient experienced permanent neurovascular damage of the extremity. Of the 306 patients, 22 (5% of 441 operations) experienced complications. One patient developed postoperative scarring that required a redo operation with a robotic-assisted transaxillary approach. The authors concluded that the endoscopic robotic-assisted transaxillary approach offers a safe and effective approach for performing thoracic outlet syndrome surgery because it provides a three-dimensional visual magnification of the anatomic area and facilitates observation of the cervical bands and the mechanism of neurovascular compression causing TOS.

2.2.2.7 Botulinum Toxin Injections in Patients with NTOS

In a retrospective analysis, Donahue et al. [26] examined the role of botulinum toxin (BTX) injections of anterior scalene (AS) and pectoralis minor (PM) muscles in patients undergoing surgery for NTOS. They hypothesized that symptomatic improvement from BTX injections correlates with favorable long-term response to surgery for NTOS. Data of NTOS patients who underwent sonographically guided chemodenervation of AS and PM using BTX type A followed by scalenectomy and first rib resection were analysed. A supraclavicular approach was chosen for the surgical procedure. There were 157 patients with 178 BTX injections. A high proportion of responders to BTX injections also responded to surgery (positive predictive value of 99%), and BTX injections showed high specificity (90%). BTX injections were moderately sensitive (66%) and accurate (67%) to determine surgical response and had low negative predictive value (14%). The study demonstrated that favorable response to sonographically guided BTX injections is associated with favorable surgical outcomes at 2 years follow-up and has high positive predictive value. While the positive predictive value of BTX injection was high, the negative predictive value was low. Only 14% of patients who did not respond to BTX injection also did not respond to surgery. The low negative predictive value obviously limits the value of the test.

2.3 Conclusions for Clinical Practice

1. Very few (randomised) studies are available on the treatment of TOS, evidence-based statements on therapy cannot be made. The Society for Vascular Surgery has adopted reporting standards. The standards define terminology, local findings, diagnostics, and severity assessment and describe the treatment and the requirements for the presentation of results.
2. The therapy must be based on the findings, whereby a strict distinction must be made between neurogenic (NTOS), venous (VTOS), arterial (ATOS) TOS, and their combinations.
3. In the major registries, first rib resection is favoured as therapy, which is probably also justified if a cervical rib is in addition resected.
4. In NTOS, first rib resection is controversial; supraclavicular decompression without resection of the first rib probably has the highest success rate in NTOS. In VTOS (Paget-Schrötter syndrome), the data suggest that first rib resection after thrombolysis is the treatment of choice in the majority of patients.
5. It is undisputed that the care of TOS patients should be reserved for specialised centres.

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Chapter 3
Distal Aortic Dissection Type Stanford B



3.1 Guidelines

3.1.1 Definition and Classification

Acute type B aortic dissection (ATBAD) is the result of a tear in the intimal arterial layer, which allows blood to propagate within the medial layer. This creates a flap, which divides the aorta into a true lumen (TL), and a false lumen (FL). The most common site for the proximal intimal tear in ATBAD is located just distal to the origin of the left subclavian artery. In 90% of cases, ATBAD has a secondary tear that allows blood to re-enter the TL at what is known as the re-entry site [1].

There are 2 commonly used anatomic classification systems for aortic dissection, the DeBakey system and the Stanford system [2].

The DeBakey system categorizes dissections into types I, II, and III, based on the origin of the intimal tear and the extent of the dissection:

- Type I: Dissection tear originates in the ascending aorta and propagates distally to include the aortic arch and typically the descending aorta.
- Type II: Dissection tear is confined only to the ascending aorta.
- Type III: Dissection tear originates in the descending thoracic aorta and propagates most often distally.
  - Type IIIa: Dissection tear is confined only to the descending thoracic aorta.
  - Type IIIb: Dissection tear originates in the descending thoracic aorta and extends below the diaphragm.

The Stanford classification system divides dissections into 2 categories according to whether the ascending aorta is involved or not, regardless of the site of origin:

- Type A: All dissections involving the ascending aorta, irrespective of the site of the intimal tear.

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- Type B: All dissections that do not involve the ascending aorta (including dissections that involve the aortic arch but spare the ascending aorta).

The European Association for Cardio-Thoracic Surgery and the European Society for Vascular Surgery published an expert consensus document [3], in which they added a third category called "non-A-non-B dissection," to be used for patients whose proximal dissection flap begins in the aortic arch.

The International Registry of Acute Aortic Dissection (IRAD) proposed that aortic dissection be divided into 4 temporal types based on time of symptom onset [4]: hyperacute (symptom onset to 24 h), acute (2–7 days), subacute (8–30 days), and chronic (>30 days). The most contemporary temporal classification system divides [2]: hyperacute (time from onset of symptoms <24 h, acute 1–14 days, subacute 15–90 days, chronic >90 days).

3.1.2 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease

The American Heart Association/American College of Cardiology practice guidelines recommend [2]:

3.1.2.1 Management of Acute Type B Aortic Dissection

- In all patients with uncomplicated acute type B aortic dissection, medical therapy is recommended as the initial management strategy. (Class of recommendation [COR] 1; Level of evidence [LOE] B-NR).
- In patients with acute type B aortic dissection and rupture or other complications (Table 3.1), intervention is recommended. (COR 1; LOE C-LD).

Table 3.1 Consensus features of complicated acute type B aortic dissection [2]

Feature	Comment
Aortic rupture	This can be either free or contained (including hemothorax, increasing periaortic hematoma, or both; or mediastinal hematoma) and should be addressed promptly
Branch artery occlusion and malperfusion	Complete or partial occlusion of a major branch, with or without clinical evidence of ischemia; this includes visceral, renal, and peripheral arterial branches
Extension of dissection	Extension of the dissection flap either distally or proximally (ie, retrograde type A dissection)
Aortic enlargement	Progressive enlargement of the true, false, or both lumens while in the acute phase may require prompt intervention
Intractable pain	
Uncontrolled hypertension	

Table 3.2 High-risk features in uncomplicated acute type B aortic dissection [2]

High-risk imaging findings
• Maximal aortic diameter > 40 mm
• False-lumen diameter > 20–22 mm
• Entry tear >10 mm
• Entry tear on lesser curvature
• Increase in total aortic diameter of >5 mm between serial imaging studies
• Bloody pleural effusion
• Imaging-only evidence of malperfusion
High-risk clinical findings
• Refractory hypertension despite >3 different classes of antihypertensive medications at maximal recommended or tolerated doses
• Refractory pain persisting >12 h despite maximal recommended or tolerated doses
• Need for readmission

- In patients with rupture, in the presence of suitable anatomy, endovascular stent grafting, rather than open surgical repair, is recommended. (COR 1; LOE C-EO).
- In patients with other complications, in the presence of suitable anatomy, the use of endovascular approaches, rather than open surgical repair, is reasonable. (COR 2a; LOE C-LD).
- In patients with uncomplicated acute type B aortic dissection who have high-risk anatomic features (Table 3.2), endovascular management may be considered. (COR 2b; LOE B-R).

  (Note: R Randomized; NR Nonrandomized; LD Limited Data; EO Expert Opinion)

3.1.3 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

The following recommendations for the management of *acute type B aortic dissections* are given [1]:

- Recommendation 12: Patients with acute type B aortic dissection who develop new or recurrent abdominal pain and where there is any suspicion of visceral, renal and/or limb malperfusion should undergo repeat CT imaging. (Class I/Level of Evidence C).
- Recommendation 13: Medical therapy should always be part of the treatment of patients with acute type B dissection. (Class I/Level of evidence C).
- Recommendation 14: In patients with acute type B aortic dissection, β-blockers should be considered as the first line of medical therapy. (Class IIa/Level of evidence C).
- Recommendation 15: In patients with acute type B aortic dissection who do not respond or are intolerant of β-blockers, calcium channel antagonists and/or

renin-angiotensin inhibitors may be considered as alternatives or complementaries. (Class IIb/Level of evidence C).

- Recommendation 16: In patients with complicated acute type B aortic dissection, endovascular repair with thoracic endografting should be the first line intervention. (Class I/Level of Evidence C).
- Recommendation 17: In complicated acute type B aortic dissection, endovascular fenestration should be considered to treat malperfusion. (Class IIa/Level of evidence C).
- Recommendation 18: To prevent aortic complications in uncomplicated acute type B aortic dissection, early thoracic endografting may be considered selectively. (Class IIb/Level of evidence B).
- Recommendation 19: In acute complicated type B aortic dissection, open repair should be considered as an alternative to endovascular therapy following failure of endovascular management or where endovascular interventions are contraindicated. (Class IIa/Level of evidence C).

Regarding *chronic* dissection, it is recommended:

- Recommendation 33: In patients with chronic aortic dissection and acute aortic symptoms, emergency repair should be considered if malperfusion, rupture, or progression of dissection is confirmed on imaging. (Class IIa/Level of Evidence C).
- Recommendation 34a: In patients with chronic aortic dissection, a descending thoracic aortic diameter between 56 to 59 mm may be considered as an indication for treatment in patients at reasonable surgical risk. (Class IIb/Level of evidence C).
- Recommendation 34b: In patients with chronic aortic dissection, a descending thoracic aortic diameter greater than 60 mm should be considered as an indication for treatment in patients at reasonable surgical risk. (Class IIa/Level of evidence C).
- Recommendation 35: In patients with chronic aortic dissection and thoracoabdominal extension, an aortic diameter greater than 60 mm should be considered as an indication for treatment in patients at reasonable surgical risk. (Class IIa/Level of evidence C).
- Recommendation 36: Open repair of aneurysmal or symptomatic chronic type B aortic dissection in patients with low surgical risk should be considered in dedicated centres with low complication rates. (Class IIa/Level of evidence C).
- Recommendation 37: In patients with chronic type B dissection undergoing operative repair, intra-procedural cerebrospinal fluid drainage, left heart bypass, and moderate hypothermia should be considered to reduce procedural mortality and spinal cord injury. (Class IIa/Level of Evidence C).
- Recommendation 38: In patients with moderate to high surgical risk or with contraindications to open repair, endovascular repair of complicated chronic type B aortic dissection should be considered in dedicated centres. (Class IIa/Level of evidence C).

- Recommendation 39: In patients at risk of further aortic complications with suitable anatomy for endografting, endovascular repair of uncomplicated chronic type B aortic dissections should be considered in the sub-acute phase, in dedicated centres. (Class IIa/Level of evidence B).

3.1.3.1 Acute Aortic Syndromes

Acute aortic syndromes (AAS) consist of three interrelated diseases: aortic dissection, penetrating aortic ulcer (PAU), and intramural haematoma (IMH). There are few details on the latter two entities in the ESVS guidelines because the evidence base for treatment is small. The recommendations are [1]:

- Recommendation 20: Uncomplicated type B intramural haematoma and penetrating aortic ulcer should be treated medically, and followed by serial imaging surveillance. (Class I/Level of evidence C) [Uncomplicated/complicated intramural haematoma means absence or presence of recurrent pain, expansion of the intramural haematoma, peri-aortic haematoma, and intimal disruption].
- Recommendation 21: Endovascular repair should be considered for complicated intramural haematoma type B. (Class IIa/Level of evidence C).
- Recommendation 22: Endovascular repair should be considered for complicated penetrating aortic ulcer type B. (Class IIa/Level of evidence C) [Complicated penetrating aortic ulcer (PAU) means presence of recurrent pain or PAU that initially measures >20 mm in diameter or > 10 mm in depth or progression of total aortic diameter].

3.1.4 Society of Thoracic Surgeons/American Association for Thoracic Surgery

The practice guidelines on the management of type B aortic dissection state [5]:

3.1.4.1 Acute Complicated Type B Aortic Dissection (TBAD)

- TEVAR (thoracic endovascular aortic repair) is indicated for complicated hyperacute, acute, or subacute TBADs with rupture and/or malperfusion and favourable anatomy for TEVAR (Class of Recommendation [COR] I/Level of Evidence [LOE] B-nonrandomised [NR]).
- Open surgical repair for complicated hyperacute, acute, or subacute TBADs should be considered for those patients with unsuitable anatomy for TEVAR (COR IIA/LOE B/NR).
- Fenestration may be considered for complicated hyperacute, acute, or subacute TBADs (COR IIB/LOE C/LD [limited data]).

3.1.4.2 Uncomplicated TBAD

- A stepwise approach to the evaluation and treatment of acute/subacute uncomplicated TBAD should be applied that includes identification of the primary entry tear site location, defining the proximity and distance of the dissection to the LSA [left subclavian artery], calibration of the maximum orthogonal aortic diameter, and confirmation of the lack of any organ malperfusion or other indications of complicated disease (COR I/LOE B-NR).
- Optimal medical therapy (OMT) is the recommended treatment for patients with uncomplicated TBAD (COR I/LOE B-NR).
- Prophylactic TEVAR may be considered in patients with uncomplicated TBAD to reduce late aortic-related adverse events and aortic-related death. (COR II B/LOE B-NR). [see Table 3.3 for details].
- Close clinical follow-up after hospital discharge is recommended for patients presenting with acute TBAD (COR I/LOE B-NR).

3.1.4.3 Chronic TBAD

- Open surgical repair should be considered for patients with chronic TBAD with indications for intervention, unless comorbidities are prohibitive or anatomy is not suitable for TEVAR (COR II A/LOE B-NR).
- TEVAR is reasonable for patients with chronic TBAD with an indication for intervention with suitable anatomy (adequate landing zone, absence of ascending or arch aneurysm) but who are at high risk for complications of open repair due to comorbidities (COR II A/LOE B-NR).
- TEVAR alone as sole therapy is not recommended in patients with chronic TBAD who have a large abdominal aortic aneurysm [AAA], an inadequate distal landing zone, and/or large distal reentry tears (COR III: no benefit/LOE C-LD).

Table 3.3 Morphological features posing high risk of late sequelae

– Primary entry tear at greater curve of distal arch
– Short proximity of entry tear to left subclavian artery ostium
– Initial aortic diameter ≥ 40 mm
– Initial false lumen diameter ≥ 22 mm
– Number/size of fenestrations between true and false lumen
– Stent graft-induced new entry
– Partial false lumen thrombosis

3.1.4.4 Timing of Intervention

- In patients with acute uncomplicated TBAD with high-risk features, it may be reasonable to consider delaying treatment (beyond 24 h up to 90 days) with TEVAR to reduce early adverse events and to improve late outcomes (COR II B/LOE C-LD).

3.1.4.5 Connective Tissue Disorders

- Open surgical repair over TEVAR is reasonable for more durable treatment in patients with connective tissue disorders and TBAD who have progression of disease despite OMT (COR I/LOE B-NR).
- TEVAR is reasonable in patients with connective tissue disorders with acute complicated TBADs and anatomy favourable for TEVAR as a bridge to delayed open reconstruction (COR IIA LOE C-LD).

3.1.4.6 Spinal Cord Protection Adjuncts to TEVAR

- Revascularisation (open surgical or endovascular) of the left subclavian artery after TEVAR coverage that obstructs antegrade LSA flow is recommended to decrease the risk of spinal cord ischaemia [SCI] (COR I/LOE B-NR).
- It is reasonable to establish CSF drainage in type B dissection patients undergoing TEVAR if they are at increased risk for spinal cord ischaemia (eg, coverage >20 cm or within 2 cm of the celic artery origin or other risk factors) and time permits (i.e., nonemergent circumstances) (COR IIA/LOE B-NR).
- It is reasonable to establish CSF drainage in type B dissection patients who develop symptoms of paraparesis/paraplegia (COR IIA/LOE B-NR).

3.1.4.7 Management of TBAD with Arch Involvement

- OMT is reasonable in patients with uncomplicated TBAD and retrograde dissection from a tear at or distal to the left subclavian artery as long as retrograde extension is limited to the arch (zones 1 and 2) (COR IIA/LOE C-LD).

3.2 Meta-Analyses/Systematic Reviews

3.2.1 Acute and Subacute Uncomplicated Type B Aortic Dissection: BMT vs. TEVAR

Hossack et al. [6] reviewed systematically the evidence in patients with acute or subacute uncomplicated TBAD (uTBAD) treated by either TEVAR and best medical therapy (BMT) or BMT alone, to see whether TEVAR improved early and late all cause and aorta related mortality. 6 studies encompassing 14,706 patients (including 1066 TEVARs) were included in this meta-analysis. Early mortality after BMT was calculated to be 7.4% overall, and 6.2% after EVAR (no significant advantage of TEVAR for early mortality). There were no statistically significant differences between TEVAR and BMT with regards to inpatient mortality, early re-intervention by TEVAR or surgery. BMT was associated with a significantly lower risk of early stroke ($p = .002$), whereas the risk of late all cause (HR 1.54, 95% CI 1.27–1.86, $p < .001$) and aorta related mortality (HR 2.71, 95% CI 1.49–4.94, $p = .001$) was significantly higher than with TEVAR. No suitable data regarding late aortic re-intervention was found for meta-analysis. Based on the limited data and studies, the authors concluded that it remains uncertain whether TEVAR is beneficial in the management of acute/subacute uTBAD.

A second meta-analysis by Wang et al. [7] came to a different conclusion. These authors compared best medical therapy (BMT) with BMT + TEVAR in acute uncomplicated Stanford TBAD based on 7 observational studies and two randomised controlled trials with a total of 15,066 patients. There were no significant differences in early outcomes (aortic rupture, retrograde dissection, paraplegia/paraparesis, reintervention and mortality) between TEVAR and BMT. However, in the long run, a significantly lower incidence of adverse events was found in the TEVAR group compared to BMT, which included aortic rupture (OR 0.26), reintervention (OR 0.45), aortic-related death (OR 0.27) and all-cause mortality (OR 0.52). In addition, complete thrombosis of the thoracic false lumen and aortic regression were significantly more pronounced (better aortic remodelling). The message was that TEVAR is not superior to BMT in the short term, but should be implemented to improve long-term prognosis. The authors explained the different results compared to Hossack et al. [6] with the larger case numbers of the studies they included and the exclusion of complicated TBAD.

3.2.2 TEVAR in Uncomplicated and Complicated TBAD

In a meta-analysis, Howard et al. [8] compared TEVAR in uncomplicated (n = 8352) and complicated (n = 7772) TBAD. Acute dissection was more frequent in the complicated TBAD group (73.55% vs. 66.91%), while chronic dissection was more common in uncomplicated TBAD patients (33.8% vs. 70.73%). Post-procedure

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stroke rate was higher in complicated TBAD than in uncomplicated TBAD (5.85% vs. 3.92%; $p < 0.01$). Conversely, the rate of post-procedure renal failure was higher in patients with uncomplicated TBAD (11.38% vs. 7.23%; $p < 0.01$). Thirty-day mortality, but not in-hospital mortality, was higher in the complicated TBAD group. Long-term 1-year survival was higher in the uncomplicated TBAD group, but this difference was not observed at 5 years. The authors concluded that despite significantly higher comorbidities in patients with complicated TBAD, both groups did not differ in hospital mortality and 5-year survival.

3.2.3 TEVAR in Acute/Chronic TBAD

Based on 92 studies with at least 10 patients each (5956 patients in total) reporting on the outcome of patients with acute/chronic TBAD, Li et al. [9] estimated the overall hospital mortality after TEVAR to be 7.0% [95% CI 6.2%–7.8%]. Major perioperative complication rates included stroke (4.2% [3.6%–4.9%]), spinal cord ischaemia (3.3% [2.8%–3.9%]), retrograde type A AD (3.2% [2.7%–3.9%]), type I endoleak (4.9% [3.8%–6.2%]), visceral ischaemia (3.1% [2.5%–3.8%]) and haemodialysis-requiring acute renal failure (5.1% [4.3%–5.9%]). Mid-term (<5 years) mortality was reported at 8.9% [7.2%–10.9%], and secondary intervention rate at 12.5% [10.5%–15.0%] with conversion to open procedure in 6.1% [5.3%–7.2%]. Institutions that reported a caseload of ≥40 endovascular procedures had significantly lower rates of in-hospital and aorta-related mortality, rates of stroke, type I endoleak, renal failure and retrograde type A AD. Patients treated in the acute phase had significantly higher incidence of in-hospital or aorta-related mortality and renal failure. Patients with chronic TBAD required significantly more secondary intervention during follow-up. Endovascular stent-graft for type B AD therefore appeared feasible and safe with a low incidence of mortality and perioperative complications, particularly for delayed intervention and centres with ≥40 caseload.

3.2.4 Acute TBAD: Open vs. Endovascular Repair

The purpose of a systematic review and meta-analysis by Harky et al. [10] was to compare perioperative and mortality outcomes of endovascular aortic repair against open repair (OR) in acute type B thoracic aortic dissection. Overall, 18,193 patients (11,618 with open and 6575 with endovascular repair) were found in a combination of 9 studies. Patients who underwent endovascular repair were older and tended to have more comorbidities. TEVAR patients had a lower rate of both paraplegia and stroke while in hospital (1.3% vs. 2.9% and 3.7% vs. 4.7%), but this difference was not statistically significant. The all-neurological complication rate was significantly ($p = 0.006$) higher (6.9% vs. 4.8%) in the open repair group. The duration of

intensive care stay (4 ± 2.1 days vs 6 ± 3.4 days; p = 0.002) and length of hospital stay (7 ± 3.1 days vs. 15 ± 7.2 days; p < 0.0001) were significantly lower in TEVAR patients than in OR patients. The rate of reintervention requirement at 1 year was reported to be higher in TEVAR patients; however, this difference did not reach any statistical significance (11.2% vs 3.3%; P = .298). Operative mortality was significantly higher after open repair (18.6% vs. 7.4%; p < 0.0001). Also at 1 year, TEVAR patients had the significantly lower all-cause mortality (14.3% vs. 24.3%; p < 0.0001). In contrast, at 1 year freedom from reintervention was significantly higher after OR (94.5% vs. 84.6%; p = 0.004). At 5 years, there were no differences in the mortality rates, with 46.7% in open repair vs 49.7% in TEVAR (p = 0.21). This meta-analysis demonstrates that TEVAR provides a significant early benefit in the setting of acute TBAD. This is also true for all-neurological events. Long-term results are pending.

3.2.5 Chronic TBAD: Open vs. Endovascular Repair

For a comparison of endovascular repair vs open surgery in patients with chronic TBAD, Boufi et al. [11] found 39 studies, including four comparative studies. Cumulative all-cause early mortality was 9.3% (95% CI 0.07% to 0.12%) in the open surgery group and 2% (95% CI 0% to 0.03%) in the endovascular repair group. The comparative meta-analysis demonstrated lower early mortality for endovascular repair (odds ratio 4.13), stroke (odds ratio 4.33), spinal cord ischaemia (odds ratio 3.3), and respiratory complications (odds ratio 6.88), but higher reintervention rate (odds ratio 0.34). Midterm survival was similar (odds ratio 1.19). Rupture rates were 1.2% with open and 3% with endovascular repair. In conclusion, endovascular repair was associated with significant early benefits, but this was not sustained at midterm.

Jordan et al. [12] planned to assess by a Cochrane Review the effectiveness and safety of thoracic aortic endovascular repair versus open surgical repair for treatment of complicated chronic Type B aortic dissection (CBAD). Due to lack of randomised controlled trials (RCTs) or controlled clinical trials (CCTs) investigating the effectiveness and safety of TEVAR compared to open surgical repair for patients with complicated CBAD, they were unable to provide any evidence to inform decision-making on the optimal intervention for these patients. High-quality RCTs or CCTs addressing this objective are necessary. However, conducting such studies will be challenging for this life-threatening disease.

3.3 Studies and Registries

3.3.1 Open Repair, Endovascular Repair, or Medical Treatment of TBAD

Lou et al. [13] examined the impact of TEVAR in the acute and chronic phases on short-term and long-term survival of patients presenting with acute TBAD (aTBAD). They identified 398 patients diagnosed with aTBAD. At index hospitalization, complicated patients underwent TEVAR (n = 80) and uncomplicated patients received optimal medical therapy (n = 318). In the uncomplicated group, 146 patients (45.9%) patients failed optimal medical therapy and underwent open repair (OR, n = 59) or endovascular repair (TEVAR, n = 87) repair in the chronic phase. Inhospital mortality was 5% and equivalent between complicated and uncomplicated aTBAD groups at index hospitalization. The mortality of patients treated later in the chronic phase with OR or TEVAR was 16.9% (OR) and 2.3% (TEVAR), respectively. In the long-term follow-up after 10 years, patients primarily treated with TEVAR in the acute phase had a survival advantage over all other patients (84.1% vs. 62.5% with OR vs. 50.4% with TEVAR in the chronic phase vs. 66.4% with BMT). According to this retrospective analysis, BMT is a suboptimal treatment for patients with uncomplicated acute type B aortic dissection due to the complication rate in the long-term course and worse survival. Endovascular therapy at the initial hospitalization for the highest risk subgroup of aTBAD patients (complicated) did not increase short-term mortality and improved longterm survival compared with the other three treatment strategies. Given these findings, the authors recommended a more aggressive strategy of TEVAR at the index hospitalization for the treatment of patients with uncomplicated aTBAD.

Schwartz et al. [14] also investigated how often patients with type B aortic dissection who were initially managed medically required subsequent aortic intervention. In this cohort of 254 patients, 97 patients (38%) required an aortic intervention in a mean follow-up of 6.8 years, 30 patients in the early phase and 67 during late follow-up (100% for aneurysmal degeneration). Predictors of late aortic intervention included entry tear >10 mm, total aortic diameter > 40 mm at time of presentation, false lumen diameter > 20 mm and increase in total aortic diameter > 5 mm between serial imaging studies. While elective TEVAR 14 to 90 days after presentation with acute TBAD should be considered in patients who present with these anatomic findings, complete thrombosis of the false lumen was protective against late operative intervention (odds ratio 0.22).

Zimmerman et al. [15] identified 15,641 patients admitted with a primary diagnosis of aortic dissection in the Nationwide Inpatient Sample (years 2003–2011) and National Inpatient Sample (year 2012) databases in the USA. 60.7% of patients were men, mean age 63.5 years. 84.1% were urgent or emergency admissions. The authors distinguished between open surgical repair (OR) of type A and type B aortic dissection and whether TEVAR was used or medical management. The results are shown in Table 3.4. As can be seen, hospital mortality was significantly higher after

Table 3.4 Complications of open repair of type A (TA-OR) and type B (TB-OR) aortic dissections as well as TEVAR and medical therapy (BMT). NIS database (according to Zimmerman et al. [15])

Variable	TA-OR n = 3253	TB-OR n = 3007	TEVAR n = 1417	BMT n = 7964
Any complication (%)	62.3	57.4	37.3	21.6
Stroke (%)	9.4	8.8	5.2	2.2
Acute renal failure (%)	29.4	29.3	18.6	15.0
Acute myocardial infarction (%)	5.4	2.8	2.1	2.2
In-hospital mortality (%)	17.5	16.6	7.9	16.0
Hospital mortality with high volume [> 6 OR/year] as odds ratio	1.03	***0.55***	0.87	0.94

open repair than after TEVAR, with no differences in mortality for OR between type A and B dissections. However, an important finding of this analysis was that patient admission to a centre with a high surgical case volume was associated with significantly lower hospital mortality (odds ratio 0.55), especially for open repair of type B dissection. The authors therefore saw a need for regionalisation of aortic dissection care.

In the NIS database from 2005 to 2012, Hsieh et al. [16] found 54,971 evaluable patients with TBAD, 12,040 (21.9%) patients received open surgery (OS), 6687 (12.2%) patients received TEVAR, and 36,244 (65.9%) received BMT. Patients with TEVAR had the lowest mortality rate among the three treatment groups (TEVAR 8.04%, OS 15.83%, BMT 13.21%). The median length of hospitalisation stay was 10 days for OS, 8 days for TEVAR and 4 days for BMT. Due to the short hospitalisation and avoidance of periprocedural complications, treatment cost was lowest for BMT (median open surgery USD 54,174, TEVAR 45,923, BMT 10,303). In this patient population, propensity score matched 3 groups were formed (OS n = 5755, TEVAR n = 5695, BMT n = 5761). TEVAR had the significantly lower mortality (8.28%) compared to OS (12.9%) and BMT (12.59%); p = 0.008. TEVAR also had the lower complication rate, shorter hospital stay and lower medical cost compared to OS. TEVAR provided superior short-term mortality benefit and cost-effectiveness in patients with type B aortic dissection, whereas OS was the least favorable option (Table 3.5).

Xiang et al. [17] analysed retrospectively 357 consecutive patients with acute uncomplicated TBAD. Among them, 191 patients underwent TEVAR, and 166 received BMT. After propensity score matching, 145 matched pairs for analysis were obtained. The 30-day mortality rate was 0.7% with TEVAR and 2.1% with BMT (p = 0.622), but the rate of early adverse events was significantly greater in the TEVAR group (11.7% vs. 2.8%; p = 0.003). At 5 years, freedom from all-cause mortality was significantly greater with TEVAR (91.9%) than with BMT (82.2%; p = 0.028). This was also true for freedom from aortic-related death (TEVAR 94.1%, BMT 86.1% at 5 years; p = 0.044). The cumulative incidence of rupture at 5 years was significantly greater in the BMT group with 13.7% than that of the TEVAR group with 5.1% (p = 0.024). The authors concluded that TEVAR may be considered as the first option for uncomplicated acute TBAD.

Table 3.5 Propensity score matched comparison of open surgery (OS), TEVAR and best medical treatment (BMT) for type B aortic dissection. National Inpatient Sample (NIS) data from 2005–2012 (according to Hsieh et al. [16])

Outcome	OS (n = 5755)	TEVAR (n = 5695)	BMT (n = 5761)	P
Mortality, n (%)	743 (12.90)	471 (8.28)	725 (12.59)	0.0008
Length of hospital stay, days	9 (6–16)	8 (4–13)	5 (2–8)	< 0.0001
Complications, n (%)	1953 (33.95)	1402 (24.62)	878 (15.24)	< 0.0001
Total cost, USD	50,931 (36,541–76,526)	46,038 (31,867–68,150)	11,780 (6415–22,667)	< 0.0001
Daily cost (USD)	5003 (3899–6605)	5689 (4183–8256)	2383 (1689–3718)	< 0.0001

3.3.2 TEVAR in Uncomplicated TBAD: Timing

In a collaborative effort with the FDA and industry sponsors, the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) developed a project to prospectively evaluate TEVAR in the treatment of all presentations of TBAD in a real-world setting. The 30-day outcomes of the project were reported by Wang et al. [18]. Data from 397 patients (204 acute (AD) and 193 chronic dissections (CD)) from 40 institutions were included in this registry. The technical success rate (including coverage of the primary entry tear) was 98% for AD patients and 99% for CD patients with a trend toward a higher 30-day mortality in acute dissection patients (AD 9.3% vs CD 5.2%; p = 0.126). Any degree of procedure-related spinal cord ischaemia occurred in 4.4% of AD patients and in 2.1% of CD patients (p = 0.261), with a deficit at discharge of 3.4% in AD patients and 0.5% in CD patients (p = 0.068). Disabling stroke (acute vs chronic) was seen in 2.5% vs. 1.6%, retrograde type A dissection in 1.1% vs. 2.6%. There was a trend toward a lower freedom from reintervention in AD patients (90.7% vs 94.8%; P = .13). In conclusion, AD patients demonstrated a trend toward a higher 30-day mortality and lower freedom from reintervention compared with CD patients. Mortality at 30 days after TEVAR for uncomplicated AD was 5.8%, and there were no clear patterns in mortality or reintervention based on timing of treatment.

Torrent et al. [19] also commented on the timing of TEVAR in patients with uncomplicated acute TBAD. The Vascular Quality Initiative (VQI) TEVAR and complex endovascular aneurysm repair registry was analyzed from 2010 to 2019. Only patients who received TEVAR within 90 days of symptom onset were included (n = 688). The 30-day mortality was 7.5% in the group receiving acute repair in the first 14 days (n = 446), compared with 2.7% in patients receiving subacute repair (n = 242) in days 15–90 after dissection (p = 0.021). To make both groups comparable, the authors performed propensity score matching with 187 patients in each of the 1- to 14-day and 15- to 90-day treatment groups. In this analysis, there was no significant difference in mortality between the two groups (acute 5.4%, subacute

3.5%), but the reintervention rate within 30 days was three-fold higher with acute repair (15.3% vs. 5.2%; p = 0.02) and the reintervention rate after 1 year was also significantly higher (acute 33.8%, subacute 14.5%; p = 0.007). However, the two matched groups did not differ significantly in mortality after 1 year (acute 12.4%, subacute 9.9%). Whether the time of intervention after dissection influences postoperative mortality and morbidity must therefore remain open. Patients in the 1- to 14-day group could represent an inherently higher anatomic or physiologic risk population that could not be entirely accounted for with propensity analysis.

Xie et al. [20] also aimed to determine the effect of intervention timing, from symptom onset to thoracic endovascular aortic repair (TEVAR), on early and late outcomes in patients with uncomplicated type B aortic dissection. They retrospectively evaluated 267 patients with high risk radiographic features (an initial false lumen diameter of ≥22 mm, a maximum aortic diameter of 40 mm at initial presentation, a patent or partially thrombosed false lumen, and an initial entry tear of >10 mm) who underwent pre-emptive TEVAR during the acute and subacute periods. 130 procedures were performed in the acute phase (1–14 days), 137 in the subacute phase (15–90 days) after initial presentation. The 30-day mortality rate was 3.8% in the acute phase group and 0.7% in the subacute phase group (p = 0.11). The complication rate was low (aortic rupture acute n = 2; retrograde type A dissection acute n = 1; disabling stroke acute n = 1; spinal cord ischaemia acute n = 1, subacute n = 3; reintervention acute n = 1, subacute n = 1). Multivariable logistic analyses showed that intervention timing was not associated with 30-day outcomes. In the multivariable Cox analysis, the time of intervention had no influence on the long-term outcome after 48.2 ± 25.9 months (mortality in the acute phase group 4.2%, in the subacute group 8.3%; aortic rupture 1.7% and 3.8%, respectively). The study indicated that TEVAR for high risk uncomplicated TBAD in the acute phase was associated with a trend toward higher rates of early complications, while the long-term outcomes were comparable with those of the subacute phase.

3.3.3 Complicated TBAD

In the TEVAR/complex endovascular aortic repair module of the VQI from 2010 to 2019 Wang et al. [21] identified 2267 patients with uncomplicated TBAD and 553 patients with malperfusion among 2820 TEVAR patients. The overall incidence of postoperative complications was greater in the malperfusion group (39.4% vs 17.1%; P < .001) and included a greater rate of spinal cord ischemia (6.3% vs 2.2%; P < .001), acute kidney injury (10.4% vs 0.9%; P < .001), and in-hospital mortality (11.6% vs 5.6%; P < .001). In-hospital reintervention was also greater for the malperfusion patients (14.5% vs 7.4%; P < .001), although the incidence of long-term reinterventions was similar between the two groups (8.7% vs 9.7%; P = .548). Patients with malperfusion exhibited more extensive dissections spanning the aorta and extending into branch vessels. They had an increased rate of in-hospital reintervention and postoperative complications compared with patients with

uncomplicated type B aortic dissection (TBAD). Despite these differences, no differences were found in the long-term survival or reintervention rates.

3.3.4 Hospital Readmission Rate After Acute TBAD

Carroll et al. [22] analysed 6937 adults with a hospitalisation due to acute type B aortic dissection between January 1, 2010, and December 31, 2014, in the Nationwide Readmissions Database. Medical management alone was the treatment for 62.6% of patients, 21.0% had open surgical repair, and 16.4% underwent TEVAR. The non-elective 90-day readmission rate was 25.1% (23.6% with initial medical management alone, 26.9% after open surgical repair, and 28.7% after TEVAR ($p < 0.001$). The most common cause for non-elective readmission was new or recurrent arterial aneurysm or dissection (24.8%). Residual arterial aneurysm or dissection accounted for a larger proportion of readmissions in the medical management alone group (35.4%) compared with the open repair group (7.1%) and TEVAR group (12.8%). Of those with unplanned readmissions, 5.2% underwent an aortic procedure. The mortality of patients with non-elective readmission was 5.0%, and the mean cost of rehospitalisation was $22,572 ± $41,598. In this population, an additional 4.7% of patients were electively readmitted. The implication is close follow-up of patients with TBAD after hospital discharge. Readmissions after acute type B aortic dissection are high regardless of initial treatment received. Interventions to reduce readmissions should be further evaluated.

3.3.5 Chimney Technique and Adjunctive Side Branch Interventions with TEVAR

Ding et al. [23] retrospectively evaluated data from 159 patients with TBAD who underwent TEVAR combined with a chimney stent for preservation of the left subclavian artery. Acute, subacute and chronic TBAD accounted for 64%, 28% and 8% of cases, respectively. Complicated TBAD accounted for 67% of the cases. The 30-day mortality and morbidity rates were 2% (3/159) and 4% (7/159), respectively. The technical success rate was 81%, with type Ia endoleak occurring in 30 (19%) patients. In the Kaplan-Meier analysis, the estimated patient survival at 1 and 3 years was 98.1 ± 1.1% and 94.4 ± 2.4%, respectively, and freedom from chimney stent occlusion at 1 and 3 years was 98.6 ± 1.0% and 96.5 ± 1.8%, respectively. The study demonstrates that the chimney technique is safe and feasible for preservation of the left subclavian artery in patients with TBAD.

Chia et al. [24] found in the VQI database a total of 426 patients who had undergone TEVAR for acute TBAD with end organ malperfusion. Of the 426 patients, 126 (29.6%) had undergone 182 adjunctive branch interventions during TEVAR. The

most common interventions were stenting (n = 86; 47.3%) and stent grafting (n = 49; 26.9%). The left renal artery was treated most frequently (n = 49; 26.9%). Patients with and without side-branch intervention had similar 30-day mortality (with side-branch intervention 12.4%, without 15.6%; p = 0.511) and in-hospital re-intervention rates (19.2% with and 20.7% without side-branch intervention; p = 0.732). With regard to postoperative complications and survival at 3 years, the two groups also did not differ. The message is to consider side-branch interventions during index TEVAR for complicated acute TBAD with end organ malperfusion that is not improved with primary entry tear coverage alone.

3.3.6 Anticoagulation and Antiplatelet Therapy After TEVAR

Chang et al. [25] investigated whether anticoagulation and antiplatelet medications affect aortic remodeling after TEVAR for type B aortic dissection (TBAD). They identified in the Vascular Quality Initiative TEVAR registry (2012–2020) 1210 patients treated for TBAD with a mean follow-up of 21.2 ± 15.7 months. One hundred sixty-six patients (14%) were on anticoagulation medications at discharge and at follow-up. There were no differences in the mean preoperative thoracic aortic diameter or the number of endografts used. At 18 months, the rates of aortic reinterventions (8% vs 9%; log-rank P = .873), complete false lumen thrombosis (52% vs 45%; P = .175), and mortality (2.5% vs 2.7%; P = .209) were similar in patients with and without anticoagulation, respectively. On a secondary analysis, antiplatelet medications did not affect the rates of aortic reintervention, complete false lumen thrombosis, and mortality. The message was that the use of anticoagulation and antiplatelet medications does not appear to negatively influence aortic remodeling and survival at midterm in patients undergoing thoracic endovascular aortic repair for treatment of type B aortic dissection. Moreover, it did not impair complete false lumen thrombosis.

3.4 Technical Issues

One of the disadvantages of TEVAR in complicated aortic dissection is that thrombosis of the false lumen is not complete—despite thrombosis of the false lumen in the zone of the stent graft—due to retrograde flow through the re-entry tear or intimal fenestrations related to branch vessels. Thus, to promote true lumen expansion and false lumen thrombosis, devices with bare metal stents that extend into the thoracoabdominal aorta have been used in an attempt to induce aortic remodeling. Two systematic reviews are available on this so-called PETTICOAT technique (The Provisional Extension To Induce Complete Attachment). Canaud et al. [26] analysed the available data on outcomes of combined proximal stent-grafting with distal bare stenting for management of aortic dissection. A total of 4 studies with 108

patients treated for management of acute (n = 54) and chronic (n = 54) aortic dissection were included. The technical success rate was 95.3%, the 30-day mortality rate was 2.7%. The morbidity rate occurring within 30 days was 51.8%. The incidence of type I endoleak was 9.2% (10/108). During follow-up, 5 (4.6%) deaths were related to aortic rupture or aortic repair. Mean re-intervention rate was 12.9%. At 12 months, complete false lumen thrombosis was observed at the thoracic level in 70.4% and at the abdominal level in 13.5% of patients. Combined proximal stent-grafting with distal bare stenting for management of aortic dissection clearly improved true lumen perfusion and diameter. However, it failed to completely suppress false lumen patency and carries not negligible risks of severe morbidity. Distal bare stenting could be proposed in case of persistence of a distal malperfusion syndrome after careful evaluation following primary entry tear closure rather than a single stage extensive repair of the thoracoabdominal aorta.

Another analysis included 11 studies (439 cases, of which 399 for type B aortic dissection) [27]. Due to the heterogeneity of the cohorts, only the perioperative results of 4 papers (143 patients) reporting a single stage PETTICOAT procedure for the treatment of acute (89 cases) or subacute (54 cases) type B dissection were pooled together. The pooled data demonstrated that the procedure is feasible and safe with an overall 30-day mortality rate of 4.9% and clinical success rate of 90.2%. However, since there is no evidence of improved short and mid-term survival as well as positive remodeling of the false lumen in the distal aorta, when compared to a simple proximal stent-grafting, a wide-spread use of the PETTICOAT technique is not justified and it should be limited to cases complicated by dynamic malperfusion as a bailout adjunctive tool.

The extent to which the PETTICOAT technique is superior to standard TEVAR for treating complicated type B aortic dissections was assessed by Rong et al. [28] in a Cochrane Review. The authors identified no randomised controlled trials and therefore could not draw any definite conclusion on this topic. Evidence from non-randomised studies appears to be favourable in the short-term, for combined proximal descending aortic endografting plus distal bare metal stenting (PETTICOAT technique) to solve the problem of unfavourable distal aortic remodeling. Randomised controlled trials are warranted to provide solid evidence on this topic. Evidence from cohort studies with large sample sizes would also be helpful in guiding clinical practice.

The stent graft used in the repair has the potential to cause intimal injury to the aorta and may result in new aortic dissection or pseudoaneurysm formation at the proximal or distal end of the stent graft. Stent graft induced new entry (SINE), which is defined as a new intimal tear caused by the stent graft, is a major complication related to TEVAR in aortic dissection. Jang et al. [29] analysed data from 79 patients who underwent TEVAR for Stanford type B aortic dissection (17 acute, 62 chronic). SINE was detected in 21 patients (26.6%) during the follow-up period of 29.7 ± 16.4 months. SINE developed at the proximal margin of the stent graft in four patients (19.0%) and at the distal margin in 17 (81.0%). The incidence of SINE after TEVAR was significantly higher in chronic aortic dissection than in acute aortic dissection (32.3% vs 5.9%; P = .032). The taper ratio and oversizing ratio by

maximal diameter, mean diameter, circumference, and area were significantly higher in the SINE group than in the non-SINE group. Distal oversizing of the stent graft was an independent predictor of the development of SINE. Appropriate size selection of stent graft without distal oversizing might reduce the risk of late SINE events.

Predisposing factors of distal stent graft-induced new entry (SINE) were also addressed by Chen et al. [30]. 73 patients with complicated type B aortic dissection who had received stent graft treatment were analysed. Distal SINE was discovered later in 13 (26%) of the 73 patients. In this study initial stent insertion with a distal-first instead of a proximal-first deployment sequence for repair of the descending thoracic aorta almost eliminated the occurrence of distal SINE. The perioperative distal oversizing ratio was significantly smaller in patients with stent insertion with a distal-first deployment than in those with proximal-first deployment. Distal SINE patients (most had proximal-first deployment) also had a greater perioperative oversizing ratio than non-distal SINE patients. Minimizing the preprocedure distal oversizing ratio with a distal small graft-first procedure could reduce the risk of late distal SINE for Stanford type B aortic dissection.

3.5 Aortic Fenestration

Since TEVAR is now considered the first-line therapy for complicated acute type B aortic dissection, reports on surgical (open) aortic fenestration are very scarce. Szeberin et al. [31] treated 42 patients with complicated type B aortic dissection by open surgical suprarenal aortic fenestration (OSSAF). In this cohort, 30-day mortality was 21.4% and 5-year survival rate was 70.6%. Eight patients (19%) died during the follow up period (6 aortic ruptures, 2 myocardial infarctions). None of the patients became paraplegic after the surgery. Further surgery or stenting was indicated in nine cases (21%). OSSAF has been performed with an acceptable early mortality and low paraplegia rate, but late mortality is frequently related to aortic rupture. Stentgraft coverage of the primary entry tear decreases late aortic related deaths, but suprarenal fenestration remains an option for cases not suitable for endovascular techniques.

Fenestration can also be performed by an endovascular approach. Vendrell et al. [32] reported on 28 patients with acute aortic dissection (type A n = 19, type B n = 9) who were treated for malperfusion with the so-called funnel technique. The funnel technique consists of deployment of an uncovered aortic stent graft placed from the false to the right lumen through an intimal flap aortic fenestration made by balloon angioplasty. The authors reported the primary technical success rate as 86% and the secondary success rate as 96%. Clinical success was achieved in 25 of 28 patients (89%). The 30-day mortality rate was 7%, two patients with severe ischemia (1 renal and bowel ischemia, 1 at all 3 sites), treated with cardiac surgery and then aortic fenestration at day 0, died before day 30. Six of 8 patients with severe ischemia survived. Of the 23 patients who were followed up, 1 proximal fracture of

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a nitinol stent was detected on the 2-year follow-up CT, with no consequences. No recurrence of ischemia was observed. Aortic diameter increased significantly over time (P = .0038) at a mean rate of 1.46 mm/year. Two patients had a significantly increased aortic thoracic diameter (9%) and needed surgical treatment.

3.6 Conclusions for Clinical Practice

1. Optimal medical therapy (OMT) is the recommended treatment for patients with uncomplicated type B aortic dissection (TBAD). To avoid aortic complications in uncomplicated acute type B aortic dissection, early endovascular repair (TEVAR) may be considered selectively.
2. TEVAR is indicated for complicated hyperacute, acute or subacute TBAD with rupture and/or malperfusion and favourable anatomy. Open surgical management should be considered in patients with complicated hyperacute, acute or subacute TBAD with anatomy unsuitable for TEVAR.
3. In chronic type B aortic dissection, there is an early survival advantage and a lower rate of major complications of standard TEVAR over open repair. The reintervention rate for TEVAR due to chronic dissection is relatively high, but the medium-term survival is similar for TEVAR and open repair.
4. Referral of the patient to a centre with a high surgical case volume is associated with significantly lower hospital mortality, especially in the case of open repair of type B aortic dissection and is urgently recommended.

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Chapter 4
Descending Thoracic Aortic Aneurysms (DTAA) and Thoracoabdominal Aortic Aneurysms (TAAA)



4.1 Guidelines

4.1.1 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

The clinical practice guidelines of the European Society for Vascular Surgery (ESVS) recommend for treatment of descending aortic aneurysms [1]:

- Open repair (OR) may be considered for fit patients, with a descending thoracic aorta between 56 to 59 mm in diameter, who are unsuitable for endovascular treatment. (Class IIb; Level of evidence C).
- OR should be considered for fit patients, with a descending thoracic aorta exceeding 60 mm in diameter, who are unsuitable for endovascular treatment. (Class IIa; Level of evidence C).
- To reduce the rate of postoperative paraplegia, left heart bypass is not recommended for patients undergoing open repair for descending thoracic aneurysm. (Class III; Level of evidence C).
- In fit and unfit patients with favourable anatomy, endovascular repair may be considered for descending thoracic aorta aneurysms between 56 and 59 mm diameter. (Class IIb; Level of evidence B).
- In fit and unfit patients with favourable anatomy, endovascular repair should be considered for descending thoracic aorta aneurysms >60 mm diameter. (Class IIa; Level of evidence B).
- In elective thoracic endografting cases when it is planned to intentionally cover the left subclavian artery, in patients at risk of neurological complications, preventive left subclavian artery revascularisation should be considered. (Class IIa; Level of evidence C).

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- In patients with ruptured descending aortic aneurysm, endovascular repair should be the first treatment option when the anatomy is appropriate. (Class I; Level of evidence B).
- In emergency ruptured descending thoracic aortic aneurysm in patients with a patent left mammary to coronary bypass or with a dominant or single left vertebral artery, left subclavian artery revascularisation should be performed prior to left subclavian artery coverage (Class I; Level of Evidence C).

These guidelines recommend for treatment of thoracoabdominal aortic aneurysms (TAAA) [1]:

- Open or endovascular treatment should be considered for patients at low to moderate surgical risk, with an atherosclerotic or degenerative TAAA of 60 mm or larger diameter, rapid aneurysm enlargement (> 10 mm/year) or aneurysm-related symptoms. (Class IIa; Level of evidence C).
- In open type I, II and III TAAA surgery, extracorporeal techniques allowing distal aortic and organ perfusion should be considered to reduce ischaemic complications, especially in extensive aneurysms requiring prolonged cross clamping time. (Class IIa; Level of evidence C).
- In patients with extensive TAAA (type I, II, III) undergoing open repair, cerebrospinal fluid (CSF) drainage should be considered as a measure to decrease the risk of neurological deficit. (Class IIa; Level of evidence B).
- An integrated approach with optimisation of mean and distal aortic arterial pressure, moderate hypothermia, neuromonitoring, and reimplantation of intercostal arteries should be considered to protect the spinal cord during thoraco-abdominal aortic aneurysm (Class IIa; Level of Evidence C).
- For thoraco-abdominal aneurysm repair, in patients unfit for open repair, an endovascular procedure should be considered. (Class IIa; Level of evidence C).
- For thoraco-abdominal aneurysm repair in patients unfit for open repair with aortic anatomy unfavourable for a branched/fenestrated endograft, a hybrid approach should be considered. (Class IIa; Level of Evidence C).
- Centralisation of endovascular repair of thoraco-abdominal aortic aneurysm in dedicated high volume centres may be considered. (Class IIb; Level of evidence C).

4.1.2 Clinical Practice Guidelines of the Society for Vascular Surgery (SVS)

Important recommendations are [2]:

- In patients who could undergo either technique [open, OR or TEVAR] (within the criteria of the device's instructions for use), we recommend TEVAR as the preferred approach to treat elective descending thoracic aorta (DTA) aneurysms,

given its reduced morbidity and length of stay as well as short-term mortality. Level of recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- We recommend TEVAR in asymptomatic patients with a descending thoracic aortic aneurysm (TAA) when the maximum aneurysm diameter has exceeded 5.5 cm in low-risk patients with favourable aortic anatomy. Level of recommendation: Grade 1 (strong). Quality of evidence B (moderate).
- We suggest using higher aortic diameter thresholds for TEVAR in patients deemed to have a particularly high risk of death, renal failure, or paraplegia from the procedure, where the benefit of treatment is lower than the risk posed by the natural history of the TAA. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- We recommend TEVAR in patients with IMH (intramural haematoma) or penetrating aortic ulcer (PAU) who have persistent symptoms or complications or show evidence of disease progression on follow-up imaging after a period of hypertension control. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

The natural history of and indications for repair in patients with PAUs are controversial, but they have been found in one series to grow 2 mm/year in their maximal aortic size and length while growing an average of only 1.2 mm/year in depth. The presence of symptoms, an associated IMH, and an increase in pleural effusion appear to be risk factors for complications. Treatment with TEVAR is indicated for patients who are symptomatic despite best medical therapy or have an increase in pleural effusion. The threshold for intervention for asymptomatic patients is also controversial. According to one study, PAU depth > 10 mm and diameter > 20 mm are risk factors for progressive disease.

Practice Statement: In the absence of clear and widely accepted parameters, the decision to intervene in asymptomatic patients with IMH and PAUs should be individualized. Asymptomatic patients treated for PAUs in the setting of a maximal aortic diameter < 5.5 cm or with PAUs <10 mm deep or < 20 mm in diameter need further study.

- We suggest TEVAR for symptomatic mycotic/infected TAAs as a temporizing measure, but data demonstrating long-term benefit are lacking. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- For elective TEVAR of a TAA where coverage of the LSA (left subclavian artery) is necessary for adequate stent graft seal, we suggest preoperative or concomitant LSA revascularization. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend nonionic, hypoosmolar contrast material with attempts at minimizing intra-arterial contrast agent use, especially in patients at high risk for contrast-induced nephropathy. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend pre-emptive SMA (superior mesenteric artery) stenting with a balloon-expandable stent in cases of >50% stenosis of the SMA in the following conditions: before or after CA (celiac artery) coverage or encroachment, with

TEVAR that is encroaching on the SMA origin, or in any patient otherwise considered at high risk for post-TEVAR mesenteric ischemia. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

- In anticipation of high risk for CA territory ischemia (nonvisualization of CA collateral branches by CTA or dedicated SMA angiography), we recommend open or endovascular revascularization of the CA before TEVAR. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- Practice Statement: Brachiocephalic access for TEVAR device delivery may be acceptable in situations in which transfemoral or iliac access is not available. However, more data are required to determine whether carotid-axillary artery access for delivery of a thoracic endograft is associated with increased complications.
- We recommend TEVAR over open repair for the treatment of ruptured DTA when it is anatomically feasible. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

4.1.3 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease

Important recommendations are [3]:

- In patients with intact descending TAA, repair is recommended when the diameter is ≥5.5 cm. (Class of recommendation [COR] 1; Level of evidence [LOE] B-NR).
- In patients with intact descending TAA and risk factors for rupture (Table 4.1), repair may be considered at a diameter of <5.5 cm. (COR 2b; LOE B-NR).
- In patients at increased risk for perioperative morbidity and mortality (Table 4.2), it may be reasonable to increase the size threshold for surgery accordingly. (COR 2b; LOE B-NR).

Recommendations for endovascular versus open repair of descending TAA:

- In patients without Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome, who have a descending TAA that meets criteria for interven-

Table 4.1 Risk factors for aortic rupture among patients with descending TAA [3]

High-risk features for rupture
• Aneurysm growth of ≥0.5 cm/year
• Symptomatic aneurysm
• Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome, or heritable thoracic aortic disease
• Saccular aneurysm
• Female sex
• Infectious aneurysm

Table 4.2 Patient characteristics associated with increased perioperative morbidity and mortality after open and endovascular repair of descending TAA [3]

Open Surgical Repair	Endovascular Repair
Advanced age	
Preoperative renal insufficiency (stage 3 or greater CKD) or hemodialysis	Thoracoabdominal aortic aneurysm extent
COPD and FEV1 $\leq$ 50% predicted	Pulmonary disease
Previous stroke	Need for iliac access
	Zone 1/2 landing for thoracic stent graft

CKD chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *FEV1* forced expiratory volume in 1 s, *TAA* thoracic aortic aneurysm

tion and anatomy suitable for endovascular repair, TEVAR is recommended over open surgery. (COR 1; LOE B-NR).

- In patients with a descending TAA that meets criteria for repair with TEVAR, who have smaller or diseased access vessels, considerations for alternative vascular access are recommended. (COR 1; LOE B-NR).
- In patients with a descending TAA that meets criteria for intervention, who have anatomy unsuitable for endovascular repair, and who are without significant comorbidities and have a life expectancy of at least 10 years, open surgical repair is reasonable. (COR 2a; LOE B-NR).

4.2 Results

4.2.1 Meta-Analyses and Systematic Reviews

4.2.1.1 Open vs. Endovascular Repair of Thoracic Aortic Aneurysms

The first systematic review to investigate two-armed studies looking only at elective endovascular stent grafting versus open surgical repair for treatment of chronic arch or descending thoracic aortic aneurysms was published by McCarthy et al. [4]. Other reviews also included dissections or ruptures. Five comparative cohort studies with 3955 endovascular stent graft procedures and 21,197 open surgical repairs (ORs) were the basis. Meta-analysis of unadjusted short-term (30-day) all-cause mortality favoured the endovascular procedure (odds ratio 0.75). Sensitivity analysis of four studies including only descending aortic aneurysms showed no significant differences, with moderate heterogeneity. Meta-analysis of adjusted short-term all-cause mortality favoured TEVAR (odds ratio 0.71), without heterogeneity. Longer-term survival (beyond 30 days) from all-cause mortality favoured OR in larger studies and TEVAR in smaller studies. Freedom from reintervention in the longer-term favoured OR. Studies reporting short-term non-fatal complications suggested fewer events following TEVAR. The authors concluded that OR is better for

long-term survival and avoidance of reintervention; conversely, TEVAR is better in terms of short-term outcome.

4.2.1.2 Open Repair of Thoracic Aortic Aneurysms

Khan et al. [5] evaluated in a single-arm meta-analysis the results of a contemporary series of open repair of TAAA and DTA in terms of operative and long-term mortality, and postoperative complications. 54 observational studies with 12,245 patients met inclusion criteria and were included in the meta-analysis. The pooled operative mortality was 10.4% (95% confidence interval [CI], 8.3–12.8): 6.6% (95% CI, 3.7–11.6) for DTA and 10.5% (95% CI, 7.5–14.5) for TAAA. The pooled incidence rate of late mortality was 0.6% per person-year. Pooled rates for postoperative outcomes were 4.9% for stroke; 5.7% and 3.0% for permanent and temporary spinal cord injury, respectively; 13.2% for renal failure; 23.3% for respiratory failure; and 2.7% for myocardial infarction. Cerebrospinal fluid (CSF) drainage was associated with lower operative mortality. Ruptured aneurysms were associated with higher mortality. The data indicate that open repair of these aneurysms is still associated with a considerable risk for operative death and perioperative complications.

4.2.1.3 Spinal Cord Ischaemia After Open and Endovascular Repair

An inclusive contemporary analysis of spinal cord injury (SCI) rates in patients undergoing aneurysm repair and the factors associated with complications has been performed by Gaudino et al. [6]. 169 studies (22,634 patients) from 2008 to 2018 on repair of descending thoracic aneurysm (DTA) and thoracoabdominal aortic aneurysm (TAAA) were pooled in this meta-analysis. The primary outcome was permanent SCI. Secondary outcomes were temporary SCI, operative mortality, long-term mortality, postoperative stroke, and cerebrospinal fluid (CSF) drain-related complications. The pooled rate of permanent SCI was 4.5%; 3.5% for DTA and 7.6% for TAAA repair, 5.7% for open repair and 3.9% (95% CI, 3.1–4.8) for endovascular repair. The pooled rates for operative mortality, late mortality at a mean follow-up of 5.0 years, stroke, and temporary SCI were 7.4%, 1.0%, 4.2% and 3.7%, respectively. The pooled rates for severe, moderate, and minor CSF-drain related complications were 5.1%, 4.1%, and 3.6% respectively. Despite improvement, both open and endovascular aneurysm repair remain associated with a substantial risk of permanent SCI. The risk is greater for TAAA repair, especially extent II, III, and V.

A second meta-analysis has been performed for the occurrence of spinal cord ischaemia after endovascular treatment of TAAA by Pini et al. [7]. A total of 27 studies with 2333 patients were included in this meta-analysis. The pooled rate of SCI was 11%. For extent I, II, III and V TAAA the pooled SCI rate was 13%, for extent IV TAAA the pooled SCI rate was 6%. A staged TAAA-endovascular repair approach was used in 20 studies and a nonstaged approach in 8 (1 study had included both). A lower rate of SCI was seen with a staged approach than with a non-staged

approach (9% vs. 18%; p = 0.02). Symptomatic CSF drainage was associated with a similar pooled SCI rate compared with prophylactic CSF drainage (10% vs. 10%). The pooled permanent SCI rate was 6% (6% for extent I, II, III and V TAAA; 3% for extent IV TAAA). The pooled 30-day mortality rate was 7%, with a similar incidence for the staged and nonstaged approaches (6% vs 9%, respectively). The authors concluded that for endovascular treatment of TAAA, the staged (two-stage) approach is likely to be associated with a lower SCI rate. The overall efficacy of CSF drainage could not be definitively assessed.

Zhang et al. [8] performed a systemic review and meta-analysis to compare the association between prophylactic CSFD vs non-CSFD in preventing spinal cord ischemia after thoracic endovascular aortic repair for aneurysm and dissection. A total of 34 studies of 3561 patients (2671 with TAA or TAAA and 890 with type B AD) were included. In the total population, the SCI rate after TEVAR with prophylactic CSF drainage was 4.45%, without drainage 3.18%. In the dissection group, the SCI rate after TEVAR with prophylactic CSF drainage was significantly lower than in the aneurysm group with CSF drainage (1.8% vs. 5.73%; $p < 0.0001$). Furthermore, for aortic dissections, the SCI rate was not different in TEVAR with and without prophylactic CSF drainage. The same was true for patients with TAA. However, in patients with TAAA and TEVAR, the rate of SCI was significantly lower with routine CSF drainage than in patients with selective drainage (p = 0.04). This meta-analysis has shown that SCI occurs more often after TEVAR for aortic aneurysms than for AD. Routine prophylactic CSFD, compared with selective CSFD, was associated with a lower rate of postoperative SCI after TEVAR for TAAAs. No significant association was found between the SCI rate and routine prophylactic CSFD for patients undergoing TEVAR for isolated TAA or AD.

4.2.1.4 Stroke Rate After Endovascular Repair of TAA

Karaolanis et al. [9] performed a systematic review and meta-analysis to assess the stroke rates after thoracic endovascular aortic repair (TEVAR) for descending thoracic aortic aneurysms and/or dissections. 43 studies (5764 patients) were identified. Overall, the pooled stroke rate was 4.4%, and 1.8% for TBAD in 12 studies. The incidence of stroke after coverage of the left subclavian artery (LSA) during TEVAR was 5.97% and was reported in 19 studies. The pooled stroke rate for the group of patients with LSA coverage and prior revascularization was 2.81% in 18 studies. For the group of patients with LSA ostial coverage without revascularization reported in 15 studies, the pooled stroke rate was 11.83%. If TEVAR was performed within or distal to zone ≥3, without coverage of LSA, the pooled stroke rate was 3.15%. These findings support the recommendation by the Society for Vascular Surgery, which has recently suggested preoperative or concomitant LSA revascularization in cases of TEVAR for which LSA coverage is necessary for an adequate stent graft seal (grade 1; quality of evidence B).

A L G r a w a n y

4.2.1.5 Gender Specific Differences in the Management of TAA

Gender-specific differences in 30-day mortality, length of hospital stay, and adverse neurological events following repair of intact degenerative descending thoracic aortic aneurysms (TAAs), by either thoracic endovascular (TEVAR) or open repair were assessed by Ulug et al. [10] in a systematic review and meta-analysis. For TEVAR, six studies were eligible for the primary outcome of 30-day mortality, including 1756 women and 2619 men. Pooled 30-day mortality was 5% in women and 3% in men. No reasons for this difference were identified. Age did not account for the difference. The hospital stay was longer in women; the two sexes did not differ in the post-interventional stroke rate. Only one study was found for open repair; it reported similar mortality in men and women.

4.2.2 Registry Data/Studies

4.2.2.1 Thoracic Aortic Aneurysm Growth

The UK National Health Service (NHS) ETTAA (Effective Treatments For Thoracic Aortic Aneurysms) study recruited 886 patients with a descending thoracic aortic aneurysm of ≥4 cm in the arch or in the descending thoracic aorta [11]. The maximum aneurysm diameter was in the descending aorta in 725 (82%) patients, growing at 0.2 (0.17–0.24) cm per year. Aneurysms of ≥4 cm in the arch increased by 0.07 (0.02 to 0.12) cm per year. During follow-up, 129 patients died (8.6% per patient-year). Of these deaths, 64 (49.4%) were aneurysm-related. Of 307 patients with aneurysms ≥6 cm, 76 (23.1% per patient-year) died. In this group, 42 deaths (12.7% per patient-year) were aneurysm-related deaths. The 1- and 3-year survival rates were 92.4% (90.2–94.1) and 77.6% (73.4–81.2), respectively. Patients with aneurysms of maximum diameter 4–6 cm had predicted 1-year mortality below 10%, which increases to 12.4% and 22.2% for 7 cm and 8 cm aneurysms, respectively. The authors concluded that large aneurysms should be treated with minimum delay since 3-year probability of death jumps from just under 12% for "average" patients with 5 cm aneurysms to over 35% if the aneurysm increases to 7 cm. These increases will be greater for women and older patients. Similarly, the 3-year risk of aneurysm-related death increases from approximately 5% for 5 cm aneurysms to over 20% for aneurysms of 7 cm.

4.2.2.2 Long-Term Outcome After Endovascular and Open Repair of TAA

To analyse the outcome after endovascular and open repair of descending thoracic aortic aneurysms, Chiu et al. [12] performed a propensity score matching on patients with intact descending thoracic aortic aneurysms who underwent TEVAR (n = 2470)

or open surgical repair (n = 1235). The Medicare database between 1999 and 2010 with follow-up through 2014 was used. The median duration of follow-up in the matched groups was 5.6 years for open surgical repair and 4.7 years for TEVAR. Mortality at 180 days was greater among open surgical repair patients, 23.8%, compared with TEVAR, 10.2%. The interaction between open surgical repair and hospital volume was significant: odds ratio for high-volume open surgical centers with respect to TEVAR: 1.97 (95% CI: 1.53 to 2.61) and for low volume open surgical centers: 3.62 (95% CI: 2.88 to 4.51), p value for interaction = 0.002. The restricted mean survival time difference favored TEVAR at 9 years, −209.2 days (95% CI: −298.7 to −119.7 days; p < 0.001) for open surgical repair. Risk of reintervention was lower for open surgical repair, hazard ratio: 0.40; p < 0.001. In conclusion, open surgical repair was associated with increased odds of early postoperative mortality but reduced late hazard of death. Despite the late advantage of open repair, mean survival was superior for TEVAR. TEVAR should be considered the first line for repair of intact descending thoracic aortic aneurysms in Medicare beneficiaries.

This conclusion was confirmed by the long-term results (median follow-up 102.8 months) of a single centre treating 946 patients with thoracoabdominal aortic aneurysms (TAAA, 79%) and descending thoracic aortic aneurysms (dTAA, 21%) [13]. Acute patients undergoing open repair had significantly higher 30-day mortality compared with endovascular (21.5% vs 4.4%; P < .01). However, there were no differences in 30-day mortality between open and endovascular repair in the non-acute cases (3.7% vs 0%; P = .06). Endovascular repair was associated with decreased perioperative mortality and significantly increased long-term survival in acute patients. Overall mortality rate at 10 years was 51.0% (n = 482), which was significantly higher than the expected 10-year mortality rate for the general age-matched United States population (29.2%) (P < .01). Once patients undergo repair of their aneurysm, aortic-related mortality remains low (aortic-related mortality was 2.1% over the study period).

From January 2000 to January 2010, 457 patients underwent open, and 596 patients underwent endovascular repair of descending TAA or TAAA at the Cleveland Clinic [14]. Propensity score matching was performed, yielding 278 well-matched pairs. In matched patients, compared with endovascular stenting, open repair achieved similar in-hospital death (8.3% vs 7.6%, P = .80) and occurrence of paralysis and stroke (3.6% vs 2.2%, P = .30), despite a longer postoperative stay (median 11 vs 6 days), more dialysis-dependent acute renal failure (8.6% vs 3.3%, P = .008), and prolonged ventilation (46% vs 6.3%, P < .0001). However, open repair resulted in better 10-year survival than endovascular repair (52% vs 33%, P < .0001), and aortic reintervention was less frequent (4% vs 21%, P < .0001). Despite a decrease in the first postoperative year, average aneurysm size did not recover to normal range after endovascular stenting. The authors concluded that because of the perioperative safety profile and lower perioperative morbidity, TEVAR is probably the method of choice in patients with TAA. However, in patients with an unfavourable landing zone or young patients with low comorbidity, the open approach should still be preferred due to better long-term outcomes.

Midterm and long-term outcomes (median follow-up 2.1 years) of TEVAR for isolated descending thoracic aortic aneurysms (n = 219), emphasizing postoperative aortic remodeling and need for reintervention were reported by Tanious et al. [15]. 30-day mortality was 10% for the cohort overall. Life-table analysis revealed an overall survival of 78% at median follow-up. At 3 years, survival was 88% (80%–93%) for those with aneurysm sac stability or regression, whereas it was 70% (49%–84%) for those with aneurysm sac growth (P = .0402). Perioperative neurologic complications occurred in 16% of patients. Significant predictors of sac growth were endoleak (odds ratio [OR], 65; P < .001), preoperative carotid-subclavian bypass (OR, 8; P = .003), and graft oversizing <20% (OR, 15; P = .046). Cox proportional hazards model showed that the only protective factor for mortality was percentage oversizing, with every 1% of oversizing having a hazard ratio (HR) of <.001 (P = .032). This was counterbalanced by the fact that patients with graft oversizing >30% had an increased odds of mortality with HR >10 (P = .049). In summary, the majority of patients (80%) experienced sac stability or regression after TEVAR, which offers a clear survival advantage. Endoleaks are predictive of sac growth, conferring increased mortality. Rigorous surveillance is necessary to prevent future aortic events through reintervention.

4.2.2.3 Open TAA Repair in Patients with Splanchnic Occlusive Disease

The influence of splanchnic occlusive disease (SOD) on outcomes after descending thoracic aneurysm (DTA) and thoracoabdominal aortic aneurysm (TAAA) open repair was reported by Gambardella et al. [16]. The occlusions were related to celiac artery, superior and inferior mesenteric arteries, and renal arteries. SOD was absent in 712 patients and present in 157 patients. Patients with SOD showed higher operative mortality (12.1% vs. 4.2%; p < 0.001), higher rates of SCI (6.4% vs. 2.2%; p = 0.004), tracheotomies (10.8% vs. 6.3%; p = 0.047), dialysis (12.1% vs. 3.7%: p < 0.001) and major complications (32.5% vs. 12.6%; p < 0.001). Survival of patients with SOD was significantly lower over 1 to 10 years after surgery. Propensity score matching led to 144 pairs each, with SOD significantly associated with SCI (6.9% vs 1.4%; P = .03) and MAE (32.6% vs 15%; P < .01). Ten-year survival was reduced in those with SOD (31.5% vs 45.2%; P < .01). The results have shown that SOD is a significant predictor of SCI in patients undergoing open DTA/TAAA repair.

4.2.2.4 Open Surgical Repair in Patients with Marfan and Loeys-Dietz Syndromes

A single centre retrospective study of 58 consecutive patients with Marfan syndromes (MS) (n = 51) or Loeys-Dietz syndromes (LDS) was presented by Adam et al. [17]. The median aortic diameter was 60 (55–74) mm. 21 patients underwent open surgical replacement of the descending thoracic aortic and 37 patients underwent open thoracoabdominal aortic replacement. The 30-day mortality was 5.2%,

permanent spinal cord injury was observed twice, permanent stroke once. The median follow-up time was 81 months. The estimated 5-year survival rate was 85% ± 5%, and freedom from distal reintervention was 94% ± 3% at 5 years. The results demonstrate that descending thoracic and thoracoabdominal aortic replacement in patients with heritable thoracic aortic disease can be performed with low perioperative morbidity and mortality, satisfactory long-term survival, and low requirement for distal reintervention. The prerequisite for these excellent results is the provision of care in specialized centres.

The largest European series to date of open thoracic and thoraco-abdominal aortic repair in patients with connective tissue disease (CTD) was presented by Keschenau et al. [18]. There were 72 procedures in 65 patients, 56 of whom had Marfan syndrome. 64 procedures (89%) were elective procedures, 8 (11%) emergency procedures. The in- hospital mortality was 14% (n = 9). Paraplegia and paraparesis were observed in 2% and 5%, respectively. Major complications were revision surgery for bleeding or haematoma (n = 20/65), sepsis (n = 10/65), myocardial infarction/severe cardiac arrhythmia (n = 2/65), and stroke (n = 2/65). Multivariate analysis identified an operating time of more than 7 h (p = 0.006) as an independent predictor of increased mortality. Median follow-up was 42 months. Freedom from re-intervention was 85%, 1 year survival was 80%, and overall survival was 75%. Open TAA(A) repair is a durable therapy for patients with CTD. It can be associated with relevant risks and should therefore be reserved for specialised centres. Staged procedures and thus reducing operating time, if applicable, should be preferred.

4.2.2.5 Risk Factors for TEVAR

Naazie et al. [19] developed a risk calculator to predict 30-day mortality after TEVAR for DTAA repair based on 2141 patients of the Vascular Quality Initiative (VQI) database. In this series, 30-day mortality was 4.2% (90 patients). Clinically relevant independent variables associated with 30-day mortality included age 75 years or older (odds ratio 2.27), coronary artery disease (odds ratio 1.60), ASA class IV/V (odds ratio 2.39), urgent vs elective procedure (odds ratio 3.47), emergent vs elective procedure (odds ratio 5.27), prior carotid revascularisation (odds ratio 3.24), and proximal landing zone <3 (odds ratio 2.51). Internal validation demonstrated a bias-corrected area under the receiver operating characteristic curve of 0.73 (95% CI, 0.66–0.79) and a calibration slope of 1.00 with a corresponding intercept of 0.00. This means a satisfactory discrimination between events and non-events. The risk calculator should be used primarily in patient information and consultation and is easy to use. It can be accessed at https://qxcalc.app.link/tevar.

Harris et al. [20] also developed a procedure-specific risk score for patients undergoing elective TEVAR for DTAA. Their calculation was based on NSQIP data from 2005 to 2016 (n = 1784 patients). The post-interventional 30-day mortality in this cohort was 4% for all patients. Significant independent risk factors for major adverse postoperative events included patient functional dependence (odds ratio

2.9), prior pulmonary disease (OR 1.6), thoracoabdominal aneurysm extent (OR 2.2), need for iliac access (OR 2.1) and stent graft placement in zone I or II (OR 1.7). According to their respective beta coefficients, each variable was assigned a single point. Based on total points, patients were stratified as low- (0 points), intermediate- (1 point), or high-risk (≥2 points), with stepwise increases in mortality (0%, 4%, and 9%) and major complications (7%, 11%, and 23%) between strata. While TEVAR is safe in low-risk patients, intermediate-risk patients warrant careful discussion of the risks and benefits of aortic intervention; under certain circumstances, high-risk patients may not benefit.

Perioperative risk factors for TEVAR may include patient obesity. Naazie et al. [21] reviewed data from 3423 patients in the VQI registry from 2014 to 2020 who had been treated with TEVAR for DTAA or type B aortic dissection (TBAD). A distinction was made between underweight (BMI <18.5 kg/m^2), obesity (BMI ≥30 kg/m^2) and normal weight (BMI ≥18.5 to <30 kg/m^2). Underweight and normal weight patients did not differ in 30-day mortality. The adjusted hazard of 1-year mortality was two-fold higher in underweight patients compared with normal weight (hazard ratio, 2.15; P < .001), driven by a higher risk of mortality among patients with thoracic aortic aneurysm (OR, 2.62; P < .001). In this study, obese patients who underwent TEVAR for DTAA had comparable 30-day and 1-year mortality risk as normal weight individuals. Obese patients who underwent TEVAR for TBAD demonstrated a 2.7-fold increase in the odds of 30-day mortality, but equivalent mortality risk as normal weight patients at 1 year. TEVAR represents a safe minimally invasive option for treatment of DTAA in obese patients.

Another risk factor might be an older age of the patient. Dakour-Aridi et al. [22] compared the outcomes of TEVAR in octogenarians vs nonoctogenarians in the treatment of thoracic aortic aneurysms and dissection. A total of 2042 patients were identified in the VQI database, including 390 octogenarians (19.1%). Compared with nonoctogenarians, octogenarians had higher percentages of females (49.5% vs 40.4%; P < .01) and white patients (75.9% vs 68.6%; P < .01) and were more likely to present with thoracic aneurysms (86.2% vs 64.3%; P < .001). They also had larger aortic diameters (maximum diameter, 60.3 ± 15.8 mm vs 53.4 ± 17.4 mm). No association was observed between octogenarians and in-hospital mortality after TEVAR for aneurysms (5.1% vs 3.3%; P = .33) or dissection (5.6% vs 4.9%; P = .63). However, for thoracic aneurysm repair, octogenarians had 44% higher adjusted odds of in-hospital complications (27.4% vs 20.7%; P = .03) compared with their younger counterparts. Octogenarians also had increased hazard of 1-year mortality. The findings suggest that elderly patients should not be denied TEVAR based on age if they are medically and anatomically fit for this procedure.

In a retrospective cohort study based on the Society for Vascular Surgery Vascular Quality Initiative (VQI) data, Deery et al. [23] identified 2574 patients who underwent TEVAR for an intact DTAA between 2011 and 2015. The goal of this study was to evaluate the association between sex and morbidity and mortality after TEVAR. 40% (n = 1038) of patients were women, and their aortic diameter was smaller (5.8 cm) compared to men (6.0 cm) (p = 0.02). However, after accounting for body size, females had larger aortic size indices. Women were more likely than

men to have COPD (33% vs. 28%; P = .01), more likely to be symptomatic (16% vs. 10%) at presentation and subsequently were less likely to have an elective procedure (79% vs. 85%). Postoperatively, the rate of major adverse events was significantly higher in women (7.6%) than in men (4.3%). Unadjusted mortality was higher in female patients at 30 days (5.4% vs 3.3%; P < .01) and 1 year (12% vs 8.1%; P < .01). Even after adjusting for differences in age and comorbidities, female patients had higher perioperative mortality and lower long-term survival after TEVAR. These findings, along with the rupture risk by sex, should be considered by clinicians in determining the timing of intervention.

4.2.2.6 Ruptured Thoracic Aortic Aneurysms

Patel et al. [24] identified in the VQI registry 3039 patients with a thoracic aortic aneurysm, 2806 (92%) had undergone repair for an intact aneurysm and 233 (8%) had undergone repair for a ruptured aneurysm (complex aneurysms excluded). Preoperative systolic blood pressure was less than 70 mmHg in 40 (17%) patients, 70–100 mmHg in 92 (40%) and > 100 mmHg in 82 (35%) patients. Compared to patients without rupture, patients with rupture were significantly less likely to have a spinal drainage placed preoperatively (17% vs. 46%; p < 0.001). EVAR for ruptured thoracic aortic aneurysms was associated with higher perioperative mortality (rupture vs intact, 27% vs 4.6%; OR, 6.6; P < .001). Patients with rupture also required more new dialysis (5.2% vs. 1.2%; p < 0.001) and had more postoperative paralysis (6.1% vs. 2.0%; p < 0.001) and stroke (8.3% vs. 4.7%: p = 0.016) compared to patients without rupture. Increasing age (per decade), increasing aortic diameter, chronic kidney disease and previous stroke were associated with higher odds of postoperative mortality. Five-year survival was lower after TEVAR for ruptured TAA than after TEVAR for intact TAA (50% vs. 76%; p < 0.001). TEVAR for ruptured thoracic aortic aneurysms resulted in increased perioperative mortality and morbidity and lower 5-year survival compared with TEVAR for intact aneurysms.

Patients admitted with a ruptured TAA (rTAA) between 1993 and 2012 were identified from the National Inpatient Sample by Ultee et al. [25]. A total of 12,399 patients were included, with 1622 (13%) undergoing TEVAR, 2808 (23%) undergoing open repair, and 7969 (64%) not undergoing surgical treatment. TEVAR has been increasingly used from 2% of total admissions in 2003–2004 to 43% in 2011–2012 (P < .001). Concurrently, there was a decline in the proportion of patients undergoing open repair (29% to 12%; P < .001) and nonoperative treatment (69% to 45%; P < .001). Overall mortality after rTAA admission decreased from 55% to 42% (P < .001). Since 2005, mortality for open repair was 33% and 22% for TEVAR (P < .001). The study demonstrates that since its introduction, endovascular repair has rapidly increased in use for the treatment of rTAA and is currently the primary mode of treatment. Aside from replacing open repair, TEVAR has led to an increase in the proportion of rTAA patients being treated surgically. TEVAR was associated with favorable outcomes compared with open repair, despite TEVAR patients being older and having more comorbidities. Because of the shift from open repair to

Table 4.3 Perioperative outcomes of patients admitted with ruptured thoracic aortic aneurysm between 2005 and 2012. National Inpatient Sample (NIS) database (according to Ultee et al. [25])

Variable	TEVAR n = 1549	Open repair n = 765	Nonoperative n = 2511	*P* OR vs. TEVAR
Death (%)	21.6	33.2	59.9	< .001
Cardiac complications (%)	16.6	31.2	17.0	< .001
Paraplegia (%)	3.7	5.6	0.6	.031
Stroke complication (%)	3.7	5.0	0.8	.165
Acute renal failure (%)	21.8	25.1	9.6	.072
Respiratory complications (%)	33.4	43.0	10.6	< .001
Wound dehiscence (%)	0.9	3.7	0.2	< .001
Postoperative infection (5)	0.6	3.8	0.2	< .001
Bleeding complication (%)	14.3	18.2	1.2	.015
Length of inpatient stay among those who did not die during hospitalisation (days)	13.7	17.2	5.2	< .001
Discharge to home (%)	27.2	21.1	9.3	.002

TEVAR and the shift from nonoperative treatment to TEVAR, overall mortality after rTAA admission declined during the study period. The perioperative outcomes after TEVAR and open repair, and the outcome of non-operative treatment of ruptured TAA for the years 2005 to 2012 are shown in Table 4.3.

4.2.3 Specific Issues with TAAA

4.2.3.1 Staged Hybrid Repair of Extent II TAAA

Hawkins et al. [26] compared morbidity, mortality, cost, and value for staged hybrid vs open repair of extent II TAAAs. Of 113 consecutive patients who underwent Crawford extent II TAAA repair, 25 (22.1%) had a staged hybrid approach with TEVAR of the proximal aorta, followed by open surgical repair of the distal aorta with a median of 129 days between procedures. The hybrid group had shorter operative time (255 vs 306 min; P = .01), shorter postoperative length of stay (10.1 vs 13.3 days; P = .02), and reduced blood loss (1300 vs 2600 mL; P = .01) at the time of open operation. Despite higher rates of acute kidney injury in the hybrid group (76.0% vs 51.1%; P = .03), there was no difference in renal failure (8.0% vs 4.5%; P = .84). The incidence of MAEs was lower in the staged hybrid group (20.0% vs 48.9%; P = .01), without a difference in hospital mortality (4.0% vs 3.4%; P = .89). The two-stage was more expensive but resulted in lower combined risk of spinal cord ischemia, renal failure, or death than standard one-stage open repair. The authors suggested two-stage hybrid repair of type II thoracoabdominal aneurysms over standard one-stage open repair.

4.2.3.2 F/BEVAR Procedures for Extensive TAAAs

299 fenestrated/branched endovascular (F/BEVAR) procedures were performed for 87 extensive TAAAs (29%) and 212 nonextensive TAAAs (71%) by Diamond et al. [27]. Between the two groups, no perioperative differences were observed in myocardial infarction, stroke, acute kidney injury, dialysis, target artery occlusion, access site complication, or type I or III endoleak ($P > .05$ for all). The incidence of perioperative paraparesis was greater in the extensive TAAA group (8.1% vs 0.5%; $P = .001$). However, the incidence of long-term paralysis was equivalent (2.3% vs 0.5%; $P = .20$), with nearly all patients with paraparesis regaining ambulatory function. On Kaplan-Meier analysis, there were no significant differences between the two groups in 1-year mortality (15.1% vs. 11.4%) and 3-year survival (61.9% vs. 62.5%). Unlike open TAAA repair, the F/BEVAR outcomes were similar for extensive and nonextensive TAAAs. The differences in perioperative paraparesis, branch instability, and type I or III endoleak likely resulted from the increasing length of aortic coverage and number of target arteries involved.

The SPIDER-graft for TAAA hybrid repair [28] was developed to minimize operative trauma, to avoid extracorporeal circulation (ECC) with related increased perioperative risk factors, to further reduce ischemic time of visceral organs, and to reduce the risk of spinal cord ischemia (SCI). The SPIDER-graft uses a combined endovascular thoracic and open abdominal aortic approach for TAAA repair in a single-stage operation, thereby avoiding the need for thoracotomy and ECC while enabling reimplantation of visceral, renal, and lumbar arteries. This device consists of a proximal stent graft for transabdominal retrograde delivery to the descending aorta combined with a distal six branched abdominal device for open abdominal aortic repair. The device has limitations, as it is not applicable to all thoracoabdominal aortic aneurysms (TAAA) and type B acute aortic dissections (TBAD). Its indication is seen predominantly in patients with type III and IV TAAA, especially in patients with unsuitable anatomy for total endovascular repair [29].

4.2.3.3 Open TAAA Repair in High Volume Centres

From October 1986 to December 2014, 3309 consecutive open TAAA repairs were performed on Baylor College of Medicine (Crawford extent I n = 914; extent II n = 1066; extent III n = 660; extent IV n = 669) [30]. 723 (21.8%) were urgent or emergency procedures. Repairs were performed to treat degenerative aneurysm (64.2%) or aortic dissection (35.8%). There were 249 operative deaths (7.5%). Permanent paraplegia and paraparesis occurred after 97 (2.9%) and 81 (2.4%) repairs, respectively. Of 189 patients (5.7%) with permanent renal failure, 107 died in the hospital. Permanent stroke was relatively uncommon (n = 74; 2.2%). The aortic diameter was approximately 1 cm larger in emergency/urgent procedures (6.9 cm) than in elective procedures (6.1 cm there). There were 1864 late deaths, with an estimated postoperative survival of 83.5% at 1 year, 63.6% at 5 years, 36.8%

at 10 years and 18.3% at 15 years. Patients who underwent surgery for dissection showed a significant survival advantage over patients with degenerative TAAA.

Between January 1991 and December 2014, Estrera et al. [31] repaired 1896 descending thoracic (DTAA) or TAAA in 1795 patients. Mean age was 64.2 ± 13.8, and 702 (37%) were women. Of 1896 operations, 646 (34.1%) were DTAA, 316 (16.7%) TAAA extent I, 310 (16.4%) TAAA extent II, 187 (9.9%) TAAA extent III, 348 (18.4%) TAAA extent IV, and 112 (5.9%) TAAA extent V. Adjunct [cerebrospinal fluid drainage (CSFD) + distal aortic perfusion (DAP)] was used in 78.4%. Postoperative stroke was 95/1896 (5%). Early mortality was 302/1896 (15.9%). Moreover, renal failure requiring dialysis occurred in 316 (16.6%). For nonemergent procedures among patients with poor baseline renal function (lowest GFR quartile <48.3), early mortality was 27% (96/356) versus 5.2% (21/405) among those with good baseline renal function (highest GFR quartile >95.3), $P < 0.0001$. For emergent procedures among patients with poor baseline renal function (lowest GFR quartile <48.3), early mortality was 51.9% (28/54) versus 16.7% (4/24) among those with good baseline renal function (highest GFR quartile >95.3), $P = 0.003$. 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.

4.3 Conclusions for Clinical Practice

1. In patients who can undergo both methods (open repair, OR or TEVAR), TEVAR is recommended as the preferred approach for elective repair of aneurysms of the descending thoracic aorta. The same applies to ruptured TAA.
2. There are no such clear recommendations for the repair of TAAA. OR and TEVAR are considered equivalent in patients with low and moderate surgical risk. Nevertheless, hybrid techniques and the use of (F/B) endografts make open repair increasingly rare.
3. CSF drainage plays a role in the prevention of paraplegia and paraparesis and should be considered for open repair of extensive TAAs. The same applies to TEVAR patients with planned extensive thoracic aortic coverage (> 200 mm) or previous abdominal aortic aneurysm (AAA) repair.
4. The experience of the surgeon and the centre is crucial for the results of TAAA repair—this applies to both OR and TEVAR—which makes it absolutely necessary to concentrate care of these patients in high volume centres.

4.4 Perioperative Management

4.4.1 Diagnostic Methods in Descending Thoracic Aortic Disease

4.4.1.1 Guideline Recommendations

European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines [1]

- All patients with clinical suspicion of thoracic aortic disease and abnormal chest radiograph should undergo computed tomographic angiography for diagnosis confirmation. (Class I recommendation/Level of evidence C).
- Multidetector computed tomography angiography from thoracic inlet to common femoral arteries should be considered as the first line diagnostic modality for descending thoracic aortic pathology. (Class IIa recommendation/Level of evidence C).
- For the diagnosis of descending thoracic aortic disease, transoesophageal echocardiography should be considered as a second line imaging when CT is unavailable, contraindicated or inconclusive. (Class IIa recommendation/Evidence level C).
- For patients at increased risk of contrast induced nephropathy, volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions should be considered before contrast administration. (Class IIa recommendation/Level of evidence C).

4.4.2 Preoperative Statin Therapy and Survival After TEVAR

Allar et al. [32] investigated the association between statin use and survival after thoracic endovascular aortic repair (TEVAR). Of 6266 patients who had undergone TEVAR and met the inclusion criteria, 3331 (53%) patients had been taking a statin preoperatively (VQI database). After propensity score matching, 1875 patients were in each cohort. Preoperative statin use was associated with lower rates of any perioperative complication (16.7% vs. 19.6%; p = .022) and also with 5-year mortality (18.8% vs. 24.5%; p = 0.001). When stratified by urgency of procedure, preoperative statin use was associated with lower 5-year mortality after elective TEVAR (14.9% vs. 22.4%), but not after urgent or emergent TEVAR (27.4% vs. 29.1%; p = 0.37). When stratified by pathology, preoperative statin use was associated with significantly lower 5-year mortality for patients with aneurysms but not for patients with dissections. (Although the mortality was also lower for patients with dissection and "other" pathology). A significant increase in statin use was observed in patients with elective TEVAR between 2014 to 2019, from 56% to 64% (p = 0.007). The data suggest that all patients with known thoracic aortic pathology should receive statin therapy unless contraindications for the drug are present. For patients

A L G r a w a n y

undergoing elective TEVAR, the statin prescription percentage should be considered a quality metric.

4.4.3 Anaesthesia and Analgesia

4.4.3.1 Epidural Analgesia, Paravertebral Block and Intercostal Nerve Cryoanalgesia

Epidural analgesia (EA) is not widely used in patients undergoing open TAAA repair, probably owing to the risks of epidural haematoma in patients who need systemic heparinisation and who are at high risk of developing perioperative coagulopathy secondary to massive bleeding. In addition, thoracic epidural anaesthesia may alter early post-operative neurological evaluation, in a setting in which neurological complications, mainly paraplegia, warrant prompt diagnosis and immediate treatment. Monaco et al. [33] reported on 459 patients undergoing open TAAA repair, of whom 409 (89%) received thoracic epidural anaesthesia. Exclusion criteria for EA included dual antiplatelet medication and clopidogrel discontinuation <7 days. After propensity score matching, 43 patients in the conventional analgesia group were compared with 43 in the thoracic epidural analgesia group. Thoracic epidural analgesia showed a significant reduction in post-operative pain ($p < .001$) and no differences in the incidence of acute kidney injury, atrial fibrillation, acute myocardial infarction, and paraplegia. In the thoracic epidural analgesia group, there were no epidural haematomas. The use of thoracic epidural analgesia, if not contraindicated, might be considered for open TAAA repair, as it could improve peri-operative management and promote recovery.

Paravertebral block is reported to be just as effective as epidural analgesia in relieving post-thoracotomy pain, with a significantly lower neurological risk. Minami et al. [34] reported on their experience with 56 consecutive patients who underwent open TAAA repair. 17 patients received the paravertebral block, 39 did not. Paravertebral block significantly reduced numeric rating scale (NRS) scores of postoperative pain at rest and while coughing, and significantly reduced the reintubation rate, the rate of noninvasive positive-pressure ventilation (NPPV), and postoperative pneumonia without complications. Paravertebral block is an effective analgesic method that may reduce postoperative respiratory exacerbations in patients undergoing TAAA repair.

Tanaka et al. [35] reviewed the efficacy of intraoperative intercostal nerve cryoanalgesia for pain control in patients undergoing open descending TAA and TAAA repairs. 241 patients underwent TAA or TAAA repair. Of those, 38 patients were treated with intraoperative cryoanalgesia to the intercostal nerves at the level of fourth to tenth under electromyography guidance and were compared with patients who did not receive cryoanalgesia. For cryoanalgesia, the CryoICE CRYO2 cryoablation probe (AtriCure) was used. One hundred twenty-six patients met the inclusion criteria: 28 in the cryoanalgesia group and 98 in the control group. Both groups

received multilevel paravertebral block and local infiltration with liposomal bupivacaine. Postoperative major complications, length of stay, and discharge to home were not significantly different in either group. However, median ventilation hours were significantly shorter in the cryoanalgesia group (5 vs 12 h, $P < .001$). Opioid use was significantly less in the cryoanalgesia group after postoperative day 4. Indexed morphine milligram equivalences, adjusted with body surface area, and numerical pain scale scores were significantly lower in the cryoanalgesia group throughout the postoperative course. Intercostal nerve cryoanalgesia provided improved pain control after TAA and TAAA repairs. One of the limitations of local anesthetic infiltration is that the effect may only last for hours to a few days. On the contrary cryoanalgesia nerve block may be effective for more than 1 month.

Another series of patients with cryoablation was reported by Clemence et al. [36]. Among 117 patients undergoing open TAA or TAAA repair, 25 patients received cryoablation of their intercostal nerves. There were no significant differences between the non-cryoablation and cryoablation groups in postoperative stroke, paraplegia (5%), pneumonia, and in-hospital mortality (0.9%). However, the average usage of narcotics was significantly reduced in the cryoablation group. Cryoablation of intercostal nerves was a safe and effective measure for postoperative pain control in TAA or TAAA repair.

4.4.4 Neurophysiological Monitoring

4.4.4.1 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) [1]

Spinal cord function monitoring:

- During open thoracic or thoracoabdominal aortic repair, perioperative monitoring of motor and/or somatosensory evoked potentials may be considered to predict spinal cord ischaemia. (Class IIb recommendation/Evidence level C).

4.4.4.2 Studies

Estrera et al. [37] reported their experience with neuromonitoring-guided open thoracoabdominal aortic aneurysm repair. 105 thoracic aorta repairs were performed; 89% of patients (93/105) underwent repair using cerebrospinal fluid drainage and distal aortic perfusion. In addition, somatosensory and motor evoked potentials were monitored during repair, and active intraoperative maneuvers were undertaken in response to changes in the signals. Intraoperative maneuvers included intercostal artery reimplantation. In-hospital mortality was 5.7% (6/105). Immediate spinal cord injury occurred in 1 patient (1%), and 3 patients (3%) had delayed neurologic deficit. Intercostal arteries were reattached in 85% of possible cases (51/60).

Somatosensory evoked potentials achieved adequate readings in 99% of cases (102/103). Loss of somatosensory evoked potential was encountered in 26% of cases (27/102), and return of somatosensory evoked potentials occurred in all cases after intraoperative maneuvers. Motor evoked potentials achieved adequate readings in 96% of cases (99/103). Loss of motor evoked potential was encountered in 50% of cases (50/99), and return of motor evoked potentials occurred in all but 1 case (95%). This patient awoke with an immediate spinal neurologic deficit. Neuromonitoring using somatosensory evoked potentials and motor evoked potentials seems useful during TAAA repair. Note: Motor evoked potentials (MEPs) disappear in the presence of neuromuscular blocking agents, and volatile anaesthetics also cause dose-dependent depression of the MEP at doses within the range used in clinical practice. Total i.v. anaesthesia is preferred if MEPs are to be used [38].

Yoshitani et al. [39] reviewed data from 1214 patients (open surgery 49.5%; endovascular repair 50.5%) with TAA or TAAA repair. MEP monitoring was performed in 631 patients and not performed in the remaining 583 patients. Postoperative motor deficits were observed in 75 (6.2%) patients at discharge, 50 (8.3%) after open and 25 (4.1%) after endovascular repair. Multivariable logistic regression analysis revealed that postoperative motor deficits at discharge did not have a significant association with MEP monitoring (adjusted odds ratio [OR], 1.13; 95% confidence interval [CI], 0.69–1.88; P = .624). The analysis revealed that a history of neural deficits due to cerebral infarction, spinal disease, spinal drainage, and other neurological diseases were associated with an increased incidence of postoperative motor deficits. Alternatively, endovascular procedures were found to be protective.

4.4.5 Prevention of Spinal Cord Ischaemia

4.4.5.1 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) [1]

Recommendations for open TAA repair:

- Cerebrospinal fluid drainage has a role in the prevention of paraplegia and paraparesis and should be considered during extensive open repair of the descending thoracic aorta. (Class IIa; Level of evidence B).
- To prevent spinal cord ischaemia, left heart bypass, allowing distal perfusion, during open type I and II thoraco-abdominal aortic aneurysm repair should be considered. (Class IIa; Level of Evidence C).
- During extensive open descending thoracic aorta repair, moderate hypothermia around 32 °C may be considered to prevent spinal cord ischaemia. (Class IIb; Level of Evidence C).
- Systemic cooling to less than 32 °C in combination with CSF drainage is ***not*** recommended during open descending thoracic aortic repair as it can increase the risk of subdural bleeding. (Class III; Level of evidence B).

Prevention of spinal cord ischaemia in thoracic endovascular repair (TEVAR):

- Patients with planned extensive thoracic aorta coverage (> 200 mm) or previous abdominal aortic aneurysm (AAA) repair have a high risk for spinal cord ischaemia and prophylactic CSF drainage should be considered in endovascular thoracic aorta repair. (Class IIa; Level of Evidence C).

4.4.5.2 Recommendations of the U.S. Aortic Research Consortium [40]

This group defined patients at high risk for spinal cord ischaemia during endovascular repair of complex aortic aneurysms as follows:

- Crawford extent I, II, III thoracoabdominal aortic aneurysms (TAAA) (intended aortic coverage).
- Previous open or endovascular infrarenal aortic surgery.
- "Shaggy" atheromatous aorta.
- Abnormal pelvic perfusion: unilateral hypogastric artery occlusion or bilateral hypogastric artery stenosis.
- Abnormal bilateral vertebral or abnormal left vertebral artery perfusion.

Recommendations for spinal cord protection practices are listed in Table 4.4. In the postoperative setting, the group recommended hourly neurovascular examinations to evaluate the patient's ability to lift each leg off the bed while a CSF drain is in place. If the patient shows any signs of weakness or deficiency in proprioception, SCI should be suspected, and rescue maneuvers should be initiated. These measures are listed in Table 4.5.

4.4.5.3 Studies

An analysis of the VQI database from 2014 to 2019 is available on CSF drain use in complex endovascular aortic repair (TEVAR/cEVAR) [41]. There were a total of 3406 TEVAR/cEVAR procedures, with an overall spinal cord ischemia (SCI) rate of 2.3%. Among 72 patients with SCI, 48 had received prophylactic CSF drain placement and 24 had received therapeutic drain placement. The SCI outcome was significantly worse for the therapeutic group because 79% had documented permanent paraplegia at discharge compared with 54% of the prophylactic group (P = .04). SCI patients receiving a postoperative therapeutic CSF drain had worse survival than those with a preoperative prophylactic CSF drain (50% ± 10% vs 71% ± 9%; log-rank P = .1; Wilcoxon P = .05). These findings speak in favour of preoperative prophylactic CSF drain placement and highlight the need for a randomized clinical trial to examine prophylactic vs therapeutic CSF drain placement in association with TEVAR/cEVAR.

Alqaim et al. [42] reported on their experience with lumbar CSF drainage in 100 patients who underwent fenestrated or branched endovascular aneurysm repair (F/

Table 4.4 Recommendations for spinal cord protection practices used by the U.S. Aortic Research Consortium during endovascular repair of complex TAAA [40]

Protective method	Recommended practice
Blood pressure elevation	ACE inhibitors should be withheld for 48 h preoperatively and resumed postoperatively when the patient is ready for discharge
	β-Blockade should be continued pre- and postoperatively
	Mean arterial blood pressure goal should be not <90 mmHg intraoperatively and continued for not >72 h postoperatively (or until removal of CSF drain is present)
	Blood pressure medication should be resumed within the first 1–2 weeks postoperatively. However, if systolic blood pressure is >200 mmHg, resumption of antihypertensive medication within the first week should be considered
Higher haemoglobin goal	Perioperative haemoglobin goal should be ≥10 mg/dl, with maintenance of haemoglobin goal of ≥10 mg/dl for not >72 h postoperatively (or until removal of CSF drain is presnt)
CSF drain placement	Placement of a preoperative prophylactic CSF drain should be considered for Crawford extent I, II, and III TAAA intended aortic coverage and for otherwise "high-risk" patients
	If a CSF drain was not placed preoperatively, a protocol should be in place for expeditious postoperative therapeutic placement
Repair in staged fashion	A staged approach should be used for Crawford extent I, II, and III TAAA
Revascularisation of spinal cord collaterals	Revascularisation of the left subclavian artery and any occluded hypogastric arteries should be performed when possible

Table 4.5 Rescue maneuvers for suspected spinal cord ischaemia. Recommendations of the U.S. Aortic Research Consortium [40]

Rescue maneuver	Recommended practice
CSF drain placement	Placement of a therapeutic CSF drain if no prophylactic drain was placed
	If a prophylactic was placed, the target CSF drain pop-off pressure should be decreased approximately 5 mmHg from baseline (but not <5 mmHg)
	Increased CSF drainage should be allowed, but not >30 ml/h, with close monitoring for signs of intracerebral haemorrhage
High haemoglobin goal	Confirmation of a haemoglobin goal of ≥10 mg/dl
Elevate mean arterial blood pressure goal	Maintenance of an elevated mean arterial blood pressure goal of not <90 mmHg
Immediate CT or MR of the spine	Evaluation for external compression on the spinal cord from a haematoma that might require surgical evacuation

BEVAR). Successful placement occurred in 98 (98%) of the cases. All lumbar drains were placed before induction of general anesthesia, using fluoroscopy guidance in 28 cases (28%). The majority (82%) were left in place ≤48 h. Nonfunctionality was the most common complication, occurring in 16 (16%) patients. Catheter dislodgment or fracture, CSF leak, and postdural puncture headache were observed in

4 (4%), 7 (7%), and 4 (4%) patients, respectively. The most common bleeding complication was the presence of asymptomatic blood in the CSF (11%), whereas subarachnoid hemorrhage combined with intraventricular hemorrhage occurred in three patients (3%); none of these patients required surgical drainage or intervention. No infectious complications were observed. These experiences demonstrate that lumbar drain placement can be performed successfully but is associated with a significant rate of nonfunctionality and a diverse range of complications. Therefore, placement of a prophylactic lumbar drain to avert SCI risk should always be weighed against the risk of drain complications.

Potential serious complications associated with perioperative lumbar drain (LD) placement for endovascular aortic repair were also highlighted by Plotkin et al. [43]. A total of 309 LDs had been placed in 268 consecutive patients for 222 thoracic endovascular aortic repairs, 85 complex endovascular aortic repairs, and 2 EVARs. Most drains were placed prophylactically (96%), with a technical success rate of 98%. The overall complication rate was 8.1% (4.2% major and 3.9% minor). Major complications included spinal haematoma with paraplegia in 1 patient, intracranial haemorrhage in 2 patients, meningitis in 2 patients, arachnoiditis in 3 and CSF leak requiring a blood patch in 3 patients. Patients who had undergone previous LD placement had experienced significantly more major LD-related complications (12.2% vs. 3%). The rate of total LD-associated complications did not differ between prophylactic and emergent therapeutic placements (8.1% vs 7.7%; P = 1.00). The complications associated with LD placement can be severe even when performed by a dedicated team. Although these risks are justified for therapeutic LD placement, the benefit of prophylactic LD placement to prevent paraplegia should be weighed against these serious complications.

The need to carefully weigh the benefits and harms of CSF drainage (CSFD) is also underlined by the findings of Kärkkäinen et al. [44]. These authors assessed CSF drainage-related complications in 187 patients undergoing first-stage or completion fenestrated branched endovascular repair for pararenal or thoracoabdominal aortic aneurysms. Nineteen patients (10%) had 22 CSF drainage-related complications after 21 aortic procedures (9%). Complications were graded as severe to moderate in 17 patients (9%). There were 12 patients (6%) with intracranial hypotension, including three (2%) who had intracranial hemorrhage and nine (5%) with post dural puncture headache requiring blood patches in six. Another six patients (3%) developed spinal hematomas resulting in paraplegia in two (1%) and transient paraparesis in two (1%). Technical difficulties were experienced in 57 drain insertions (24%). Of 13 study patients who developed spinal cord injuries during aortic procedures, 4 (31%) were attributed to CSFD. Because of the high rate of spinal hematomas, the authors no longer recommend CSFD during first-stage TEVARs or for patients with pararenal or extent IV TAAAs who require shorter segments of supraceliac coverage. In addition, CSFD is individualized for patients with extent III TAAAs and used routinely for extent I and II TAAAs. Given the potential for serious complications, the risks of prophylactic CSFD should be carefully weighed against its potential benefits.

The report by Kitpanit et al. [45] is also critical. They analysed 106 consecutive patients with TAAAs treated with F/B-EVAR. Prophylactic CSFD was used in 78 patients (73.6%), and 28 patients (26.4%) underwent F/B-EVAR without CSFD. Four patients (3.8%) with prophylactic drainage developed spinal cord ischaemia (SCI), including two patients with permanent paraplegia and two patients with paraparesis. Multivariate analysis revealed that greater extent of thoracic aortic coverage and intraoperative blood loss were the significant risk factors for SCI. Six patients (7.6%) experienced major CSFD-related complications, including subarachnoid hemorrhage in 2.6% (2), spinal hematoma in 2.6% (2), cerebellar hemorrhage in 1.3% (1), and spinal drain fracture requiring surgical laminectomy in 1.3% (1). Technical difficulties during CSFD catheter placement were noted in seven patients (9.0%). The incidence of SCI after F/B-EVAR with selective CSFD was low, and risk factors for SCI were greater with extent of thoracic aortic coverage and intraoperative blood loss. However, the incidence of major CSFD-related complications exceeded the incidence of SCI, and CSFD significantly increased both intensive care unit and total hospital length of stay. Therefore, routine prophylactic CSFD may not be justified, and a prospective randomized trial of CSFD in patients undergoing F/B-EVAR seems appropriate.

4.4.6 Transfusion Strategy

Monaco et al. [46] performed a propensity score matched study to assess whether the introduction of a rotational thromboelastometry (ROTEM) based transfusion strategy reduces allogenic blood transfusion and affects morbidity in patients undergoing open TAAA repair. 547 consecutive patients were included. After propensity score matching, 77 patients in the ROTEM algorithm group were successfully matched with 77 patients in the standard algorithm group. During the study period, all patients received intraoperative infusion of tranexamic acid (1 g over 20 min followed by 250 mg/h) to prevent hyperfibrinolysis. A cellsaver machine was used to process and re-infuse salvaged blood. If needed, left heart bypass was used. The target activated clotting time (ACT) during bypass was >190 s. Heparin was administrated at a maximum starting dose of 70 IU/kg and reversed at the end of surgery with protamine in a 1:1 ratio. ACT was serially assessed during surgery and additional heparin was administered as necessary. Packed RBCs were transfused if the haematocrit was <30%. ROTEM tests were performed in all patients after heparin reversal with protamine. As the aim of ROTEM is to treat peri-operative coagulopathy associated with microvascular bleeding, the test was only performed after all surgical sources of bleeding were under control. In the event of a maximum clotting firmness in the EXTEM (extrinsic) < 45 mm and in the FIBTEM (fibrinogen) < 8 mm, 2 g of fibrinogen were administered. Conversely with a clotting firmness in the FIBTEM >10 mm, platelets were transfused. Patients managed with ROTEM received fewer red blood cells units (and a lower volume of fresh frozen plasma. In addition, fewer patients received fresh frozen plasma (35% vs. 97%;

p < .001). Patients in the ROTEM group showed a significant decrease in the occurrence of pulmonary complications (44% vs. 83%; p = .01). In conclusion, a ROTEM guided transfusion strategy significantly limited the quantity of transfused blood products during open TAAA repair, improving clinical outcomes while reducing costs, allowing for better resource distribution in a setting where blood loss is relevant.

4.4.7 Minimally Invasive Segmental Artery Coil Embolisation to Prevent Spinal Cord Ischaemia

Sequential coil embolisation of intercostal arteries has been suggested as a method to protect the spinal cord after TEVAR through stimulation of collateral flow of the spinal cord [47]. The value of the procedure cannot yet be assessed [48], but a feasibility study is now available in 57 patients who underwent ischaemic preconditioning using minimally invasive segmental coil embolisation prior to endovascular TAAA repair [49]. The time interval between the last session of coiling and the complete exclusion of the aneurysm was a median of 65 days (mean 83 ± 62 days) with a wide range (7–248). Endovascular exclusion of the thoracoabdominal aneurysm was performed in 55 patients. 1 patient died postoperatively, and none of the 54 patients alive after the complete exclusion of their aneurysm developed spinal cord ischaemia. Minimally invasive segmental artery coil embolisation (MISACE) to precondition the paraspinous collateral network is clinically feasible, but the ultimate proof of MISACE's success requires a randomised trial. The trial protocol for a randomised controlled multicentre has been published, where 500 patients will be randomised in a 1:1 ratio to standard aneurysm repair or to MISACE in 1–3 sessions followed by repair. The study intends to include endovascular or open repair of TAAA, Crawford type II or III [50].

4.4.8 Thromboprophylaxis

4.4.8.1 Guidelines

There are no specific guideline recommendations for thromboprophylaxis in patients with endovascular or open TAA repair. Only the guidelines of the American College of Chest Physicians [51] recommend for patients with TAAA repair VTE (Venous Thromboembolism) prophylaxis with low molecular weight heparin (LMWH) by analogy to major abdominal-pelvic surgery patients. The risk of thrombosis must be balanced against the risk of bleeding, especially with concomitant anticoagulant therapy and platelet aggregation inhibition.

4.4.8.2 Studies

Ramanan et al. [52] used the NSQIP database to define the incidence of overall and postdischarge VTE after major vascular operations and assess risk factors associated with VTE development. 45,548 vascular procedures were identified including 361 patients with open thoracoabdominal aortic aneurysm (TAAA) repair and 732 thoracic endovascular aortic repairs (TEVAR). Open TAAA repair and TEVAR had the highest rates of VTE among all vascular procedures identified, at 4.2% and 2.2%, respectively. The authors attributed this to the fact that spinal drains are placed for protection from paraplegia in most patients undergoing TAAA repairs and in many undergoing TEVARs, and consequently, they do not receive VTE prophylaxis for the first 48 to 72 h. As a significant proportion of VTE events were observed after discharge, the authors recommended continuing VTE prophylaxis even beyond patient discharge. Aziz et al. [53] also emphasised the high incidence of VTE after vascular surgery, which was higher among cardiac surgery (2%) and vascular surgery (0.99%) patients as compared with that of general surgery patients (0.66%). They emphasised that apparently intraoperative anticoagulation does not prevent the occurrence of deep venous thrombosis (DVT) in the postoperative period. They recommended that these patients should receive DVT prophylaxis in the perioperative period, like other surgical patients, but did not provide data specifically on TAA.

4.4.9 Endoleak

4.4.9.1 The European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines Recommend [1]

- Any early or late type I or III endoleak after endovascular repair of the descending thoracic aorta should undergo prompt intervention (recommendation class 1, level of evidence C).
- Type II and IV endoleaks may be followed by serial CTA/MRI at 3 and 6 months. If the aneurysm sac grows >10 mm, endovascular or open repair is required. If the aneurysm sac growth is <10 mm, CTA/MRI is indicated at 3 and 6 months.

4.4.9.2 Reviews

Ameli-Renani et al. [54] reviewed the treatment options for secondary endoleaks after EVAR and TEVAR, defined as those detected more than 30 days after the procedure and after previous negative imaging. They summarized classification of endoleaks and their management as shown in Table 4.6.

Belvroy et al. [55] performed a systematic review of the literature on endoleak type 1b, in patients with aortic aneurysm after TEVAR based on 16 studies. The

Table 4.6 Summary of classification of endoleaks and their management [54]

Endoleak	Cause of sac perfusion	Management
1	Flow from the proximal or distal graft attachment site	Prompt
1a	Proximal graft attachment site	Angioplasty, Palmaz or cuff extension, chimney extension and embolisation
1b	Distal graft attachment site	Angioplasty and extension of distal limb
1c	Endoleak at the site of an iliac occluder plug	Insertion of an additional iliac occluder plug or embolisation
2	Retrograde flow through patent aortic side branch vessels	Conservative if sac size stable. Embolisation if sac size increase
3	Mechanical graft failure	Prompt
3a	Modular disconnection Leak at a fenestration, branch or visceral stent	Placement of additional endograft components
3b	Fabric tear	Relining the endograft by deploying a new endograft within the preexisting graft
4	Graft porosity	Conservative Transient phenomenon
5	Sac size increase with no visible Endoleak (Endotension)	May consider catheter angiography with cone beam CT

reported incidence of early endoleaks (< 30 days after intervention) was 1.3–8.1% and that of late endoleaks (> 30 days after intervention) 3.1% to 5%. Treatment was required in most cases and was usually performed with distal extension of the stent graft.

A systematic review and meta-analysis summarises the evidence for endoanchor use in EVAR and TEVAR to treat type Ia endoleak (TIaE) and graft migration [56]. In patients where endoanchors were used during the primary EVAR procedure, the rate of TIaE was 3.5% at a mean follow up of 15.4 months. A total of 107 EVAR patients underwent secondary fixation with a technical success of 91.8%. 74 patients were available at a mean follow up of 10.7 months. Of the 74 secondary patients available, 22.6% had a post-operative TIaE. Of those treated exclusively for TIaE, 39.3% continued to have persistent endoleak despite endoanchors. Alternative strategies such as proximal endograft extension may have better outcomes for treating established TIaE. Evidence for endostapling in TEVAR was sparse. A total of 66 TEVAR patients underwent endoanchor fixation (29 primary, 31 secondary, six indeterminate). Technical success in endoanchor deployment was 90.3%. The overall rate of TIaE was 8.7%. The weighted all cause 30-day mortality was 11.9%. Compared to EVAR, endostapling in TEVAR is associated with lower technical success, higher perioperative mortality, and potential serious adverse events. The current evidence is hindered by short term follow up and lack of case controlled trials, among other drawbacks, to recommend endoanchor use in routine clinical practice.

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Chapter 5
Abdominal Aortic Aneurysm (AAA)



5.1 Guidelines

5.1.1 European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms [1]

5.1.1.1 General Information

- Recommendation 3: Abdominal aortic aneurysm repair should only be considered in centres with a minimum yearly caseload of 30 repairs. (Class IIa recommendation; Level of evidence C)
- Recommendation 4: Abdominal aortic aneurysm repair should **not** be performed in centres with a yearly caseload <20. (Class III; Level B)
- Recommendation 9: In patients with abdominal aortic aneurysms computed tomography angiography is recommended for therapeutic decision making and treatment planning, and for the diagnosis of rupture. (Class I; Level C)

5.1.1.2 Screening/Surveillance

- Recommendation 12: Population screening for abdominal aortic aneurysm with a single ultrasound scan for all men at age 65 years is recommended. (Class I; Level A)
- Recommendation 14: Population screening for abdominal aortic aneurysm in women is **not** recommended. (Class III; Level B)
- Recommendation 15: All men and women aged 50 years and older with a first degree relative with an abdominal aortic aneurysm may be considered for abdominal aortic aneurysm screening at 10 year intervals. (Class IIb; Level C)

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- Recommendation 17: Ultrasonography is recommended for aneurysm surveillance; every 3 years for aneurysms 3–3.9 cm in diameter, annually for aneurysms 4.0–4.9 cm, and every 3–6 month for aneurysms ≥5.0 cm. (Class I; Level B)

5.1.1.3 Indication for Elective Repair

- Recommendation 22: In men, the threshold for considering elective abdominal aortic aneurysm repair is recommended to be ≥5.5 cm diameter. (Class I; Level A)
- Recommendation 23: In women with acceptable surgical risk the threshold for considering elective abdominal aortic aneurysm repair may be considered to be ≥5.0 cm diameter. (Class IIb; Level C)
- Recommendation 24: When rapid abdominal aortic aneurysm growth is observed (≥1 cm/year), fast track referral to a vascular surgeon with additional imaging should be considered. (Class IIa; Level C)
- Recommendation 25: Emergency referral to a vascular surgeon of patients with symptomatic abdominal aortic aneurysm is recommended. (Class I; Level C)
- Recommendation 65: Symptomatic non-ruptured abdominal aortic aneurysms should be considered for deferred urgent repair ideally under elective repair conditions. (Class IIa; Level B)
- Recommendation 26: Patients who initially are not candidates for abdominal aortic aneurysm repair should be considered for continued surveillance, referral to other specialists for optimisation of their fitness status and then reassessed. (Class IIa; Level C)
- Recommendation 116: Early treatment may be considered for saccular abdominal aortic aneurysms, with a lower threshold for elective repair than for standard fusiform abdominal aortic aneurysms. (Class IIb; Level C)

5.1.1.4 Elective AAA Repair

- Recommendation 60: In most patients with suitable anatomy and reasonable life expectancy, endovascular abdominal aortic aneurysm repair should be considered as the preferred treatment modality. (Class IIa; Level B)
- Recommendation 61: In patients with long life expectancy, open abdominal aortic aneurysm repair should be considered as the preferred treatment modality. Class IIa; Level B)
- Recommendation 62: In patients with limited life expectancy, elective abdominal aortic aneurysm repair is **not** recommended. (Class III; Level B)

5.1.1.5 Techniques for Elective AAA Open Repair

- Recommendation 50: Intravenous heparin (50–100 IU/kg) is recommended before aortic cross clamping. (Class I; Level C)
- Recommendation 52: In selected cases of suspected insufficient perfusion of pelvic organs with risk of colonic ischaemia, reimplantation of the inferior mesenteric artery may be considered during open abdominal aortic aneurysm repair. (Class IIb; Level C)
- Recommendation 53: In open abdominal aortic aneurysm repair, it is recommended to preserve the blood flow to at least one internal iliac artery to reduce the risk of buttock claudication and colonic ischaemia. (Class I; Level C)
- Recommendation 54: In patients treated for abdominal aortic aneurysm by open repair, prophylactic use of mesh reinforcement of midline laparotomies may be considered for patients at high risk of incisional hernia. (Class IIb; Level A)

5.1.1.6 Techniques for Elective AAA Endovascular Repair

- Recommendation 55: An ultrasound guided percutaneous approach should be considered in endovascular aortic aneurysm repair. (Class IIa; Level B)
- Recommendation 56: Preservation of large accessory renal arteries (>3 mm) or those that supply a significant portion of the kidney (>1/3) may be considered in endovascular aneurysm repair. Class IIb; Level C)

5.1.1.7 Management of Ruptured AAA

- Recommendation 63: In haemodynamically stable patients with suspected ruptured abdominal aortic aneurysm, prompt thoracoabdominal computed tomography angiography is recommended as the imaging modality of choice. (Class I; Level B)
- Recommendation 74: In patients with ruptured abdominal aortic aneurysm and suitable anatomy, endovascular repair is recommended as a first option. (Class I; Level B)
- Recommendation 69: In patients undergoing endovascular repair for ruptured abdominal aortic aneurysms, a bifurcated device, in preference to an aorto-uniiliac device, should be considered whenever anatomically suitable. (Class IIa; Level C)

5.1.2 Society for Vascular Surgery

These guidelines recommend [2]:

5.1.2.1 Screening/Surveillance

- We recommend a one-time ultrasound screening for AAAs in men or women 65–75 years of age with a history of tobacco use. Level of recommendation 1 (strong), quality of evidence A (high).
- We suggest ultrasound screening for AAA in first degree relatives of patients who present with an AAA. Screening should be performed in fist degree relatives who are between 65 and 75 years of age or in those older than 75 years and in good health. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest a one-time ultrasound screening for AAAs in men or women older than 75 years with a history of tobacco use and in otherwise good health who have not previously received a screening ultrasound examination. Level of recommendation 2 (weak), quality of evidence C (low).
- If initial ultrasound screening identified an aortic diameter >2.5 cm but <3 cm, we suggest rescreening after 10 years. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest surveillance imaging at 3-year intervals for patients with an AAA between 3.0 and 3.9 cm. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest surveillance imaging at 12-month intervals for patients with an AAA between 4.0 and 4.9 cm in diameter. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest surveillance imaging at 6-month intervals for patients with an AAA between 5.0 and 5.4 cm in diameter. Level of recommendation 2 (weak), quality of evidence C (low).

5.1.2.2 Indication for Elective Repair

- We recommend repair for the patient who presents with an AAA and abdominal or back pain that is likely to be attributed to the aneurysm. Level of recommendation 1 (strong), quality of evidence C (low).
- We recommend elective repair for the patient at low or acceptable surgical risk with a fusiform AAA that is ≥5.5 cm. Level of recommendation 1 (strong), quality of evidence A (high).
- We suggest elective repair for the patient who presents with a saccular aneurysm. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest repair in women with AAA between 5.0 cm and 5.4 cm in maximum diameter. Level of recommendation 2 (weak), quality of evidence B (moderate).

These guidelines generally recommend EVAR for elective AAA repair. OAR of an AAA is suggested for patients who do not meet the anatomic requirements for endovascular repair, including short or angulated landing zones, excessive thrombus, multiple large accessory renal arteries, and small and tortuous access vessels with concomitant occlusive disease. However, fenestrated, branched, and chimney or

snorkel grafts have expanded the range of complex aortic anatomy potentially treatable by EVAR. OAR may be required for treatment of a persistent endoleak and aneurysm sac growth after EVAR or for treatment of a mycotic aneurysm or infected graft.

5.1.2.3 Management and Perioperative Outcome of Elective Repair

- We suggest that elective EVAR be performed at centers with a volume of at least 10 EVAR cases each year and a documented perioperative mortality and conversion rate to OAR of 2% or less. Level of recommendation 2 (weak), quality of evidence C (low).
- We suggest that elective OAR for AAA be performed at centers with an annual volume of at least 10 open aortic operations of any type and a documented perioperative mortality of 5% or less. Level of recommendation 2 (weak), quality of evidence C (low).

5.1.2.4 Management of Ruptured AAA

- We recommend immediate repair for patients who present with a ruptured aneurysm. Level of recommendation 1 (strong), quality of evidence A (high)
- We suggest a door-to-intervention time of <90 min, based on a framework of 30–30–30 min, for the management of the patient with a ruptured aneurysm. Level of recommendation: Good Practice Statement, quality of evidence: Ungraded
- An established protocol for the management of ruptured AAA is essential for optimal outcomes. Level of recommendation: Good Practice Statement, quality of evidence: Ungraded
- We recommend implementing hypotensive hemostasis with restriction of fluid resuscitation in the conscious patient. Level of recommendation 1 (strong), quality of evidence B (moderate).
- If it is anatomically feasible, we recommend EVAR over open repair for treatment of a ruptured AAA. Level of recommendation 1 (strong), quality of evidence C (low).

5.1.2.5 Management in Symptomatic Patients

- Should repair of a symptomatic AAA be delayed to optimize coexisting medical conditions, we recommend that the patient be monitored in an ICU setting with blood products available. Level of recommendation 1 (strong), quality of evidence C (low).

- We suggest renal artery or SMA angioplasty and stenting for selected patients with symptomatic disease before EVAR or OAR. Level of recommendation 2 (weak), quality of evidence C (low).

5.1.3 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease

These guidelines recommend [3]:

- In patients with nonruptured AAA with low to moderate operative risk and who have anatomy suitable for either open or EVAR, a shared decision-making process weighing the risks and benefits of each approach is recommended. Class of recommendation [COR] 1; Level of evidence [LOE] A)
- In patients undergoing elective endovascular repair for nonruptured AAA, adherence to manufacturer's instructions for use is recommended. (COR 1; LOE B-NR)
- In patients with nonruptured AAA and a high perioperative risk, EVAR is reasonable to reduce the risk of 30-day morbidity, mortality, or both. (COR 2a; LOE B-NR)
- For patients with nonruptured AAA, a moderate to high perioperative risk, and anatomy suitable for an FDA-approved fenestrated endovascular device, endovascular repair is reasonable over open repair to reduce the risk of perioperative complications. (COR 2a; LOE B-NR)
- In patients presenting with ruptured AAA who have suitable anatomy, endovascular repair is recommended over open repair to reduce the risk of morbidity and mortality. (COR 1; LOE B-R)

5.2 Results

5.2.1 AAA-Screening

5.2.1.1 Systematic Review/Meta-Analysis

In 2014, the US Preventive Services Task Force (USPSTF) recommended one-time ultrasound screening for AAA in asymptomatic men aged 65–75 years who had ever smoked (B recommendation). Guirguis-Blake et al. [4] prepared a systematic review based on 50 studies (n = 323,279) to inform an updated recommendation by the USPSTF on the evidence related to the effectiveness of 1-time and repeat screening for AAA and possible related harms, as well as the effectiveness and related harms of treatment (pharmacotherapy or surgery) of small AAAs (3.0–5.4 cm in diameter). Meta-analysis of population-based randomized clinical trials (RCTs) estimated that a screening invitation to men 65 years or older was associated with a

A L G r a w a n y

reduction in AAA-related mortality over 12–15 years (OR 0.65), AAA-related ruptures over 12–15 years (OR, 0.62), and emergency surgical procedures over 4–15 years (OR, 0.57). In contrast, no significant association with all-cause mortality benefit was seen at 12- to 15-year follow-up (relative risk 0.99). One-time screening was associated with significantly more procedures over 4–15 years in the invited group compared with the control group (OR, 1.44). One-time AAA screening in men 65 years or older was associated with decreased AAA-related mortality and rupture rates but was not associated with all-cause mortality benefit. Higher rates of elective surgery but no long-term differences in quality of life resulted from screening. Overdiagnosis and overtreatment were not addressed in these trials but may be important considerations given that most screen detected aneurysms are small.

5.2.1.2 Screening for AAA in Women

The aim of the Female Aneurysm screening STudy (FAST) was to determine the uptake of screening and prevalence of AAA in a group of women deemed at high risk of having an AAA using data that were readily available in UK primary care records (white European ethnicity, current/ex-smokers and/or past history of coronary artery disease) [5]. Women aged 65–74 years deemed at high risk of having an AAA were invited to attend ultrasound screening (July 2016 to March 2019) for AAA. Of the 5998 women invited for screening, 5200 (86.7%) attended their screening appointment and 5190 (86.5%) had ultrasound screening. 15 AAAs larger than 29 mm were detected (prevalence 0.29%). Current smokers had the highest prevalence (0.83%) but lowest attendance (75.2%). Three AAAs greater than 5.5 cm were identified and referred for consideration of surgical repair; one woman underwent repair. AAA prevalence in women with risk factors for AAA was lower than 0.35%, the prevalence threshold below which AAA screening for men is likely to be ineffective. Screening women at high risk for AAA is unlikely to be either cost-effective or clinically effective if those AAA detected have a low likelihood of repair. A reduction in quality-of-life outcomes was identified after screening. This suggests that a screening programme for AAA in women may cause harm. Health services worldwide should exercise great caution before considering implementation of targeted screening of women for AAA.

5.2.1.3 Screening Effectiveness

The NHS Abdominal Aortic Aneurysm Screening Programme (NAAASP) has been implemented since 2013. Men with a large aneurysm >54 mm, either at first screen or during surveillance, are referred for intervention. The aim of a study presented by Meecham [6] was to explore outcomes in these men and to see whether there was any regional variation in treatment rates and type of repair. Some 3026 men were referred for possible intervention. Some 2624 (87%) men had planned AAA repair,

with a peri-operative mortality of 1.3%. The mean age of this cohort was 67.6 years (range 64–92 years), with a 30-day mortality of 0.4% after EVAR and 2.1% after open repair. The method of repair remained consistent year on year, with roughly equal numbers undergoing endovascular (50%) and open surgical repair (48%); 2% unknown. However, there was a very wide range of EVAR use for screen detected AAA (from 22 to 97%). Considering the high mortality rate of ruptured AAA (rAAA), the authors described the English AAA screening programme as effective.

Using the National Inpatient Sample from 2004 to 2015, Dansey et al. [7] identified 65,125 admissions for ruptured AAAs and 461,191 repairs for intact AAAs. The number of patients admitted for rAAA decreased significantly over the observation period, from 6461 in 2004 to 4848 in 2015 ($p < 0.001$). Of all patients with rAAA undergoing repair, 14,012 (31%) underwent EVAR and 31,693 (69%) underwent open repair. Overall in-hospital mortality following repair of ruptured AAA was 35%. However, there was a decrease in mortality over the study period, from 42% in 2004 to 28% in 2015 ($P < .001$). Of the 65,125 patients admitted with a diagnosis of rupture, 44,155 (68%) would have been ineligible for screening. Of the patients who did not qualify, 27,653 (63%) were aged >75 years, 10,603 (24%) were aged <65 years, and 16,103 (36%) were women. In conclusion, the majority of patients with a ruptured AAA did not meet criteria for screening, suggesting a need for reconsideration of the current screening paradigm. Of those admitted with a ruptured AAA, over half were older than 75 and almost a quarter were younger than 65 and with women making up a significant portion of the population. Based on prior risk factors such as age, cardiovascular disease and tobacco use, further studies are needed to design a more sensitive screening algorithm to capture the high-risk patients in these excluded populations.

The identical question of the extent to which rAAA patients would have been covered by the US screening programme was addressed by Mota et al. [8] using the Vascular Quality Initiative (VQI) patient population from 2003 to 2019. A total of 5340 patients underwent rAAA repair. The majority (66%) were screening-ineligible according to the Centers for Medicare and Medicaid reimbursement guidelines. The largest contributors to screening ineligibility were males less than 65 years of age with a smoking history or family history of AAA (25%), males greater than 75 years of age with a smoking history (25%), and females older than 65 years of age with a smoking history (19%). The data suggest that three high-risk populations may benefit from expansion of AAA screening guidelines: males with a smoking history or family history of AAA between ages 55 and 64 years, female smokers older than 65 years, and male smokers older than 75 years who are otherwise in good health.

5.2.1.4 Screen Detected Sub-Aneurysmal Aortas

A population-based Swedish cohort study [9] aimed to evaluate the long-term natural course of men with a screen detected sub-aneurysmal aorta (SAA), that is an aortic diameter of 25–29 mm, regarding development to an AAA, with a focus on

the proportion progressing to the threshold diameter for surgical repair (≥55 mm). Between 1 January 2006 and 31 December 2014, a total of 52,221 men were screened. A total of 1020 men with SAA were detected (2.0%), of whom 940 (92.2%) had any follow up scan after the baseline screening. The Kaplan-Meier estimated incidence of AAA ≥ 30 mm development after the 5 year follow up was 65.8%, all <55 mm. The incidence after the 10 year follow up was 95.1%, and 29.7% reached ≥55 mm. All 41 SAAs that reached >55 mm in diameter were >30 mm at the 5-year follow-up. 32 of these patients underwent AAA repair, with 100% survival. According to this study, a majority of SAAs eventually progress to an AAA, of which 30% are estimated to eventually reach the threshold for repair within 10 years. The results indicate that the cohort of men with SAAs at risk of later AAA repair can safely be identified by a single scan 5 years after their initial screening.

5.2.2 Intact AAA: Randomized Trials

5.2.2.1 OVER-Trial

The Open versus Endovascular Repair (OVER) trial included a total of 881 randomized patients with asymptomatic AAA, 444 with EVAR and 437 with open repair (OAR). The primary outcome was all-cause mortality. The 30-day mortality had been 0.5% with EVAR and 2.5% with OAR. Lederle et al. [10] published long-term results of this study. Patients were followed for up to 14 years after randomisation. A total of 302 patients (68.0%) in the endovascular-repair group and 306 (70.0%) in the open-repair group died. During the first 4 years of follow-up, overall survival appeared to be higher with endovascular repair than with open repair; from year 4 through year 8, overall survival was higher in the open-repair group; and after 8 years, overall survival was once again higher in the endovascular-repair group. None of these trends were significant. In this study, long-term survival was similar for EVAR and OAR, but the number of patients requiring a second procedure was higher for EVAR (117/439; 26.7%) vs OAR (85/429; 19.8%). These results were not consistent with the findings of worse performance of endovascular repair with respect to long-term survival that was seen in the two European trials. Of note, deaths from cancer were not more common in the endovascular-repair group than in the open-repair group, despite the presumed higher exposure to ionizing radiation among patients in the endovascular-repair group. There were a total of 80 deaths from cancer in the endovascular-repair group (18%) and 85 in the open-repair group (19.5%).

5.2.2.2 EVAR-2 Trial

The randomized EVAR-2 trial is the sole randomized trial to identify whether EVAR reduces mortality in patients physically ineligible for open repair [11]. Between September 1, 1999 and August 31, 2004, 404 patients were recruited. Patients of both sexes who were at least 60 years of age with large aneurysms (≥5.5 cm in diameter) and deemed physically ineligible for open repair were randomly assigned (1:1) to undergo either endovascular repair (n = 197) or no-intervention (n = 207). Mean follow-up until death or censoring was 4.2 years. There were 187 deaths (22.6 per 100 person-years) in the EVAR group and 194 (22.1 per 100 person-years) in the no-intervention group. By 12 years of follow-up the estimated survival was 5.3% in the EVAR group and 8.5% in the no-intervention group; there was no significant difference in life expectancy between the groups (both 4.2 years; P = 0.97). However, overall aneurysm-related mortality was significantly lower in the EVAR group (3.3 deaths per 100 person-years compared with 6.5 deaths per 100 person-years in the no-intervention group, P = 0.019). In this trial, EVAR did not increase overall life expectancy in patients ineligible for open repair, but could reduce aneurysm-related mortality.

5.2.2.3 Mesenteric Artery Embolisation/Aneurysm Sac Coil Embolisation

Samura et al. [12] aimed to evaluate the effect of inferior mesenteric artery (IMA) embolization during endovascular aneurysm repair (EVAR) in patients at high risk of type II endoleak (T2EL) in a randomized controlled trial (RCT). High risk T2EL was defined as IMA patency with (1) IMA ≥ 3 mm, (2) lumbar arteries >2 mm, or (3) an aortoiliac-type aneurysm. For embolistion mainly the Amplatzer Vascular Plug was used. 106 patients were randomized. The incidence of T2EL was significantly lower in the embolisation group with 24.5% vs. 49.1% in the control group (p = 0.009). The median follow-up time was 20.0 ± 10.8 months in the intention-to-treat analysis. The aneurysm sac shrunk significantly more in the treatment group (−5.7 ± 7.3 mm vs. −2.8 ± 6.6 mm; p = 0.037) and the incidence of aneurysm sac growth related to a T2EL was significantly lower with embolisation (3.8% vs. 17.0%; p = 0.030). Complications or reinterventions due to IMA embolisation were not seen. The data recommend the method for prevention of T2EL in the defined risk group.

A second randomised study [13] also addressed the prevention of T2-EL. In this so-called SCOPE 1 (Sac COil embolisation for Prevention of Endoleak) study, patients at high risk of type II EL were randomised to standard EVAR (n = 47) or EVAR with non-selective aneurysm sac coil embolisation (ASCE; n = 47). Before deployment of the contralateral iliac extension, a guidewire was pushed in the aneurysm sac. After deployment of the contralateral iliac extension, a microcatheter was placed in the sac to perform non-selective embolisation using removable coils. There were no intraoperative complications. At 12 months, a significant reduction in T2EL rate was seen, 40.5% with standard EVAR vs. 14.3% with coil

embolisation. Freedom from EL and reinterventions was significantly higher with embolisation (26/47 events with standard EVAR vs.11/47 with coil embolisation). Aneurysm sac volume and diameter decreased significantly in the embolisation group compared to control. Spinal cord ischaemia, colonic infarction or coil migration were not observed after coil embolisation. For selected patients at risk of EL, ASCE seems effective in preventing EL at 1, 6, and at 12 months. However, the difference was not statistically significant at 24 months. ASCE decreases the reintervention rate 2 years after EVAR. A significantly faster aneurysm volume shrinkage was observed at 1 and 2 years following surgery. Non-selective embolisation of the aneurysm sac seems safe and not technically demanding.

5.2.3 Intact AAA: Meta-Analyses

5.2.3.1 Surgery for Small Asymptomatic Abdominal Aortic Aneurysms

Guidelines recommend repair of large asymptomatic AAAs (greater than 5.5 cm in diameter). Debate continues over the roles of early repair versus surveillance with repair on subsequent enlargement in people with asymptomatic AAAs of 4.0–5.5 cm diameter. A Cochrane review was prepared to compare mortality and costs, as well as quality of life and aneurysm rupture as secondary outcomes, following early surgical repair versus routine ultrasound surveillance in people with asymptomatic AAAs between 4.0 and 5.5 cm in diameter [14]. Four trials with 3314 participants fulfilled the inclusion criteria. There was no evidence of an advantage to early repair for small AAA (4.0–5.5 cm), regardless of whether open repair or EVAR is used and, at least for open repair, regardless of patient age and AAA diameter. Thus, neither early open nor early EVAR of small AAAs is supported by currently available evidence.

5.2.3.2 EVAR vs. Open Surgical Repair

A meta-analysis was undertaken of published high-quality long-term data of EVAR vs. open surgical repair for unruptured AAA [15]. Seven RCTs reporting a total of 2983 patients, 1518 of whom underwent EVAR and the remaining 1465 open repair, were included in quantitative synthesis. Meta-analysis found significantly lower odds of 30 day (OR, 0.36; 95% CI 0.20–0.66) and in hospital mortality with EVAR. Meta-analysis of the three trials reporting long term follow up found no significant difference in all cause mortality at any time between EVAR and open repair. The hazard of all cause (HR 0.62; 95% CI 0.42–0.91) and aneurysm related death within 6 months (HR 0.42; 95% CI 0.24–0.75) was significantly lower in patients who underwent EVAR, but with further follow up, the pooled hazard estimate moved in favour of open surgery; in the long term (>8 years) the hazard of aneurysm related mortality was significantly higher after EVAR (HR 5.12; 95% CI

1.59–16.44). Compared with open surgery, EVAR results in a better outcome during the first 6 months but carries an increased risk of aneurysm related mortality after 8 years.

Another meta-analysis of long-term outcomes of EVAR vs open repair was based on 3 randomised trials and 68 observational studies including 151,092 (EVAR) and 148,692 (OAR) patients, respectively [16]. In this analysis, EVAR was associated with higher long-term all-cause mortality, reintervention and secondary rupture rates compared to OAR. However, subanalysis of more recent studies, with last year of patient recruitment 2010 or after, demonstrated no long-term mortality differences between EVAR and OAR.

Finally, Bulder et al. [17] included 53 studies in a meta-analysis. They reported lower 30-day mortality rate for EVAR (1.16%) compared to OAR (3.27%). There were no significant differences in long-term survival between the two procedures (hazard ratios 1.01, 1.00 and 0.98 for 3, 5 and 10 years respectively; p = 0.721, p = 0.912 and P = 0.777, respectively). Correction of age inequality by means of relative survival analysis showed equal long-term survival: 0·94, 0·91 and 0·76 at 3, 5 and 10 years for EVAR, and 0·96, 0·91 and 0·76 respectively for OAR. Although the relative survival analysis took age and sex differences into account, other patient characteristics that may influence the choice of treatment between EVAR and OAR could not be corrected for. Yet, asymmetrical medical decision-making as result of the higher intervention threshold for OAR presumably results in over-representation of 'healthier' patients in the OAR group. As such, conclusions from this meta-analysis may underestimate the benefit of EVAR. Available data do not allow extension beyond the 10-year survival window or analysis of specific subgroups.

5.2.3.3 Gender-Specific Differences in Outcome

Liu et al. [18] conducted a comprehensive systematic review and meta-analysis of all available studies reporting sex differences after EVAR for infrarenal AAA. Thirty-six cohorts were included in this meta-analysis. 25 cohorts investigated intact AAA, 7 investigated ruptured AAA, and 4 investigated indeterminate AAA. The pooled results showed that women were associated with a significantly increased risk of 30-day mortality (crude OR, 1.67; P < .001; adjusted OR, 1.73; P < .001), in-hospital mortality (OR, 1.90), limb ischemia (OR, 2.44), renal complications (OR, 1.73), cardiac complications (OR, 1.68), and long-term all-cause mortality (hazard ratio, 1.23) compared with men after EVAR for infrarenal AAA. However, no significant difference was observed between sexes for visceral/mesenteric ischemia, 30-day reinterventions, late endoleaks and late reinterventions. Women should be enrolled in a strict and regular long-term surveillance after EVAR.

A second meta-analysis [19] and systematic review of sex specific differences in 30-day mortality and complications demonstrated that the risk of worse outcomes in women (vs. men) after elective abdominal aortic aneurysm repair has not ameliorated with time and the risk ratio for mortality is higher for EVAR than open repair. 26 studies (371,215 men, 65,465 women) were included. Mortality risk was higher

in women for OAR (OR 1.49) and more so for EVAR (OR 1.86). Over the last 20 years, this difference remained unchanged. Transfusions, pulmonary complications, and bowel ischaemia were more common in women after OAR and EVAR. Better pre-operative optimisation might reduce the higher risk of systemic complications in women. Arterial injury, renal, and other ischaemic complications (limb and bowel ischaemia), which probably contribute to mortality, are higher in women, especially after EVAR, and may be avoidable with strategic planning.

5.2.3.4 EVAR: Reintervention Rate

A systematic review and meta-analysis of the available literature to determine long-term freedom from reintervention after EVAR and the change in reintervention rates over time was performed by Wanken et al. [20]. A total of 30 studies (randomized trials, n = 3; observational studies, n = 27) comprising 32,126 patients were included. The probability of freedom from reintervention was 81% at 5 years, 70% at 10 years and 64% at 14 years. Freedom from reintervention improved linearly over time, from 90% to 94% after 1 year (years 1998 vs 2008), from 77% to 90% after 3 years, and from 68% to 81% after 5 years. At 7 years, estimated freedom from reintervention improved from 51% in 1998 to 86% in 2011. EVAR patients remain at risk for reintervention indefinitely, and therefore lifelong surveillance is imperative. Encouragingly, reintervention rates have improved over time, with newer devices exhibiting lower rates. Reintervention rate remains an important metric for new devices and registries.

5.2.4 Ruptured AAA: Meta-Analyses

5.2.4.1 EVAR vs. OAR

A meta-analysis by Kontopodis et al. [21] is available on the perioperative mortality of endovascular aneurysm repair (EVAR) vs. open repair (OAR) for ruptured abdominal aortic aneurysm (rAAA). 136 studies were included in quantitative synthesis reporting a total of 267,259 patients (EVAR 58273; open surgery 208,986). The pooled peri-operative mortality of EVAR and OAR was 0.245 (95% CI 0.234–0.257) and 0.378 (95% CI 0.364–0.392), respectively. EVAR was associated with reduced peri-operative mortality (OR 0.54, 95% CI 0.51–0.57, $p < .001$). If EVAR can be done, it is a better treatment for ruptured AAA in view of the reduced perioperative mortality compared with OAR. The outcomes of both EVAR and OAR have improved over the years, and the difference in perioperative mortality in favour of EVAR has become more pronounced. There is a significant association between peri-operative mortality and institutional case load for open repair of rAAA. The data support the statement that, when feasible, EVAR is the preferred procedure in the management of rAAA.

Kontopodis et al. [22] also prepared a systematic review with meta-analysis on late outcomes of EVAR vs. OAR for rAAA. Three randomized controlled trials and 22 observational studies reporting a total of 31,383 patients were included in the quantitative synthesis (mean follow-up ranged from 232 days to 4.9 years). The overall all-cause mortality was significantly lower after EVAR than after OAR (HR, 0.79; 95% CI, 0.73–0.86). However, the post discharge all-cause mortality was not significantly different (HR, 1.10; 95% CI, 0.85–1.43). Similarly, aneurysm-related mortality, reported in only one randomised trial, was not different between EVAR and OAR (HR, 0.89; 95% CI, 0.69–1.15). The mortality difference in favour of EVAR was more pronounced in the more recent trials. The data demonstrate that the perioperative survival advantage of EVAR over OAR is maintained at follow-up, which argues for a wider adoption of an EVAR first strategy for rAAA.

5.2.4.2 Procedure Volume and Outcomes After rAAA Repair

The objective of a systematic review by Kontopodis et al. [23] was to test the hypothesis that institutions or surgeons with higher AAA case volumes confer improved outcomes for patients with rAAA. Thirteen studies reporting a total of 120,116 patients were included. Patients treated in low-volume centres had a statistically significantly higher perioperative mortality than those treated in high-volume centres (odds ratio 1.39; 95% CI 1.22–1.59). Subgroup analysis showed a mortality difference in favour of high volume centres for both EVAR (OR 1.61, 95% CI 1.11–2.35) and OAR (OR 1.50, 95% CI 1.25–1.81). Adjusted analysis showed a benefit of treatment in high volume centres for OAR but not for EVAR. Differences in perioperative mortality between low and high volume surgeons were not statistically significant for either EVAR or OAR. A high institutional volume may result in a reduction in perioperative mortality following surgery for rAAA. These findings have implications for vascular service provision, with an emphasis on the centralisation of aortic services and the potential to enhance clinical outcomes.

5.2.4.3 rAAA in Octogenarians

A meta-analysis sought to identify the mortality and ambulatory state 30 days and 1 year postoperatively in octogenarians treated for rAAA by EVAR or OAR [24]. Eight retrospective studies could be included, reporting on 7526 patients. Meta-analysis showed a pooled 30-day mortality of 43% (95% confidence interval (CI) 33–53) and a 1-year mortality of 47%. Compared with OAR, patients after EVAR had a significant lower mortality at 30 days (risk ratio (RR) 0.50, 95% CI 0.38–0.67) and at 1 year (RR 0.65, 95% CI 0.44–0.96). The 30 day and 1 year mortality rates for rAAA repair in octogenarians are similar to the outcome at all ages, with a significant survival advantage of EVAR over OAR. Patients should therefore not be denied treatment of a rAAA based on age alone.

5.2.4.4 Weekend Admission of rAAA

A meta-analysis was undertaken to determine whether weekend admission for rAAA is associated with poorer outcomes [25]. Twelve observational cohort studies published between 2001 and 2019 comprising 14 patient cohorts with a total of 95,856 patients were eligible for quantitative synthesis. Patients presenting on a weekend had a significantly higher risk of unadjusted in-hospital (OR 1.20, 95% CI 1.10–1.31, p < .001). Both the unadjusted 30 day mortality risk (OR 1.16, 95% CI 0.98–1.39, p = .090) and unadjusted 90 day mortality risk (OR 1.12, 95% CI 0.90–1.40, p = .30) were higher for those presenting at a weekend, but neither reached statistical significance. There was a significantly greater risk of combined unadjusted in hospital, 30 and 90 day mortality for those presenting at a weekend (OR 1.17, 95% CI 1.09–1.27, p < .001). Hospital length of stay was not statistically different between groups. There is an association between weekend admission and higher mortality in patients presenting with rAAAs. Services should be reviewed to ensure that high quality emergency vascular care can be provided reliably at the weekend at an equitable level to the weekday service.

5.2.5 Studies and Registries

5.2.5.1 Long-Term Outcomes of EVAR vs. OAR

Long-term outcomes of endovascular vs open repair of abdominal aortic aneurysm were identified in a multicenter retrospective cohort study using data with 6-year follow-up from the Medicare-matched Vascular Quality Initiative Vascular Implant Surveillance and Interventional Outcomes Network database [26]. Among a total of 32,760 patients who underwent surgical abdominal aortic aneurysm repair, 28,281 patients underwent endovascular repair and 4479 patients underwent open repair. After propensity score matching, there were 2852 patients in each group. OAR was associated with significantly lower 6-year mortality (35.6%) compared with EVAR (41.2%; P = .002). OAR, compared with EVAR, also was associated with significantly lower rates of 6-year rupture and reintervention. Open repair was associated with significantly higher odds of 30-day mortality (OR, 3.56; 95% CI, 2.41–5.26; P < .001) and complications (Table 5.1). The authors concluded that although EVAR remains a highly valuable treatment modality, especially in patients who are not candidates for open surgery, OAR should be carefully considered in patients who may be poor candidates for EVAR.

Long-term outcomes of EVAR compared with open surgical repair for unruptured AAAs were analyzed by Epple et al. [27] in a retrospective cohort study using health insurance data from Germany. Among 20,683 patients, 15,792 (76.4%) underwent EVAR and 4891 (23.6%) underwent OAR. From these patients, 4886 well-balanced propensity score–matched pairs of patients were defined. Perioperative mortality was 1.9% after endovascular and 5.9% after open repair (P ≤ .001). The

Table 5.1 Outcomes after elective endovascular (EVAR) and open (OAR) abdominal aortic aneurysm repair. Vascular Quality Initiative data from 2003 to 2018. Propensity score matched comparison (according to [26])

Parameter	EVAR (n = 2842)	OAR (n = 2842)	P
Perioperative outcome			
– Death, n (%)	33 (1.2)	114 (4.0)	<.001
– Leg ischaemia, n (%)	25 (0.9)	58 (2.0)	<.001
– Intestinal ischaemia, n (%)	10 (0.4)	121 (4.3)	<.001
– Respiratory complications, n (%)	57 (2.0)	302 (10.6)	<.001
– Nonhome discharge, n (%)	207 (7.3)	813 (28.6)	<.001
Death			
– 1 year, n (%)	241 (9.2)	253 (9.3)	.49
– 6 years, n (%)	608 (41.2)	548 (35.6)	.002
Rupture			
– 6 years, n (%)	149 (8.3)	117 (5.8)	.03
Reintervention			
– 6 years, n (%)	267 (16.0)	190 (11.6)	<.001

benefit of lower mortality with EVAR was seen in all analyzed age groups and in both, men and women. The length of hospital stay was significantly shorter (EVAR mean: 13.0 days, OAR mean: 20.3 days, $P \leq .001$) and the rate of patients requiring blood transfusions was significantly lower with EVAR (14.0% vs 60.8%, $P \leq .001$). The early survival benefit after endovascular repair persisted for approximately 3 years (EVAR estimated survival rate 82.3%, OAR 80.9%, P = .021). After that time the estimated survival curves were similar. After 9 years estimated survival was 51.2% among patients in the EVAR cohort as compared to 52.8% in the OAR cohort (P = .102). The decision between EVAR or OAR may depend on patient preference, surgeons' experience, and the institutions' ability to handle complications.

Varkevisser et al. [28] used the Society of Vascular Surgery Vascular Quality Initiative (VQI) clinical registry to investigate the differences in long-term all-cause mortality between EVAR and open repair for infrarenal AAA stratified by age. 48,074 patients undergoing elective infrarenal abdominal aneurysm repair (89% EVAR) were identified, including 7940 patients aged less than 65, 29,555 aged between 65 and 79, and 10,579 aged 80 years or more. EVAR was associated with a higher propensity score-adjusted long-term hazard of mortality compared with open repair in the cohort aged less than 65 years (HR 1.39; P = .026). The mortality was similar in the age cohort between 65 and 79 (HR 0.94; P = .43), whereas EVAR was associated with a lower hazard of mortality in the cohort aged 80 years or more (HR 0.63; P = .004). These results suggest that a young, healthy patient with low operative risk and a long life expectancy may be considered for open AAA repair, whereas EVAR remains the preferred treatment for most AAA patients.

5.2.5.2 Long-Term Reintervention After EVAR

The long-term reintervention rate after EVAR was described by Columbo et al. [29] in 12,911 patients using the Vascular Quality Initiative registry, including both elective procedures (89.1%) and urgent or emergent procedures. The 3-year reintervention rate was 15%, and the 10-year rate was 33%. Five factors predicted reintervention: operative time ≥ 3.0 h; aneurysm diameter ≥6.0 cm; an iliac aneurysm ≥2.0 cm; emergency surgery; history of prior aortic surgery. Patients with no risk factors had a 3-year reintervention rate of 12% and a 10-year reintervention rate of 26%. Patients with multiple risk factors had a 3-year reintervention rate of 72%. Suprarenal fixation was not associated with reintervention. It can be concluded that 1 in 3 patients underwent reintervention in the first decade after EVAR. Almost two-thirds of these reinterventions were associated with an inpatient hospital stay of 3 or more days. 5% of patients experienced a late rupture. The data support open repair for AAA rather than EVAR in patients at high risk of reintervention and with good long-term prognosis. They also confirm the need for long-term monitoring of the EVAR patient.

Columbo et al. [30] also analysed the cumulative financial impact of reintervention after EVAR in a cohort of 1207 Medicare patients enrolled in the Vascular Quality Initiative registry. The reintervention rate after EVAR was 18% at 5 years. Of these patients, 154 (73.7%) had a single reintervention, 40 (19.1%) patients had two reinterventions, and 15 (7.2%) had three or more reinterventions. The median cost to Medicare for the index EVAR hospitalisation was $25,745 (interquartile range $21,131–$28,774) and the median cost for subsequent reinterventions was $22,165 (interquartile range $17,152–$29,605). The cost of reintervention was thus roughly the same as for the initial procedure itself. For multiple reinterventions, cumulative cost increased further, with each reintervention being similar in cost to the index EVAR. The authors called for further cost-effectiveness studies surrounding the utilization of EVAR and reintervention.

5.2.5.3 EVAR in Patients Deemed Unfit for Open Surgical Repair

Of 16,183 EVAR patients registered in the Vascular Quality Initiative database, 1782 had been deemed unfit for open surgical repair (OR) because the operating surgeon considered them too high risk for OR [31]. The reasons the patient had been deemed unsuitable for OR were cardiac or pulmonary instability, frailty, a hostile abdomen, or any of these combinations. Postoperatively, the unfit cohort was more likely to have experienced cardiopulmonary complications (6.5% vs 3%; $P < .001$), with greater perioperative mortality (1.7% vs 0.6%; $P < .001$) and 1- and 5-year mortality (13% and 29% for the unfit vs 5% and 14% for the fit cohorts, respectively; $P < .001$). Reintervention-free survival at 1 and 5 years was significantly greater in the fit cohort compared with those considered unfit (93% and 82% vs. 85% and 68%, respectively; $P < .001$). Despite low perioperative mortality, the long-term mortality of those designated by operating surgeons as unfit for OR was

rather high for patients undergoing elective EVAR, likely owing to the competing risk of death from medical frailty. An unfit designation because of a hostile abdomen did not confer any additional risks after EVAR. Judicious estimation of the patient's life expectancy is essential when considering the treatment options for this subset of patients deemed unfit for OR. Shared decision-making is imperative when evaluating an unfit patient with an AAA for EVAR.

5.2.5.4 Elective AAA Repair and Cancer

In a cohort of 8663 patients who had undergone AAA repair Roush et al. [32] identified 270 patients with a cancer diagnosis and 8393 without a cancer diagnosis. Male reproductive organ (24.8%) and lung (24.4%) cancer were the most common cancer diagnoses in the cohort. Patients with cancer were more likely to undergo EVAR (88.2%) compared to patients without cancer (82.1%). Elective AAA repair for patients with a cancer diagnosis was associated with a prolonged length of stay and the development of infection, respiratory failure, and vascular-specific complications during the inpatient hospitalization. Given that differences in outcomes stratified by gender and treatment modality have been shown for patients with a cancer diagnosis, careful patient selection is important and reinforces the finding that cancer exerts negative systemic postoperative effects even when treated or quiescent.

Patient survival and cancer incidence were recorded by Ettengruber et al. [33] for 18,802 patients (16,086 men, 2716 women) who underwent EVAR (n = 14,218) and open repair (n = 4584.) All patients were preoperatively and in their history cancer-free. 30.1% of EVAR and 27.6% of OR patients ($p \leq .001$) developed cancer after a follow-up period of up to 9 years. The estimated survival of patients with and without cancer was 27.0% and 55.4%, respectively ($p < .001$). Survival of men and women did not differ significantly. In the Cox regression analysis, the postoperative cancer incidence was not significantly different between EVAR and OR (HR 1.09; 95% CI 1.00–1.18, p = .051). However, EVAR showed an increased risk of postoperative development of abdominal cancer (HR 1.20; 95% CI1.07–1.35, p = .002). Cancer significantly worsened the long-term outcome after EVAR and OR, without significant differences between the two repair methods in the overall cancer incidence. However, the higher abdominal cancer incidence with EVAR can affect quality of life including oncological therapy and therefore should be considered when determining the indication for surgery, and the patient should be informed about it.

5.2.5.5 Case Volume and Outcome in Abdominal Aortic Aneurysm Repair

Brown et al. [34] identified a total of 67,073 procedures for nonruptured AAA in the Vascular Quality Initiative database from 2003 to 2019, including 11,601 (17.3%) open procedures. The median annual case volume for hospitals was 7.4 (interquartile range 3.0–13.3) for OR and 35.4 (interquartile range 18.8–59.8) for EVAR. Of

the 223 hospitals that had performed open surgery, only 11 (4.9%) had performed >15 ORs annually. The authors reviewed the risk-adjusted mortality rates for each hospital and found a perioperative mortality rate of 1.3–8.2% for OR and of 0.3–2.8% for EVAR. A decreasing trend in mortality was found with increasing an annual case volume for open repair with each additional annual case associated with a 0.012% decrease in mortality (P = .05); however, the relationship was not significant for endovascular repair (P = .793). The message of this study was that most hospitals did not perform a sufficient number of annual cases to generate a reliable center-specific mortality rate for open aneurysm repair. Center-specific mortality rates for low-volume centers should be viewed with caution, because a substantial proportion of the variation for these outcomes will be statistical noise rather than true center-level differences in the quality of care.

A cross-sectional evaluation of the association between the average hospital and surgeon volume and 30-day postoperative mortality using a hierarchical Bayesian model was performed by Sharma et al. [35] using the Vascular Quality Initiative registry. A total of 3078 patients had undergone elective AAA open repair by 520 surgeons at 128 hospitals. Of the 520 surgeons, 489 (94%) had averaged fewer than four open elective AAA repairs annually. The 30-and 90-day risks of postoperative mortality after open repair were 4.1% (n = 126) and 5.4% (n = 166), respectively. The mean surgeon volume and hospital volume both correlated inversely with the 30-day mortality (Table 5.2). With a 96% probability, surgeons who performed an average of four or more repairs per year achieved a 30-day mortality <5%. On average, higher volume surgeons achieved the SVS guideline-recommended ≤5% mortality, regardless of hospital volume. In contrast, lower volume surgeons only achieved such results at higher volume hospitals. A 91% probability was found that hospitals that performed ≥10 repairs annually would achieve <5% 30-day adjusted mortality. Of the 128 hospitals, 116 (91%) averaged <10 repairs annually. The authors emphasized that patient safety organisations have advocated for minimum annual volume thresholds for open AAA repair of 10 cases per hospital and 7 cases

Table 5.2 Association of surgeon and hospital volume with mortality after open abdominal aortic aneurysm repair. Vascular Quality Initiative registry (according to [35])

Surgeon/cases per year (n)	Mean 30-day mortality (%)	Probable mortality <5%	Mean 90-day mortality (%)
2	4.7	0.68	6.2
4	3.5	0.97	4.4
6	2.3	>0.99	2.8
8	1.4	>0.99	1.6
10	1.0	>0.99	1.0
Hospital/cases per year (n)			
5	4.3	0.85	5.5
10	4.2	0.91	5.4
20	3.9	0.87	5.2
40	2.7	0.97	3.8

per surgeon. Recently updated SVS guidelines have recommended open AAA repair only occur at hospitals with ≥10 open aortic procedures of any type annually. However, only a small portion of even the highest volume surgeons and hospitals would be able to satisfy these volume requirements in the USA.

Scali et al. [36] examined the association between surgeon annual case volume and years of practice experience with open aneurysm repair. All infrarenal ORs (n = 11,900; elective, 70%; nonelective, 30%) included in the Society for Vascular Surgery VascularQuality Initiative from 2003 to 2019 were examined. Surgeon experience was defined as years in practice after training. The experience level at repair was categorized chronologically (≤5 years, n = 1667; 6–10 years, n = 1887; 11–15 years, n = 1806; ≥16 years, n = 6540). The annual case volume was determined by the number of ORs performed by the surgeon annually (median, five cases). Practice experience had no association with unadjusted 30-day mortality. However, more experienced surgeons had fewer complications after elective OR (25% with ≥16 years vs 29% with ≤5 years; P = .004). Total procedure time, estimated blood loss, and renal and/or visceral ischemia times were all greater for less experienced surgeons (P-trend <.0001). The annual surgeon case volume appeared to be more impactful than the years of practice experience for predicting OR outcomes. The authors found that a threshold of five OR cases annually was sufficient in real world practice to achieve consistently improved outcomes, irrespective of the surgeon experience level.

The volume-outcome relationship in elective open AAA repair was also studied by Geiger et al. [37] in a cohort of 7594 procedures performed by 542 surgeons in 137 hospitals during a 12-year period. The mean annual volume for the centers performing elective open abdominal aortic surgery was 12.9 cases/year, with a median annual volume of 7 cases per center per year. The mean annual volume for the surgeons performing elective open abdominal aortic surgery was five cases per year, with a median annual volume of three cases per surgeon per year. Multivariate survival analysis revealed a hazard ratio for a surgeon volume of ≥7, hospital volume of ≥10, and hospital 3-year perioperative mortality of ≤5% of 0.80, 0.91, and 0.72, respectively. Additionally, procedures performed by surgeons with a yearly average volume of open aortic operations of at least seven and at hospitals with an established elective open AAA repair perioperative mortality rate of ≤5% showed improved 1-year (33.2% relative risk reduction; P < .001) and 30-day (P = .001) all-cause survival and improved postoperative complication rates. A surgeon open aortic volume of at least seven procedures and an established hospital perioperative mortality of ≤5% each independently predicted for 1-year survival after open AAA repair, with the hospital volume less important. These results indicate that surgeons with an annual volume of at least seven open aortic operations of any type should perform elective open AAA repair at centers with a documented perioperative mortality of ≤5%.

5.2.5.6 AAA Diameter and Elective Endovascular Aortic Aneurysm Repair

Scali et al. [38] analyzed all elective repairs in the SVS Vascular Quality Initiative (VQI) EVAR registry from 2015 to 2019 (n = 25,112) and included patients with aneurysms confined to the infrarenal abdominal aorta. Center and surgeon variation with clinical practice diameter guidelines (CPG) compliance was examined. Patients were stratified into predicted 1-year mortality risk tertiles and comparisons were made between patients meeting diameter guidelines (men ≥5.5; women ≥5.0 cm) and those who did not. Non-diameter-compliant EVAR occurred in 38.5% (n = 9675; diameter compliant, 61.5% [n = 15,437]). Notably, 82% of VQI surgeons (n = 852 of 1048) were non-diameter-compliant in more than 20% of their repairs. Furthermore, 22% of patients undergoing noncompliant repair deemed to be at high physiologic risk. The 1-year survival for the high physiologic risk patients receiving non-guideline-compliant EVAR was worse compared with low- to intermediate-risk patients who were treated within recommended CPGs (92 ± 2% vs 97 ± 1%; log-rank P < .0001). This analysis highlights that a significant percentage of US EVARs are performed for a non-diameter-compliant indication. Efforts to constrain deviation from SVS CPG diameter treatment thresholds can potentially improve AAA care in the United States and eliminate unnecessary care provision.

Differences in patient selection, operative technique, and outcomes for AAA repair in Canada versus United States were assessed by Li et al. [39] using the VQI database. There were 51,455 US patients and 1451 Canadian patients. Patients in the USA were more likely to undergo endovascular repair (83.7% vs. 68.4%). The percentage of AAAs repaired below recommended thresholds was 38.8% in the USA and 15.2% in Canada ($p < 0.001$). Factors associated with repair below recommended thresholds were USA region, male sex and EVAR. The in-hospital mortality rate was low (USA 1.0% vs. Canada 0.8%) and the 1-year mortality rate was similar between the two countries (hazard ratio 0.96; $p = 0.79$). The authors attributed the difference in indications mainly to the more frequent use of EVAR in the USA. Patients who underwent endovascular repair were more often deemed unfit for open surgery in Canada compared with the United States (62.3% vs 14.5%). Intervening on smaller AAAs did not afford a survival advantage in this study. Perioperative and 1-year mortality rates remained similar between the two countries and there was no difference in the ruptured AAA repair rate between the United States and Canada.

5.2.5.7 Endovascular vs. Open Repair of Juxtarenal AAAs

The perioperative outcome with EVAR and OR in patients with juxtarenal AAAs (JRAAAs) was reported by von Meijenfeldt et al. [40] using the Dutch Surgical Aneurysm Audit (DSAA), a mandatory nationwide audit in the Netherlands. In this retrospective study, in all 455 primary treated patients with JRAAAs could be included. 258 patients underwent open repair and 197 complex EVAR (chimney

EVAR or fenestrated EVAR). Patients treated with OR had significantly more major complications (45% vs. 21) and minor complications (34% vs. 23%) as well as a higher chance of early mortality (6.6% vs. 2.5%; p = 0.046). After primary elective open surgical repair for juxtarenal abdominal aortic aneurysms, the odds for major complications, minor complications, and short-term mortality were all significantly higher compared with complex endovascular repair. Although this study reflects daily practice in The Netherlands, selection bias and number of included patients should be taken into account when interpreting the generalizability of this study.

5.2.5.8 Small Abdominal Aortic Aneurysm Rupture

Bellamkonda et al. [41] investigated the proportion of AAAs that rupture at sizes less than elective operative thresholds and compared the outcomes of repair with those of aneurysms that had ruptured at a larger size using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2011 to 2018. Of the 1612 rAAA repairs, 167 (10.4%) were small rAAAs. For men, inclusion in the large rAAA group was contingent on an AAA diameter of ≥5.5 cm and, for women, ≥5.0 cm. Cases that did not meet this threshold were classified as small rAAAs. The large rAAA group was more likely to have juxtarenal or suprarenal aneurysms compared with the small rAAA group (27% vs 16%; P = .001). A comparison of infrarenal rAAAs only demonstrated that the mean small rAAA (n = 141) diameter was 4.1 cm in the women and 4.5 cm in the men compared with the large rAAAs (n = 1051), with a mean diameter of 7.1 cm in women and 8.3 cm in men (P < .01 for the women; P < .01 for the men). EVAR was more commonly used for the repair of small rAAAs (78.7% vs 65.2%; P < .01). Patients treated for small rAAAs had experienced significantly lower mortality compared with those with large rAAAs (17.0% vs 24.7%; P = .04). Multivariable analysis was performed on mortality, which revealed that the AAA size was not independently associated with mortality, and patients with small rAAAs were less likely to present with hypotension. Open surgery was also associated with higher mortality compared with EVAR.

5.2.5.9 Survival After EVAR and Open Repair for Ruptured AAAs

Varkevisser et al. [42] identified 4638 rAAA repairs in the Vascular Quality Initiative registry and compared outcomes (5-year survival) in an early (years 2004–2012) with those in a late cohort (years 2013–2018). There were 409 EVARs and 558 ORs in the early cohort and 2250 EVARs and 1421 ORs in the late cohort. Propensity matching resulted in 366 matched pairs of late vs early EVAR and 391 matched pairs of late vs early open repair. When comparing EVAR with open repair, propensity matching resulted in 277 matched pairs of early EVAR versus open, and 1177 matched pairs of late EVAR versus open. In matched EVAR patients, 5-year survival was higher in the late cohort (63% vs 49% [HR], 0.77), whereas there was no

difference between matched late vs early for open repair patients (52% vs 59%; HR, 1.04). In the early cohort, there was no survival difference between EVAR and open repair (51% vs 46%). However, in the late cohort EVAR was associated with higher survival compared with open repair (63% vs 54%; HR, 0.69; 95% CI, 0.60–0.79; P < .001). Consequently, the relative survival benefit of EVAR over open repair has increased over time, which should encourage further adoption of EVAR for ruptured AAA.

All ruptured cases of open surgical repair (rOR) and endovascular aneurysm repair (rEVAR) in the Vascular Quality Initiative were analyzed (2003–2018) by Wang et al. [43]. There were 4929 rAAA repairs performed, 2749 rEVAR and 2180 rOR. Compared with rEVAR patients, rOR patients had higher rates of myocardial ischemic events (15% vs 10%; P < .001), major adverse events (67% vs 37%; P < .001), and 30-day death (34% vs 21%; P < .001). After 1:1 matching, the study cohort consisted of 724 pairs of rOR and rEVAR. Multivariable regression analysis of the propensity-matched pairs demonstrated that rOR was associated with double the 30-day mortality compared with rEVAR (odds ratio, 2.0). All-cause 1-year survival was 73% and 59% after rEVAR and rOR in the propensity-matched cohort, respectively (P < .001). Clear short-term and midterm survival benefits of endovascular over open surgical repair were demonstrated. The study suggests a more aggressive endovascular approach for ruptured abdominal aortic aneurysm in patients with suitable anatomy.

5.3 Conclusions for Clinical Practice

1. In men, the threshold for considering elective abdominal aortic aneurysm repair is recommended to be ≥5.5 cm diameter, in women ≥5.0 cm diameter. When rapid abdominal aortic aneurysm growth is observed (>1 cm/year), fast track referral to a vascular surgeon with additional imaging should be considered. There is no evidence to go below these thresholds with endovascular repair.
2. In most patients with suitable anatomy and reasonable life expectancy, endovascular abdominal aortic aneurysm repair should be considered as the preferred treatment modality.
3. If anatomically feasible, EVAR over open repair for treatment of a ruptured AAA is recommended.
4. Minimum annual volume thresholds for open AAA repair of 10 cases per hospital and 7 cases per surgeon have been suggested.

5.4 Perioperative Management

5.4.1 Modifiable Risk Factors

In a systematic review, Khashram et al. [44] assessed the effect of modifiable risk factors on late survival following AAA repair. Twenty-four studies which comprised 53,118 patients, published between 1989 and 2015, were included in the analysis. The use of statin, aspirin, beta-blockers, and a higher hemoglobin level was all significant predictors of improved survival following repair. Smoking history and uncorrected coronary disease were associated with a worse long-term. Addressing cardiovascular risk factors in patients preoperatively improves long-term survival following AAA repair.

In a review, researchers from Cochrane [45] examined the long-term effectiveness of antiplatelet, antihypertensive, or lipid-lowering medication in reducing mortality and cardiovascular events in people with abdominal aortic aneurysm. They concluded that due to the limited number of included trials, there is insufficient evidence to draw any conclusions about the effectiveness of cardiovascular prophylaxis in reducing mortality and cardiovascular events in people with AAA.

5.4.1.1 Smoking

The Society for Vascular Surgery practice guidelines [2] recommend:

- We recommend smoking cessation to reduce the risk of AAA growth and rupture. Level of recommendation 1 (Strong). Quality of evidence B (Moderate)

Studies

The Vascular Quality Initiative was reviewed for all patients with a documented smoking history and who underwent an elective lower extremity bypass or open AAA repair from 2010 to 2017 [46]. 5215 patients who underwent an elective open AAA repair were identified. Long-term smoking cessation defined as quitting smoking ≥8 weeks before surgery resulted in a 51% decreased risk of pulmonary complications compared with current smokers. In conclusion, longer periods of smoking cessation should be encouraged before open abdominal aortic aneurysm repair to decrease the risk of pulmonary complications.

5.4.1.2 Statin Therapy

The ESVS guidelines [1] recommend:

- Recommendation 44: Statins are recommended before (if possible, at least 4 weeks) elective abdominal aortic aneurysm surgery to reduce cardiovascular morbidity. (Recommendation class I, evidence level A)

Studies

Two systematic reviews with meta-analyses are available. Based on one case-control study and 21 cohort studies (80,428 patients) Salata et al. [47] found that statin use was associated with a mean AAA growth rate reduction of 0.82 mm/y (95% confidence interval 0.33, 1.32, P = 0.001). Statins were also associated with a lower rupture risk (odds ratio 0.63, 95% confidence interval 0.51, 0.78, P < 0.0001), and preoperative statin use was associated with a lower 30-day mortality following elective AAA repair (odds ratio 0.55, 95% confidence interval 0.36, 0.83, P = 0.005). Statin therapy may be associated with reduction in AAA progression, rupture, and lower rates of perioperative mortality following elective AAA repair. These data argue for widespread statin use in AAA patients.

A second systematic review and meta-analysis revealed 14 eligible cohort studies of which 11 were judged to be of high quality [48]. The pooled estimate showed that statin treatment among 69.790 AAA patients with a median follow up of 3.1 years was associated with a 35% relative reduction in total mortality (rate ratio 0.65, 95% confidence interval 0.57–0.73) with moderate heterogeneity and no small study effect. Evidence from this systematic review indicates a beneficial effect of statins on long term survival in patients treated by AAA repair.

The association between perioperative statin intensity and in-hospital mortality following open abdominal aortic aneurysm (AAA) repair was examined by Alshaikh et al. [49] in a cohort of 6497 patients undergoing open AAA repair. 3217 (49.5%) patients received perioperative statin. Multivariable analysis showed that statin use was associated with lower odds of death (odds ratio 0·41). Moderate, high and supratherapeutic statin intensities were not associated with lower odds of death or major adverse events compared with low-intensity statin therapy. In this study, high-intensity statins were not associated with lower morbidity or mortality.

In a registry-based study of all patients undergoing repair of AAAs in the Vascular Quality Initiative between 2003 and 2017 [50] preoperative statin therapy was associated with higher long-term survival but not perioperative mortality and morbidity in patients undergoing AAA repair. Overall, 25,997 patients (69%) were taking a statin preoperatively, with patients undergoing endovascular aneurysm repair more frequently taking a statin than those undergoing open repair (69% compared with 66%; P < .001). After propensity weighting, preoperative statin therapy was not associated with 30-day death or in-hospital stroke or myocardial infarction. However, patients taking statins preoperatively experienced higher adjusted 1-year (94% vs 90%) and 5-year (85% vs. 81%) survival from the date of surgery compared with those who were not (P < .001 overall). In a secondary analysis of the subset of patients not taking statins preoperatively, those initiated on a statin before discharge experienced higher survival at 1 year (94% vs 91%) and 5 years (89% vs

81%; P < .001 overall) than those who remained off statin therapy, with the greatest absolute long-term survival difference in patients with rupture (87% vs 62%; P < .001 overall). Initiating statin therapy in previously statin-naive patients is associated with markedly higher survival. All patients with AAAs without contraindications should receive statin therapy. In patients not taking a statin at the time of AAA repair, clinicians should consider initiating one before discharge.

5.4.1.3 Antiplatelet Therapy

The ESVS guidelines [1] recommend:

- Recommendation 21: Blood pressure control, statins and antiplatelet therapy should be considered in all patients with abdominal aortic aneurysm. (Class IIa, Level B)

Studies

There is a review available by Cameron et al. [51] on antithrombotic therapy in patients with AAA. The authors concluded that antiplatelet therapy is standard in most cardiovascular diseases and is therefore also used in patients with AAA. However, retrospective studies have not yet demonstrated an improvement in patient outcomes with ASA. Randomised trials do not exist.

In a matched cohort study [52] with 11,094 Danish patients who underwent acute or elective open AAA repair from January 1986 through June 2009, each aneurysm patient undergoing open surgery was matched as of the day of operation with four individuals from the general population (controls n = 44,364). AAA patients had an annual MI incidence of 2.5% (hazard ratio, 2.1; 95% confidence interval [CI], 1.9–2.2 compared with the general population). The annual incidence of stroke was 2.9% (hazard ratio, 1.8; 95% CI, 1.6–1.9), and there was a 2.4-fold (95% CI, 2.3–2.4) increase in the hazard of all-cause mortality compared with the general population. The authors concluded that AAA patients of both sexes have a high risk of atherosclerotic events (MI, stroke) and death, so lifelong prophylaxis must be considered from these epidemiologic data. The initiation of lifelong aspirin and statin therapy should be considered as soon as a diagnosis of AAA is made. Randomized trials investigating the potential benefit of aspirin and statin therapy in AAA patients are needed.

A Danish nationwide, combined case-control and follow-up study aimed to examine the association between ASA use and the risk of presenting with rAAA on hospital admission and subsequent mortality after rAAA [53]. There were 4010 patients with an incident diagnosis of rAAA and 4010 age- and sex-matched AAA patients identified in the Danish National Registry of Patients. In this large, population-based study, no association between use of ASA and the risk of presenting with rAAA on hospital admission was found. However, ASA use was associated

with a poorer 30-day prognosis after rAAA. The finding of an adverse outcome in ASA users after rAAA has not previously been reported. In this study, only patients who had open surgical repair or no repair after rAAA were considered. The adverse outcome after rAAA among ASA users could likely relate to complications of excessive bleeding due to ASA-induced altered coagulation or ineffective clotting in the immediate perioperative period after rAAA. However, these results do not provide sufficiently strong evidence to recommend against the use of ASA in patients with asymptomatic AAAs, given that the anticipated general cardiovascular protective effect is considered to outweigh the risk of an adverse outcome if the patient should suffer a rAAA.

5.4.1.4 Beta-blocker

The European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA) guidelines [54] recommend:

- Pre-operative initiation of beta-blockers may be considered in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status 3. (Class II b, Level B)
- Pre-operative initiation of beta-blockers is **not** recommended in patients scheduled for low-risk surgery. (Class III, Level B)

The ESVS guidelines [1] recommend:

- Recommendation 43: Commencement of beta blockers is not recommended prior to abdominal aortic aneurysm repair. (Class III, Level A)

Studies

Hajibandeh et al. [55] performed a systematic review of the literature and meta-analysis of reported outcomes to evaluate the effect of beta blockers on perioperative outcomes in patients undergoing vascular and endovascular surgery. The results of their analyses indicated that perioperative beta-blocker use did not reduce the risk of all-cause mortality, cardiac mortality, MI, unstable angina, stroke, arrhythmias,CHF, composite cardiovascular events, renal failure, rehospitalisation, or reoperation in vascular surgery. Perioperative use of beta-blockers should not be routinely used in vascular and endovascular surgery.

The objection to the cautious recommendations of the ESC [54] is that they are not specifically designed for the AAA. Alshaikh et al. [56] assessed the effect of perioperative beta blocker (BB) use on postoperative in-hospital mortality after open repair of abdominal aortic aneurysms. Of 6515 patients admitted for OR, 5423 (83.2%) received perioperative BBs. Patients who received BBs were more likely to develop major adverse events compared with those who did not (45.6% vs 35.2%; $P < 0.001$); however, failure to rescue was lower among BB users (7.6% vs 19.5%;

P < 0.001). In a multivariable logistic regression model, BB use was associated with 57% and 81% lower odds of mortality among patients without and with a history of coronary artery disease, respectively. The predicted mortality (95% CI) for patients who did not receive BBs, or received low, intermediate, or high-intensity BBs was 11.6% (8.0%–15.2%), 5.4% (4.4%–6.5%), 2.5% (1.9%–3.0%), and 3.3% (2.3%–4.3%), respectively. They concluded that in-hospital use of BBs was associated with a significant reduction in postoperative mortality after OR. This was the first study to demonstrate a dose-response relationship between BBs and postoperative mortality after OR. Randomized studies are necessary in order to be able to make a definitive recommendation.

5.4.2 Preoperative Coronary Revascularisation

5.4.2.1 Guidelines

The Society for Vascular Surgery practice guidelines [2] recommend:

- In patients with significant clinical risk factors, such as coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic renal insufficiency, and unknown or poor functional capacity (metabolic equivalent [MET] < 4), who are to undergo OR or EVAR, we suggest noninvasive stress testing. [Level of recommendation 2 (Weak); Quality of evidence B (Moderate)]
- We suggest coronary revascularization before aneurysm repair in patients with acute ST-segment or non-STsegment elevation myocardial infarction (MI), unstable angina, or stable angina with left main coronary artery or three-vessel disease. [Level of recommendation 2 (Weak); Quality of evidence B (Moderate)]

The ESVS guideline [1] recommend:

- Recommendation 29: In patients with stable coronary artery disease, routine coronary revascularisation before elective abdominal aortic aneurysm repair is **not** recommended. (Class III; Level B)
- Recommendation 30: In patients with unstable coronary artery disease or considered to be at high risk of cardiac events following abdominal aortic aneurysm repair, prophylactic preoperative coronary revascularisation should be considered. (Class IIa; Evidence Level B)

5.4.2.2 Studies

McFalls et al. [57] randomly assigned patients at increased risk for perioperative cardiac complications and clinically significant coronary artery disease to undergo either revascularization or no revascularization before elective major vascular surgery. The primary end point was long-term mortality. Coronary-artery

revascularization before elective vascular surgery did not significantly alter the long-term outcome. On the basis of these data, a strategy of coronary-artery revascularization before elective vascular surgery among patients with stable cardiac symptoms cannot be recommended.

The prognostic implication of coronary revascularization (CR) on overall and cause-specific mortality in vascular surgery patients was determined by Ultee et al. [58]. A total of 1104 patients were included in this retrospective study. The study confirmed the significance of ischaemic heart disease (IHD) for postoperative survival of vascular surgery patients. CR was associated with lower IHD-related death rates. However, it failed to provide an overall survival benefit because of an increased rate of cardiovascular mortality unrelated to IHD.

This confirms the results of the randomised DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V trial. In this trial, preoperative coronary revascularisation did not lead to improved postoperative and long-term survival compared to "best medical therapy" in high-risk vascular surgery patients with extensive stress-induced ischaemia [59, 60].

5.4.3 Preoperative Carotid Intervention

5.4.3.1 Guidelines

The ESVS guidelines [1] recommend:

- Recommendation 40: Routine screening for asymptomatic carotid stenosis prior to abdominal aortic aneurysm repair is **not** recommended. (Class III; Level C)
- Recommendation 41: Patients with abdominal aortic aneurysms and concomitant symptomatic carotid stenosis within the last 6 months should be considered for carotid intervention before aneurysm repair. (Class IIa; Level A)
- Recommendation 42: Routine prophylactic carotid intervention for asymptomatic carotid stenosis prior to abdominal aortic aneurysm repair is **not** recommended (Class III; Level C)

5.4.3.2 Studies

There are no specific studies on this issue in patients with AAA. Sonny et al. [61] tested the primary hypothesis that degree of carotid artery stenosis is associated with in-hospital stroke or 30-day all-cause mortality after noncardiac surgery. As carotid artery stenosis is also a marker for cardiovascular disease, the secondary hypothesis was that degree of carotid artery stenosis is associated with postoperative myocardial injury. Adults who had noncardiac, noncarotid surgery at Cleveland Clinic from 2007 to 2011 and had carotid duplex ultrasound performed either within 6 months before or 1 month after surgery were included in this study. Of 2110

patients included, 112 (5.3%) died within 30 days and 54 (2.6%) suffered postoperative in-hospital stroke. There was no association between carotid artery stenosis and perioperative stroke or 30-day mortality after noncardiac surgery.

5.4.4 Open Repair of Nonruptured AAA

5.4.4.1 Perioperative Antibiotic Prophylaxis

The ESVS guidelines [1] recommend:

- Recommendation 46: In all patients undergoing open or endovascular abdominal aortic aneurysm repair, peri-operative systemic antibiotic prophylaxis is recommended. (Class I; Level A)

5.4.4.2 Fast Track Concept (ERAS)

The ESVS guidelines [1] note:

- Early or "enhanced" recovery after surgery (ERAS) programmes have been designed to accelerate the postoperative recovery of surgical patients by reducing the surgical stress response. The methodology of ERAS has been well established in colorectal surgery and other areas of general surgery. A limited number of studies have assessed ERAS protocols in the context of open AAA surgery and have reported shorter hospital stays and decreased pulmonary complications.

Studies

McGinigle et al. [62] performed a systematic review to characterize the use and effectiveness of ERAS in all types of vascular and endovascular operations. In the final analysis, 19 studies were included. Twelve studies provided information on the effectiveness of ERAS-like clinical care pathways in aortic surgery. Combined, these studies included 2107 patients. All studies used pathways involving epidural analgesia, oral intake on the day of surgery or postoperative day 1, and ambulation on postoperative day 1. In addition to these elements, two studies also allowed intake of clear liquids up to 2 h before surgery and limited postoperative intravenous fluid to 1 L/day; two other studies included scheduled metoclopramide in the postoperative period. Although the risk of bias is high in most of the studies done to date, all of them observed improvements in length of stay, postoperative diet, and ambulation. It is reasonable to consider the implementation of ERAS pathways in the care of vascular surgery patients, specifically those undergoing open aortic

Table 5.3 Fast-track ("Enhanced Recovery After Surgery", ERAS) protocol in open abdominal aortic aneurysm repair (according to [63])

Protocol elements	Element description
Preoperative	
Counselling	Meeting with a trained nurse at least 3 weeks prior surgery. Modification of risk factors. Informative booklet
Avoidance of fasting	Intake of fluids up to 2 h and solids up to 6 h before surgery
Carbohydrate loading	800 mL of 12.5% maltodextrin-containing clear drink on the preceeding evening + 400 mL up to 2 h before anaesthesia
Intraoperative	
Avoid central venous catheter	Minimally invasive monitoring in radial artery
Active normothermia	Forced-air cover, warmed i.v. fluids
Goal-directed fluid	Strictly controlled intraoperative fluid administration according to the haemodynamic monitoring
Preemptive analgesia	Preincisional subcutaneous infiltration with lidocaine + ropivacaine
Avoid evisceration	Positioning of self-retaining retractors for optimal access while avoiding evisceration
Avoid drainage	
Postoperative	
Opioid-sparing analgesia	Perifascial analgesic catheter until POD 2, NSAIDs or paracetamol upon request
PONV prophylaxis	Ondansetron (4–8 mg i.v.)
Restrictive ICU	Indicated only for high-risk patients depending on their pre- and intraoperative course; in-ward telemetry monitoring
Early nasogastric tube removal	At the end of surgery, before reversal of anesthesia
Early urinary catheter removal	In the operating room at the end of surgery (or on the consecutive morning)
Avoid prokinetic drugs	
Early enteral feeding	In the evening of the day of the surgery
Avoid i.v. hydration	i.v. fluid abolition immediately after the surgery
Early mobilisation	4 h after surgery; assisted to sit in an armchair

ICU Intensive Care Unit, *PONV* Postoperative nausea and vomiting, *NSAID* nonsteroidal anti-inflammatory drug, *POD* postoperative day

operations, but many of the details will be based on limited data and extrapolation from other surgical specialties until further research is done.

A single centre's experience with a fast-track protocol for open abdominal aortic aneurysm repair (OR) was reported by Malik et al. [63]. The protocol (Table 5.3) was fully implemented in 103 patients, with a postoperative complication rate of 8% across all and no deaths. Median hospitalization time was 3 days, with only 17% requiring ICU admission. Perioperative protocol implementation in AAA open repair is feasible; the clinical outcomes may be improved when strictly adhering to the protocol.

A single-center, prospective, nonrandomized cohort study with the use of the enhanced recovery after surgery protocol in open abdominal aortic aneurysm repair was presented by Giacomelli et al. [64]. During surgery, the ERAS patients were administered a combination of thoracic epidural analgesia and short-acting anesthetic agents. The indwelling bladder catheter and nasogastric tube were immediately removed after AAA repair, and the central venous catheter and retroperitoneal drain were removed on the first postoperative day. The use of the ERAS protocol for 17 patients provided perioperative outcomes similar to those obtained for 18 patients who had undergone endovascular aneurysm repair. Both groups had had a reduced time to discharge and decreased postoperative pain compared with an historical control group of 32 patients who had undergone open repair of AAAs with the standard protocol of care.

5.4.4.3 Epidural Anaesthesia

The Society for Vascular Surgery practice guidelines [2] recommend:

- We recommend multimodality treatment, including epidural analgesia, for postoperative pain control after OR of an AAA. Level of recommendation 1 (Strong). Quality of evidence A (High)

The ESVS guidelines [1] recommend:

- Recommendation 47: In patients undergoing open abdominal aortic aneurysm repair, peri-operative epidural analgesia should be considered, to maximise pain relief and minimise early post-operative complications. (Class IIa; Level B)

A NICE evidence review and guideline [65] noted that the identified evidence relating to elective open repair did not allow to draw many distinctions between the use of general anaesthesia alone, general anaesthesia with an epidural, and general anaesthesia with an intrathecal injection of opioid. However, the addition of an epidural to general anaesthesia was associated with a lower need for additional analgesia compared with the use of general anaesthesia alone. In the absence of explicit contraindications, possible reasons not to undertake an epidural might include possible side effects (including cardiac, respiratory, or gastrointestinal complications), the failure rate of epidurals, and the need for relatively intensive postoperative management to maximise benefits of an epidural. However, the committee did not feel that these concerns, when properly accounted for in the management of the patient, outweighed the possible benefits of using an epidural in conjunction with general anaesthesia in people undergoing open repair of an unruptured AAA. The overall recommendation was therefore positive.

The recommendation is different for ruptured AAA (rAAA). The committee agreed that the use of epidurals in addition to general anaesthesia is not considered safe or appropriate in the context of ruptured aneurysm. This is for a number of reasons; including a lack of sufficient time to administer an epidural when a patient

is losing blood quickly, as well as the fact that people with ruptured AAA are generally not in a condition to tolerate administration of an epidural.

Studies

Greco et al. [66] investigated the effects of supplemental epidural analgesia (EA) on postoperative outcomes after open AAA repair using the National Surgical Quality Improvement Program (NSQIP) database. A total of 2145 patients were included in this analysis, of whom 1492 patients received general anesthesia (GA) only and 653 patients received EA-GA. Major postoperative outcomes included mortality, pulmonary cardiac and renal complications, infections, thrombosis, and blood transfusion requirement (including Cell-Saver usage). Additional overall outcomes included hospital length of stay, return to the operating room, and readmission. EA + GA was not associated with decreased mortality or decreased rates of major postoperative pulmonary, cardiac, or renal complications. EA + GA was associated with increased transfusion requirements and decreased rates of hospital readmission. The better pain relief provided by EA alone may justify its use.

5.4.4.4 Perioperative Pain Management

The Society for Vascular Surgery practice guidelines [2] recommend:

- Central regional opioids, systemic opioid patient-controlled analgesia, and peripheral regional techniques are recommended for pain management, including multimodal techniques such as central regional blockage with local anesthetics. The geriatric population warrants special consideration, and incorporation of acetaminophen is recommended in the postoperative pain plan.

Studies

Jessula et al. [67] compared the postoperative opioid intake in patients undergoing open AAA repair across three analgesic modalities: systemic analgesia (SA) without regional anesthesia, paravertebral catheters (PVC) and thoracic epidural analgesia (TEA). Secondary objectives were to compare the time to discharge from the ICU across analgesic modalities and to compare postoperative pain scores and the opioid-related adverse event profiles of PVC and TEA. Surgically positioned paravertebral catheters used for anesthesia in 117 of 355 patients undergoing abdominal aortic aneurysm repair were associated with earlier discharge from intensive care compared to patients who underwent only systemic analgesia; these patients had similar rates of opioid-related adverse events than those who had thoracic epidural anesthesia. The study contained limitations. Because PVC is feasible only through a retroperitoneal incision, all patients in the PVC group had a retroperitoneal

incision and most patients in the TEA group had a transperitoneal incision (76.9%). Because these two incision types may be associated with different pain profiles, the benefits of PVC may be secondary to the incision type rather than the analgesic modality.

Nejim et al. [68] reported on 6394 patients in the Premier Healthcare Database who underwent elective OAR. 806 patients (12.6%) received the non-selective COX inhibitor ketorolac. The study demonstrated 40% mortality reduction with intravenous ketorolac following open abdominal aortic aneurysm repair. Ketorolac use was safe and was not accompanied by the expected NSAID-related side effects such as postoperative hemorrhage, GI bleeding nor cardiac complications. The authors explained the survival benefit with the anti-inflammatory and opioid-sparing properties of ketorolac. Limitations of the study include the potential selection bias because the administration of ketorolac was not random.

5.4.4.5 Blood Transfusion and Blood Management

The Society for Vascular Surgery practice guidelines [2] recommend:

- In the absence of ongoing blood loss, we suggest a threshold for blood transfusion during or after aneurysm repair at a hemoglobin concentration of 7 g/dL or below. Level of recommendation 2 (Weak). Quality of evidence C (Low)

The ESVS guidelines [1] recommend:

- Recommendation 49: Intra-operative cell salvage and re-transfusion should be considered during open abdominal aortic aneurysm repair. (Class IIa; Level B)

NICE guidance [69]

- Consider alternatives to blood transfusion in surgical patients.
- Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (>500 mL). Do not use cell salvage alone without tranexamic acid.
- For patients who need red blood cell transfusions and do not have major haemorrhage or acute coronary syndrome, use a restrictive haemoglobin concentration threshold of 70 g/L and a haemoglobin concentration target of 70–90 g/L after transfusion.
- Consider single unit red blood cell transfusions for patients who do not have active bleeding and reassess patients after each transfusion.

Studies/Meta-analysis

A Cochrane review assessed the effectiveness and safety of anti-fibrinolytic and haemostatic drugs and agents in reducing bleeding and the need for blood transfusion in people undergoing major vascular surgery or vascular procedures with a risk

of moderate or severe (>500 mL) blood loss [70]. Seven trials of three systemic drugs (aprotinin, desmopressin and tranexamic acid) were identified. The trials of aprotinin and desmopressin were small with very low-certainty evidence for all of outcomes. Tranexamic acid versus placebo was the systemic drug comparison with the largest number of participants (2 trials; 1460 participants), both at low risk of bias. The largest of these included a total of 9535 individuals undergoing a number of different higher risk surgeries and reported limited information on the vascular subgroup (1399 participants). Neither trial reported the number of units of red cells transfused per participant up to 30 days. Three outcomes were associated with very low-certainty evidence due to the very wide confidence intervals (CIs) resulting from small study sizes and low number of events. These were: all-cause mortality up to 30 days; number of participants requiring an allogeneic blood transfusion up to 30 days; and risk of requiring a repeat procedure or operation due to bleeding. Most trials of topical drug treatments were at high risk of bias due to their open-label design (compared with usual care, or liquids were compared with sponges). All of the trials were small, and few reported clinically relevant outcomes in the postoperative period. There is uncertainty whether any systemic or topical treatments used to reduce bleeding due to major vascular surgery have an effect on: all-cause mortality up to 30 days; risk of requiring a repeat procedure or operation due to bleeding.

Red blood cell (RBC) transfusions are associated with increased mortality and morbidity. The long-term effects of perioperative blood transfusions in patients with elective open abdominal aortic aneurysm repair (OAR) were reported by Wedel et al. [71] using data from The Danish Vascular Registry from 2000 to 2015. There were 801 patients who did not receive blood transfusion among 3876 patients (median survival 9.1 years). Overall 30-day mortality was 3.1 and 3.6% for all transfused patients. For five subgroups 30-day mortality was: No transfusions 1.1%, 1 RBC 1.2%, 2–3 RBC 2.2%, 4–5 RBC 1.9% and >5 RBC 7.9%. After receiving RBCs, the hazard ratio for death was 1.54 (95% CI 1.27–1.85) compared to non-transfused patients. There was a dose-dependent association between RBC transfusions received during elective AAA repair and an increase in short- and long-term mortality. The conclusion was to set the transfusion trigger as low as possible in OAR to avoid unnecessary blood transfusions. According to a Cochrane Review [72], RBCs can be avoided in most patients with hemoglobin thresholds above 7–8 g/dL. There was no evidence that a restrictive transfusion strategy impacts 30-day mortality or morbidity.

Since open elective abdominal aortic aneurysm repair is associated with significant blood loss, the intraoperative use of the cell saver (intraoperative autotransfusion) is recommended for these procedures. The cell saver should be used as follows [73]:

- When anticipated blood loss is >1 L or 20% of the patient's estimated blood volume (EBV)
- In patients with a low haemoglobin concentration or who are at increased risk of bleeding

- In patients with multiple antibodies or rare blood types (cross-match compatible blood is unobtainable)
- In patients who are unwilling to accept allogeneic blood (e.g., Jehovah's Witnesses)
- If>10% of patients undergoing the procedure will require transfusion
- If the mean transfusion requirement for the planned procedure exceeds one unit of blood.

A systematic review on the role of cell savers in AAA surgery has been compiled by Shantikumar et al. [74]. Twenty-three studies were identified. Whilst some data are conflicting, cell salvage appears to reduce overall use and exposure to allogeneic blood and reduces length of intensive care unit and hospital stay after elective AAA repairs. There may be additional benefit by combining cell salvage with other blood-conservation techniques. Use of cell salvage in ruptured AAA repairs consistently reduced blood-product requirement.

5.4.4.6 Graft Infection

The Society for Vascular Surgery practice guidelines [2] recommend:

- In patients presenting with an infected graft in the presence of extensive contamination with gross purulence, we recommend extra-anatomic reconstruction followed by excision of all graft material along with aortic stump closure covered by an omental flap. Level of recommendation 1 (Strong). Quality of evidence B (Moderate)
- In patients presenting with an infected graft with minimal contamination, we suggest in situ reconstruction with cryopreserved allograft. Level of recommendation 2 (Weak). Quality of evidence B (Moderate)
- In a stable patient presenting with an infected graft, we suggest in situ reconstruction with femoral vein after graft excision and débridement. Level of recommendation 2 (Weak). Quality of evidence B (Moderate)
- In unstable patients with infected graft, we recommend in situ reconstruction with a silver- or antibiotic-impregnated graft, cryopreserved allograft, or PTFE graft. Level of recommendation 1 (Strong). Quality of evidence B (Moderate)

The ESVS guidelines [1] recommend:

- Recommendation 77: For radical treatment of aortic graft or stent graft infection complete graft/stent graft explantation is recommended. (Class I; Level C)
- Recommendation 78: In selected high risk patients with graft/stent graft infection, conservative and/or palliative options should be considered. (Class IIa; Level C).

ALGrawany

Studies

A Cochrane review [75] on abdominal aortic graft infections states:

- Abdominal aortic graft infections can be treated surgically or conservatively using medical management. The two most common surgical techniques are in situ replacement of the graft and extra-anatomical bypass. Medical management most commonly consists of a course of long-term antibiotics. There is currently no consensus on which intervention is the most effective in managing abdominal aortic graft infections. Whilst in emergency or complex situations such as graft rupture surgical management is the only option, in non-emergency situations it is often personal preference that influences the clinician's decision-making. There is currently insufficient evidence to draw conclusions to support any treatment over the other. Multicentre clinical trials are required to compare different treatments for the condition.

A systematic review on the management of open abdominal aortic graft infections was performed by Post and Vos [76]. They included 32 publications with a total of 1316 patients. The meta-analysis showed that overall 30 day mortality and 1 year survival for treatment of aortic graft infection is 13.5% and 73.6%, respectively. Extraanatomic repair, once the gold standard, had the highest 30-day mortality (26.7%) and lowest 1 year survival (54.3%) rates. Limb salvage rates were high (95%) for all subgroups and recurrent infection rates were low (approximately 5%) except for those studies in which partial graft removal was performed (39.3%). Subgroup analyses of graft material used for in situ replacement demonstrated better survival and mortality rates for prosthetic grafts, although these grafts performed worse compared with superficial femoral veins and arterial allografts in terms of limb salvage and infection recurrence rates. Patency at 1 year was comparable between all subgroups studied.

The first systematic review with meta-analysis of all data (31 studies, 1377 patients) available on in situ reconstruction with cryopreserved allografts for arterial reconstruction after aortoiliac infection was performed by Antonopoulos et al. [77]. 30-day mortality was 14.9%. Peri-anastomotic rupture/allograft disruption rate was 5.9%, while pooled aneurysmal degeneration/allograft dilatation was 4.99%. A pooled rate of 3.11% was estimated for pseudoaneurysm formation after the use of cryopreserved arterial allografts, while the allograft thrombotic/stenotic complication rate and perianastomotic infection were 12.19%, respectively. Mortality during follow up was 19.24%, while allograft related mortality during follow up was 3.58%. A pooled allograft related re-operation rate was estimated at 24.87%. The authors considered in situ reconstruction with the use of cryopreserved allografts as a safe and durable option with acceptable outcomes for treatment of aorto-iliac infection

Alonso et al. [78] reported the surgical strategy and early outcomes of abdominal aortic reconstruction in both native and graft-related aortic infection with in situ xenopericardial grafts. In situ xenopericardial aortic reconstruction in 21 patients resulted in 4.7% 30-day mortality, 19% overall mortality, and 95% primary patency

with a median follow up of 14 months. Combined with debridement and an appropriately long course of antibiotics, in situ xenopericardial aortic reconstruction was a safe and effective management strategy for both native and graft-related abdominal aortic infection with good short-term results.

Bovine pericardium was also used by Almási-Sperling et al. [79] for in situ reconstruction of infected grafts. Graft reconstructions were related to the descending aorta (n = 1), abdominal aorta (n = 5), iliac arteries (n = 4) and femoral arteries (n = 9). Ten patients (53%) had a complication perioperatively and postoperatively. The 30-day mortality was 10.5%; the total mortality rate after 1 year was 32%. There was no reinfection after bovine reconstruction observed. Graft occlusions were detected in two cases during follow-up (median, 6 months; range, 1–47 months).

A third retrospective analysis of patients in whom bovine pericardial grafts (BPGs) had been used for the management of aortic graft infection or aortic reconstructive surgery in the presence of systemic infection was presented by Burghuber et al. [80]. Twenty-one patients had received BPGs. The 30-day mortality was 9.5% and the 2-year survival rate was 75%, with a primary assisted patency rate of 94% and freedom from reinfection of 89%. Considering that antibiotic-impregnated/silver-coated polyester grafts are reported to have a higher reinfection rate than biological materials, the authors considered bovine pericardial prostheses to be a good alternative. However, case series without a control group do not allow a final conclusion.

5.4.5 Endovascular Repair of Nonruptured AAA

5.4.5.1 Anaesthesia

Studies

A systematic review is available for the effect of mode of anesthesia on outcome from EVAR [81]. 16 studies in 23,202 patients compared local anaesthesia (LA) to general anaesthesia (GA) and reported in-hospital mortality/30-day mortality. The unadjusted risk of death after emergency EVAR with LA was lower than with GA. Trends in elective surgery were less clear. Randomised trials were lacking.

The aim of a systematic review and meta-analysis performed by Harky et al. [82] was to compare the clinical outcomes of using local/regional anesthesia (LA/RA) versus GA in nonemergency EVAR. A total of 12,024 patients (n = 1664 LA/RA, n = 10,360 GA) were analyzed from 12 observational studies included in this analysis. Shorter total surgical time in LA/RA patients was reported (135 ± 40 min v 164 ± 43 min; $p < 0.00001$). Shorter hospital stay was observed in LA/RA patients (3.6 ± 3.3 d v 4.6 ± 5 d; $p = 0.002$). No difference in cardiac or renal complications was noted between the LA/RA and GA groups postoperatively. Similarly, no difference in vascular complications was noted in LA/RA versus GA patients. Thirty-day morality was not different between the two cohorts. Use of LA/RA in selective

endovascular abdominal aortic aneurysm repair procedures provides satisfactory and comparable perioperative outcomes with those of GA, with the advantage of a shorter hospital stay. A large randomized controlled trial or multicenter study is required to confirm these findings.

Van Orden et al. [83] identified 8141 percutaneous EVARs in the Vascular Quality Initiative (VQI) database. GA was used in 7387 (90.7%) cases, whereas LA was used for 754 (9.3%) of cases. Multivariable analysis showed that GA compared with LA was associated with more pulmonary complications (odds ratio, 2.8; 95% confidence interval, 1.49–5.43; P = .002) and prolonged operative time (means ratio, 1.11; 95% confidence interval, 1.08–1.52; P < .001). There was no independent effect on overall complications, cardiac complications, or mortality. Surgeons should consider expanding the use of LA for percutaneous EVAR when feasible.

Data from the UK's National Vascular Registry were analysed by Dovell et al. [84]. A total of 9783 patients received an elective, standard infrarenal EVAR (GA, n = 7069; RA, n = 2347; and LA, n = 367) across 89 hospitals. Thirty-day mortality was significantly lower in the RA group compared with the GA group, but mode of anaesthesia was not associated with increased complications for patients undergoing elective standard infrarenal EVAR. The previously observed reduction in pulmonary complications associated with LA in elective EVAR was not reproduced in this cohort. This retrospective analysis of a contemporary national database contributes to the evolving evidence base and clinical equipoise surrounding the choice of anaesthetic technique for EVAR.

5.4.5.2 Percutaneous Access

The ESVS guidelines [1] recommend:

- Recommendation 55: An ultrasound guided percutaneous approach should be considered in endovascular aortic aneurysm repair. (Class IIa; Level B)

Studies

In the so-called PiERO study [85], patients with an abdominal aortic aneurysm suitable for EVAR were randomized to open or percutaneous access of the main device (MD) through the common femoral artery (CFA). Both groups contained 137 groins. A major strength of the PiERO trial was the comparison of two techniques in one patient. No difference in surgical site infections or wound complications was found, but a reduction of pain and wound inflammation was observed in the percutaneous access group. The patient's comfort did improve.

Perioperative outcomes of percutaneous EVAR were analysed by Siracuse et al. [86] using the Vascular Quality Initiative (VQI) database. In 8340 patients (64%), endovascular aneurysm repair through a percutaneous approach resulted in reductions in operative time, blood loss, and length of stay compared with results in 4747

patients who underwent abdominal aortic aneurysm repair by open surgical access. The percutaneous approach failed in 4%, most frequently with previous bypass procedures, ruptured aneurysms, general anesthesia, female sex, obesity, coronary disease, and preoperative aspirin use. Early results of this study suggest that a percutaneous approach should be used for endovascular aortic aneurysm repair.

A meta-analysis comparing open vs. percutaneous access in EVAR is now available [87]. Four RCTs were identified, reporting a total of 368 patients and 530 access sites. Meta-analysis showed no difference in access site complications or infection, post-operative bleeding/haematoma, access related arterial injury, femoral artery occlusion, pseudo-aneurysm, or peri-operative mortality between percutaneous and cutdown EVAR. Seroma/lymphorrhoea was significantly less frequent after percutaneous EVAR compared with cutdown EVAR and the procedure time was significantly shorter, but hospital length of stay was not different between treatments. The evidence is very uncertain about the effect of percutaneous EVAR on clinically important outcomes.

5.4.5.3 EVAR Outside the Instructions for Use

Studies

In a systematic review, Antoniou et al. [88] investigated whether patients undergoing standard endovascular aneurysm repair outside the instructions for use (IFU) have worse outcomes than patients treated within IFU. 17 observational cohort studies published between 2011 and 2017, reporting a total of 4498 patients were identified. The pooled prevalence of EVAR performed outside the IFU was 40%. Nonadherence to IFU was not associated with increased risk of perioperative mortality, aneurysm rupture, aneurysm-related mortality, technical failure, requirement for adjunctive procedures, type I endoleak, aneurysm sac expansion, or aneurysm-related reintervention. The overall mortality was significantly higher in patients treated outside the IFU. Meta-regression showed that the prevalence of EVAR performed outside the IFU has increased over time (P = .019). Standard EVAR outside the IFU could be considered in selected patients who are deemed high risk for complex open or endovascular surgery.

The long-term results of outside IFU EVAR were examined by Oliveira-Pinto et al. [89]. 13 studies were included in this review. Although overall mortality and aneurysm-related mortality did not seem to differ significantly at long-term, higher rates of type I endoleaks may be expected, mainly in short necks. However, for patients with severe angulation or high thrombus load in the proximal neck, results of outside IFU EVAR seem to match the results of EVAR within IFU.

5.4.5.4 Prevention of Contrast-Induced Nephropathy (CIN) with EVAR

The ESVS guidelines [1] recommend:

- Recommendation 38: Patients with renal impairment should be adequately hydrated before elective abdominal aortic aneurysm repair, and estimated glomerular filtration rate, fluid input, and urine output should be monitored after abdominal aortic aneurysm repair to recognise and manage reduced kidney function. (Class I; Level C)

The guideline of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) [90] recommends:

- Especially if glomerular filtration rate (GFR) is <40 mL/min/1.73 m^2, all patients with chronic kidney disease who undergo diagnostic catheterization should receive preventive hydration with isotonic saline, to be started approximately 12 h before angiography and continued for at least 24 h afterwards to reduce the risk of contrast-induced nephropathy (CIN). The implementation of high-dose statin before diagnostic catheterization has been shown to reduce the incidence of CIN and should be considered as an additional preventive measure in patients without contraindications.

Studies

Ma et al. [91] conducted a network meta-analysis to evaluate the relative efficacy of pharmacological interventions for the prevention of CIN. They found 107 trials comprising 21,450 participants and 11 pharmacological interventions. Compared with intravenous saline, intravenous saline + statin + *N*-acetylcysteine (NAC) seemed to be the most effective treatment for the prevention of CIN in patients after coronary angiography. NAC + intravenous saline may have a protective role against short-term all-cause mortality. However, none of these drugs has effectively decreased the requirement for dialysis and the rate of major cardiac and cerebrovascular adverse events.

A second meta-analysis compared the preventive effect of strategies to reduce CIN, including subgroup analyses based on route of administration of contrast media and the type of contrast media used [92]. In this study, evidence for a clinically important and statistically significant benefit regarding CIN prevention was found for three strategies:

- Low-dose NAC + intravenous saline compared with intravenous saline alone.
- NAC + i.v. saline vs. i.v. saline in patients receiving low-osmolar contrast media.
- Statins + NAC + i.v. saline vs. NAC + i.v. saline.

A clinically important difference that was not statistically significant was seen for:

- Sodium bicarbonate vs. i.v. saline in patients receiving low osmolar contrast media.
- Statins + i.v. saline vs. i.v. saline alone.
- Ascorbic acid + i.v. saline vs. i.v. saline alone.

Strength of evidence was generally insufficient for comparisons of the need for renal replacement, cardiac events, and mortality. The greatest reduction in CIN was seen with *N*-acetylcysteine plus i.v. saline in patients receiving low osmolar contrast media and with statins plus *N*-acetylcysteine plus i.v. saline.

5.4.5.5 Preservation of Flow to the Internal Iliac Artery

The Society for Vascular Surgery practice guidelines [2] recommend:

- We recommend preservation of flow to at least one internal iliac artery. Level of recommendation 1 (Strong). Quality of evidence A (High)
- We recommend using FDA-approved branch endograft devices in anatomically suitable patients to maintain perfusion to at least one internal iliac artery. Level of recommendation 1 (Strong). Quality of evidence A (High)
- We recommend staging bilateral internal iliac artery occlusion by at least 1–2 weeks if required for EVAR. Level of recommendation 1 (Strong). Quality of evidence A (High)

Studies

A significant proportion (up to 40%) of patients with AAA have an ectatic or aneurysmal common iliac artery (CIA). In the absence of an adequate iliac artery landing zone, EVAR requires exclusion of one or both internal iliac arteries (IIAs) and extension of the stent graft to the external iliac artery. In most of these patients, embolization of one or both IIAs is required to prevent backbleeding from the IIA. The aim of a study presented by Kouvelos et al. [93] was to review all studies on IIA sacrifice during EVAR and analyze the clinical effect of IIA interruption. Furthermore, all reported cases that involved preservation of IIA were reviewed to investigate technical and clinical outcome. In this systematic review the pooled 30-day buttock claudication rate was 29.2%. Patients undergoing bilateral IIA interruption had a higher incidence of buttock claudication than patients with unilateral IIA interruption (36.5% vs. 27.2%; p = .01). During a median follow up of 17 months, the pooled rate of persistent buttock claudication was 20.5%. In patients with an iliac branched device, technical success was 96.2%. Within 30 days of EVAR, 4.3% of internal iliac branches occluded. The pooled buttock claudication rate on the side of the IIA revascularization during follow up was 4.1%. IIA preservation techniques represent a significant improvement in the treatment of aorto-iliac aneurysms and have been associated with high technical success and low morbidity.

According to a systematic review by Bosanquet et al. [94], 15% of EVARs require internal iliac artery (IIA) sacrifice. Buttock claudication occurred in 27.9% of patients, although 48% resolved after a mean of 21.8 months. Erectile dysfunction was reported in 10.2% of males, with higher rates after coiling. Buttock claudication rates were 32.6% with coils, 23.8% with plugs, and 12.9% with coverage

alone, and less with unilateral (vs. bilateral) IIA treatment. More proximal coil placement resulted in lower rates of buttock claudication. Type II endoleaks were more frequent after covering alone; however, re-interventions were rare. Significant ischaemic events (bowel/gluteal/spinal ischaemia) were very rare. Plugs were quicker to place and required less radiation ($p < .001$) than coils. Where both options are technically possible, plugs could be considered preferential to coils, and placed as proximally in the IIA as possible.

Medium-term results are available for two techniques to maintain blood flow in the IIA, the use of iliac-branched prostheses and the so-called parallel graft techniques (sandwich graft, chimney). The most used technique here is the internasnorkel technique, in which a covered stent is inserted into the IIA parallel to the main graft, allowing retrograde perfusion of the IIA [95]. In a review, Oliveira-Pinto et al. [96] found similar short-term outcomes for the iliac branch extension device (IBED) and the parallel graft—"sandwich" technique (PG-ST). Both IBED and PG-ST have proven to be safe and valid approaches. However, while IBED has established as a durable procedure, mid-term data lacks on PGs performance and further studies are required to attest durability of the latter procedure.

5.4.5.6 Stent Graft Migration

Studies

Device migration is a common complication that requires secondary intervention following EVAR. It is defined as displacement of the endograft by more than 5–10 mm from its original position. It is often due to progressive dilatation of the aneurysm neck but can also be related to aortic tortuosity, aortic wall degeneration after endograft placement or may be secondary to graft over- or undersizing. Device migration is associated with endoleaks, aneurysm sac expansion and possible rupture. Device migration has been reported to occur following 1.0–2.8% of TEVAR procedures and 1–10% of endovascular repair of the abdominal aorta at 1 year post-intervention. In cases of aortic endograft migration, treatment is very similar to management of a type I endoleak. Endovascular treatment options include the use of aortic extension cuffs or placement of large balloon-expandable stents to augment the fixation of the endograft to the native aortic wall and thus extend the fixation zone. Another option is that of using endostaples to secure the graft to the aortic wall [97].

Muhs et al. [98] examined whether prophylactic use of EndoAnchors contributes to improved outcomes after endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms. In propensity-matched cohorts (99 pairs matched), most with hostile neck, prophylactic use of EndoAnchors during elective endovascular aortic aneurysm repair resulted in similar rates of freedom from type I endoleak, neck dilation, or sac enlargement but a significantly higher rate of sac regression during a 2-year follow-up.

A retrospective review of a prospective database of 42 patients with hyperangulated necks (>60°) who underwent EVAR with supplementary endostapling was undertaken by Chaudhuri et al. [99]. The study specifically examined hostile neck anatomy in the context of hyperangulated necks, and whether using targeted adjunct fixation with the Heli-FX EndoAnchor (EA) system can achieve acceptable sealing augmentation and prevent complications such as type Ia endoleaks and migration. Mean follow-up time was 18.5 months. One patient had persistent type Ia endoleak, successfully banded. There was 6.8 ± 10.2 mm sac size reduction ($p < .001$). There were no other neck-related reinterventions, despite continued neck dilatation (3.2 ± 3.7 mm, $p < .001$). The study suggested successful EVAR with adjunct endostapling for AAA with hyperangulated necks, with significant sac shrinkage and low rates of endoleaks, migration and reinterventions.

5.4.5.7 Endoleak

The ESVS guidelines [1] recommend:

- Recommendation 86: In patients with Type I endoleak after endovascular abdominal aortic aneurysm repair, re-intervention to achieve a seal, primarily by endovascular means, is recommended. (Class I; Level B)
- Recommendation 87: Expansion of sac diameter ≥ 1 cm detected during follow up after endovascular abdominal aortic aneurysm repair using the same imaging modality and measurement method may be considered as a reasonable threshold for significant growth. (Class IIb; Level C)
- Recommendation 88: Re-intervention for Type II endoleak after endovascular abdominal aortic aneurysm repair should be considered in the presence of significant aneurysm growth (see Recommendation 87), primarily by endovascular means. (Class IIa; Level C)
- Recommendation 89: In patients with Type III endoleak after endovascular abdominal aortic aneurysm repair, re-intervention is recommended, primarily by endovascular means. (Class I; Level C)
- Recommendation 90: Significant aneurysm sac growth after endovascular abdominal aortic aneurysm repair, without visible endoleak on standard imaging, should be considered for further diagnostic evaluation with alternative imaging modalities to exclude the presence of an unidentified endoleak, and should be considered for treatment. (Class IIa; Level C)

Studies

Cannavale et al. [100] outlined the most recent concepts on imaging follow-up, pathophysiology/risk factors, and management of endoleaks. The results of this review are shown in Table 5.4. Prevention and treatment of endoleaks have reached high success rates, with low complication and endoleak recurrence rates. Type 2

Table 5.4 Treatment modalities in type I and II endoleaks (according to [100])

Treatment modality	Technical success	Freedom from recurrent endoleak
Endoleak type Ia		
• Aortic balloon angioplasty + cuff/ stent-extension-reinforcement	100%	87%
• Embolisation (coils and glue)	90–100%	80%
• Endo-Anchors	90–100%	95–97%
• Parallel stent grafts	90–94.4%	90–100%
• Surgical conversion	>90%	Not reported
Endoleak type Ib		
– Limb extension	100%	94% without embolisation
– Embolisation internal iliac artery	100%	75%
– Surgical/hybrid access	>90%	Not reported
Endoleak type II		
– Transarterial embolisation	62.5–84%	64.2%
– Translumbar direct sac puncture	81–98.7%	81%
– Transcaval embolisation	93.7%	Not reported
– Surgical laparoscopic/open	90%	100%

endoleaks (T2EL), caused by backflow of collateral arteries into the aneurysm sac, are the most frequently encountered and may account for the need for secondary interventions after EVAR in up to 40% of the cases. Support for conservative management of T2EL derives from the relatively high percentage of T2EL that will resolve spontaneously over a variable period (more than 30%) and the estimated low risk of post-EVAR rupture secondary to isolated T2EL (less than 1%) [101].

Dijkstra et al. [102] reported the incidence, natural history, and outcome of type II endoleaks in the largest prospective real-world cohort to date. The ENGAGE registry included 1263 patients. Through 5 years of follow-up, a total of 197 (15.6%) patients with isolated type II endoleaks were identified. Most were detected within the first 30 days (37.1%) and through the first year (37.1%), with the remainder being detected after 1 year of follow-up (25.8%). Patients with a type II endoleak had a higher incidence of aneurysm growth and more secondary endovascular procedures (15.4% vs 7.5% at 5 years; $P < .001$). Overall survival was higher in the isolated type II endoleak group compared with patients with no endoleak (77.2% vs 67.0% at 5 years; $P = .010$). Twenty-two patients (10%) with a type II endoleak were diagnosed with a late type I endoleak (type IA, $n = 10$; type IB, $n = 12$), with a secondary intervention rate of 67.5% through 5 years. Most of the type II endoleaks do not require secondary intervention. However, a small group of patients with a type II endoleak will present with a type I endoleak, resulting in a high secondary intervention rate and significant risk of aneurysm-related complications.

A systematic review and meta-analysis on pre-emptive aortic sidebranch embolization to prevent T2EL after EVAR was performed by Yu et al. [103]. Together with 13 studies from a previous search, a total of 17 studies were included in this updated analysis. Pre-emptive embolization was performed 1–28 days before the

EVAR procedure in six studies. In seven studies, embolization of aortic side branch(es) was performed simultaneously with the EVAR procedure. Four studies did not specify the timing of pre-emptive embolization in relation to the EVAR procedure. Based on 16 studies, the incidence of T2EL was 19.7% (145/735) in the embolization group vs 37.4% (456/1220) in the control group (OR, 0.38), after a median follow-up of 21.3 months. Based on 12 studies, the incidence of reintervention for T2EL was 1.2% (7/570) in the embolization group vs 11.2% (84/753) in the control group (OR, 0.12) after a median follow-up of 24.1 months. With a lower incidence of T2EL, aneurysm sac growth, and reintervention rate, pre-emptive embolization can potentially reduce the frequency of surveillance and improve the long-term durability of EVAR. However, a higher level of evidence is still required to support a broad change of practice, including data on cost-effectiveness and on the potential effect on rupture.

5.4.5.8 Stent Graft Infection

Studies

A meta-analysis based on 12 studies reporting on 362 patients is available on the outcome of endograft infection after EVAR [104]. The incidence of graft infection was 0.6%. Surgical treatment was performed in the majority of patients (n = 293, 81%; 233 [64%] in situ reconstructions, 58 [16%] extra-anatomical bypasses, 2 endovascular interventions). Aortic replacement with a prosthetic graft was performed in 58%, whereas cryopreserved allografts and autologous grafts were used in 31% and 11%, respectively. The pooled estimate of 30-day/in-hospital mortality was 26.6%. The pooled 30-day/in-hospital mortality for nine patients treated conservatively was 63.3%. The pooled overall follow-up mortality was 45.7% vs 58.6% for the nine patients receiving conservative treatment. Surgical treatment with complete explantation of the infected endograft seems to be the optimal management in selected patients.

Another meta-analysis is based on 11 studies with 402 patients [105]. Most of the endografts were implanted for EVAR (351/402, 87%), while the other 51 (13%) endografts were infected following TEVAR. Among the 402 patients, 39 (9.7%) patients presented with aortic rupture. Ninety-two of 380 (24.2%) patients with available data had aortoenteric fistula (AEF). 69 patients (17%) died in hospital or within 30 days after operation. 114 patients (28%) died during follow-up. 42 patients (10%) received conservative treatment, whereas 359 (90%) patients underwent surgical treatment, including stent graft removal with in situ reconstruction or extra-anatomical bypass, and secondary endovascular procedure. Patients in the surgical group had a higher survival rate compared with conservative group (58% vs. 33%, P = 0.002). This analysis suggests that surgical treatment is a better option compared with conservative management in selected patients with aortic endograft infection.

5.4.5.9 Short Stay EVAR

Studies

Shaw et al. [106] aimed to examine evidence for the safety and utility of a short stay care pathway for EVAR. Inclusion criteria were asymptomatic patients, favourable anatomy, patient consent, technical success, able to mobilise post-operatively, transfer time to hospital if readmission <60 min, and adult observer for first 24 h. From five suitable studies, 450 (75%) patients were successfully discharged the same or next day after EVAR. Complications most often occurred within 3 h of surgery, and major complications requiring intensive treatment unit admission occurred within 6 h. Readmission rates were 0–5% for those discharged early, with no difference in 30-day readmission. Early discharge led to a statistically significant cost saving of £13,360 (LOS 4 days) to £9844 (LOS 1 day).

The objective of a retrospective, single-center cohort study presented by Montross et al. [107] was to assess the possibility of developing a preoperative profile to select potential candidates for ambulatory admission with early discharge (≤6 h after surgery) or to have EVAR performed in a free-standing ambulatory surgery center (ASC). Analysis of 272 elective endovascular aortic aneurysm repairs (EVAR) cases revealed that failed percutaneous EVAR (odds ratio, 2.37) and percutaneous EVAR performed outside of the manufacturer's instructions for use (odds ratio, 2.84) were risk factors associated with ambulatory EVAR ineligibility. Early discharge after EVAR is possible in more than one-half of patients, permitting ambulatory hospital admission and discharge. However, preoperative profiling is not yet sufficient to endorse performing EVAR at free-standing ambulatory surgery centers at this time.

5.4.6 Ruptured Abdominal Aortic Aneurysm (rAAA)

5.4.6.1 Anaesthesia for EVAR

The ESVS guidelines [1] recommend:

- Recommendation 67: Local anaesthesia should be considered as the anaesthetic modality of choice for endovascular repair of ruptured abdominal aortic aneurysm whenever tolerated by the patient. (Class IIa; Level B)

Studies

Mouton et al. [108] reported on 3101 patients with rAAA captured in the UK National Vascular Registry. 2306 underwent on open procedure and 795 had EVAR (local anaesthesia, LA, n = 319; general anaesthesia, GA, n = 435; regional

anaesthesia, RA, n = 41). Overall, 56 of 72 hospitals (78%) offered LA for EVAR of rAAA. Patients who had surgery under LA had a lower in-hospital mortality rate than patients who received GA (18.5% vs 28.0%), and this was unchanged after adjustment for factors known to influence survival (adjusted hazard ratio 0·62; P = 0·003). Median hospital stay and postoperative morbidity from other complications were similar. The study provided further evidence of the benefit of LA for patients undergoing emergency EVAR for rAAA.

Using the Vascular Quality Initiative database, Faizer et al. [109] compared LA vs GA in EVAR for rAAA. Among 3330 patients with rAAA, 226 (6.8%) underwent EVAR in LA and 1510 (45.3%) underwent EVAR in GA. Hospital mortality rates were significantly lower with EVAR in LA compared with EVAR in GA (15.5% vs. 23.3%; p = 0.04). Patients undergoing EVAR who were <75 years old and those without preoperative hypotension had the greatest survival benefit from LA compared with GA.

Propensity score matching techniques were used by Bennett et al. [110] to compare the 30-day postoperative outcomes of patients from the 2007 to 2015 American College of Surgeons National Surgical Quality Improvement Program database who underwent endovascular repair of rAAA under locoregional vs general anaesthesia. 130 general anaesthesia patients were well matched with their locoregional anaesthesia counterparts. The 30-day postoperative mortality rates for patients in the matched cohort were 14.6% for patients in the locoregional anaesthesia group compared with 29.2% for patients in the general anaesthesia group (P = .002).

The first meta-analysis focusing on the effect of the anaesthesia modality on perioperative mortality in endovascular repair of ruptured abdominal aortic aneurysms was performed by Deng et al. [111]. A total of eight studies were included in this analysis. Three different pooled analyses of the data from the included studies revealed robust results that endovascular repair of ruptured abdominal aortic aneurysms (REVAR) under locoregional anesthesia is associated with a lower 30-day/in-hospital mortality than REVAR under general anaesthesia. However, because the included studies may have had some observation bias, further randomized controlled trials are warranted to validate these results. Despite the perioperative survival benefit of REVAR under LA vs GA observed, clinicians must exercise caution when adopting this procedure. LA was associated with some potential disadvantages, including patient anxiety, discomfort, and movement artifacts caused by pain or un-intubated respiration. In addition, awake patients might have a limited tolerance of time on the operating table, which increases the urgency of the REVAR. These factors may result in inaccurate or incorrect deployment of the stent grafts.

5.4.6.2 Access Type for EVAR in Ruptured Abdominal Aortic Aneurysms

Studies

Cheng et al. [112] identified 1206 patients with EVAR for rAAA in the VQI database. 739 (61.3%) EVARs were performed by percutaneous access, 416 (34.5%) by open access, and 51 (4.2%) by failed percutaneous that converted to open access. Percutaneous access, compared with open access and failed percutaneous access, respectively, had the shortest operative time (min, median) (111 vs. 138 vs. 180, $P < 0.001$) and was most often performed under local anesthesia (16.7% vs. 5% vs. 9.8%, $P < 0.001$). Multivariable analysis did not show access type to have a significant effect on cardiac complications, pulmonary complications, any complications, return to the operating room, or perioperative mortality. However, open access was independently associated with a prolonged length of stay ($P = 0.012$). Access during these emergent procedures should be based on surgeon preference and experience.

5.4.6.3 Permissive Hypotension

The ESVS guidelines [1] recommend:

- Recommendation 66: In patients with ruptured abdominal aortic aneurysm, a policy of permissive hypotension, by restricting fluid resuscitation, is recommended in the conscious patient. (Class I; Level B)

Studies

In the management of people with rAAA, controlled hypotension resuscitation aims to replace sufficient fluid to maintain the blood pressure between 50 and 100 mmHg during the preoperative and intra-operative period. The controlled hypotension strategy avoids large volumes of crystalloid replacement. It may help to prevent blood loss by avoiding: the clot disruption caused by a rapid increase in systolic blood pressure; the dilution of clotting factors, platelets, and fibrinogen; and the temperature decrease that inhibits enzyme activity involved in platelet and clotting factor function. The principle of controlled hypotension is widely adopted for people with trauma and has been applied for people with rAAA. A Cochrane Review [113] found no RCTs that compared controlled hypotension and normotensive resuscitation strategies in the management of haemorrhagic shock in patients with ruptured abdominal aortic aneurysm that assessed mortality, presence of coagulopathy, intensive care unit length of stay, and the presence of myocardial infarct and renal failure. In conclusion, high quality studies that evaluate the best strategy for managing haemorrhagic shock in ruptured abdominal aortic aneurysms are required.

NICE published an evidence review on permissive hypotension during transfer of people with rAAA to regional vascular services [114]. Although there was a lack

of evidence on permissive hypotension during transfer of people with ruptured AAA, the committee noted that a recommendation in the clinical guideline on assessment and management of major trauma (NICE guideline NG39) recommended the use of restrictive approaches to volume resuscitation in this population. They agreed that the rationale underpinning the use of restrictive fluid rescuscitation in people after major trauma was applicable to people with ruptured AAA, as both groups experience profuse bleeding. As a result, the committee considered it reasonable to adapt the recommendation from NICE guideline NG39 so it can be used within the context of AAA. Excessive fluid resuscitation can dilute clotting factors, cause hypocalcaemia and reduce a patient's body temperature. The committee agreed that a potential benefit of a permissive hypotensive resuscitation strategy is that it can make surgery easier by reducing the size of haematomas. Furthermore, patients will retain the ability to form clots, making postoperative management easier.

5.4.6.4 Aortic Occlusion Balloon

The ESVS guidelines [1] recommend:

- Recommendation 68: Aortic balloon occlusion for proximal control should be considered in haemodynamically unstable ruptured abdominal aortic aneurysm patients undergoing open or endovascular repair. (Class IIa; Level C)

Studies

Karkos et al. [115] aimed to investigate whether the use of aortic occlusion balloon (AOB) has an impact on mortality of patients undergoing endovascular repair of ruptured abdominal aortic aneurysms. Included in this meta-analysis were 39 eligible studies reporting 1277 patients. The pooled perioperative mortality was 21.6%. A total of 200 patients required AOB with an estimated pooled proportion of 14.1%. There was a statistically significant negative correlation between AOB and mortality and a positive effect of hemodynamic instability on mortality. In practical terms, mortality was significantly higher in studies with a higher proportion of hemodynamically unstable patients and lower in studies with a higher rate of AOB use. The study provided meta-analytical evidence that the use of an AOB in unstable rAAA patients undergoing endovascular repair may improve the results.

5.4.6.5 Abdominal Compartment Syndrome

The ESVS guidelines [1] recommend:

- Recommendation 71: In all patients undergoing open or endovascular treatment for ruptured abdominal aortic aneurysm, monitoring of intra-abdominal pressure

for early diagnosis and management of intra-abdominal hypertension/abdominal compartment syndrome is recommended. (Class I; Level B)

- Recommendation 72: In the presence of abdominal compartment syndrome after open or endovascular treatment of ruptured abdominal aortic aneurysm, decompressive laparotomy is recommended. (Class I; Level B)
- Recommendation 73: In the management of open abdomen following decompression for abdominal compartment syndrome after open or endovascular treatment of ruptured abdominal aortic aneurysm, vacuum assisted closure system should be considered. (Class IIa; Level B)

Studies

A population-based Swedish study described the incidence, treatment, and outcome of abdominal compartment syndrome (ACS) after rAAA [116]. ACS developed in 6.8% after OR versus 6.9% after EVAR. In the rAAA group, the 30-day mortality rate with ACS was 42.4%. Without ACS, the 30-day mortality rate was 23.5%. There was no difference in mortality between EVAR and OR among those who developed ACS. After rAAA and OR the mortality rate was 37.5% at 30 days, the corresponding mortality rates after EVAR were 50% at 30 days. In all, approximately 14.9% (10.7% prophylactic treatment + 4.2% after decompression laparotomy) required open abdomen treatment after rAAA repair. Thus, ACS is a devastating complication after rAAA repair, regardless of whether an open or endovascular technique is used. This knowledge is particularly important given the fact that ACS developed as often after EVAR as after OR (although prophylactic open abdomen treatment was common after OR).

In a second Swedish study, during 2008–2015, 120 of 8765 patients undergoing surgery for infrarenal AAA developed postoperative ACS (1.4%). Among 1718 repairs for rAAA and 7009 repairs for iAAA, the risks of ACS were 45/1212 (3.7%) after OR for rAAA, 38/506 (7.5%) after EVAR for rAAA, 307/2859 (1.0%) after OR for iAAA, and 7/4150 (0.2%) after EVAR for iAAA [117]. The duration of intraabdominal hypertension before treatment predicted the need for renal replacement therapy. This emphasises the need to focus on prevention, through careful monitoring of intra-abdominal pressure, strategies for pre-emptive treatment of intraabdominal hypertension, and swift treatment when ACS develops.

The aim of a propensity-matched retrospective cohort study was to investigate whether leaving the abdomen open with delayed closure can improve outcome in terms of mortality and major complications in patients treated for rAAA with open repair, compared to closing the abdomen at the end of the primary operation [118]. In total, 79 patients treated with a primarily open abdomen were compared to a control group of 148 patients. There was no difference in 30-day mortality between patients treated with a primarily open abdomen and the controls, 21 (26.6%) versus 49 (33.1%), $p = 0.37$. No difference was observed between the groups regarding 90-day mortality, postoperative renal failure requiring renal replacement therapy, postoperative intestinal ischaemia necessitating bowel resection or postoperative

bleeding requiring reoperation. Therefore, this study did not lend support to routine use of open abdomen treatment after surgical rAAA repair.

5.4.6.6 Colonic Ischemia After rAAA Repair

Sigmoidoscopy

Jalalzadeh et al. [119] determined the value of sigmoidoscopy to detect colonic ischaemia (CI) after repair of ruptured abdominal aortic aneurysm. Sigmoidoscopies were carried out based on clinical judgment. Endoscopy results were classified as "no ischaemia," "mild CI," or "moderate to severe CI." In 43 of 351 patients (12%) any grade of CI, as detected by sigmoidoscopy or laparotomy, was diagnosed. The study suggested that the diagnostic value of sigmoidoscopy to detect CI after rAAA repair is high in patients with a clinically moderate suspicion of CI. First, it is effective in ruling out the presence of CI. Second, when doubts exist about the presence of CI, the probability of identifying a patient with transmural ischaemia increases from approximately 22–73% when moderate to severe CI is detected at sigmoidoscopy.

Extraluminal pH Measurement

Postoperative surveillance to detect colonic ischemia using extraluminal pH measurement (pHe) was performed by Ersryd et al. [120] in 27 subjects who had undergone surgery for intact or ruptured abdominal aortic aneurysms. At the end of the primary open AAA repair, before abdominal closure, a balloon catheter was tunneled through the abdominal wall of the left fossa, lateral to the inferior epigastric artery, and placed in the peritoneal fold adjacent to the sigmoid colon. The balloon was positioned in contact with the sigmoid serosa. The catheter was connected to a Tonocap device (GE Healthcare, Helsinki, Finland), and the pCO_2 was measured inside the balloon catheter. Measurements of pHe using colonic tonometry indicated malperfusion in all four patients who had developed clinically significant CI. Extraluminal pH measurement is a promising technique for surveillance of colonic ischemia after open abdominal aortic aneurysm repair, but larger studies are warranted.

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Chapter 6
Renal Artery Stenosis

6.1 Guidelines

6.1.1 American College of Cardiology Foundation/American Heart Association

Renal artery disease guideline recommendations of the American Heart Association [1] are:

Clinical Clues to the Diagnosis of Renal Artery Stenosis (Class I recommendations)

1. The performance of diagnostic studies to identify clinically significant renal artery stenosis (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, ie, 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).

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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 2 kidneys of greater than 1.5 cm. (Level of Evidence: B).
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).

Diagnostic Methods (Class I recommendations)

1. Duplex ultrasonography is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B).
2. CTA (in individuals with normal renal function) is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B).
3. MRA is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B).

Indications for Revascularization (Class IIb recommendations)
Asymptomatic stenosis

1. Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS. (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. (Level of Evidence: C).

Hypertension (Class IIa recommendation)

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. (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/Level of Evidence: B).
2. Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS. (Class IIb/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/Level of Evidence: B).
2. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina. (Class IIa/Level of Evidence: B).

Endovascular treatment for RAS (Class I recommendations)

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

Surgery for RAS (Class I recommendations)

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. (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. (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). (Level of Evidence: C).

6.1.2 European Society of Cardiology (ESC) and European Society for Vascular Surgery (ESVS)

The ESC and ESVS guidelines [2] consider renal artery disease (RAD) when renal artery stenosis (RAS) is ≥60%, although additional functional assessment by haemodynamic criteria is advisable.

6.1.2.1 Clinical Situations Raising Suspicion for Renal Artery Disease

- Onset of hypertension before the age of 30 years.
- Onset of severe hypertension after the age of 55 years, when associated with chronic kidney disease or heart failure.
- Hypertension and abdominal bruit.
- Rapid and persistent worsening of previously controlled hypertension.
- Resistant hypertension (i.e. other secondary form unlikely and target not achieved despite four drug classes including a diuretic and mineralocorticoid-receptor antagonist in appropriate doses).
- Hypertensive crisis (i.e. acute renal failure, acute heart failure, hypertensive encephalopathy, or grade 3 to 4 retinopathy).
- New azotemia or worsening of renal function after treatment with renin-angiotensin-aldosterone system (RAAS) blockers.

- Unexplained atrophic kidney or discrepancy in kidney size, or unexplained renal failure.
- Flash pulmonary oedema.

6.1.2.2 Diagnostic Strategies

- Duplex ultrasound (as first-line), CTA and MRA are recommended imaging modalities to establish a diagnosis of RAD. (Class I recommendation/Evidence level B).
- DSA may be considered to confirm a diagnosis of RAD when clinical suspicion is high and the results of non-invasive examinations are inconclusive. (Class IIb recommendation/Level of evidence C).
- Renal scintigraphy, plasma renin measurements before and after angiotensin-converting enzyme inhibitor (ACEI) provocation and vein renin measurements are ***not*** recommended for screening of atherosclerotic RAD. (Class III recommendation/Evidence level C).

6.1.2.3 Recommendations for Treatment Strategies for Renal Artery Disease

Medical therapy

- ACEIs/ARBs (angiotensin receptor blockers) are recommended for treatment of hypertension associated with unilateral RAS. (Class I recommendation/Evidence level B).
- Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with renal artery disease. (Class I recommendation/Level of evidence C).
- ACEIs/ARBs may be considered in bilateral severe RAS and in the case of stenosis in a single functioning kidney, if well-tolerated and under close monitoring. (Class IIb recommendation/Level of evidence B).

Revascularisation

- Routine revascularisation is ***not*** recommended in RAS secondary to atherosclerosis. (Class III recommendation/Level of evidence A).
- In cases of hypertension and/or signs of renal impairment related to renal arterial fibromuscular dysplasia, balloon angioplasty with bailout stenting should be considered. (Class IIa recommendation/Level of evidence B).
- Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema. (Class IIb recommendation/Level of evidence C).
- In the case of an indication for revascularisation, surgical revascularisation should be considered for patients with complex anatomy of the renal arteries,

after a failed endovascular procedure or during open aortic surgery. (Class IIa recommendation/Level of evidence B).

6.1.3 Society for Cardiovascular Angiography and Interventions (SCAI)

6.1.3.1 Clinical Scenarios in Which Treatment of Significant RAS May Be Considered [3]

Appropriate care:

- Cardiac disturbance syndromes (flash pulmonary oedema or acute coronary syndrome with severe hypertension).
- Resistant hypertension (uncontrolled hypertension with failure of maximally tolerated doses of at least 3 antihypertensive agents, one of which is a diuretic, or intolerance to medications).
- Ischaemic nephropathy with chronic kidney disease (CKD) with estimated GFR < 45 ml/min and global renal ischaemia (unilateral significant RAS with a solitary kidney or bilateral significant RAS) without other explanation.

May be appropriate care:

- Unilateral RAS with CKD (eGFR <45 ml/min).
- Unilateral RAS with prior episodes of congestive heart failure (stage C).
- Anatomically challenging or high-risk lesions (early bifurcation, small vessel, severe concentric calcification, and severe aortic atheroma or mural thrombus).

Rarely appropriate care:

- Unilateral, solitary or bilateral RAS with controlled blood pressure and normal renal function.
- Unilateral, solitary or bilateral RAS with kidney size <7 cm in pole-to-pole length.
- Unilateral, solitary or bilateral RAS with chronic end-stage renal disease on hemodialysis >3 months.
- Unilateral, solitary or bilateral renal artery chronic total occlusion.

(Note: significant RAS is an angiographically moderate lesion (50–70%) with physiologic confirmation of severity or a > 70% stenosis).

6.1.4 Fibromuscular Dysplasia- Statement from the AHA

A scientific statement from the American Heart Association [4] specifies the following indications for renal arterial revascularization in patients with renal artery fibromuscular dysplasia (FMD):

1. Resistant hypertension (failure to reach goal blood pressures in patients on an appropriate 3-drug regimen including a diuretic).
2. Hypertension of short duration with the goal of a cure of hypertension.
3. Renal artery dissection; rarely is intervention needed, but if so, stenting is generally the procedure of choice.
4. Renal artery aneurysm(s); surgical resection, endovascular coiling, or placement of a covered stent is usually used.
5. 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.
6. Preservation of renal function in the patient with severe stenosis, especially in the pediatric population with perimedial fibroplasia or intimal fibroplasia.

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 2 vascular disorders. The natural history of medial fibroplasia is generally benign.

PTA of the renal artery is the procedure of choice for patients with renal artery FMD and hypertension in the appropriate clinical setting. The typical FMD patient with multifocal disease of the main renal artery is first offered PTA. There are patients, however, 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.

6.2 Results

6.2.1 Endovascular Intervention

6.2.1.1 Systematic Reviews/Meta-Analyses

A Cochrane Review compared the effectiveness of balloon angioplasty (with and without stenting) with medical therapy for the treatment of atherosclerotic renal artery stenosis in patients with hypertension [5]. Eight randomised controlled trials (RCTs) comparing balloon angioplasty with medical therapy in 2222 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. The available data were insufficient to conclude that revascularisation in the form of balloon angioplasty, with or without stenting, is superior to medical therapy for the treatment of atherosclerotic renal artery stenosis in patients with

hypertension. However, balloon angioplasty resulted in a small improvement in diastolic blood pressure and a small reduction in antihypertensive drug requirements. Balloon angioplasty appeared safe and resulted in similar numbers of cardiovascular and renal adverse events to medical therapy.

A systematic review by Piaggio et al. [6] replicated the same research methods and meta-analysis as described by Jenks et al. while expanding it to include papers between 2014 and 2018. One of the trials included in the previous review published results in the interim. Additionally, 2 ongoing trials identified in the 2014 review are yet to publish any result. Meta-analysis of the reports showed no heterogeneity between trials and no significant improvement shown by balloon angioplasty, with or without stenting, versus medical therapy.

Mohan and Bourke [7] assessed the literature on intervention for RAS, with special emphasis on the last two and largest randomized trials, the ASTRAL and CORAL trials. According to this systematic review, best evidence still supports 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;
- those with truncal rather than ostial stenosis;
- patients with a rapid deterioration of renal function;
- flash pulmonary oedema;
- and post-transplant RAS.

The Agency for Healthcare Research and Quality (AHRQ) has published a systematic review with a comparative analysis of the effectiveness and safety of percutaneous transluminal renal angioplasty with stent placement (PTRAS) versus medical therapy, and also versus surgical revascularization, to treat RAS [8]. They included 9 randomized controlled trials (RCTs), 11 nonrandomized comparative studies, 67 cohorts (in 63 studies) of PTRAS; 20 cohorts (in 17 studies) of medical therapy alone; and 4 cohorts of surgery. There was a low strength of evidence of no statistically significant or minimal clinically important differences in important clinical outcomes (death, cardiovascular events, renal replacement therapy) or blood pressure control between PTRAS and medical therapy alone, and that kidney function may improve with PTRAS. Clinically important adverse events related to PTRAS are rare; however, studies generally did not report medication-related adverse events. Based on the evidence, subsets of patients benefit from revascularization, but the evidence does not clearly define who these patients are, except that case reports demonstrate that some patients with acute decompensation benefit from revascularization. The RCTs had limited applicability to many patients for whom PTRAS is recommended, particularly those who present with pulmonary edema or rapidly declining kidney function. As summarized in Table 6.1, for all outcomes, the strength of evidence is low regarding the relative benefit of PTRAS versus medical therapy alone for patients with RAS, across both comparative and noncomparative studies.

Table 6.1 Angioplasty with stent versus medical therapy alone for the treatment of RAS: Strength of evidence. (According to Balk et al. [8])

Outcome	Strength of evidence	Design No of studies	Finding
Death	Low	RCT:4 NRCS: 5	Comparative studies: No evidence of a difference
RRT/ESRD	Low	RCT:4 NRCS: 5 Case reports 18	Comparative: No evidence of a difference Case reports: RRT averted with revascularisation
Cardiovascular event	Low	RCT: 5 NRCS: 3 Case reports:18	Comparative: No evidence of a difference Case reports: Cardiovascular symptoms resolved immediately with revascularisation
Kidney function	Low	RCT: 6 NRCS: 7 Case reports:18	RCT: No evidence of a difference NRCS: Heterogeneous effect on kidney function after PTRAS, favouring PTRA Case reports: Improvement with revascularisation
Blood pressure control	Low	RCT: 6 NRCS: 6 Case reports: 18	Comparative: Inconsistent Case reports: Improvement with revascularisation
Adverse events	Low	RCT: 4 NRCS:4 Cohort PTRAS: 34 Cohort medical therapy alone: 0	Severe adverse events rare, but reported only in PTRAS studies

RRT renal replacement therapy, *ESRD* end-stage renal disease, *RCT* randomised controlled trials, *NRCS* nonrandomised comparative studies, *PTRAS* percutaneous transluminal renal angioplasty with stent placement

6.2.1.2 Randomised Trials

The Cardiovascular Outcomes in Renal Athero-sclerotic Lesions (CORAL) study was a multi-center, open-label, randomized, controlled trial that compared medical therapy alone (480 patients) with medical therapy plus renal-artery stenting (467 patients) in patients with atherosclerotic renal-artery stenosis and elevated blood pressure, chronic kidney disease, or both [9]. 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. Over a median follow-up period of 43 months, the rate of the primary composite end point did not differ significantly between participants who underwent stenting in addition to receiving medical therapy and those who received medical therapy alone (35.1% and 35.8%, respectively). 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 renal-artery stenosis and hypertension or chronic kidney disease. Key findings

from this largest randomised trial of renal-artery stenting in patients with renal artery stenosis are given in Table 6.2.

Under the assumption that the outcomes in randomized trials were due to overly liberal inclusion criteria, e.g. inclusion of hemodynamically insignificant lesions with a stenosis diameter < 70%, the RADAR study aimed to evaluate the clinical impact of percutaneous renal artery stenting on renal function measured by estimated glomerular filtration rate (eGFR) in patients with hemodynamically significant atherosclerotic RAS, based on duplex ultrasonographic patient screening [10]. In RADAR, outcomes of renal artery stenting were similar to BMT. These results have to be interpreted with the caveat that the study did not reach its statistically based sample size. Due to slow enrollment, RADAR was terminated early after inclusion of 86 of the scheduled 300 patients (28.7%). Change in eGFR between baseline and 12 months was 4.3 ± 15.4 ml/min/1.73 m^2 (stent group) and 3.0 ± 14.9 ml/min/1.73 m^2 (BMT group), $p > 0.999$.

6.2.1.3 Uncontrolled Trials

While the randomised trials demonstrated no benefit of PTRAS versus medical therapy in patients with renal artery stenosis, the uncontrolled trials showed more positive results. The Safety and Effectiveness Study of the Herculink Elite Renal Stent to Treat Renal Artery Stenosis (HERCULES) trial is a prospective,

Table 6.2 Stenting and medical therapy for atherosclerotic renal artery stenosis. Outcomes of the randomised CORAL trial/median follow-up period 43 months. (According to Cooper et al. [9])

End Point	Stenting + Medical Therapy (n = 459) n (%)	Medical Therapy only (n = 472) n (%)
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)
– Hospitalisation for congestive heart failure	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)

[a] Primary end point: Death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalisation for congestive heart failure, progressive renal insufficiency, or permanent renal-replacement therapy

multicenter trial evaluating the safety, effectiveness, and durability of the RX Herculink Elite renal stent system in select patients with atherosclerotic renal artery stenosis and uncontrolled hypertension [11]. A total of 202 patients were enrolled between August 2007 and October 2009. The primary endpoint, 9-month binary restenosis, was 10.5%. At 36 months, freedom from death, nephrectomy, and target lesion revascularisation were 90.1%, 100%, and 91.8%, respectively. The mean baseline systolic blood pressure of 162 ± 18 mmHg significantly decreased post procedure and through 36 months (mean systolic blood pressure 141 mmHg ($P < .0001$) and 146 mmHg ($P < .0001$), respectively). The trial demonstrated sustained clinically and statistically significant reduction in systolic blood pressure in patients with uncontrolled hypertension.

In another observational study, 54 patients with resistant hypertension and angiographically confirmed renal artery stenosis >70% were followed for 4 years after renal stenting [12]. Blood pressure decreased rapidly after renal stenting and was normalized in 67% of patients at 6 months, with significant reduction in the number of antihypertensive drugs. Creatinine clearance increased in 39% of patients, decreased in 52% and remained stable in 9%. Urinary albumin excretion did not change throughout the study. After 4 years, left ventricular wall thickness and concentric geometry decreased significantly and variables of left ventricular diastolic function improved. The authors concluded that timely identification and correction of RAS in patients with resistant hypertension could modify the natural history of the disease with significant benefits for both renal and cardiovascular outcomes.

Atherosclerotic renal artery stenosis (RAS) is associated with high mortality rates, but large randomized trials have not shown improvement in survival with renal artery stenting. These results suggest that factors other than ongoing renal hypoperfusion are important in determining survival in patients with RAS. Using logistic regression models, Meredith et al. [13] performed a single-center, case-control study that included 188 patients with ≥70% RAS; 118 patients (63%) underwent renal artery stenting. A total of 89 patients (47%) died during an average follow-up of 5.1 years. The risk associated with left ventricular ejection fraction (LVEF) ≤35% and previous myocardial infarction were additive with mortality of 40%, 54%, and 85%, respectively, with 0, 1, or both these factors. Renal artery stenting was associated with a 43% reduction in mortality in patients with 0 or 1 mortality risk factors (defined as LVEF ≤35%, previous MI, and glomerular filtration rate ≤ 45 ml/min/1.73 m^2) but had no effect on mortality in patients with 2 or 3 mortality risk factors. This retrospective analysis suggests that clinical, in addition to anatomic and physiological, factors should be considered in future studies examining effects of renal artery stenting on survival.

Bradaric et al. [14] assessed the impact of drug-eluting stents (DES) compared to bare metal stents (BMS) for the endovascular treatment of atherosclerotic renal artery stenosis (RAS). Overall, 338 renal arteries were treated in 298 patients. BMS were implanted in 163 (48%), and DES in 175 lesions (52%). Of the 175 lesions treated with DES, 55 (31%) were treated with a BMS-in-DES hybrid technique. After 12 months, the rate of in-stent restenosis >50% was 18.6% in the BMS group and 7.2% in the DES group ($p = 0.031$). None of the BMS-in-DES-treated (hybrid)

lesions developed in-stent restenosis. Systolic BP and number of antihypertensive drugs remained unchanged in the BMS group but declined in the DES group ($p = 0.02$). Renal function significantly deteriorated in the BMS group ($p = 0.03$) but did not change significantly in the DES group ($p = 0.188$). Overall, the BMS-in-DES-technique (hybrid) achieved the lowest risk for in-stent restenosis.

6.2.1.4 Endovascular Treatment of Transplant Renal Artery Stenosis

Transplant renal artery stenosis (TRAS) following kidney transplantation is a possible cause of graft failure. A review summarized the evidence about physiopathology, diagnosis and early and late effectiveness of endovascular treatment, including angioplasty and stenting procedures [15]. Fifty-six studies with 1442 patients were included. TRAS incidence ranged from 1% up to 12% in transplanted kidneys and was usually observed in the first year after transplantation. Treatment indications were non-adjustable hypertension or/and deterioration of graft function. The most frequent localization of stenosis was para-anastomotic (ranging from 25% to 78%). In 9 studies, all patients were treated by percutaneous transluminal angioplasty (PTA), in 16 studies all patients received percutaneous transluminal stenting (PTS) and in 21 series patients received either PTA or PTS. The 12 months patency rates after endovascular treatment ranged from 72% to 94%. The complication rates of the procedures varied between 0 and 25%, the reintervention rates between 0% and 53%. Pseudoaneurysms and hematomas were the most frequent complications. TRAS can be successfully and safely treated through an endovascular approach. Stent delivery seems to guarantee a higher patency rate compared to simple angioplasty, however further studies are needed to confirm these results.

Patel et al. [16] compared long-term graft and patient survival after PTA or stent placement for TRAS with a control cohort without TRAS in a retrospective matched cohort study of 41 patients. Twenty-four patients underwent PTA and 17 received stent placements. Ten-year graft survival was 92.1% versus 81.4% (P = .56), and 10-year patient survival was 89.9% vs. 84.7% (P = .49), for the study and control groups, respectively. Five patients (12%) resumed dialysis in each group and a total of 17 patients died (eight in the study group and nine in the control group). Most patients died with a functioning graft (seven of eight in the study group and seven of nine in the control group). In conclusion, long-term graft and patient survival after endovascular correction of transplant renal artery stenosis (TRAS) was similar to that without TRAS and most patients avoided returning to dialysis.

6.2.2 Registry Data

The Nationwide Inpatient Sample, 1988–2009, was used by Liang et al. [17] to identify patients with a diagnosis of renal artery atherosclerosis undergoing open surgical repair (bypass or endarterectomy) or percutaneous transluminal

angioplasty with or without stenting (PTRA/S). 308,549 PTRA/S and 33,147 open surgical repairs were identified. PTRA/S increased from 1.9/100 K adults in 1988 to 13.7 in 2006 followed by a decrease to 6.7 in 2009. Open surgical repair steadily decreased from 1.3/100 K adults in 1988 to 0.3 in 2009. In 2009, PTRA/S procedures (6.4/100 K adults) greatly outnumbered procedures done by open repair alone (0.1/100 K), combined open renal and aortic repair (0.2/100 K), and combined PTRA/S and endovascular aneurysm repair (0.3/100 K). The total number of PTRA/S performed in the outpatient setting remained stable from 2005 (3.8/100 K) to 2009 (3.7/100 K), whereas the total number of inpatient procedures mirrored the national trend, declining from 2006 (7.9/100 K) to 2009 (4.2/100 K). PTRA/S had lower in-hospital mortality (0.9% vs. 4.1%; $P < .001$) compared with open repair. Mortality was higher after combined open renal and open aortic surgery compared to open repair alone (6.5% vs. 4.1%; $P < .001$). Mortality was similar for combined PTRA/S and endovascular aneurysm repair compared with PTRA/S alone (1.2% vs. 0.9%; $P = .04$). The performance of PTRA/S procedures for the management of RAS has decreased significantly after 2006. An increasing proportion of these procedures are performed in the outpatient setting. PTRA/S remains the dominant revascularization procedure for RAS with lower in-hospital mortality and morbidity than surgery.

6.2.3 Fibromuscular Dysplasia (FMD)

A meta-analysis by Tian et al. [18] is available on the outcomes following endovascular treatment of renal artery stenosis caused by FMD. 36 relevant studies of 1916 total repairs conducted in 1191 patients were identified. The overall technical success rate across these studies was 94.3%. Rates of total, major, and minor complications in these pooled studies were 12.9%, 4.6%, and 7.4%, respectively. Pooled rates of cured hypertension and improved hypertension following angioplasty, defined according to study-specific criteria, were 37.0% and 80.0%, respectively, although these rates varied highly among studies. Cure rates in studies using current definitions of cured hypertension (blood pressure < 140/90 mmHg without treatment) were just 18.1% following angioplasty. Cure rates fell markedly with increasing mean patient age (OR associated with an increase in mean age of 10 years: −0.24 [95% CI: −0.44 to −0.04, $P = 0.019$] and with mean known duration of hypertension (OR associated with an increase in mean hypertension duration of 5 years: −0.09 [95% CI: −0.12 to −0.05, $P = 0.001$]). These findings suggest that endovascular treatment yielded moderate benefits to renal artery FMD patients, with substantial variation across studies. The blood pressure outcome was strongly influenced by patient age.

In the prospective ARCADIA registry (Assessment of Renal and Cervical Artery Dysplasia), symptomatic patients with renal artery (RA) FMD underwent tomographic- or magnetic resonance-angiography from the aortic arch to the intracranial arteries and those with cervical FMD from the diaphragm to the pelvis [19]. Of 469

patients (84.0% women), 225 (48.0%) had multisite FMD. The mean age at diagnosis of FMD was 53 ± 13.4 years. The clinical presentation of FMD was renal in 304 (64.8%) patients, including 268 with hypertension and 11 with acute renal infarction. It was cerebrovascular in 165 (35.2%) patients, including 100 with acute cerebrovascular events. Among the 165 patients with a cerebrovascular presentation, the prevalence of RA FMD was 63 of 95 (66.3%) if they had a history of hypertension and 29 of 70 (41.4%) in the absence of such history (OR, 3.4; 95% CI, 1.99–6.15). Most patients with multisite FMD had bilateral RA (59.7%) or extracranial carotid and vertebral (72.5%) FMD lesions. These findings have implications for the guidelines concerning vascular screening of patients with FMD. Patients with FMD should be informed of the possibility of lesions affecting asymptomatic vascular beds, particularly older patients and those with a cerebrovascular presentation because age and cerebrovascular symptoms are independently associated with multisite FMD. Among patients with a cerebrovascular presentation, those with hypertension are 3× more likely to have RA FMD than those without hypertension. Such patients should be screened with RA imaging because hypertension could be amenable to RA angioplasty in selected cases.

Fibromuscular dysplasia is a non-atherosclerotic, noninflammatory vascular disease that affects children from infancy throughout childhood. In children, it most commonly affects the renal arteries, but also frequently involves the mesenteric arteries and abdominal aorta. The most common signs and symptoms in children are hypertension, headache, abdominal bruits, and dizziness. Green et al. [20] described the demographics, presenting symptoms and signs, and diagnostic and treatment modalities utilized in pediatric patients with FMD. As of October 2014, there were 1032 patients in the United States Registry for FMD. Of those patients, 33 were classified as pediatric (less than 18 years of age at the time of diagnosis). Mean age at diagnosis was 8.4 ± 4.8 years. Compared with adults, pediatric FMD occurred in more males (42.4 vs. 6%, $p < 0.001$). Hypertension (100%), headache (55%), and abdominal bruits (10.7%) were the most common presenting signs and symptoms. FMD affects renal vasculature in almost all children (97 vs. 69.7%, $p = 0.003$), whereas the extra-cranial carotid vessels are less commonly involved in children (23.1 vs. 73.3%, $p < 0.001$). At the time of enrollment, 87.9% of pediatric patients were medically managed with antihypertensive agents, and 54% had undergone therapeutic procedures related to their FMD diagnosis. Of the pediatric patients who required intervention, 78.9% underwent balloon angioplasty alone. 15.8% of children who underwent therapeutic procedures had stent placement, in addition to their balloon angioplasty. Stent placement should be avoided whenever possible as the initial management of FMD in children, as they have a high incidence of significant morbidity in this scenario. Stent placement, however, may be required to manage dissection or other complications.

6.3 Conclusions for Clinical Practice

1. Medical therapy is recommended for treatment of hypertension associated with unilateral renal artery stenosis (RAS). Routine revascularization is not recommended in RAS secondary to atherosclerosis.
2. Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema.
3. PTA +/− stenting have largely replaced the indication for open surgery, as can be seen from the lack of current publications in this field.
4. Surgical revascularization should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure or during open aortic surgery.
5. 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.
6. The European Renal Association (ERA)/European Society of Hypertension (ESH) summarized the indications of percutaneous transluminal renal artery angioplasty with or without stenting in patients with atherosclerotic renovascular disease [21]. The indications are shown in Table 6.3.

Table 6.3 Indications of percutaneous transluminal renal artery angioplasty with or without stenting in patients with atherosclerotic renovascular disease (according to Sarafidis et al. [21])

Strong indications
• High-grade (>70%) RAS in association with one of the following criteria:
– Resistant hypertension
– New-onset or recently uncontrolled hypertension
– Acute pulmonary oedema or acute decompensated heart failure
– Rapid decline of eGFR (bilateral stenosis or solitary kidney)
– ACEI or ARB intolerance (≥30% eGFR reduction)
– Renal replacement treatment (with possibly viable renal parenchyma) if stenosis detected <3 months after renal replacement treatment or if uncontrolled hypertension with multiple (five or more) antihypertensive agents
– AKI due to acute renal artery occlusion or high-grade stenosis
– Kidney transplant with RAS
Moderately strong indications
• High-grade (>70%) RAS in association with one of the following criteria:
– Chronic heart failure
– Asymptomatic but either bilateral or supplying a solitary kidney with viable renal parenchyma (non-atrophic kidney, distinct renal cortex)

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Chapter 7
Visceral Artery Aneurysms (Including Renal Artery Aneurysms)



7.1 Guidelines

The Society for Vascular Surgery Clinical Practice Guidelines describe the care of patients with aneurysms of the visceral arteries [1]. Important recommendations are:

7.1.1 Renal Artery Aneurysm (RAA)

- In patients who are thought to have RAAs, we recommend computed tomography angiography (CTA) as the diagnostic tool of choice. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- In patients who are thought to have RAA and have increased radiation exposure risks or renal insufficiency, we recommend non-contrast-enhanced magnetic resonance angiography (MRA) to establish the diagnosis. Level of recommendation: Grade 1 (Strong), Quality of Evidence: C (Low).
- In patients with noncomplicated RAA of acceptable operative risk, we suggest treatment for aneurysm size >3 cm. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- We recommend emergent intervention for any size RAA resulting in patient symptoms or rupture. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- In patients of childbearing potential with noncomplicated RAA of acceptable operative risk, we suggest treatment regardless of size. Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- In patients with medically refractory hypertension and functionally important renal artery stenosis, we suggest treatment regardless of size. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).

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- We suggest daily antiplatelet therapy (ie, aspirin, 81 mg) for patients with RAA. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- We suggest open surgical reconstructive techniques for the elective repair of most RAAs in patients with acceptable operative risk. Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- We suggest ex vivo repair and autotransplantation for complex distal branch aneurysms over nephrectomy when it is technically feasible. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- We suggest endovascular techniques for the elective repair of anatomically appropriate RAAs to include stent graft exclusion of main RAAs in patients with poor operative risk and embolization of distal and parenchymal aneurysms. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- For patients managed nonoperatively, we suggest annual surveillance imaging until two consecutive studies are stable; thereafter, surveillance imaging may be extended to every 2 to 3 years. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).

7.1.2 Splenic Artery Aneurysm (SAA)

- We recommend emergent intervention for ruptured SAAs. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- We recommend treatment of nonruptured splenic artery pseudoaneurysms of any size in patients of acceptable risk because of the possibility of rupture. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend treating nonruptured splenic artery true aneurysms of any size in women of childbearing age because of the risk of rupture. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend treating nonruptured splenic artery true aneurysms >3 cm, with a demonstrable increase in size, or with associated symptoms in patients of acceptable risk because of the risk of rupture. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low).
- We suggest observation over repair for small (<3 cm), stable asymptomatic splenic artery true aneurysms or those in patients with significant medical comorbidities or limited life expectancies. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- In patients with ruptured SAA discovered at laparotomy, we suggest treatment with ligation with or without splenectomy, depending on the aneurysm location. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- In patients with ruptured SAA diagnosed on preoperative imaging studies, we suggest treatment with open surgical or appropriate endovascular techniques based on the patient' s anatomy and underlying clinical condition. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).

- We suggest elective treatment of SAA using an endovascular approach if it is anatomically feasible. However, elective treatment may appropriately involve open surgical, endovascular, or laparoscopic methods of intervention, depending on the patient's anatomy and underlying clinical condition. Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- In treatment of SAA, we suggest that the splenic artery does not routinely require preservation or revascularization. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- In treatment of distal SAA adjacent to the hilum of the spleen, we suggest open surgical techniques including possible splenectomy as opposed to endovascular methods, given concern for the possibility of endorgan ischemia, including splenic infarction and pancreatitis. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).

7.1.3 Celiac Artery Aneurysm (CAA)

- We recommend treatment of nonruptured celiac artery true aneurysms >2 cm, with a demonstrable increase in size, or with associated symptoms in patients of acceptable risk because of the risk of rupture. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low).
- For the elective treatment of CAA, we suggest using an endovascular intervention if it is anatomically feasible. However, elective treatment may appropriately involve open surgical, endovascular, or laparoscopic methods of intervention, depending on the patient's anatomy and underlying clinical condition. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- To determine the need for revascularization of the celiac artery and its branches in treating CAA, we suggest evaluating the status of the superior mesenteric artery, gastroduodenal artery, and other relevant collateral circulation, which must be carefully documented on preoperative CTA or angiography. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).

7.1.4 Gastric and Gastroepiploic Artery Aneurysms

- We recommend treatment of all gastric artery and gastroepiploic artery aneurysms of any size. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend endovascular embolization for firstline treatment of gastric artery and gastroepiploic artery aneurysms. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

- We suggest abdominal axial imaging to screen for concomitant abdominal aneurysms. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).

7.1.5 Hepatic Artery Aneurysm (HAA)

- In patients with HAA who are considered for intervention, we recommend mesenteric angiography for preoperative planning. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- Given the high propensity of rupture and significant antecedent mortality, we recommend that all hepatic artery pseudoaneurysms, regardless of cause, be repaired as soon as the diagnosis is made. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- We recommend repair of all symptomatic HAAs regardless of size. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- In asymptomatic patients without significant comorbidity, we recommend repair if true HAA is >2 cm, Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High), or if aneurysm enlarges >0.5 cm/year, Level of Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low). In patients with significant comorbidities, we recommend repair if HAA is >5.0 cm. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We recommend an endovascular-first approach to all HAAs if it is anatomically feasible (ie, if this approach maintains arterial circulation to the liver). Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- In patients with extrahepatic aneurysms, we recommend open and endovascular techniques to maintain liver circulation. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- In patients with intrahepatic aneurysms, we recommend coil embolization of the affected artery, Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate). In patients with large intrahepatic aneurysms, we recommend resection of the involved lobe of liver to avoid significant liver necrosis, Level of Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low).

7.1.6 Superior Mesenteric Artery Aneurysm (SMAA)

- We recommend repair of all true SMAAs and pseudoaneurysms as soon as the diagnosis is made regardless of size. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- We recommend an endovascular-first approach to all SMAAs if it is anatomically feasible. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

7.1.7 Jejunal, Ileal, and Colic Artery Aneurysms

- We recommend elective intervention for jejunal and ileal artery aneurysms >2 cm in maximal diameter and for all colic artery aneurysms, any size. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We suggest open surgical ligation or aneurysm excision for cases of jejunal, ileal, and colic artery aneurysms when laparotomy is being considered for hematoma evacuation or bowel assessment for viability. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- We suggest endovascular embolization for cases of jejunal, ileal, and colic artery aneurysm. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).

7.1.8 Pancreaticoduodenal Artery Aneurysm (PDAA) and Gastroduodenal Artery Aneurysm (GDAA)

- In patients with noncomplicated GDAA and PDAA of acceptable operative risk, we recommend treatment no matter the size of the aneurysm because of the risk of rupture. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- In patients with intact and ruptured aneurysms, we recommend coil embolization as the treatment of choice. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- In patients in whom coil embolization is not feasible, we suggest covered stenting or stent-assisted coil embolization as a treatment option in select cases of GDAA and PDAA. Level of Recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).

7.2 Results

7.2.1 Meta-Analyses/Systematic Reviews

Barrionuevo et al. [2] conducted a systematic review and meta-analysis to summarize the best available evidence of comparing open to endovascular approaches for visceral artery aneurysms (VAAs). 80 observational studies that were mostly noncomparative were included. Data were available for 2845 aneurysms, comprising 1279 renal artery, 775 splenic artery, 359 hepatic artery, 226 pancreaticoduodenal and gastroduodenal arteries, 95 superior mesenteric artery, 87 celiac artery, 15 jejunal, ileal and colic arteries, and 9 gastric and gastroepiploic arteries. Differences in mortality between open and endovascular approaches were not statistically

significant. The endovascular approach was associated with shorter hospital stay and lower rates of cardiovascular complications but higher rates of reintervention. Post embolization syndrome (PES) rates ranged from 9% (renal) to 38% (splenic). After procedures of renal artery aneurysms, PES was defined as hyperpyrexia, abdominal pain, nausea, and vomiting, and after splenic artery aneurysms, it was defined as left upper-quadrant pain, with or without a documented splenic infarct, or as fever, abdominal pain, and slow bowel transit after a splenic infarction. Coil migration ranged from 8% (splenic) to 29% (renal). Otherwise, access site complications were low (<5%). Pseudoaneurysms tended to have higher mortality and reintervention rates. Numerous complications are more likely to occur with the open approach and may justify a recommendation for pursuing the endovascular approach as a first choice. Open reconstructive techniques for the elective repair of most of these aneurysms are reasonable when the endovascular approach is not feasible. An obvious limitation in this body of evidence is the small sample size of case series of these rare conditions and the noncomparative uncontrolled nature of the available studies.

A systematic review of the literature from 2004 to 2018 and the personal experience of the authors with management of giant splenic artery aneurysms (GSAAs) > 5 cm were presented by Hamid et al. [3]. A total of 92 GSAA cases were reviewed. 73% were symptomatic at presentation. Abdominal pain was the presenting symptom in >50% of cases; 34% were ruptured, with an overall mortality rate of 12.5%. This group often presented with gastrointestinal bleeding or hemodynamic collapse. Surgical intervention was performed in 47 patients with a success rate of 97.9%. Open surgical treatment included aneurysmectomy with splenectomy (30/47), ligation with or without splenectomy (8/47), and aneurysmectomy with vascular reconstruction (7/47). Two other patients had laparoscopic aneurysmectomy with splenectomy. Overall, endovascular intervention was attempted in 39 patients and was successful in 35 (89.7%). Sandwich exclusion, which involves occlusion of the parent vessel proximal and distal to the aneurysmal neck, was the most commonly used endovascular procedure (19/39). Overall, surgical treatment had a lower morbidity (P = .041) than endovascular therapy and comparable reintervention and mortality rates. Surgery remains the standard treatment of these lesions. Endovascular intervention is a viable alternative in high-risk patients, particularly those with lesions <10 cm or with anomalous origin.

The efficacy of endovascular embolization of pancreatitis-related pseudoaneurysms was evaluated in another review with meta-analysis based on 29 studies with 638 pseudoaneurysms [4]. The pooled incidence rates of pseudoaneurysms in acute and chronic pancreatitis were 0.05% and 0.03%, respectively. The most common site of pseudoaneurysm was splenic artery (37.7%), followed by gastroduodenal artery (23.6%) and pancreaticoduodenal artery (10.6%). The pooled technical success rate was 96%, with no significant differences between acute and chronic pancreatitis. The most common complication was splenic infarction (n = 47). Of these, 3 patients developed an abscess, two of whom died. The mean follow-up period was 54.7 weeks. Re-bleeding was seen in 98/600 patients, re-embolisation was attempted in 63/94 patients. Clinical success rates at ≤3 months, 3–12 months, and > 12 months

were 82%, 86%, and 88%, respectively. The pooled mortality in 582 embolised patients was 10%. The authors highlighted the high technical success rate of embolisation.

Data from a single center for patients with necrotizing pancreatitis who developed a visceral artery pseudoaneurysm (VA-PSA) were reviewed by Maatman et al. [5]. Twenty-eight of 647 patients with necrotizing pancreatitis (4.3%) developed a VA-PSA. The artery most commonly involved was the splenic artery (36%), followed by the gastroduodenal artery (24%). The most common presenting symptom was bloody drain output (32%), followed by incidental computed tomographic findings (21%). The median time from onset of necrotizing pancreatitis to diagnosis of a VA-PSA was 63.5 days (range 1–957 day). 25 of 28 patients (89%) were successfully treated with percutaneous angioembolization. Three patients (11%) required surgery. Percutaneous angioembolization effectively treated most cases; however, mortality from VA-PSA was high (14%).

Ossola et al. [6] investigated the features of minimally invasive surgical approaches in vascular surgery for SAAs: robotic surgery and laparoscopy. A total of 40 studies, including 107 patients (laparoscopy n = 94, robotic surgery n = 13), were considered eligible for the review. The mean operative time was 164.2 ± 75.9 min (laparoscopy) and 150 min (±87.7 min) for robotic procedures. Four cases of conversion (4.8% of all laparoscopic procedures) were reported; no conversion in the robotic series was reported. Laparoscopic procedures included resection of the aneurysm in approximately half of the cases, followed by aneurysm ligation. Overall morbidity was 11.2%; the most common complications were postoperative spleen infarction and pancreatitis. Neither mortality nor reinterventions were observed in these series. Advantage of robotic surgery over laparoscopy was said to be the facilitation of intracorporeal vascular sutures and anastomoses. Ultimately, only the feasibility of robotic surgery could be demonstrated.

7.2.2 Registries

7.2.2.1 Endovascular and Open Surgical Treatment

In the Agency for Healthcare Research and Quality (AHRQ) National Inpatient Sample (NIS) database, there were 9260 interventions for VAAs from 2003 to 2013, including 5166 endovascular and 4094 open [7]. Endovascular repairs increased from 5.3 to 24.7 per ten million U.S. population ($P < .001$), surpassing open repairs in 2008, which decreased from 14.3 to 9.2 per ten million ($P < .001$). In-hospital mortality (4.1% vs. 4.5%; $P = .618$) and overall complication rates (37.8% vs. 38.8%; $P = .688$) were similar between groups; however, pulmonary complications were decreased for endovascular patients (10.6% vs. 19.7%; $P < .001$). Endovascular patients had shorter hospital stays (6.5 vs. 8.7 days; $P < .001$). Multivariate adjustment for mortality predictors (Table 7.1) showed that open treatment was associated with increased mortality (OR, 1.70; CI, 1.03–2.81; $P = .04$). Analysis of overall

Table 7.1 Predictors of in-hospital mortality in endovascular and open surgical treatment of visceral artery aneurysms (VAAs). Multivariate logistic regression. (According to Chin et al. [7])

Characteristic	Odds ratio	*P* value
Age > 60 years	1.54	.07
Open intervention	1.70	.04
Teaching hospital	0.75	.25
Elective admission	0.32	.00
AIDS	4.97	.13
Coagulopathy	4.34	.00
Liver disease	2.25	.01
Fluid and electrolyte disorders	2.84	.00
Metastatic cancer	2.18	.22
Peripheral vascular disorders	1.67	.15
Solid tumour without metastasis	2.81	.03
Weight loss	0.81	.59

Table 7.2 Periprocedural outcomes after elective endovascular and open renal artery aneurysm treatment in the National Inpatient Sample (NIS) database 2000 to 2011 (according to Buck et al. [8])

Parameter	Open (n = 1627)	Endovascular (n = 1082)	P
Hospital mortality, %	0.9	1.8	.037
Cardiac complications, %	2.2	0.6	.001
Respiratory complications, %	4.6	4.3	.658
Peripheral vascular complications, %	0.6	0.0	.014
Acute renal failure, %	10	6.8	.001
Wound dehiscence, %	0.3	0.0	.068
Complications of bleeding, %	5.2	5.0	.842
Infection, %	0.9	0.8	.983
Any complication, %	12.4	10.5	.134
Duration of hospital stay, days	6.0	4.6	< .001

complications revealed that open treatment was again associated with increased complications (OR, 1.78; CI, 1.43–2.21; P < .001). Despite patients' having worse comorbidities and more nonelective admissions, endovascular therapy appears to be associated with decreased mortality and complications and shorter hospital stays.

Buck et al. [8] identified a total of 6234 isolated renal artery aneurysm repairs in the National Inpatient Sample (NIS) database between 1988 and 2011. Total repairs increased after the introduction of endovascular repair (8.4 in 1988 to 13.8 in 2011 per ten million U.S. population; P = .03). Endovascular repair increased from 0 in 1988 to 6.4 in 2011 per ten million U.S. population (P < .0001). However, there was no concomitant decrease in open surgery (5.5 in 1988 to 7.4 in 2011 per ten million U.S. population; P = .28). From 2000 to 2011, there were 1627 open and 1082 endovascular elective repairs (Table 7.2). Patients undergoing endovascular repair were more likely to have a history of coronary artery disease (18% vs. 11%; P < .001),

prior myocardial infarction (5.2% vs. 1.8%; P < .001), and renal failure (7.7% vs. 3.3%; P < .001). In-hospital mortality was 1.8% for endovascular repair, 0.9% for open reconstruction (P = .037), and 5.4% for nephrectomy (P < .001 compared with all revascularizations). Complication rates were 12.4% for open repair vs. 10.5% for endovascular repair (P = .134). This retrospective review demonstrated that more renal artery aneurysms were being treated after the introduction of endovascular techniques, without a reduction in operative mortality or a reduction in open surgery. Therefore, re-evaluation of the indications for repair of isolated renal artery aneurysms is warranted.

7.2.3 Studies

7.2.3.1 Endovascular and Open Surgical Treatment

Wolk et al. [9] reported their experience in the management of 60 true VAAs (including RAAs) in 59 patients over an observation period of more than 20 years. Open surgery was performed in 37 patients and endovascular repair in 23 patients. The mean aneurysm diameter was 30.5 ± 15.6 mm. In 18 patients (30.5%), a ruptured VAA was diagnosed. The most performed endovascular procedure was coil embolization in 20 aneurysms. Three patients were treated with a stent graft. Endovascular treatment was favored in ruptured VAA (61.1%). The most common open surgical procedures were resection with end-to-end anastomosis in 12 patients, vein graft interposition in 8, prosthetic graft interposition in 6, organ resection in 8, and ligation without revascularization in 3 cases, respectively. Mortality in the total cohort was 1.7% (1 patient with open surgical treatment of a ruptured VAA) and morbidity was 18.6%. The length of inpatient stay was significantly shorter with endovascular procedures; conversely, the primary technical success rate was significantly higher with open procedures at 100% vs. 79.3%. During the mean follow-up of 53.5 months, 4 patients died (6.8%), but no aneurysm-related death was observed.

Aneurysms of the pancreaticoduodenal arcades including the gastroduodenal artery (PDAAs) are rare, and best treatment evidence is lacking. Illuminati et al. [10] reported pooled data from three centers to compare the results of open surgical repair of true PDAA with celiac axis (CA) release or bypass vs. coil embolisation of PDAA and CA stenting or laparoscopic release of median arcuate ligament (MAL). Between 1994 and 2019, 57 consecutive patients, including 35 men (61%), with a mean age of 56 ± 11 years underwent elective PDAA treatment. This multicentre study suggested that in patients with PDAAs and compression of the coeliac axis (CA) by a median arcuate ligament (MAL), the choice between transcatheter embolisation or open exclusion of PDAAs should be tailored according to the location of the aneurysm, favouring open surgical repair for aneurysms located on the gastroduodenal and anterior pancreaticoduodenal arteries and embolisation for aneurysms located on the posterior pancreaticoduodenal artery. This study also demonstrated that in this setting CA stenting should be avoided. Open and

endovascular treatment of PDAA yield excellent post-operative results, with zero mortality and low morbidity in both groups. However, midterm follow up showed differences, with late recanalisation of three PDAAs (11%) following embolisation vs. none following open repair, and worrying results of CA stenting, with a crude 50% occlusion rate (n = 6/12) at 6 years. Open surgical release of MAL offered satisfactory long-term results in all patients without fibrosis or CA occlusion (n = 21). In the remaining 10 patients, fibrosis due to long lasting compression by MAL required direct reimplantation of the CA on the coeliac aorta or revascularisation by an aortohepatic bypass leading to durable results, except for one patient with asymptomatic bypass occlusion discovered at the 5 year follow up CTA.

A single centre experience with endovascular therapy and open surgery in 125 patients with true VAAs was reported by Martinelli et al. [11]. Fifty-six patients (44.8%) underwent endovascular treatment, mainly by coil embolization (n = 26) and covered stenting (n = 29). The hospital mortality was 0%, complications occurred in 5 cases (8.9%). In 69 (55.2%) cases, surgical treatment was preferred, with 24 VAA resections and 45 arterial reconstructions. In 20 cases (29%), open surgery was performed in emergency conditions. In the surgical group, 8 emergency patients (40%) died intraoperatively. The mortality after elective surgical interventions was nil. Complications after surgery were 4 graft late thromboses (5.8%): asymptomatic in three cases and requiring splenectomy in one. At follow-up, freedom from complications at 36 months was 94.6% in the endovascular group and 98.6% in the open surgery group. The authors considered the endovascular approach as the first choice because of its reduced invasiveness, faster way to access and bleeding control; this accounted for the lower morality of the interventional therapy compared to open surgery.

The experience of a single centre with endovascular (n = 22) and open (n = 20) repair of intact splenic artery aneurysms was presented by Zhu et al. [12]. Endovascular treatment was exclusively with coil embolization, while the surgical group included splenectomy, aneurysm resection and aneurysm resection combined with arterial reconstruction. The 30-day mortality rate was 0%, and the technical success rate was 100%. There was one major complication, 1 patient suffered multiple splenic abscesses after endovascular embolization. Endovascular repair had significantly shorter procedure time (82.5 ± 27.6 vs. 191.9 ± 62.7 min, $P < 0.001$) and hospital stay (5.6 ± 3.1 vs. 10.8 ± 5.2 days, $P < 0.001$) compared with open repair. No late complications or reinterventions were seen after open surgery during the median follow-up period of 34.5 months. In the endovascular group, there were three asymptomatic splenic infarctions and two reperfusions of the aneurysm sac, requiring repeat coil embolisations. The authors gave priority to the endovascular approach because of its less invasiveness, but also pointed out its weaknesses, with a higher reintervention rate and increased late complications compared to the open approach.

7.2.3.2 Endovascular Treatment

154 consecutive patients with visceral and renal artery aneurysms (VRAAs) were treated with endovascular therapy, with a technical success rate of 96.9% by Ren et al. [13]. Of the 154 patients with successful endovascular therapy, 3 patients died within 30 days of treatment, with a 30-day mortality rate of 1.9%. The clinical success rate was 98.1%. 97 patients (63.0%) received coils embolization alone, 38 patients (24.7%) received coils combined with gelatin sponge embolization, 13 patients (8.4%) received coils combined with stent, and 6 patients (3.9%) received stent implantation alone. Fifty-seven patients underwent emergency intervention due to ruptured aneurysm. One patient died within 1 month after intervention, and 5 patients were transferred to surgical treatment after failure of interventional therapy. The remaining patients were all hemodynamically stable and bleeding stopped after endovascular treatment. The authors emphasized the safety of the endovascular approach as first-line therapy for these aneurysms, especially since treatment failure does not preclude further open surgical repair.

Endovascular treatment of hepatic artery pseudoaneurysms was performed in 30 patients (24 males, 6 females) with a median age of 64 years (IQR: 53; 73 years) by Pedersoli et al. [14]. Previous pancreaticobiliary surgery had been performed in 28/30 cases, with a median time lapse of 18 days between the surgery and the diagnosis of hepatic pseudoaneurysm. Vessel erosion caused by perihilar cholangiocarcinomas was the cause of pseudoaneurysm in the remaining 2/30 patients. Pseudoaneurysms arising proximal to the hepatic bifurcation (25/30 patients) were treated by stent graft implantation. Coil embolization was performed with pseudoaneurysms of the left or right hepatic artery (5/30 patients). The 30-day mortality after stent graft implantation was 28% (7 of 25 patients), due to the underlying disease, no patient died stent graft related. Stent graft implantation was an effective treatment for pseudoaneurysms of the hepatic artery, with a technical success rate of 92% in pseudoaneurysm exclusion, with maintenance of the hepatic arterial flow in 88% cases. High stent patency rates (81%) were observed at short-term follow-up with a decrease to 40% at mid-to-long-term follow-up. Stent occlusion was mainly asymptomatic and characterized by sufficient collateralization in most patients (86%).

7.2.3.3 Open Surgical Treatment

National Surgical Quality Improvement Program data from 2013 to 2019 were queried for patients who had undergone open repair of visceral artery aneurysms by DeCarlo et al. [15]. Of the 304 aneurysms, 263 were nonruptured (137 mesenteric, 66 renal, 60 splenic) and 41 were ruptured (24 mesenteric, 1 renal, 16 splenic). For those with nonruptured aneurysms, the 30-day mortality was 1.9% and the major complication rate was 12.9%. A return to the operating room (5.3%) and prolonged ventilator support (3.8%) were especially common. Rupture was associated with significantly greater mortality (22.0%; $P < .001$) and major complications (34.1%; $P = .001$). In nonruptured aneurysms, male sex (odds ratio [OR] 2.93; $p = 0.011$),

anticoagulation (not discontinued before surgery) or bleeding disorder (OR 4.52; p = 0.012) and albumin <3.0 g/dL (OR 4.66; p = 0.029) were significant risk factors. Neither age nor aneurysm location were significant risk factors. Open repair of visceral aneurysms was associated with acceptable morbidity and mortality. Male sex, bleeding risk, and low albumin were all risk factors for adverse events and should be considered for operative planning and postoperative care. In view of the high mortality rate of ruptured VAA the treatment recommendations of the SVS [1] regarding the aneurysm size should be necessarily considered.

Marone et al. [16] reported technical details of robotic surgery in 4 patients with splenic artery aneurysms. All patients, after aneurysm excision, received reconstruction of the splenic artery by direct anastomosis. All cases were treated successfully without mortality. Reintervention-free survival at 24-month mean follow-up was 100%, and no systemic complication of clinical relevance was reported. The mean time of organ ischemia was 45 min. Robotic surgery was safe and provided the possibility to reconstruct the splenic artery after aneurysm excision.

7.2.4 Special Issues

7.2.4.1 Aneurysm Growth Rate

The growth rate of 87 VAAs in 74 patients who had at least two CTs during follow-up was analyzed by Batagini et al. [17]. The median follow-up period was 46.7 (± 35.3) months, and the median of growth for all aneurysms was 0.63 mm/year (±2.19). Only the splenic aneurysms presented growth with statistical significance of 1.08 mm per/year (±1.99) (P < 0.001). Multivariate analysis for variables associated with splenic aneurysm growth ≥1 mm/year showed that portal hypertension was the only variable with statistical significance (P < 0.01). Most VAAs tend to remain stable in size through follow-up. Portal hypertension was the only risk factor found for true splenic aneurysm growth, and so those patients must have a closer follow-up.

VAAs grow rarely, and rather slow. This was also shown by V. Rose et al. [18]. They identified in a 17-year-period from January 2003 to March 2020, 30 splenic artery aneurysms, 14 celiac trunk aneurysms, 11 renal artery aneurysms and 4 other VAA in 59 patients who underwent chemotherapy for malignancy. Eight patients had relevant growth of their VAA and one patient showed diameter regression (average growth rate 0.1 ± 0.5 mm/year). Twenty-nine patients with 14 splenic, 11 RAAs (seven right) and 4 celiac trunk aneurysms were available in the non-cancer comparison cohort (average growth rate 0.5 ± 0.9 mm/year, p = 0.058). However, the growth rate of patients receiving operative treatment for relevant VAA growth was significantly higher (p = 0.004). Cancer and/or chemotherapy do not significantly influence the annual growth rate. Additional control examinations seem unnecessary.

7.2.4.2 Ex Vivo Renal Artery Repair for Renal Artery Branch Aneurysms

Duprey et al. [19] evaluated the long-term outcome of renal revascularization by ex vivo renal artery reconstruction and autotransplantation for renal artery branch aneurysms (RABAs). Between 1991 and 2015, 67 ex vivo renal artery reconstructions followed by kidney autotransplantation were performed in 55 adults (mean age 47 years) and 10 children to repair 87 RABAs. The main underlying disease was fibromuscular dysplasia in 34 patients. Other etiologies were systemic congenital disease in eight patients, spontaneous dissecting aneurysms in five, iatrogenic aneurysms in three, atheromatous aneurysms in two and unknown etiology in 13. Median RABA diameter was 20.5 mm. Fifty-three patients (82%) were hypertensive, 60 had normal renal function and no patient was on hemodialysis. Seven patients (11%) were operated on after failure of an endovascular procedure. The mean number of renal artery branches repaired per patient was 3.5 and multiple aneurysms were treated in 14 patients (22%). No deaths occurred during the first 30 days. Primary patency at 30 days was 90.8% following to six early thromboses. No deaths occurred during the first 30 days. At 8 years, the primary and primary-assisted patency were 88% and 91%, respectively. Survival was 95% at 9 years. Among the 53 hypertensive patients, two were lost to follow up. At 9 years, 22 (43%) were cured and nine (18%) were improved with a significant reduction of antihypertensive medication ($p < .05$). Ex vivo renal artery reconstruction for complex RABAs eliminates the risk of rupture, confers a benefit to hypertension, and preserves renal function with a satisfactory long-term patency. Ex vivo repair is an appropriate technique to treat complex renal artery branch lesions, particularly in the young adult and children without atheromatous disease.

7.3 Conclusions for Clinical Practice

1. Visceral artery aneurysms can be treated by endovascular intervention and open repair, there are no definite treatment recommendations. However, numerous complications are more likely to occur with the open approach and may justify a recommendation for pursuing the endovascular approach as a first choice.
2. The indication for invasive treatment of VAAs depending on aneurysm size is uncertain due to their low growth rate. Pseudoaneurysms, on the other hand, should usually be treated regardless of the diameter.
3. In patients with asymptomatic non-complicated renal artery aneurysms and splenic artery aneurysms and acceptable risk, treatment is recommended for aneurysm size >3 cm, and for aneurysms of the celiac artery and hepatic artery >2 cm. For gastric and gastroepiploic aneurysms and those of the superior mesenteric and gastroduodenal and pancreaticoduodenal arteries, treatment is advised for any size.

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Chapter 8
Acute Mesenteric (Intestinal) Ischaemia



8.1 Guidelines

8.1.1 American College of Cardiology Foundation/American Heart Association

The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines recommend [1]:

8.1.1.1 Acute Intestinal Ischaemia Caused By Arterial Obstruction

1. Patients with acute abdominal pain out of proportion to physical findings and who have a history of cardiovascular disease should be suspected of having acute intestinal ischemia. (Class I recommendation/Level of evidence B).
2. Patients who develop acute abdominal pain after arterial interventions in which catheters traverse the visceral aorta or any proximal arteries or who have arrhythmias (such as atrial fibrillation) or recent MI should be suspected of having acute intestinal ischemia. (Class I recommendation/Level of evidence C).
3. In contrast to chronic intestinal ischemia, duplex sonography of the abdomen is not an appropriate diagnostic tool for suspected acute intestinal ischemia. (Class III recommendation/Level of evidence C).

Surgical treatment:

- Surgical treatment of acute obstructive intestinal ischemia includes revascularization, resection of necrotic bowel, and, when appropriate, a "second look" operation 24 to 48 h after the revascularization. (Class I recommendation/Level of evidence B).

Endovascular treatment:

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- Percutaneous interventions (including transcatheter lytic therapy, balloon angioplasty, and stenting) are appropriate in selected patients with acute intestinal ischemia caused by arterial obstructions. Patients so treated may still require laparotomy. (Class IIb recommendation/Level of evidence C).

8.1.1.2 Acute Non-occlusive Intestinal Ischaemia

1. Nonocclusive intestinal ischemia (NOMI) should be suspected in patients with low flow states or shock, especially cardiogenic shock, who develop abdominal pain. (Class I recommendation/Level of evidence B).
2. Nonocclusive intestinal ischemia should be suspected in patients receiving vasoconstrictor substances and medications (e g, cocaine, ergots, vasopressin, or norepinephrine) who develop abdominal pain. (Class I recommendation/Level of evidence B).
3. Nonocclusive intestinal ischemia should be suspected in patients who develop abdominal pain after coarctation repair or after surgical revascularization for intestinal ischemia caused by arterial obstruction. (Class I recommendation/Level of evidence B).

Diagnosis:

- Arteriography is indicated in patients suspected of having nonocclusive intestinal ischemia whose condition does not improve rapidly with treatment of their underlying disease. (Class I recommendation/Level of evidence B).

Treatment:

1. Treatment of the underlying shock state is the most important initial step in treatment of nonocclusive intestinal ischemia. (Class I recommendation/Level of evidence C).
2. Laparotomy and resection of nonviable bowel is indicated in patients with nonocclusive intestinal ischemia who have persistent symptoms despite treatment. (Class I recommendation/Level of evidence B).
3. Transcatheter administration of vasodilator medications into the area of vasospasm is indicated in patients with nonocclusive intestinal ischemia who do not respond to systemic supportive treatment and in patients with intestinal ischemia due to cocaine or ergot poisoning. (Class IIa recommendation/Level of evidence B).

8.1.2 Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS)

The ESVS clinical practice guidelines for the management of the diseases of mesenteric arteries and veins [2] recommend, among other things:

8.1.2.1 Acute Mesenteric Ischaemia (AMI)

- In patients with acute abdominal pain, D-dimer measurement is recommended to exclude acute mesenteric ischaemia (AMI). (Class I recommendation/Level of evidence B).
- Use of L-lactate measurement is ***not*** recommended to diagnose or rule out acute occlusive mesenteric ischaemia. (Class III recommendation/Level of evidence B).
- In patients with suspected AMI, a triphasic CTA with 1 mm slices (or thinner) should be used to detect mesenteric arterial occlusion. (Class I recommendation/Level of evidence B).
- In patients with acute mesenteric arterial ischaemia, open or endovascular revascularisation should be considered before bowel surgery. (Class IIa recommendation/Level of evidence B).
- In patients undergoing laparotomy for AMI, clinical judgement should be considered as the preferred method for assessing bowel viability. (Class IIa recommendation/Level of evidence C).
- Patients requiring bowel resection because of intestinal infarction should be treated with antibiotics. (Class I recommendation/Level of evidence A).
- In patients undergoing acute intestinal revascularisation, second-look laparotomy and damage control surgery should be considered. (Class IIa recommendation/Level of evidence C).
- In patients with acute thrombotic superior mesenteric artery (SMA) occlusion, endovascular therapy should be considered as first-line therapy because of lower mortality and bowel resection rates compared with open revascularisation. (Class IIa recommendation/Level of evidence B).
- In patients with AMI and stented mesenteric arteries, imaging follow-up should be considered. (Class IIa recommendation/Level of evidence C).
- In patients surviving AMI, secondary medical prevention, including smoking cessation, statin therapy, and antiplatelet or anticoagulation treatment, is recommended. (Class I recommendation/Level of evidence C).

8.1.2.2 Non-occlusive Mesenteric Ischaemia

Definition:

- NOMI is defined as a hypoperfusion syndrome that occurs when severe ischaemia of the intestines develops despite the mesenteric arteries being patent. It is caused by either mesenteric vasoconstriction secondary to conditions such as heart failure, vasoconstrictive medication and hypvolaemia or by increased intra-abdominal pressure.

Diagnosis:

- In patients suspected of having NOMI, clinical suspicion should be considered the mainstay of diagnosis. (Class IIa recommendation/Level of evidence C).
- In patients suspected of having NOMI, use of biomarkers to diagnose or rule out the condition is ***not*** recommended. (Class III recommendation/Level of evidence C).
- In patients suspected of having NOMI, DSA should be considered the most reliable method to verify the diagnosis. (Class IIa recommendation/Level of evidence C).
- In patients with known risk factors for intra-abdominal hypertension/abdominal compartment syndrome, a protocol for monitoring of intra-abdominal pressure is recommended to prevent NOMI. (Class I recommendation/Level of evidence B).

Therapy:

- In patients suspected of having NOMI, stenoses of the mesenteric arteries should be identified and treated. (Class I recommendation/Level of evidence C).
- Patients with intra-abdominal pressure above 12 mmHg should be treated medically to prevent abdominal compartment syndrome and NOMI. (Class I recommendation/Level of evidence B).
- In patients with abdominal compartment syndrome (defined as an intra-abdominal pressure > 20 mmHg and newly developed organ dysfunction or failure), decompression laparotomy should be performed to prevent NOMI. (Class I recommendation/Level of evidence B).
- Patients with life threatening NOMI should be taken to an operating room with the capacity for open and endovascular surgery, where angiography, with stenting in the case of a stenosis, and/or intra-arterial administration of vasodilators and/or laparotomy for bowel resection can be performed (Class I recommendation/Level of evidence C).

8.1.3 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS)

The ESC/ESVS guidelines for diagnosis and treatment of AMI recommend [3]:
Diagnosis:

- In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended. (Class I recommendation/Level of evidence C).

- In patients with suspicion of acute mesenteric ischaemia, the measurement of D-dimer should be considered to rule out the diagnosis. (Class IIa recommendation/Level of evidence B).

Therapy:

- In patients with acute thrombotic occlusion of the superior mesenteric artery, endovascular therapy should be considered as first-line therapy for revascularization. (Class IIa recommendation/Level of evidence B).
- In patients with acute embolic occlusion of the superior mesenteric artery, both endovascular and open surgery therapy should be considered. (Class IIa recommendation/Level of evidence B).

8.2 Results

8.2.1 Meta-Analyses/Systematic Reviews

Hou et al. [4] performed a meta-analysis to evaluate the outcomes of different treatment approaches for AMI in the last 20 years based on 39 studies (2369 patients). The mortality associated with open surgical treatment, endovascular therapy, and retrograde open mesenteric stenting tended to be similar in the last 20 years. The pooled mortality estimates for open surgery, endovascular therapy, and retrograde open mesenteric stenting were 40% (95% CI, 0.33–0.47), 26% (95% CI, 0.19–0.33), and 32% (95% CI, 0.21–0.44), respectively. The conclusions were limited by the fact that these were exclusively observational studies with high heterogeneity and, especially in the endovascular group, different techniques.

Preoperative risk factors for postoperative mortality after open surgery for AMI were analysed by Wu et al. [5]. 20 studies with 5011 patients were included in this meta-analysis. Short-term postoperative mortality was 44.38% (range 18.80%–67.80%). Significant risk factors for short-term postoperative mortality were older age (OR 1.90), arterial occlusive mesenteric ischemia versus mesenteric venous thrombosis (OR, 2.45, 95% CI 1.12–5.33), heart failure (OR 1.33, 95% CI 1.03–1.72), renal disorders (OR 1.61, 95% CI 1.24–2.07), and peripheral vascular disease (OR 1.38, 95% CI 1.00–1.91). Non-survivors had lower platelet counts.

Emile et al. [6] reviewed the current literature for predictors of transmural bowel necrosis in patients with AMI and investigated whether it is feasible to establish a scoring system to predict bowel necrosis in AMI. This systematic review comprised nine articles that included 963 patients of a median age of 57 years. Irreversible bowel necrosis was found in 402 (41.7%) patients. 21 predictive parameters with significant Odds Ratio were found and were included into the predictive scoring system. The predictive parameters were:

- 8 clinical parameters (SIRS, long duration between symptoms and surgery, high BMI, coronary heart disease, shock, pulmonary embolism, mesenteric arterial occlusion, organ failure).
- 7 biochemical parameters (elevated serum lactate, acidosis, leukocytosis, haemoconcentration, hyperamylasemia, increased neutrophil to lymphocyte ratio, increased platelet to lymphocyte ratio).
- 6 radiological parameters (bowel loop dilatation, pneumatosis intestinalis, thrombosis of the superior mesenteric vein, free intraperitoneal fluid, portal vein thrombosis, splenic vein thrombosis).

Murphy et al. [7] presented a systematic review of current literature addressing endovascular management of acute mesenteric ischaemia. The population of interest was adult patients presenting with acute mesenteric ischaemia diagnosed by either radiological imaging or intra-operatively. Studies in which patients underwent intervention via endovascular means alone or studies comparing endovascular to open intervention were included. The 30-day mortality for endovascular approach from all 13 studies was 16–42%. Of the 7 comparative studies including results of open revascularisation, the 30-day mortality for patient treated with an endovascular approach was 15–39% versus 33–50% for open revascularisation. Laparotomy rates post-initial endovascular intervention ranged from 13 to 73%. Bowel resection post-endovascular therapy ranged from 14 to 40% among studies. Concerning 7 comparative studies for open versus endovascular revascularisation, the rate of bowel resection in the endovascular group ranged 14–28% and 33–63% in the open cohort. Endovascular intervention also demonstrated lower median length(s) of bowel resected. Endovascular management may be associated with reduced mortality and need for/length of bowel resection compared with the traditional open approach, but there remains a paucity of robust data to support this. The available literature illustrates that a subgroup of patients without haemodynamic compromise and more insidious onset may garner benefit from endovascular intervention.

8.2.2 Studies

8.2.2.1 Open Surgery

Swerdlow et al. [8] performed a retrospective cohort study of patients in the American College of Surgeons National Surgical Quality Improvement Program database undergoing open mesenteric revascularization for AMI from 2005 to 2017. The primary outcome was 30-day mortality. The study cohort included 918 patients; their median age was 70 years, 62% were female. Thirty-day mortality after open revascularization for AMI was 32%, specifically 35% after embolectomy, 31% after thromboendarterectomy, and 28% after mesenteric bypass (Table 8.1). Mortality was higher in patients requiring concomitant bowel resection (38% vs. 29%, respectively, $P < 0.01$). The preoperative factor most strongly associated with 30-day

Table 8.1 30-day mortality after open revascularisation for AMI. National Surgical Quality Improvement Program database from 2005–2017 (adapted from Swerdlow et al. [8])

Parameter	Bowel resection rate (%)	Mortality with concomitant bowel resection (%)	Mortality without bowel resection (%)	P
All (n = 918)	35%	38%	29%	< .001
Bypass (n = 341)	27%	39%	24%	.01
– Aorto-mesenteric (vein) (n = 109)	46%	41%	34%	.52
– Aorto-mesenteric (graft) (n = 147)	31%	43%	20%	.01
– Ilio-mesenteric (n = 85)	23%	29%	22%	.53
Thromboendarterectomy (n = 98)	26%	36%	29%	.50
Embolectomy (n = 479)	43%	38%	33%	.28

mortality was disseminated cancer (odds ratio = 8.8, 95% confidence interval = 2.4–32, P = 0.001). Other factors independently associated with mortality were renal dysfunction, preoperative intubation, preoperative blood transfusion, diabetes, elevated preoperative international normalized ratio, elevated preoperative white blood cell count, and increasing age.

Acosta-Mérida [9] reported on a total of 323 consecutive patients who underwent open surgery for AMI at a single centre between 1990 and 2015. The aim of this study was to analyze whether there have been changes in terms of patient characteristics and operative mortality in the same institution over a long period of time. Of the 323 patients, 178 were men (55%) and 145 were women (45%). The average age of the sample cohort was 73 years (±12.7). Regarding the etiology of AMI, mesenteric arterial embolism was found to be the primary cause in 95 patients (29.4%), followed by mesenteric arterial thrombosis in 94 patients (29.1%); 44 patients (16.9%) had mesenteric venous thrombosis, and 28 patients (10.7%) had NOMI. In 62 patients (19.5%), it was not possible to exactly determine the cause. Global operative mortality was 59% (192 patients). Cumulative survival at 1, 3 and 5 years was 30.8%, 26% and 23%, respectively. Over time, an increasing linear trend was observed in Charlson score ($p = 0.008$), antiplatelet medication ($p < 0.001$), use of CT scan ($p < 0.001$), arterial thrombosis ($p < 0.001$) and intestinal resection ($p = 0.047$), while a decreasing linear trend was observed in digoxin intake ($p < 0.001$), angiography use ($p = 0.004$), and embolism ($p < 0.001$). Changes in operative mortality have also been detected, showing a tendency toward a progressive and significant decrease, but remained high overall.

Data from another single institution were presented by Chou et al. [10]. This study involved 303 AMI patients from the years 1993 to 2016, venous thrombosis patients were excluded. Primary outcome was 30-day mortality. Patients were stratified by etiology and diagnosis date (before 2004 versus 2004 and later). AMI mechanisms included: embolic (49%), thrombotic (29%), and non-occlusive

(NOMI) (22%). 345 procedures were performed in 242 patients: 321 open and 24 hybrid/endovascular. Among the 189 embolic/thrombotic patients who were managed operatively, 45% (n = 85) underwent mesenteric revascularization while 39 (21%) had findings of non-survivable bowel necrosis (NSBN). Among the 104 patients who did not undergo revascularization, 64 (62%) died within 30-days compared to 36 out of 85 (42%) patients who were revascularized (P = 0.01). Thirty-day mortality was 61% and stable over time (P = 0.91); 1-year survival was 28%, and overall survival at 3 and 5 years was 22% and 17%, respectively, without significant differences between temporal cohorts. When stratified by AMI etiology, the thrombotic cohort had worse survival than embolic and NOMI patients (P = 0.04). Since 2000, there was a significant decrease in the percentage of embolic AMI events (P = 0.04). The percentage of patients who underwent operative management decreased also over time (P = 0.01, 81% → 61%). The study demonstrated the continued poor prognosis of AMI over a 25-year period.

Andraska et al. [11] reported on 148 patients who had undergone revascularization for AMI from 2010 to 2020. 26% of patients were admitted with peritonitis, 32% were clinically septic. Surgery was performed within 16 h of admission in 96% of patients. 89 patients underwent open surgical revascularization, most commonly with embolectomy (n = 72), and 17 patients with open bypass. Bowel resection had to be performed in 49 of these patients (55.1%). Cumulative mortality was 44/89 (49.4%) with open surgery, 19/36 (52.8%) with endovascular management and 9/23 (39.1%) with retrograde open mesenteric stenting, for a total of n = 72 (48.6%) for AMI. The conclusion was that an open approach should remain the reference standard for AMI because it reduces the likelihood of bowel resection.

The objective of a study from Pittsburgh was to identify hospital-based determinants of delayed revascularization and their effects on postoperative morbidity and mortality in AMI [12]. All patients who underwent any surgery for AMI from a multi-center hospital system between 2010 and 2020 were divided into two groups based on timeliness of mesenteric revascularization after presentation. Early revascularization (ER) was defined as having both vascular consultation ≤12 h of presentation and vascular surgery performed at the patient's initial operation. Delayed revascularization (DR) was defined as having either delays to vascular consultation or vascular surgery. A total of 212 patients were analyzed. Ninety-nine patients received ER, whereas the remaining 113 patients experienced a DR after hospital presentation. Thirty-day mortality in patients who had DR was significantly higher when compared with ER (39.6% vs. 25.0%; P = .02). There was a two- to three-fold increased risk of 30-day mortality and short bowel syndrome and an almost eightfold increased risk of bowel resection in patients who had DR compared with those who had ER. Delayed vascular consultation and vascular surgery are both significant hospital-based determinants of postoperative mortality and short bowel syndrome in patients with AMI.

8.2.2.2 Open Mesenteric Bypass and Retrograde Open Mesenteric Stenting

Scali et al. [13] reviewed their experience with open mesenteric bypass (OMB) in the treatment of AMI and compared outcomes between patients undergoing either antegrade (supraceliac aortic inflow) or retrograde (infrarenal aortoiliac inflow) bypass.

Eighty-two patients (female 54%; age 63 ± 12 years) underwent OMB for AMI. An antegrade bypass configuration was used in most cases (76%; n = 62). The incidence of bowel resection at the index operation did not differ based on bypass configuration (antegrade, 45%; retrograde, 45%) and 37% (n = 30) underwent subsequent resection during second look operations. The overall in-hospital mortality rate was 37%, with no difference between retrograde/antegrade cohorts. The median follow-up was 8 months. The 1- and 3-year primary patency rates were both 82% ± 6%, with 10 patients requiring reintervention. 1-year freedom from reintervention rates were 89% ± 5% and 57% ± 10% for antegrade and retrograde bypass patients, respectively. Overall survival, including follow-up after discharge, was 57% ± 6% and 50% ± 6% at 1 and 5 years and did not differ between patients undergoing antegrade/retrograde OMB. The study suggested that antegrade aortomesenteric bypasses are preferred over retrograde bypasses because of a lower reintervention rate.

Retrograde open mesenteric stenting (ROMS) is an alternative to traditional bypass in patients who present with AMI. Andraska et al. [14] compared outcomes of ROMS with those of conventional mesenteric bypass. A total of 34 patients were included in the study; 16 underwent mesenteric bypass, and 18 underwent ROMS. The majority of patients in both groups required bowel resection at the time of presentation (bypass, 56.25%; ROMS, 77.78%). Average operative time was significantly higher in the bypass arm (302 vs. 189 min; $P < .010$). In the bypass group, dacron graft was the most commonly used conduit (62.5%), followed by autologous vein conduit. All ROMS procedures were performed with balloon expandable stents. The majority of ROMS procedures were performed with covered stents (55.56%). In-hospital mortality was comparable between groups (bypass, 43.75%; ROMS, 38.89%; $P = .459$). Primary patency at 2 years did not differ significantly between groups (bypass, 66.67%; ROMS, 87.50%; $P = .600$). Similarly, all-cause mortality at 2 years did not differ between groups (bypass, 62.50%; ROMS, 55.56%; $P = .476$). Given similar postoperative outcomes and ability to perform these procedures in a conventional operating room but with significantly shorter operative times, ROMS should be considered a first-line option in acute situations when the operator is comfortable performing the procedure.

Oderich et al. [15] reviewed the clinical data and outcomes of all consecutive patients treated by ROMS in seven academic centers from 2001 to 2013. There were 54 patients, 13 male and 41 female, with a mean age of 72 ± 11 years. Indications for ROMS were AMI in 44 patients (81%) and subacute-on-chronic mesenteric ischemia with flush mesenteric occlusion in 10 patients (19%). Bowel resection was needed in 29 patients (66%) with AMI because of perforation or gangrene. Technical

success was achieved in all (98%) except one patient for whom ROMS failed, who was treated by bypass. Early mortality was 45% (20/44) for AMI and 10% (1/10) for subacute-on-chronic mesenteric ischemia (P = .04). Patient survival for the entire cohort was 43% ± 9% at 2 years. Freedom from symptom recurrence and freedom from reinterventions were 72% ± 8% and 74% ± 8% at the same interval. The study suggests that retrograde open mesenteric stenting is an appropriate alternative for patients with mesenteric ischemia requiring a laparotomy for exploration or treatment of perforated or gangrenous bowel.

In most cases of AMI, intestinal inspection and resection of nonviable bowel are required through laparotomy. Thus, ROMS, which is a hybrid technique, combines the benefits of both techniques: prompt blood flow restoration with an endovascular approach and inspection and resection of the small bowel. Roussel et al. [16] retrospectively enrolled all consecutive patients who underwent ROMS revascularization for occlusive AMI in three participating tertiary care centers. Twenty-five patients were included. In two patients, ROMS was not possible because of failure of re-entry in the aortic lumen (technical success, 92%).13 patients (52%) required bowel or colon resection. The 30-day operative mortality rate was 25%, and the overall 1-year survival rate was 65%. The 1-year primary patency rate was 92%. The study suggested that retrograde open mesenteric stenting is a reasonable procedure for selected patients with acute mesenteric ischemia not amenable to percutaneous stenting.

8.2.2.3 Mesenteric Ischaemia in Patients with COVID-19

The aim of a systematic review by Ojha et al. [17] was to assess the most common CT imaging features of AMI in COVID-19 patients. A total of 47 studies comprising 75 patients were included in the review. In COVID-19 patients with AMI, small bowel ischemia is the most prevalent imaging diagnosis and NOMI is the most common pattern of bowel involvement. Small bowel ischemia was seen in 46.7% of the patients, followed by ischemic colitis (37.3%). Non-occlusive mesenteric ischemia (NOMI) indicating microvascular involvement was found in 67.9% of patients with AMI. 50% of the patients receiving conservative/medical management died, highlighting high mortality without surgery.

Pirola et al. [18] provided further information. They analyzed the small bowel radiological manifestations of SARS-CoV-2 infection in abdominal imaging studies. Of 62 patients, mesenteric ischemia was diagnosed in 31 cases (50%), small bowel wall thickening in 10 cases (16%), pneumatosis in nine cases (15%), intussusception in eight cases (13%), pneumoperitoneum in two cases (3%) and paralytic ileus in two cases (3%). Treatment of AMI was reported in 17 cases. Thirteen (76%) were treated by segmental resection of small bowel, and anticoagulant therapy alone was administered in four cases. Of the nineteen patients with a reported outcome, nine (47%) died.

8.3 Conclusions for Clinical Practice

For the conclusions, we follow the recommendations of Björck et al. [19] in the Trans-Atlantic Debate, whether an endovascular-first strategy is the optimal approach for treating acute mesenteric ischemia:

After having diagnosed the condition, most often with multislice computed tomography images, and if an acute occlusion of the superior mesenteric artery (SMA) is diagnosed, the treatment is organized in the following way:

1. The patient is taken to a hybrid operating room, thereby providing the option for using both open and endovascular techniques. Angiography and endovascular treatment is attempted, with access from the groin or the brachial artery, or both, preferably under local anesthesia.
2. After endovascular revascularization, the abdomen is evaluated, and if there is any suspicion of bowel gangrene, a laparotomy is performed; otherwise, close surveillance follows for at least 48 h. If percutaneous endovascular revascularization fails, laparotomy and hybrid retrograde recanalization of the SMA and stenting, or open revascularization should be undertaken, without delay.
3. Completion angiography, followed by adjunctive endovascular procedures (where necessary), including further aspiration embolectomy of SMA branches, percutaneous transluminal angioplasty/stenting of residual stenosis, thrombolysis of occluded side branches.
4. Second-look angiography or laparotomy, or both, may be necessary, and should be performed liberally.

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Chapter 9
Chronic Mesenteric (Intestinal) Ischaemia



9.1 Guidelines

Preliminary note: in the following, the terms "chronic intestinal ischaemia" and "chronic mesenteric ischaemia" are used synonymously, as specified in the literature database (MEDLINE, PubMed). Chronic mesenteric ischaemia (CMI) is the more commonly used term and is preferred here.

9.1.1 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS)

The ESC/ESVS guidelines recommend [1]:

Chronic mesenteric artery disease includes stenosis or chronic occlusion of the coeliac trunk or the mesenteric arteries. Its prevalence increases with age, especially in the presence of other atherosclerotic diseases and abdominal aortic aneurysms (AAAs). In patients with an AAA and lower extremities arterial disease significant stenosis (mostly asymptomatic) of at least one of the three arteries was detected in 40% and 27%, respectively.

9.1.1.1 Diagnosis

- In patients with suspected chronic mesenteric ischaemia (CMI), duplex ultrasound is recommended as the first-line examination. (Class I recommendation/ Level of evidence C).

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- In patients with suspected CMI, occlusive disease of a single mesenteric artery makes the diagnosis unlikely and a careful search for alternative causes should be considered. (Class IIa recommendation/Level of evidence C).

9.1.1.2 Treatment

- In patients with symptomatic multivessel CMI, revascularization is recommended. (Class I recommendation/Level of evidence C).
- In patients with symptomatic multivessel CMI, it is ***not*** recommended to delay revascularization in order to improve the nutritional status. (Class III recommendation/Level of evidence C).

These guidelines do not specify the revascularization procedure (open surgery or endovascular intervention), but they note:

Although endovascular treatment has been increasingly used, open surgery is still indicated in the following situations:

- After failed endovascular therapy without possibility for repeat endovascular treatment.
- Extensive occlusion, calcifications or other technical difficulties.
- Young patients with non-atherosclerotic lesions due to vasculitis or mid-aortic syndrome.

9.1.2 Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS)

The ESVS guidelines recommend [2]:

- Recommendation 13: The diagnosis of CMI should be considered less likely in the absence of multi-vessel stenosis or occlusion and warrants careful investigation for alternative causes. (Class IIa recommendation/Level of evidence C).
- Recommendation 14: In patients with otherwise unexplained abdominal symptoms, and occlusive disease of two or three mesenteric arteries, CMI should be considered to be the cause of the symptoms. (Class IIa recommendation/Level of evidence C).
- Recommendation 15: In patients with suspected CMI, duplex ultrasound of the mesenteric arteries is recommended as the first-line examination. (Class I recommendation/Level of evidence B).
- Recommendation 16: In patients with a moderate to high suspicion of CMI, CTA (computed tomography angiography) is recommended to map the occlusive disease, and to detect or exclude other intra-abdominal pathology. (Class I recommendation/Level of evidence C).

- Recommendation 17: MRA (magnetic resonance angiography) may be considered as an alternative to CTA for diagnosis of suspected CMI, although there is some evidence that images obtained with MRA are not as accurate or complete as those obtained with CTA. (Class IIb recommendation/Level of evidence C).
- Recommendation 18: In patients with symptomatic CMI caused by multi-vessel occlusive disease, revascularisation is recommended. (Class I recommendation/Level of evidence B).
- Recommendation 19: In patients with symptomatic single vessel disease, revascularisation may be considered. (Class IIb recommendation/Level of evidence B).
- Recommendation 20: In patients with advanced CMI (severe weight loss, diarrhoea, continuous pain), it is ***not*** recommended that revascularisation is delayed by attempts to improve the nutritional status. (Class III recommendation/Level of evidence C).
- Recommendation 21: In patients with CMI, needing revascularisation, the superior long-term results of open surgery must be offset against a possible early benefit of endovascular intervention with regard to peri-procedural mortality and morbidity. (Class I recommendation/Level of evidence B).
- Recommendation 22: In patients requiring revascularisation for CMI, the superior mesenteric artery is the main target vessel using either open or endovascular techniques. (Class I recommendation/Level of evidence B).
- Recommendation 23: In patients requiring endovascular treatment of CMI, routine mesenteric stenting should be used, as opposed to plain balloon angioplasty. (Class I recommendation/Level of evidence C).
- Recommendation 24: In patients requiring mesenteric artery stenting, covered stents as opposed to bare metal stents, may be considered. (Class IIb recommendation/Level of evidence C).
- Recommendation 25: In patients with CMI, open revascularisation should be considered in the following situations:

  – In a patient who has failed endovascular therapy or
  – In patients who are not candidates for endovascular intervention because of extensive occlusion and calcification precluding safe angioplasty and stenting or
  – In young patients with complex non-atherosclerotic lesions caused by vasculitis or mid-aortic syndrome.

  (Class IIa recommendation/Level of evidence B)

- Recommendation 26: In patients needing mesenteric revascularisation, ROMS (retrograde open mesenteric stenting) should be considered when trans-aortic stenting and open reconstruction are impossible. (Class IIa recommendation/Level of evidence C).
- Recommendation 27: In patients after revascularisation for CMI, repeated follow-up by clinical assessment to detect symptomatic restenosis might be considered. (Class IIb recommendation/Level of evidence C).

- Recommendation 28: In patients after revascularisation for CMI, repeated long-term follow-up by imaging to detect asymptomatic restenosis might be considered. (Class IIb recommendation/Level of evidence C).
- Recommendation 29: In patients after revascularisation for CMI, antiplatelet therapy is recommended. (Class I recommendation/Level of evidence A).
- Recommendation 30: In patients after endovascular revascularisation for CMI, dual antiplatelet therapy might be considered for 3 to 12 months. (Class IIb recommendation/Level of evidence C).
- Recommendation 31: Patients with CMI should preferably be investigated and treated at specialised centres that can offer a multidisciplinary assessment, as well as both open and endovascular treatment. (Class I recommendation/Level of evidence C).

9.1.3 Clinical Practice Guidelines of the Society for Vascular Surgery

These are the most recently published guidelines [3]. To avoid repetition, only a few recommendations are highlighted.

- We recommend revascularization in patients with CMI to reverse their presenting symptoms (ie, weight loss, food fear, diarrhea, postprandial pain) and improve their overall quality of life. Level of recommendation: Grade 1 (Strong), Quality of Evidence: A (High).
- We recommend that total parenteral nutrition is not an acceptable alternative to revascularization for patients with CMI owing to the risk of clinical deterioration, bowel infarction, and catheter-related complications. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).
- We suggest that the superior mesenteric artery (SMA) is the primary target for revascularization. Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- We suggest that the celiac axis and inferior mesenteric artery are secondary targets for revascularization and that revascularization may aid in symptom relief if the SMA is not suitable for intervention or the technical result is not acceptable. Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).
- In patients with symptoms consistent with CMI and occlusive disease isolated to a single mesenteric vessel, particularly the SMA, we suggest a shared decision-making approach between the patient and provider to discuss revascularization as a treatment option. Level of recommendation: Grade 2 (Weak), Quality of Evidence: C (Low).
- We recommend endovascular revascularization as the initial treatment for patients with CMI and suitable lesions. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

- We recommend reserving open surgical revascularization for patients with CMI who have lesions that are not amenable to endovascular therapy, endovascular failures, and a select group of younger, healthier patients for whom the long-term benefits may offset the increased perioperative risks. Level of recommendation: Grade 1 (Strong), Quality of Evidence: B (Moderate).

9.1.4 European Guidelines on Chronic Mesenteric Ischaemia: Joint United European Gastroenterology et al.

These gastroenterology guidelines recommend [4]:

- Chronic mesenteric ischaemia should be considered in patients with unexplained postprandial abdominal pain, weight loss (>5% body weight), adapted eating pattern (to avoid abdominal complaints) or diarrhoea. Strong recommendation/Low quality of evidence.
- In symptomatic patients with single-vessel disease of either the CA or SMA, a ≥ 70% stenosis could be considered relevant. Weak recommendation/Very low quality of evidence.
- In symptomatic patients with extensive multivessel mesenteric artery disease, a ≥ 50% stenosis of the SMA could be considered relevant. Weak recommendation/Very low quality of evidence.
- Mesenteric bypass procedures might be reserved for patients in whom endovascular revascularization is not suitable. Weak recommendation/Low quality of evidence.
- In patients with chronic mesenteric ischaemia, it might be disadvantageous to increase oral intake, start enteral tube feeding or start total parenteral nutrition before revascularization. Weak recommendation/Very low quality of evidence.
- In patients with occlusive disease of both the CA and SMA, endovascular revascularization of both vessels might be attempted. The SMA is the preferred target artery followed by the CA. Weak recommendation/Very low quality of evidence.
- After endovascular mesenteric artery stenting, we suggest administering dual antiplatelet therapy for at least 1 month, followed by life-long antiplatelet monotherapy. Weak recommendation/Very low quality of evidence.

9.2 Results

9.2.1 Registries

Lima et al. [5] sought to compare in-hospital major adverse cardiac and cerebrovascular events (MACCE) following endovascular therapy with open surgery for chronic mesenteric ischemia (CMI). Data were obtained from the 2007 to 2014

National Inpatient Sample (NIS). Of 4150 patients with CMI, 3206 (77.2%) underwent endovascular therapy and 944 (22.8%) underwent surgery (weighted national estimates of 15,850 and 4687, respectively). In a propensity score-matched cohort comparison of 880 patients in each group, the incidence of MACCE was significantly lower among patients undergoing endovascular therapy than surgery (8.6% vs. 15.9%; $p < 0.001$), driven mainly by significantly lower in-hospital mortality (5.1% vs. 9.9%; $p < 0.001$) and post-operative cardiac complications (<1.1% vs. 4.3%; $p < 0.001$). The composite, any in-hospital complications, occurred significantly less often with endovascular therapy than surgery (15.3% vs. 20.3%; $p = 0.006$). Median total hospital costs during the study period were lower for patients undergoing endovascular treatment compared with open surgery. The data suggest that endovascular therapy should be the preferred revascularization modality for patients with CMI (Table 9.1).

In addition, Lima et al. [6] sought to determine the contemporary rates, reasons, predictors, and costs of 30-day readmissions following endovascular or surgical revascularization for CMI in the US. In the overall cohort, the mean age was 71.4 ± 11.1 years and 70.6% were women. Approximately one in five patients overall underwent surgery as the mode of revascularization at index hospitalization. A total of 35% of the overall index hospital admissions were elective. Among 4671 patients with CMI who underwent mesenteric revascularization, 19.5% were readmitted within 30 days after discharge at a median time of 10 days. The observed unadjusted readmission rates were higher for the endovascular than surgical group (20.6% vs. 14.7%, $p < 0.001$). The most frequent reasons for 30-day readmissions were cardiovascular and cerebrovascular conditions (27%), non-hemorrhagic gastrointestinal conditions (19%), and treatment-related complications (14%). Overall median LOS during readmission hospitalizations was 5 (IQR 3–9) days. Median overall cost per readmission stay was US $9586 (IQR $5670–$20,770). The national estimate of aggregate costs for readmission after CMI revascularization was

Table 9.1 In-hospital adverse events after endovascular (ER) versus open (OR) revascularization for chronic mesenteric ischemia. NIS database from 2007 to 2014. Propensity score-matched comparison (according to Lima et al. [5])

Parameter	ER (n = 880)	OR (n = 880)	*P*
MACCE, n (%)	76 (8.6)	140 (15.9)	< 0.001
Any in-hospital complication, n (%)	135 (15.3)	179 (20.3)	0.006
Death, n (%)	45 (5.1)	87 (9.9)	< 0.001
Myocardial infarction, n (%)	27 (3.1)	33 (3.8)	0.430
Stroke, n (%)	12 (1.4)	10 (1.1)	0.667
Other cardiac post-operative complications, n (%)	< 10 (< 1.1)	38 (4.3)	< 0.001
Peripheral vascular post-operative complications, n (%)	11 (1.3)	< 10 (< 1.1)	0.031
Major bleeding, n (%)	18 (2.0)	30 (3.4)	0.079
Gastrointestinal hemorrhage, n (%)	53 (6.0)	27 (3.1)	0.002
Bowel resection, n (%)	0 (0.0)	< 10 (< 1.1)	0.157

MACCE major adverse cardiac and cerebrovascular events

$14,634,678. Non-elective index admission, CKD, and discharge disposition, but not revascularization modality, predicted 30-day readmission.

9.2.2 Studies

9.2.2.1 Open vs. Endovascular Revascularization

A retrospective study was performed by Zacharias et al. [7] of all consecutive patients with CMI (161 patients, 215 vessels) treated from 2008 to 2012. There were 116 (72%) patients who were first treated with endovascular revascularization (ER) and 45 (28%) patients with open revascularization (OR). Overall mortality was 6.8% (11/161). Among the ER patients, 27 developed restenosis and required OR (23%). Patients treated with ER were older (73 vs. 66 years; P = .014), had similar comorbidities, and had higher rate of short lesions (≤2 cm) on preoperative angiograms (23% vs. 47%; P = .004). Primary patency at 3 years was higher in the OR group compared with the ER group (91% vs. 74%; P = .018). Long-term survival rates were higher in the ER group (95% vs. 78%; P = .003). Hospital length of stay and intensive care unit length of stay were shorter in the ER group (<.001). Perioperative mortality (30-day) was not statistically significant between the groups (5.2% vs. 11%; P = .165). Patients with short lesions ≤2 cm who have higher operative risk are 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 (Table 9.2).

A study from Pittsburgh included 259 patients treated for CMI from 2010 to 2020 [8]. 56 (22%) of these patients underwent open bypass surgery, usually (70%) antegrade (aortic inflow), with a Dacron graft (82%). 230 patients underwent endovascular intervention, usually at the SMA (63%), with bare-metal stents (64%), mostly balloon-expandable (97%). Postoperative major adverse events were

Table 9.2 Endovascular revascularization (ER) vs. open revascularization (OR) for chronic mesenteric ischemia (according to Zacharias et al. [7])

Parameter	ER (n = 116)	OR (n = 45)	P
Patient age, years (mean ± SD)	73 ± 10	66 ± 13	.014
Gender, female, %	70	76	.459
Multivessel disease ≥2, %	83	66	.059
Location of vessel occlusion >2 cm from origin, %	33	18	.059
Length of stenosis >2 cm, %	23	47	.004
Perioperative mortality, %	5.2	11	.165
Intensive care unit length of stay, days	2 ± 5	12 ± 19	<.001
Hospital length of stay, days	5 ± 8	23 ± 20	<.001
Primary patency at 3 years, %	74	91	.018
Survival at 3 years, %	95	78	.003

observed in 12% (27% after open, 9% after endovascular interventions ($p < 0.01$). 30-day mortality was 10.7% vs. 4.4%. Primary patency rates at 1 year were 85% after endovascular intervention and 96% after open bypass. However, primary assisted patency rates showed little difference (94% in the endovascular and 96% in the open bypass group). The conclusion was to pursue an endovascular first approach in patients with CMI, but with strict post-interventional monitoring.

The impact of malnutrition on the outcomes of open and endovascular revascularization in 54 patients with CMI was investigated by Allain et al. [9]. The prevalence of malnutrition was 70% (38 patients), including 9 severely malnourished patients. Twenty-nine patients (53.7%) underwent endovascular revascularization, while 25 (46.3%) underwent conventional surgery. The 30-day mortality was null in the non-malnourished group, whereas ten patients (26.3%) died in the malnourished group ($P = 0.02$). The mean duration of follow-up was 639 (±660) days. The 3-year survival was not different between the endovascular group and the open surgery group (43% vs. 52%, $P = 0.7$). The 3-year survival was statistically higher in the non-malnourished group (87%) than in the malnourished group (49.6%) ($P = 0.01$). The authors suggested perioperative nutrition for severely malnourished patients with CMI, but according to guidelines this should not delay intervention.

9.2.2.2 Open Revascularization

72 patients with open mesenteric bypass (OMB) for CMI were reported by Crawford et al. [10]. Previous mesenteric stent placement or bypass had been performed in 39%. An antegrade configuration (93%) was most common (retrograde configuration, 7%), with revascularization of the superior mesenteric artery/celiac vessels in 85% (superior mesenteric artery only in 15%). The 30-day mortality was 4% ($n = 3$) and in-hospital morbidity was 53%. The clinical follow-up period was 16 ± 20 months. The 1- and 3-year primary bypass patency and freedom from reintervention was 91% ± 5% and 83% ± 7%, respectively, with no association with the Multiple Organ Dysfunction Scores (MODS) or sequential organ failure assessment (SOFA) scores. The 1- and 3-year survival was 86% ± 4% and 71% ± 6% with significantly worse outcomes for patients with higher MODSs and/or SOFA scores. Most CMI patients undergoing OMB will experience significant metabolic derangements resulting from sequelae of the ischemia-reperfusion phenomenon postoperatively. These can be objectively assessed in the early postoperative period using simply applied scoring systems to reliably predict the early and long-term outcomes.

9.2.2.3 Endovascular Revascularization

Long-term outcomes of percutaneous angioplasty and stenting of the superior mesenteric artery (SMA) for CMI in 76 consecutive were reported by Awouters et al. [11]. Catheter-angiography revealed an ostial or non-ostial >90% stenosis in $n = 23$ (29.7%) and $n = 53$ (69.7%) of included patients, respectively. Immediate clinical

success was achieved in n = 68 (89.5%), and procedural complications were observed in n = 13 (17.1%) patients. Long-term follow-up revealed relapse of symptoms in n = 21 (28.8%) patients, and overall survival estimates are 81.8%, 57.0% and 28.2% after 2, 5 and 10 years of follow-up, respectively. A trend towards longer relapse-free survival was found in the circumferential stenosis group (78.2% at 5 years) compared with the non-circumferential stenosis group (55.5%) (P = 0.063). Angioplasty and stenting of the SMA for CMI is relatively safe and effective despite a substantial number of patients experiencing clinical relapse over time.

Haben et al. [12] conducted a retrospective review of patients with CMI treated with angioplasty and stenting with bare-metal stents from 2003 to 2014. There were 150 patients (39 men, 111 women; age, 70.7 ± 11.1 years) with CMI who underwent interventions on the CA (56 vessels) and the SMA (133 vessels); 38 patients had both CA and SMA intervention. Primary patency for the CA was 86% at 1 year and 66% at 3 years; for the SMA, primary patency was 81% at 1 year and 69.0% at 3 years. Chronic total occlusion in the SMA conferred worse patency compared with stenosis (HR, 2.38; 95% CI, 1.03–5.47; P = .042), and younger patients (<70 years) had a higher proportion of SMA occlusion (38.9% vs. 22.8; P = .045). Intervention for CMI has acceptable midterm results. Patients older than 70 years have better results than younger patients, and this may reflect a more malignant presentation in the younger patients. Ostial flaring proved to be the single factor on multivariate analysis associated with improved patency.

Zhou et al. [13] analyzed the outcomes of patients treated for mesenteric artery in-stent restenosis (MAISR). Clinical data from a single center between 2004 and 2017 were presented. During the study period, 91 patients underwent primary mesenteric angioplasty and stenting (MAS). In total, 113 mesenteric vessels were treated with 20 covered stents and 93 bare-metal stents. Overall primary patency was 69% at 2 years. At 2 years, primary patency was 83% for covered stents compared with 65% for bare-metal stents (P = .17). Of these 91 primary MAS patients, 27 (30%) were treated for MAISR (32 vessels). Two covered stent patients developed significant restenosis (11%) compared with 25 (34%) bare-metal stent patients (P = .02). The 30-day mortality rate after reintervention for mesenteric stent restenosis was 0%. Postoperative complications occurred in 15% of patients. The 2-year patency was similar after balloon angioplasty alone and repeated stenting. Data suggest use of covered vs. bare-metal stents for mesenteric artery stenosis. Restenosis treatment has low mortality and acceptable morbidity, and angioplasty alone appears as effective as repeated stenting.

9.3 Conclusions for Clinical Practice

1. Chronic mesenteric ischaemia (CMI) should be considered in patients with unexplained postprandial abdominal pain, weight loss (>5% body weight), adapted eating pattern (to avoid abdominal complaints) or diarrhoea.

2. In patients with symptomatic CMI caused by multi-vessel occlusive disease, revascularization is recommended.
3. In symptomatic patients with single-vessel disease of either the celiac artery (CA) or superior mesenteric artery (SMA), a > 70% stenosis could be considered relevant.
4. In patients with advanced CMI (severe weight loss, diarrhoea, continuous pain), it is not recommended that revascularization is delayed by attempts to improve the nutritional status.
5. In most centres angioplasty and stenting have become the primary treatment modalities, relegating open surgical bypass to patients who are not candidates or who fail endovascular therapy.
6. The SMA is the main primary target for revascularization, whenever possible. Revascularization of the CA or IMA has also been performed, particularly when the SMA is chronically occluded and not suitable for recanalisation.

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Chapter 10
Median Arcuate Ligament Syndrome (MALS)



Preliminary Note In the following, the term "median arcuate ligament syndrome" (MALS), the most common term in PubMed, is used. MALS is also known as Dunbar syndrome or coeliac artery compression syndrome.

10.1 Guidelines

10.1.1 The Appropriateness Criteria of the American College of Radiology [1] Recommend

Diagnostics:

- CTA or MRA should be performed prior to catheter angiography.
- Mesenteric angiography in lateral projection during both inspiration and expiration.

Treatment:

- Surgery with median arcuate ligament release, with or without bypass. This procedure is performed once diagnosis is confirmed by angiography.
- Percutaneous transluminal angioplasty with stent placement. This procedure is the second-line intervention in patients with recurrent or persistent symptoms despite surgical decompression and where there is evidence of celiac artery narrowing.

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10.1.2 European Guidelines on Chronic Mesenteric Ischaemia—Joint United European Gastroenterology. These Guidelines Recommend [2]

- CA compression in MALS can be diagnosed by inspiration/expiration duplex ultrasound, CTA or CE-MRA. In patients of younger age, suspected of having MALS, both duplex ultrasound and CE-MRA (2 mm slices with 3D reconstructions) in inspiration and expiration are recommended imaging techniques. Strong recommendation / Very low quality of evidence
- Patients with MALS might be considered for surgical coeliac artery release. Weak recommendation / Very low quality of evidence
- In patients with MALS (and no preceding adequate coeliac artery release) endovascular stenting of the CA is contraindicated. Strong recommendation/Very low quality of evidence

10.2 Results

10.2.1 Reviews

A review aimed to outline the anatomy and pathophysiology of MALS. Evidence pertaining to its clinical presentation, diagnosis, and management was also reported [3]:

- Anatomy

  The median arcuate ligament (MAL) is a tough fibrous arch connecting the right and left crura of the diaphragm at the level of the aortic hiatus (T12-L1). It traverses anterior to the aorta and is usually cranial to the celiac artery. The position of the MAL and the origin of the celiac artery vary between individuals.
- Presentation

  The true prevalence of MALS is unclear, which is partly due to its variable clinical presentation. There is a tendency toward a female phenotype (4:1), and the median age typically lies between 30 and 50 years. Cases have also been reported in pediatric. Frequently reported symptoms include epigastric pain, nausea, vomiting, weight loss, and postprandial or exercise-induced abdominal pain. Clinical signs may include abdominal bruits (amplified with expiration), epigastric tenderness, and marked weight loss.
- Diagnosis

  Duplex ultrasound (DUS) is the first-line recommended investigation. In patients in whom there is a moderate to high suspicion of chronic mesenteric ischemia, CTA is recommended to map occlusive disease and to detect or to

exclude other intra-abdominal disease. CTA features in MALS include focal narrowing of the proximal celiac artery with a characteristic hooked appearance. Magnetic resonance angiography and digital subtraction angiography (DSA) can provide similar appreciation of vessel stenosis as CTA. Magnetic resonance angiography, DSA, and CTA should be performed in inspiration and expiration to demonstrate the changes in celiac artery compression with the phases of respiration. Interestingly, a convincing correlation between degree of angiographic stenosis and likelihood of being symptomatic from MALS is lacking.

- Management

  Surgical management involves decompression of the median arcuate ligament's constriction of the celiac artery; robotic, laparoscopic, endoscopic retroperitoneal, and open surgical intervention can provide effective symptom relief, but long-term follow-up data (>5 years) are lacking. Patients treated nonoperatively appear to have worse outcomes.

- Evidence

  The available evidence is highly suggestive that MALS exists. Despite no definitive group consensus agreement as to the diagnostic criteria or management of MALS, patient presentation and radiologic signs appear generally consistent across the literature.

Kim et al. [4] reviewed the literature to define an algorithm for accurate diagnosis and successful treatment for patients with MAL syndrome. They concluded that although diagnosis and treatment of MAL syndrome are unclear, symptom resolution has been achieved with multiple surgical modalities, including open, laparoscopic, or robotic ligament release as well as celiac ganglionectomy, which often requires celiac artery revascularization. Based on current literature and own experience, they proposed an algorithm for diagnostic evaluation and intervention in patients with MAL syndrome which is shown in Fig. 10.1.

10.2.2 Studies

10.2.2.1 Surgical Vs. Nonoperative Management

The only recent study describing the outcome after surgical decompression and nonoperative management of MALS comes from Australia [5]. There were 67 patients, 43 (64%) treated surgically and 24 (36%) managed without surgery, with a median follow-up of 25 months and 24 months, respectively. Laparoscopic decompression was performed in 38 cases (88%). One case (3%) was converted to an open operation because of left gastric artery bleeding. Open decompression was performed in five cases (12%). One patient had a percutaneous angioplasty and stent insertion 1 month after open decompression because of persistence of symptoms.

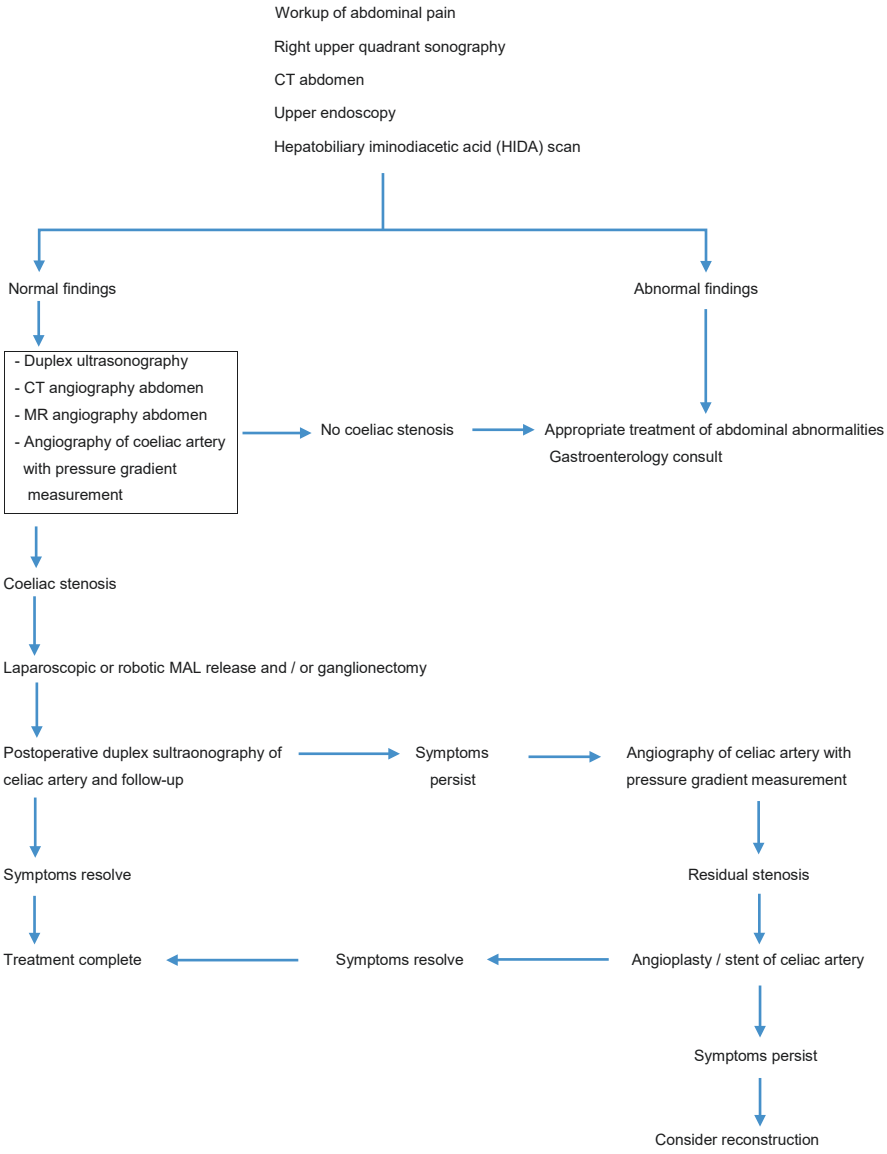

Fig. 10.1 Algorithm for diagnosis and management of median arcuate ligament (MAL) syndrome proposed by Kim et al. [4]

One patient received a patch angioplasty during open decompression because the celiac artery did not expand after decompression. After surgical treatment, 16 (37%) patients were asymptomatic, 24 (56%) were partially improved, 3 (7%) had no changes in symptoms, and none had worsening of symptoms. Postexertional abdominal pain was associated with better surgical outcomes, whereas unprovoked

abdominal pain (i.e., abdominal pain that was not related to meals or exercise) and vomiting were associated with poor surgical outcomes. There was no association between postprandial pain and outcome.

After nonoperative management, 1 (4%) was asymptomatic, 7 (29%) were partially improved, 12 (50%) had no changes in symptoms, and 4 (17%) had worsening of symptoms. The available evidence suggests that patients with postexertional abdominal pain, without unprovoked abdominal pain, and without vomiting appear more likely to achieve favorable surgical outcome. Other factors that were previously found to be predictive of surgical outcomes, such as gender, postprandial abdominal pain, and weight loss of >9 kg, were not found to be associated with surgical outcomes in this study but should be taken into consideration.

10.2.2.2 Laparoscopic and Open MAL Release

Using the National Inpatient Sampling database, Alnahhal et al. [6] identified all patients surgically treated for MALS between 2008 and 2018 through conventional open and laparoscopic approaches. A total of 630 patients were included and analyzed: 487 (77.3%) patients underwent open surgery while 143 (22.7%) patients underwent laparoscopic decompression. The majority of the study population consisted of female patients (74.8%) with a mean age of 40.6 ± 19 years. Patients who underwent laparoscopic decompression had significantly less all-cause perioperative complications compared to their open surgery counterparts (0.7% vs. 9.9%; $P = 0.001$). Additionally, prolonged hospitalization was noted in the open group compared to the laparoscopic (5.8 days vs. 3.5; $P < 0.001$, respectively) with a significantly higher mean of total hospital charges ($70,095.8 vs. 56,113.5; $P = 0.016$). This paper demonstrates the safety and improved outcomes during the index hospitalization of the laparoscopic approach as the standard of care. Although this work shows that it can be done safely, it does not provide evidence on indications for surgery, open or laparoscopic, and furthermore does not provide evidence on the efficacy of the short or long-term symptom relief postoperatively.

The Vascular Low Frequency Disease Consortium is an international, multi-institutional research consortium. Data on open, laparoscopic, and robotic MAL release (MALR) performed from 2000 to 2020 were gathered by DeCarlo et al. [7]. Of 516 patients treated at 24 institutions, 227 (44.0%), 235 (45.5%), and 54 (10.5%) had undergone open, laparoscopic, and robotic MALR, respectively. Of the 488 patients (94.6%) with follow-up data available, 287 (58.8%) had had full relief, 119 (24.4%) had had partial relief, and 82 (16.8%) had derived no benefit from MALR. The 3-year freedom from treatment failure for the overall cohort was 51.9% (95% confidence interval, 46.1%–57.3%). The factors associated with an increased hazard of treatment failure included robotic MALR, a history of gastroparesis, a history of abdominal cancer, dysphagia or odynophagia, no relief from a celiac plexus block, and the number of pain locations. Age and an increasing number of preoperative diagnostic gastrointestinal studies were associated with a lower hazard of failure. No radiographic parameters were associated with differences in treatment

failure. No difference was found in long-term failure after open vs laparoscopic MALR; however, open release was associated with higher perioperative morbidity. These results support the use of a preoperative celiac plexus block to aid in patient selection. The overall rate of treatment failure was high, and operative candidates for MALR should be counseled regarding the factors associated with treatment failure.

Romero-Velez et al. [8] examined the trends in MAL release in the United States in the past 10 years using the American College of Surgeons-National Surgical Quality Improvement Project from 2010 to 2020. A total of 578 open cases (76%) and 185 laparoscopic cases (24%) were identified. There was an increase adoption of the laparoscopic approach, with 22% of the cases employing this technique at the end of the study period, compared to 7% at the beginning of the study period. The open group had a higher prevalence of hypertension (26% vs 18%, $p = 0.04$) and bleeding disorders (5% vs 2%, p 0.03). Laparoscopic approach had a shorter length of stay (2.3 days vs 5.2 days, $p < 0.0001$), lower major complication rates (0.5% vs 4.0%, $p = 0.02$) and lower reoperation rates (0% vs 2.6%, $p = 0.03$). Overall mortality was 0.1%. Increased surgical treatment of MALS was detected in the past decade in the United States.

Patel et al. [9] described 32 patients who underwent laparoscopic MAL release. The average age of the patients at time of treatment was 37.8 years (range, 22–60 years). No operative complications occurred, and none required conversion to open surgery. Technical success rate, defined as origin of the celiac artery being visually free of external stricture and with improvement in intraoperative DUS velocity, was 100%. There were 29 patients (91%) who completed follow-up with a 1-year clinical evaluation. 19 patients (66%) reported improvement in symptoms, and 18 (62%) decreased their use of analgesics. No celiac artery DUS finding (peak celiac artery velocity, angle of deflection, or change in preoperative to postoperative velocity) was predictive of successful clinical outcomes ($P > .05$). Similarly, no CTA finding (characteristic morphology, cross-sectional area, diameter, or location of the focal stenosis of the celiac artery) was associated with clinical outcomes ($P > .05$). This small series of patients who underwent laparoscopic MAL release experienced good outcomes comparable to those reported in the literature. However, no DUS or CTA findings were able to predict response to treatment. MALS is a complex condition that may be multifactorial in etiology, including both vascular and neurogenic components. This study did not confirm a vascular etiology for median arcuate ligament syndrome. The leading alternative pathophysiologic mechanism for MALS involves neurogenic pain from compression of the celiac nerve plexus.

In a single-center, 52 consecutive MALS patients were followed-up, prospectively, after transperitoneal laparoscopic decompression. All operations were performed by one surgeon [10]. Mean age of the patients was 47 ± 21 years, and 65% were females. Complete (67%) or partial (23%) relief from symptoms was found in 47 patients (90%) after 3–6 months of follow-up. Five patients (10%) had operative complications. Only two patients had recurrent symptoms requiring intervention during a mean follow-up period of 2.4 years. Despite controversies about its

pathophysiology, laparoscopic decompression of the celiac artery seems to provide persistent relief from symptoms in most patients with median arcuate ligament syndrome.

Long-term results in 100 patients with MALS (mean age, 38 ± 18 years; 75% female) were presented by Pather et al. [11]. Open surgical release was performed in 81 and laparoscopic release in 19 patients. There was no mortality. Major adverse events at 30 days had occurred in 21 patients (open 19, laparoscopic 2) including myocardial infarction (n = 1), pancreatitis (n = 2), respiratory failure (n = 4), estimated blood loss of more than 1 L (n = 8), and postoperative ileus (n = 8). A cross-sectional questionnaire using the Visick score, the Gastrointestinal Quality of Life Index, and Short Form (SF)-12v2 questionnaires was performed to assess long-term outcomes. Forty-six patients responded to the questionnaire with a mean follow-up of 8 ± 4 years. Initial symptom resolution or improvement was reported by 38 patients (83%), whereas eight patients (17%) reported treatment failure. Seven of the 38 patients (18%) with initial treatment success reported symptom recurrence. The estimated 5-year freedom from symptoms was 67 ± 7%. Forty respondents (87%) reported that they would still undergo operative management if given the choice, including all respondents who reported symptom recurrence.

10.2.2.3 Open Surgery for Abdominal Compression Syndromes

An observational study was undertaken on 169 patients who underwent 196 open operations for abdominal compression syndromes (CS) between 2010 and 2020 by Sandmann et al. [12]. Arising not only in the abdomen and causing pain (median arcuate ligament syndrome [MALS] and superior mesenteric artery syndrome [SMAS]), CS also occur in the retroperitoneum and the pelvis (nutcracker syndrome and May-Turner syndrome), these latter conditions causing chronic pelvic congestion syndrome (PCS). Out of 169 patients with CS, 132 (78.1%) were female, 37 (21.9%) were male. The mean age was 31.36 years (female 33.82 years, male 29.44 years). The majority (n = 123, 72.8%) of 169 patients presented with multiple types of CS. Eighty-one patients were operated for primary or recurrence of MALS, that is 47.9% of the total number of patients undergoing surgery for abdominal-retroperitoneal and pelvic CS. 122 patients with either MALS as a mono-lesion or in combination with other CS underwent partial resection of the MAL. In all but 4 patients, the typical symptoms disappeared or had significantly improved after 2 to 3 weeks. A subgroup of 43 (25.4%) patients underwent superior mesenteric artery transposition (SMATX) from suprarenal into the infrarenal aorta for treatment of SMAS. Thirty-eight (90.5%) patients in this SMAS subgroup having undergone SMASTX reported pain-free eating and weight gain within 6 months post operation. Based on their experience, the authors argued against the laparoscopic approach for MALS, which could either—performed too close to the aorta—lead to bleeding that is difficult to control or - if the procedure is too cautious—may leave fibres in place that make decompression incomplete. Just dividing but not resecting a segment of the MAL can cause recurrence due to strong scar tissue.

10.2.2.4 Robotic Surgery

Gerull et al. [13] presented a retrospective cohort study analyzing adult patients who underwent robotic median arcuate ligament release (MALR) performed by a single surgeon at a tertiary academic hospital from 2014 to 2021. A total of 74 patients underwent robotic MALR during the study period. The mean age was 27.3 ± 7.9 years and the majority of patients were female (n = 60/74, 81.1%). The most common presenting symptom was post-prandial abdominal pain (n = 65/74, 87.7%). The mean operative time was 52.6 ± 18.1 min. There were no conversions to open surgery and minimal blood loss (mean = 13.9 ± 8.4 mL). At 3-months, 12% (n = 9/74) of patients had persistent abdominal pain and underwent additional imaging. 5 of these 9 patients had persistently elevated DUS expiratory PSV and were referred for angioplasty. At 1-year follow up, 90.3% (n = 56/62) continued to have no abdominal pain. The robotic approach to MALR is safe and feasible, with good patient outcomes.

In a retrospective study, Khrucharoen et al. [14] compared surgical outcomes between laparoscopic and robotic-assisted MAL release. A total of 16 laparoscopic and 18 robotic cases were included. Median operative time was shorter in the robotic group (106 vs. 179.5 min). The rates of conversion to open procedure in both groups were similar (6.3% in the laparoscopic group and 5.6% in the robotic group). Postoperative complication rates were similar (12.5% vs. 16.7%, p = 0.99), major complications were not seen in either group. There was no difference in the immediate postoperative outcome. Complete abdominal pain relief was found in 37.5% (laparoscopic group) and 44.4% (robotic group), respectively, and no improvement in 12.5% and 16.7%. This study demonstrated that laparoscopic and robotic-assisted MAL release offer comparable surgical outcomes and similar short- and intermediate-term clinical outcomes. Robotic MAL release can be associated with a substantially shorter operative time than laparoscopic MAL release with the hypothesis of improved dexterity offered by the robotic instrument's multi-articulated joints.

In another retrospective study, the results of 26 robotic MALR and 24 laparoscopic MALR performed by a single surgeon were reported [15]. In this study, the mean operative time was significantly shorter for laparoscopic surgery (86 min) compared to robotic surgery (134 min; $p < 0.0001$). There were no open conversions and mean length of hospital stay was 1 day for both groups. While robotic MALR had significantly higher reduction of chronic abdominal pain postoperatively (76.9% vs 50%) there were no significant differences in other postoperative symptom relief between groups. In comparison with laparoscopic MALR, robotic MALR cases were associated with more junior first assistants, fewer second assistants, and longer operative times. Both approaches are safe and feasible for well-selected patients in experienced centers.

10.2.2.5 MALS in the Pediatric Population

Mak et al. [16] prospectively evaluated 46 pediatric patients (42 females, 4 males; ages 8.6–20.5 years; median 16.6; mean 16.2 ± 0.5 years). All patients had previously been diagnosed with chronic functional abdominal pain (CFAP). Patients were evaluated for celiac artery compression by duplex ultrasound and diagnosis was confirmed by computed tomography. All patients underwent a technically satisfactory laparoscopic surgical release resulting in a significant improvement in blood flow through the celiac artery. There were no deaths and a total of 9 complications, 8 requiring a secondary procedure; 33 patients were administered QOL surveys. Eighteen patients completed the survey with 15 (83%) patients reporting overall improvement in the QOL. Overall, 31/46 patients (67%) reported improvement of symptoms since the time of surgery. Laparoscopic release of the celiac artery can be performed safely in the pediatric population. Surgical release of the artery and resultant neurolysis resulted in significant improvement in the blood flow, symptoms, and overall QOL in this cohort. The overall improvement in QOL outcome measures after surgery leads the authors to conclude that MALS might be earlier diagnosed and possibly treated in patients with CFAP.

In another retrospective study, six pediatric patients underwent laparoscopic release for MALS [17]. 5 patients were female (83.3%), with an average age of 15.7 ± 1.5 years. Presenting symptoms lasted on average 16.5 ± 12.7 months prior to treatment. Average pre- and postsurgical ultrasound celiac artery peak velocities with inspiration were 332.0 ± 34.1 cm/s and 224.3 ± 31.2 cm/s, respectively, with a statistically significant decrease of 107.67 cm/s ($P = 0.03$). The results demonstrated that laparoscopic MALR in the pediatric population is safe and effective. In carefully selected patients, laparoscopic release for MALS without additional celiac artery reconstruction normalizes blood flow in the celiac artery and improves physical and psychosocial quality of life for the child and his or her parents.

10.3 Conclusions for Clinical Practice

1. MALS is a controversial disease; this applies to pathogenesis and treatment. There are no guidelines, meta-analyses, or controlled trials, so that evidence-based treatment recommendations cannot be made.
2. Despite no definitive group consensus agreement as to the diagnostic criteria or management of MALS, patient presentation and radiologic signs appear generally consistent across the literature. The available evidence is highly suggestive that MALS exists.
3. Celiac artery compression in MALS can be diagnosed by inspiration/expiration duplex ultrasound, CTA or CE-MRA.
4. Surgical management involves decompression of the median arcuate ligament's constriction of the celiac artery; robotic, laparoscopic, endoscopic retroperitoneal, and open surgical intervention can provide effective symptom relief, but

long-term follow-up data (>5 years) are lacking. Patients treated nonoperatively appear to have worse outcomes.
5. Percutaneous transluminal angioplasty with stent placement is the second-line intervention in patients with recurrent or persistent symptoms despite surgical decompression and where there is evidence of celiac artery narrowing.
6. A mental disorder is not uncommon in these patients and must be carefully ruled out before any intervention.

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Chapter 11
Intermittent Claudication



11.1 Guidelines

11.1.1 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS)

The European Society of Cardiology in collaboration with the European Society for Vascular Surgery (ESVS) guidelines [1] recommend for the management of intermittent claudication (IC):

- On top of general prevention, statins are indicated to improve walking distance. (Class I recommendation/Level of evidence A).
- In patients with intermittent claudication supervised exercise training is recommended. (Class I recommendation/Level of evidence A).
- Unsupervised exercise training is recommended when supervised exercise training is not feasible or available. (Class I recommendation/Level of evidence C).
- When daily life activities are compromised despite exercise therapy, revascularization should be considered. (Class IIa recommendation/Level of evidence C).
- When daily life activities are severely compromised, revascularization should be considered in association with exercise therapy. (Class IIa recommendation/Level of evidence B).

The recommendations on revascularization of aorto-iliac occlusive lesions and the recommendations on revascularization of femoro-popliteal occlusive lesions in this guideline apply for patients with intermittent claudication and severe chronic limb threatening ischemia and are given in Chap. 12.

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11.1.2 American College of Cardiology/American Heart Association

The American College of Cardiology/American Heart Association guidelines [2] recommend:

11.1.2.1 Medical Therapy

- Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). (Recommendation class I/Level of evidence A).
- Treatment with a statin medication is indicated for all patients with PAD. (Recommendation class I/Level of evidence A).
- The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. (Recommendation class IIb/Level of evidence B-R).
- Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. (Recommendation class I/Level of evidence A).
- Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program. (Recommendation class I/Level of evidence A).

11.1.2.2 Structured Exercise Therapy

- In patients with claudication, a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms. (Recommendation class I/Level of evidence A).
- A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization. (Recommendation class I/Level of evidence B-R).
- In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status. (Recommendation class IIa/Level of evidence A).
- In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum claudication while walking, can be beneficial to improve walking ability and functional status. (Recommendation class IIa/Level of evidence A).

11.1.2.3 Revascularization for Claudication

- Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to GDMT (guideline-directed management and therapy). (Recommendation class IIa/Level of evidence A).
- Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease. (Recommendation class I/Level of evidence A).
- Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease. (Recommendation class IIa/Level of evidence B-R).
- The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown. (Recommendation class IIb/Level of evidence C-LD).
- Endovascular procedures should ***not*** be performed in patients with PAD solely to prevent progression to CLI. (III: Harm/Level of Evidence B-NR).
- When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material. (Recommendation class I/Level of evidence A).
- Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication with inadequate response to GDMT, acceptable perioperative risk, and technical factors suggesting advantages over endovascular procedures. (Recommendation class IIa/Level of evidence B-NR).
- Femoral-tibial artery bypasses with prosthetic graft material should ***not*** be used for the treatment of claudication (III: Harm/Level of evidence B-R).
- Surgical procedures should ***not*** be performed in patients with PAD solely to prevent progression to CLI. (III: Harm/Level of Evidence B-NR).

Note: R = randomized; NR = Nonrandomized; LD = Limited data.

11.1.3 Society for Vascular Surgery (SVS)

The SVS guidelines [3] are in accordance with the other guidelines referred here regarding medical therapy and noninterventional management. These recommendations are therefore—in order to avoid redundancy—not listed here. Recommendations for revascularization are among others:

11.1.3.1 General Recommendations

- We recommend EVT (endovascular therapy) or surgical treatment of IC for patients with significant functional or lifestyle-limiting disability when there is a reasonable likelihood of symptomatic improvement with treatment, when phar-

macologic or exercise therapy, or both, have failed, and when the benefits of treatment outweigh the potential risks.

(Recommendation grade I/Level of evidence B).

- We recommend an individualized approach to select an invasive treatment for IC. The modality offered should provide a reasonable likelihood of sustained benefit to the patient (>50% likelihood of clinical efficacy for at least 2 years). For revascularization, anatomic patency (freedom from hemodynamically significant restenosis) is considered a prerequisite for sustained efficacy. (Recommendation grade I/Level of evidence C).

11.1.3.2 Recommendations for Interventions in Aortoiliac Occlusive Disease (AIOD) in IC

- We recommend endovascular procedures over open surgery for focal AIOD causing IC. (Recommendation grade1/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. (Recommendation grade 1/Level of evidence B).
- We recommend the selective use of BMS (bare-metal stent) 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. (Recommendation 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. (Recommendation grade 1/Level of evidence C).
- In all patients undergoing revascularization for AIOD, we recommend assessing the CFA (common femoral artery). If hemodynamically significant CFA disease is present, we recommend surgical therapy (endarterectomy) as first-line treatment. (Recommendation grade 1/Level of evidence B).
- 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. (Recommendation grade 1/Level of evidence B).

11.1.3.3 Recommendations for Intervention for Femoropopliteal Occlusive Disease (FPOD) in IC

- We recommend endovascular procedures over open surgery for focal occlusive disease of the SFA (superficial femoral artery) not involving the origin at the femoral bifurcation. (Recommendation 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. (Recommendation 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. (Recommendation grade 1/Level of evidence B).
- We recommend ***against*** [negative recommendation] EVT of isolated infrapopliteal disease for IC because this treatment is of unproven benefit and possibly harmful. (Recommendation 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. (Recommendation grade 1/Level of evidence B).
- We recommend using the saphenous vein as the preferred conduit for infrainguinal bypass grafts. (Recommendation 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. (Recommendation grade 2/Level of evidence C).

11.1.4 "Appropriate Use": Criteria of the SVS for IC

Appropriate use criteria (AUC) for the management of intermittent claudication were created by the SVS [4]. The recommendations are:

- First, exercise therapy is the preferred initial management strategy for all patients with IC.
- Second, for patients who have not completed exercise therapy, invasive therapy might provide net a benefit for selected patients with IC who are nonsmokers, are taking optimal medical therapy, are considered to have a low physiologic and technical risk, and who are experiencing severe lifestyle limitations and/or a short walking distance.
- Third, considering the long-term durability of the currently available technology, invasive interventions for femoropopliteal disease should be reserved for patients with severe lifestyle limitations and a short walking distance.
- Fourth, in the common femoral segment, open common femoral endarterectomy will provide greater net benefit than endovascular intervention for the treatment of IC.
- Finally, in the infrapopliteal segment, invasive intervention for the treatment of IC is of unclear benefit and could be harmful.

11.1.5 Reporting Standards of the SVS for Endovascular Treatment of Chronic Lower Extremity Peripheral Artery Disease

The purpose of this document is to provide an overview and summary for the reporting of endovascular revascularization techniques in the setting of chronic disease [5].

11.1.5.1 Intervention

1. Reports should characterize anatomic location (vessel-specific reporting) and primary vs. secondary intervention.
2. Angioplasty trials should report definitive balloon diameter and length.
3. Stent trials should document predilation and other adjuncts in addition to definitive diameter and length.
4. Atherectomy trials should report device-specific data, such as treatment time, quantitative measures of plaque excision, and use of embolic protection device.
5. Radiation dose, contrast volume, total treatment time, and intraprocedural pharmacology should be recorded.

11.1.5.2 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 (see later).
2. Hemodynamic success is defined as a pressure gradient <10 mmHg 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.

11.1.5.3 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.

11.1.5.4 Complications

1. Complications are categorized into procedural or device related.
2. A minimum of 30 days of complication reporting is required; subacute and late complication reporting is suggested.

11.1.6 Optimal Exercise Programs for Patients with Peripheral Artery Disease: A Scientific Statement from the American Heart Association [6]

Although SET (supervised exercise therapy) programs for patients with PAD should be individualized with regard to duration, intensity, frequency of exercise, and the work-to-rest ratio, currently available evidence suggests parameters for these program elements. Exercise sessions should progress up to a target goal of accumulating 30 to 45 min of treadmill walking per session. Exercise should be carried out at an intensity that elicits mild claudication pain within 5 min and moderate to moderately severe claudication within 10 min followed by rest until claudication pain subsides. Randomized trials of SET that demonstrate significant improvement in walking performance have typically asked patients with PAD to walk for exercise 3 times per week.

Exercise prescription for supervised exercise treadmill training in patients with claudication:

- Intensity: 40%–60% maximal workload based on baseline treadmill test or workload that brings on claudication within 3–5 min during a 6-min walk test (6-MWT).
- Session duration: 30–50 min of intermittent exercise; goal is to accumulate at least 30 min of walking exercise.
- Claudication intensity: moderate to moderate/severe claudication as tolerated.

- Work-to-rest ratio: walking duration should be within 5–10 min to reach moderate to moderately severe claudication followed by rest until pain has dissipated (2–5 min).
- Frequency: 3 times per week supervised.
- Program duration: at least 12 weeks.
- Progression: every 1–2 week. Increase duration of training session to achieve 50 min. As individuals can walk beyond 10 min without reaching prescribed claudication level, manipulate grade or speed of exercise prescription to keep the walking bouts within 5–10 min.
- Maintenance: Lifelong maintenance at least 2 times per week.

11.1.7 French Guidelines for the Management of Ambulatory Endovascular Procedures for Lower Extremity Peripheral Artery Disease

The French Society of Vascular and Endovascular Surgery (SCVE) established guidelines to facilitate the development of ambulatory procedures in France [7].
Eligibility for ambulatory peripheral arterial repair:
Medical

- No limit of age is imposed.
- Body mass index >40 kg/m^2 should be considered as a contraindication, except in specific patients after extensive evaluation.
- Only ASA I, II and III stable patients.
- Critical limb ischemia and complex lesions have not been considered as exclusion criteria.
- Evaluate the need for hyperhydration in case of chronic renal failure.
- The use of antiplatelet is not considered as a contraindication.

Sociological

- Sufficient comprehension skills.
- Proper compliance to the medical prescriptions.
- Equivalent hygiene and housing conditions to those available during hospitalization.
- Available person on hand to accompany the patient.
- Medical care should be available less than 1 h from patient's home.
- Convenient and rapid telephone access.

Recommendations regarding the procedure

- Ultrasound-guided femoral artery puncture is recommended.
- Radial or brachial approaches can be used in addition to the femoral approach for complex procedures.

- The use of percutaneous closure devices is recommended for ambulatory intervention involving 7F or more sheath and/or in the presence of clinical elements raising concerns to get hemostasis at the puncture point (obesity, coagulation disorder, and so forth).
- For 7F sheaths or less, manual compression with compression dressing or arterial closure device could be considered.

Recommendations for postoperative monitoring

- A minimum of 4 h of monitoring after the procedure is required to allow patient's discharge from hospital after approved clinical assessment.
- A medical letter reporting the reason for hospitalization, a brief summary of the procedure and potential complications, as well as the detailed prescriptions and scheduled follow-up has to be issued to the patient.
- Emergency telephone number, reachable 24/7, has to be provided. Phone call or text message, on the day after the procedure, is recommended and might be charted.

11.2 Results

11.2.1 Meta-Analyses/Systematic Reviews/Randomised Trials

11.2.1.1 Exercise Therapy

The effects of alternative modes of supervised exercise therapy compared to traditional walking exercise in patients with intermittent claudication were assessed by Jansen et al. [8] in a Cochrane Review. 10 studies that randomised a total of 527 participants with IC were included. The studies compared supervised walking programmes against exercises to strengthen the leg muscles, Nordic walking, cycling, arm ergometry (pedalling with the arms on an exercise machine), and a combination of different types of exercise. According to GRADE criteria, the certainty of the evidence was downgraded to low, due to the relatively small sample sizes, clinical inconsistency, and inclusion of three studies with risk of bias concerns. This review found no clear difference between alternative exercise modes and supervised walking exercise in improving the maximum and pain-free walking distance in patients with intermittent claudication.

Supervised exercise programs (SEP) are effective for improving walking distance in patients with IC, but provision and uptake rates are suboptimal. The aim of a review by Pymer et al. [9] was to provide a comprehensive overview of the evidence for home-based exercise programs (HEP). 23 studies with 1907 participants were included. HEPs were inferior to SEPs which was reflected in the meta-analysis. Monitoring was an important component, because HEPs adopting this strategy were equivalent to SEPs. For HEPs vs. basic exercise advice, narrative review suggested HEPs can be superior, although not always significantly so. Other elements such as

appropriate frequency (≥3× a week), intensity (to moderate-maximum pain), duration (20 progressing to 60 min) and type (walking) of exercise were important, as was education, self-regulation, goal setting, feedback, and action planning. Remote and self-monitoring should be done via pedometers, step activity monitoring or techniques that include these components (e.g. smartphones). Monitor information should be recorded, either by the patient in an exercise diary or remotely, with regular feedback to the patient.

11.2.1.2 Exercise Therapy and Endovascular Revascularization

The aim of a meta-analysis presented by Shirasu et al. [10] was to analyze the risk of progression to chronic limb-threatening ischemia (CLTI), amputation and subsequent interventions after revascularization versus noninvasive therapy in patients with intermittent claudication (IC). A total of 9 RCTs comprising 1477 patients (invasive, 765 patients; noninvasive, 712 patients) were eligible. During a mean of 3.6-year follow-up, progression to CLTI after invasive and noninvasive treatment were not statistically different Incidence of amputation (RR: 1.69; 95% CI, 0.54–5.26; P = 0.36, I2 = 0%) and all-cause mortality (hazard ratio: 1.26; 95% CI, 0.91–1.74; P = 0.16, I2 = 0%) also did not differ between the groups. However, the invasive treatment group underwent significantly more revascularizations (RR: 4.15; 95% CI, 2.80–6.16; P < 0.00001, I2 = 83%). This meta-analysis of RCTs for treatment of IC found that progression to CLTI, risk of major amputation, and all-cause mortality were not affected by the choice of invasive versus noninvasive initial treatment strategy. The study supports the current guideline recommendation that noninvasive, exercise-based treatment in addition to best medical therapy should be first-line treatment for IC.

Thanigaimani et al. [11] conducted a network meta-analysis of randomized trials comparing the relative efficacy of cilostazol, home exercise therapy, supervised exercise therapy (SET), endovascular revascularization (ER) and ER + SET in improving maximal walking distance over short (< 1 year), moderate (1 to <2 years) or long-term (> 2 years) follow-up in people with IC. 46 trials involving 4256 patients were included. At short-term follow-up, home exercise therapy, SET, and ER + SET, but not ER and cilostazol significantly improved maximum walking distance (MWD) (in meters) compared with controls. At moderate-term follow-up, SET and ER + SET, but not home exercise therapy or ER, significantly improved MWD compared to controls. At long-term follow-up, none of the tested treatments significantly improved MWD compared to controls. This network meta-analysis suggested that SET and ER + SET are effective at improving MWD over the moderate term (<2 year) but not beyond this. More durable therapies are needed for intermittent claudication.

The ERASE trial is the largest randomized trial assessing the long-term effectiveness of endovascular revascularization plus SET (n = 106) or SET alone (n = 106) in patients with IC [12]. Median long-term follow-up was 5.4 years.

Whereas the difference in maximum walking distance significantly favored combination therapy at 1-year follow-up, the difference at 5-year follow-up was no longer significant. No difference in pain-free walking distance, ankle-brachial index, and quality of life was found during long-term follow-up. Supervised exercise was associated with an increased hazard of a revascularization procedure during follow-up. Combination therapy resulted in a lower number of revascularization procedures during follow-up but a higher total number of revascularizations including the randomized treatment. In the treatment of patients with intermittent claudication, there is an advantage of combination therapy compared with supervised exercise only during the first year. These results do not support a sustained advantage at 5-year follow-up (Table 11.1).

The randomized SUPER trial compared the effectiveness of SET vs. endovascular revascularization (ER) in patients with IC caused by iliac artery obstruction [13]. 114 patients were allocated to SET, and 126 to ER. The trial was terminated prematurely after 240 patients were included. Compliance with SET was 57/114 (50%) after 6 months. Ten patients allocated to ER (8%) did not receive this intervention. One year follow up was complete for 90/114 (79%) SET patients and for 104/126 (83%) ER patients. The mean MWD improved from 187 to 561 m in SET patients and from 196 to 574 m in ER patients (p = .69). VascuQol sumscore improved from 4.24 to 5.58 in SET patients, and from 4.28 to 5.88 in ER patients (p = .048). After a mean of 5.5 years, 49% of SET patients and 27% of ER patients underwent an additional intervention for IC. This multicentre RCT found no statistically

Table 11.1 Endovascular revascularization plus supervised exercise compared with supervised exercise only for intermittent claudication. Results of the randomized ERASE trial (according to Klaphake et al. [12])

Functional performance measures	Supervised exercise only (n = 106)	Combination therapy (n = 106)	P
Maximum walking distance (meters)			
– Baseline	285 (244–326)	246 (228–300)	
– 12 months	955 (786–1124)	1237 (1058–1418)	0.001
– 5 years	981 (764–1199)	1034 (825–1244)	0.620
Pain-free walking distance (meters)			
– Baseline	135 (113–157)	117 (96–138)	
– 12 months	712 (549–876)	1120 (948–1293)	< 0.001
– 5 years	865 (657–1074)	976 (773–1178)	0.281
Ankle-brachial index at rest			
– Baseline	0.68 (0.64–0.72)	0.71 (0.67–0.76)	
– 12 months[a]	0.03 (−0.02–0.08)	0.16 (0.11–0.21)	< 0.001
– 5 years[a]	0.08 (−0.15–0.06)	0.13 (0.07–0.19)	0.149

[a]Data are expressed as mean improvement compared with baseline

significant differences in maximum walking distance after 1 year follow up, and a small difference in quality of life in favour of ER, which supports current guidelines to start with SET in patients with mild IC, including when the obstruction is in the iliac arteries. These investigators also compared the cost effectiveness of endovascular revascularization and supervised exercise therapy as primary treatment for patients with intermittent claudication due to iliac artery obstruction in the SUPER study [14]. This cost effectiveness analysis showed that ER as a primary treatment results in slightly better health outcome and higher QALYs and HRQOL during 12 months of follow up. Although these differences are statistically significant, clinical relevance must be discussed due to the small differences and relatively high cost of ER as primary treatment. The results of this analysis also support the recommendations to start with SET in patients with IC, if caused by an iliac artery obstruction.

In another trial from Sweden, 100 patients with IC due to lesions in the superficial femoral artery (SFA) were randomized to treatment with primary stenting, best medical treatment (BMT) and exercise advice (stent group), or to BMT and exercise advice alone (control group) [15]. The mean cost per patient was €11,060 in the stent group and €4787 in the control group, resulting in a difference of €6273 per patient between the groups. The difference in mean QALYs between the groups was 0.26, in favour of the stent group, which resulted in an incremental cost effectiveness ratio (ICER) of € 23,785 per QALY. After 2 years of follow up, primary stenting as an adjunct to exercise training advice was a cost-effective treatment option, according to Swedish national guidelines, and approaching the National Institute of Health and Care Excellence's threshold for willingness to pay. From a cost effectiveness standpoint, primary stenting of the SFA can, in many countries, be used as an adjunct to exercise training advice. However, longer follow up may alter these findings. In another trial, after 5 years of follow-up, a revascularization strategy had lost its early benefit and did not result in any long-term improvement in health-related quality of life or walking capacity compared to a noninvasive treatment strategy [16]. In this IRONIC trial (Invasive Revascularization or Not in Intermittent Claudication) altogether 158 patients with mild-to-severe intermittent claudication were randomized to either revascularization + best medical therapy + structured exercise therapy (the revascularization group) or best medical therapy + structured exercise therapy alone (the nonrevascularization group). No intergroup differences were observed in the vascular quality of life questionnaire total and domain scores or in treadmill walking distances. A revascularization strategy resulted in almost twice the cost per patient compared with a noninvasive treatment approach ($13,098 versus $6965, P = 0.02) and was not a cost-effective treatment option from a payer/healthcare point of view.

11.2.1.3 Medical Therapy for Intermittent Claudication

Brown et al. [17] examined the evidence to see if cilostazol improved walking distance, quality of life and other important outcomes compared to placebo (dummy pill) or other drugs used for intermittent claudication in a Cochrane Review. 16

double-blind, RCTs (3972 participants) comparing cilostazol with placebo, of which five studies also compared cilostazol with pentoxifylline were included. Treatment duration ranged from 6 to 26 weeks. Cilostazol dose ranged from 100 mg to 300 mg; pentoxifylline dose ranged from 800 mg to 1200 mg. Cilostazol has been shown to improve walking distance in patients with IC. However, participants taking cilostazol had higher odds of experiencing headache. There was insufficient evidence about the effectiveness of cilostazol for serious events such as amputation, revascularization, and cardiovascular events. Despite the importance of QoL to patients, meta-analysis could not be undertaken because of differences in measures used and reporting. Very limited data indicated no difference between cilostazol and pentoxifylline for improving walking distance and data were too limited for any conclusions on other outcomes.

A Cochrane review based on 24 studies (3377 participants) is available on the efficacy of pentoxifylline in improving the walking capacity (i.e., pain-free walking distance and total (absolute, maximum) walking distance) of people with stable intermittent claudication, Fontaine stage II [18]. Seventeen studies compared pentoxifylline versus placebo. The seven remaining studies compared pentoxifylline with flunarizine (one study), aspirin (one study), Gingko biloba extract (one study), nylidrin hydrochloride (one study), prostaglandin E1 (two studies), and buflomedil and nifedipine (one study). There is a lack of high-certainty evidence for the effects of pentoxifylline compared to placebo, or other treatments, for IC. There is low-certainty evidence that pentoxifylline may improve pain-free walking distance (PFWD) and total walking distance (TWD) compared to placebo, but no evidence of a benefit to ABI or QoL (moderate-certainty evidence). Pentoxifylline was reported to be generally well tolerated (low-certainty evidence). Given the large degree of heterogeneity between the studies, the role of pentoxifylline for people with IC Fontaine class II remains uncertain.

In a Cochrane review, Kamoen et al. [19] determined whether propionyl-L-carnitine (PLC) is efficacious compared with placebo, other drugs, or other interventions used for treatment of intermittent claudication, Fontaine stage II. 12 studies were included in this review with a total number of 1423 randomized participants. A majority of the included studies assessed PLC versus placebo (11 studies, 1395 participants), and one study assessed PLC versus L-carnitine (1 study, 26 participants). Participants received PLC 1 g to 2 g orally (9 studies) or intravenously (3 studies) per day or placebo. When PLC was compared with placebo, improvement in walking distance was mild to moderate and safety profiles were similar, with moderate overall certainty of evidence. Although in clinical practice, PLC might be considered as an alternative or an adjuvant to standard treatment when such therapies are found to be contraindicated or ineffective, no RCT evidence comparing PLC with standard treatment was found to directly support such use.

11.2.1.4 Rivaroxaban and Aspirin in Patients Undergoing Surgical Revascularization

Bauersachs et al. [20] evaluated the total burden of vascular events in patients with PAD after lower extremity revascularization (LER) and the efficacy of low-dose rivaroxaban on total events in the VOYAGER PAD trial (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD). Patients undergoing surgical or endovascular LER received either 2.5 mg rivaroxaban twice daily plus aspirin 100 mg daily or aspirin alone. Among 6564 randomized events, there were 4714 total first and subsequent vascular events including 1614 primary endpoint events and 3100 other vascular events. Rivaroxaban reduced total primary endpoint events (HR: 0.86; 95% CI: 0.75–0.98; P = 0.02) and total vascular events (HR: 0.86; 95% CI: 0.79–0.95; P = 0.003). An estimated 4.4 primary and 12.5 vascular events per 100 participants were avoided with rivaroxaban over 3 years.

The effect of rivaroxaban and aspirin in patients with PAD undergoing surgical revascularization in the VOYAGER PAD trial was reported by Debus et al. [21]. A total of 6564 patients underwent randomization. Of these, 2185 patients (33%) underwent surgical LER, and 4379 (67%) were treated with an endovascular or hybrid procedure. Patients were randomized after LER for symptomatic PAD to rivaroxaban 2.5 mg twice daily or matching placebo on top of background antiplatelet therapy (aspirin to be used in all and clopidogrel at the treating physician's discretion), and patients were followed for a median of 28 months. After surgical LER, the primary efficacy outcome occurred in 199 (18.4%) patients in the rivaroxaban group and 242 (22.0%) patients in the placebo group with a cumulative incidence at 3 years of 19.7% and 23.9%, respectively (hazard ratio, 0.81 [95% CI, 0.67–0.98]; P = 0.026. After surgical LER, the principal safety outcome occurred in 11 (1.0%) patients in the rivaroxaban group and 13 (1.2%) patients in the placebo group; 3-year cumulative incidence was 1.3% and 1.4%, respectively (hazard ratio, 0.88 [95% CI, 0.39–1.95]; P = 0.75). Among surgical patients, the composite of fatal bleeding or intracranial hemorrhage (P = 0.95) and postprocedural bleeding requiring intervention (P = 0.93) was not significantly increased. In conclusion, in symptomatic PAD after LER, nearly 1 in 5 patients will develop cardiovascular or limb ischemic events at 3 years—a risk that is even higher (1 in 4) after surgical LER. The addition of rivaroxaban 2.5 mg twice daily to aspirin in patients with symptomatic PAD undergoing surgical LER reduced cardiac and limb risk, with robust benefits apparent early and consistent over time.

11.2.2 Studies/Registries

11.2.2.1 Exercise First Approach and Peripheral Vascular Intervention

A nationwide retrospective data analysis of health insurance claims of patients newly diagnosed with IC between January 2013 and December 2017 was presented by Jansen et al. [22]. The 5-year cohort included 54.504 patients with IC (primary SET n = 39.476, primary ER n = 11. 769, and primary open surgery n = 3.259). SET as primary treatment increased from 63% in 2013 to 87% in 2017. Patients who underwent ER or open surgery as a primary treatment had a higher risk of secondary revascularizations and a higher mortality risk compared with SET as a primary treatment. This study demonstrates that guideline adherence improved to 87% in Dutch patients with IC, probably as a result of optimized organization of SET and greater awareness among healthcare providers. Revascularization after primary SET was only necessary in 17% after 5 year follow up. These results support the feasibility of a SET first strategy in real world settings. Efforts should be made to make exercise accessible to all patients with peripheral artery disease. Additionally, a new focus for improvement was identified. As a disappointingly low 10% received SET in the first year following primary revascularization, although considered standard care according to the recommendations, future endeavours should be directed towards increasing this rate of participation.

Hicks et al. [23] examined physician practice patterns of early peripheral vascular interventions (PVI) performed within 6 months of a new diagnosis of claudication using 100% Medicare fee-for service claims. Of 194,974 patients who had a first-time diagnosis of claudication during the study period, 6286 (3.2%) underwent early PVI. Among the 5664 physicians included in the analysis, the median physician-level early PVI rate was low at 0% (range, 0%–58.3%). However, there were 320 physicians (5.6%) who had an early PVI rate $\geq$ 14%. Physicians with higher intervention rates performed a greater percentage of their interventions in an ambulatory center or office-based laboratory compared with a hospital setting. The association between higher early PVI rate and high volume ambulatory surgery center or office based laboratory services supports the concern that some procedures for claudication may be overused for financial gain. This study suggests that practice patterns in large data can identify outlier physicians with high utilization of early peripheral vascular intervention for patients newly diagnosed with claudication.

11.2.2.2 Endovascular Interventions

Bath et al. [24] examined the outcomes of endovascular management of IC reported in the Vascular Quality Initiative and compared them with the Society for Vascular Surgery guidelines for IC treatment to determine whether real-world results are within the guidelines. A total of 16,152 patients were included in the study, and 28% had been discharged without antiplatelet or statin medication. Treatment of more

than two arteries was associated with a shorter time to IC recurrence and a shorter time to repeat procedures. The use of atherectomy was also associated with a shorter time to IC recurrence and a shorter time to repeat procedures. Discharge with antiplatelet and statin medications was associated with a longer time to IC recurrence time to repeat procedures. Life-table analysis at 2 years revealed that only 32% of patients were free from IC recurrence, although 76% had not undergone repeat procedures. Stratified by anatomic treatment level, 37% of isolated aortoiliac interventions, 22% of aortoiliac and femoropopliteal interventions, 30% of isolated femoropopliteal interventions, and 20% of femoropopliteal and tibial interventions had remained free from IC recurrence at 2 years. In conclusion, most patients treated with an endovascular approach to IC did not meet the Society for Vascular Surgery guidelines for long-term freedom from recurrent symptoms of >50% at 2 years. Many lacked preprocedure optimization of medical management. The use of atherectomy and treatment of more than two arteries were associated with poor outcomes after peripheral vascular intervention for IC, because only 32% of these patients were free from recurrent symptoms at 2 years.

Siracuse et al. [25] characterized IC treatment patterns in the commercially insured non-Medicare population. There were 300,590 patients newly diagnosed with IC. The prevalence of statin use was 48% among patients at the time of IC diagnosis and increased to 52% among patients after 1 year from diagnosis. Interventions were performed in 14.3%, of whom 20% and 6% underwent two or more and three or more interventions, respectively. The median time from diagnosis to intervention decreased from 230 days in 2008 to 49 days in 2016. There were 16,406 inpatient and 102,925 ambulatory interventions for IC over the study period. Among ambulatory interventions, 7.9% were performed in office-based/surgical centers. The proportion of atherectomies performed in the ambulatory setting increased from 9.7% in 2007 to 29% in 2016. In office-based/surgical centers, 57.6% of interventions for IC used atherectomy in 2016. Inpatient atherectomy rates remained stable over the study period. Open and endovascular tibial interventions were performed in 7.9% and 7.8% of ambulatory and inpatient IC interventions, respectively. Tibial bypasses were performed in 8.2% of all open IC interventions. The use of atherectomy has dramatically increased, despite limited supporting evidence. This point is particularly true in the outpatient setting, including office-based/surgical centers. The trend is thought to be due to higher relative value units for the procedure as well as disproportionately higher reimbursement in office-based laboratories and ambulatory surgical centers which incentivize its use. Procedures of unclear clinical benefit in patients with IC were performed in both inpatient and ambulatory settings, and statin use remained low.

11.2.2.3 Smoking and Postprocedural Complications

Reitz et al. [26] assessed if preprocedural smoking is associated with an increased risk of early postprocedural complications following elective open and endovascular revascularization. The study used nearest-neighbor (1:1) propensity score

matching of 2011 to 2019 data from the Veterans Affairs Surgical Quality Improvement Program. Of 14,350 included cases of revascularization with a primary diagnosis of IC, a total of 7820 patients (54.5%) were smoking within the preprocedural year. There were a total of 4417 endovascular revascularizations (30.8%), 4319 hybrid revascularizations (30.1%), and 5614 open revascularizations (39.1%). A total of 1594 patients (11.1%) had complications, and 57 (0.4%) died. Compared with nonsmokers, any complication was higher for smokers following endovascular revascularization, hybrid revascularization, and open revascularization. In a sensitivity analysis, compared with active smokers (n = 5173; smoking within 2 weeks before the procedure), the risk of any complication was decreased by 65% for never smokers (n = 1197; adjusted odds ratio, 0.45; 95% CI, 0.34–0.59) and 29% for former smokers (n = 4755; cessation more than 1 year before the procedure; adjusted odds ratio, 0.71; 95% CI, 0.61–0.83; P = .001 for interaction). In this cohort study, following elective open and endovascular revascularization for IC, smoking was associated with an increased risk of any and respiratory-specific early postprocedural complications. The data highlight the persistently and unacceptably high rate of smoking in patients with IC and strongly suggest patients should receive comprehensive smoking cessation counseling prior to revascularization (including endovascular modalities).

11.2.3 Drug-Coated Devices

Sridharan et al. [27] conducted a systematic literature search for randomized clinical trials reporting primary patency (PP) or target lesion revascularization (TLR) for drug-eluting stent (DES), or dug-coated balloon (DCB, compared with any alternative therapy in the superficial femoral artery (SFA) or popliteal artery. Meta-analysis was performed first. Second, results from these studies were pooled and aggregated with additional literature-based parameter estimates to create a decision model to simulate cost-effectiveness of index therapy options (plain old balloon angioplasty [POBA], bare-metal stent [BMS], DCB, or DES) for SFA-popliteal disease. Effectiveness was defined as patency. Eight studies (1352 patients) met inclusion criteria for meta-analysis. DCB outperformed POBA with respect to target lesion revascularization over time (pooled hazard ratio, 0.41; P < .001). Risk of major amputation at 12 months was not significantly different between groups. There was significantly improved 1-year PP in the DCB group compared with POBA (pooled odds ratio, 3.30; P < .001). In the decision model, the highest PP at 1 year was seen in the DES index therapy strategy (79%), followed by DCB (74%), BMS (71%), and POBA (64%). The primary BMS option is dominated by being more expensive and less effective than DCB. Based on the projected PP at 1 year in the decision model, the number needed to treat for DES compared with DCB is 20. At current reimbursement, the use of more than two DCBs per procedure would no longer be cost-effective compared with DES. At 2 years, DCB emerges as the most cost-effective index strategy with the lowest overall cost and highest patency rates over

that time horizon. Current data and reimbursements support the use of DCB as a cost-effective strategy for endovascular intervention in the SFA; any additional effectiveness of DES comes at a high price.

A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed by Katsanos et al. [28]. The primary safety measure was all-cause patient death. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; −number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; −number-needed-to-harm, 14 patients [95% CI, 9–32]). In conclusion, there was an increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs.

This statement gave rise to various publications.

Nordanstig et al. [29] conducted an unplanned interim analysis of the data from a multicenter, randomized, open-label, registry-based clinical trial (SWEDEPAD). The trial includes two cohorts of patients who undergo randomization separately: patients with chronic limb-threatening ischemia and patients with intermittent claudication. At the time of the analysis, 2289 patients had been randomly assigned to treatment with drug-coated devices (the drug-coated-device group, 1149 patients) or treatment with uncoated devices (the uncoated-device group, 1140 patients). At 1 year, all-cause mortality was 10.2% (117 patients) in the drug-coated-device group and 9.9% (113 patients) in the uncoated-device group. During the entire follow-up period, there was no significant difference in the incidence of death between the treatment groups among patients with chronic limb-threatening ischemia (33.4% [249 patients] in the drug-coated-device group and 33.1% [243 patients] in the uncoated-device group) or among those with intermittent claudication (10.9% [44 patients] and 9.4% [38 patients], respectively). In this randomized trial in which patients with peripheral artery disease received treatment with paclitaxel-coated or uncoated endovascular devices, the results did not show a difference between the groups in the incidence of death during 1 to 4 years of follow-up.

SAFE-PAD (Safety Assessment of Femoropopliteal Endovascular Treatment With Paclitaxel-Coated Devices) was a retrospective cohort study designed with the US Food and Drug Administration to evaluate the noninferiority of mortality between DCDs and non–drug-coated devices (NDCDs) for femoropopliteal revascularization performed in 2978 inpatient and outpatient facilities in the US from April 1, 2015, through December 31, 2018 [30]. Of 168,553 patients, 70,584 (41.9%) were treated with a DCD. Median follow-up was 2.72 years (interquartile range, 0.87–3.77; longest, 5.16 years). After weighting, the cumulative incidence of all-cause mortality was 53.8% with DCDs and 55.1% with NDCDs (hazard ratio [HR], 0.95; 95% CI, 0.94–0.97; noninferiority $P < .001$). No harm associated with

DCDs was observed among subgroups, including those treated with stents (HR, 0.97; 95% CI, 0.95–1.00) or balloons (HR, 0.94; 95% CI, 0.92–0.96), with or without CLI (CLI: HR, 0.95; 95% CI, 0.93–0.97; non-CLI: HR, 0.97; 95% CI, 0.95–0.99), and those within the lowest quartile of total comorbidities (HR, 0.95; 95% CI, 0.92–0.99). In this initial report from the SAFE-PAD cohort study, DCDs were found to be noninferior to NCDCs in respect to mortality through a median follow-up of 2.72 years. SAFE-PAD will continue until the median follow-up of all patients surpasses 5 years and will provide the FDA a mechanism for the ongoing safety evaluation of these devices.

Bertges et al. [31] compared 1-year mortality after treatment of superficial femoral-popliteal artery disease with paclitaxel and nonpaclitaxel devices. Patients (N = 8376) in the Society for Vascular Surgery Vascular Quality Initiative were studied. In propensity-matched analyses, mortality was similar after plain balloon angioplasty (12.6%) and paclitaxel-coated balloon angioplasty (9.6%; HR = 0.84 [95% CI, 0.66–1.06], P = 0.14). In propensity-matched groups, mortality was similar after bare-metal stenting (9.8%) and paclitaxel-eluting stenting (8.8%; HR = 0.93 [95% CI, 0.62–1.41], P = 0.75). In the combined, matched analysis mortality was significantly lower in the paclitaxel device group (8.5%) compared with the nonpaclitaxel device group (11.5%; HR = 0.82 [95% CI, 0.68–0.98], P = 0.03). Secondary interventions were similar after nonpaclitaxel (N = 1113/4149, 26.8%) and paclitaxel device use (N = 1113/4227, 26.3%). For intermittent claudication, mortality was lower after paclitaxel device use (1.6%) compared with nonpaclitaxel devices (4.4%; adjusted HR = 0.59 [95% CI, 0.39–0.89], P = 0.01). For chronic limb-threatening ischemia, the mortality difference was not significant; paclitaxel (12.8%) versus nonpaclitaxel devices (15.5%; adjusted HR = 0.85 [95% CI, 0.72–1.00], P = 0.05). At 1 year, mortality was similar if not lower after treatment of femoral-popliteal occlusive disease with paclitaxel versus nonpaclitaxel devices.

A retrospective health insurance claims analysis was presented by Behrendt et al. [32] to determine the survival of patients after use of paclitaxel coated devices (PCX). Index femoropopliteal arterial interventions between 1 January 2010 and 31 December 2018 were identified. The study cohort was stratified into patients with chronic limb threatening ischaemia (CLTI) and intermittent claudication (IC), then into balloons vs. stents cohorts. There were 37,914 patients (mean age 73.3 years; 48.8% female) included in the study. The annual proportion of PCX use increased from 3% to 39% during the study period for CLTI and from 4% to 48% for IC (both $p < .001$). Paclitaxel coated balloons and stents were associated with improved overall survival (hazard ratio [HR] 0.83), amputation free survival (HR 0.85), and freedom from major cardiovascular events (HR 0.82) vs. uncoated devices at 5 years for CLTI. In IC cohort, mortality was significantly lower after using drug coated balloons (DCB) (HR 0.87) or combined DCB and drug eluting stents (HR 0.88). In this large health insurance claims analysis, rapid adoption of PCX, higher long-term survival, better amputation free survival, and lower rates of major cardiovascular events were seen after their use for the treatment of CLTI.

Data from the Veterans Health Administration were used by Gutierrez et al. [33] to evaluate the association between paclitaxel-coated devices (PCDs; drug-coated

balloon or drug-eluting stent), long-term mortality, and cause of death in patients with peripheral endovascular intervention (PVI). 10,505 patients underwent femoropopliteal peripheral endovascular intervention: 2265 (21.6%) with a PCD and 8240 (78.4%) with a non-PCD. Following femoropopliteal PVI, the median follow-up for the remaining living patients (n = 8503) was 20.3 months (interquartile range, 10.0–31.8 months). Survival rates at 2 years (77.4% versus 79.7%) and 3 years (70.7% versus 71.8%) were similar between the PCD and non-PCD groups, respectively. Patients presenting with CLI had lower survival rates at any given time point compared with patients presenting for claudication. The hazard ratio (HR) for all-cause mortality for patients treated with a PCD versus a non-PCD was 1.05 (95% CI, 0.94–1.16; P = 0.4045). After adjustment with inverse probability–weighted estimates, the hazard for all-cause mortality remained similar (HR, 1.06; 95% CI, 0.95–1.18; P = 0.3013). Among patients undergoing femoropopliteal peripheral endovascular intervention within the Veterans Administration Health Administration, there was no increased risk of long-term, all-cause mortality associated with PCD use. Cause-specific mortality rates were similar between treatment groups.

In the VOYAGER PAD trial, among 4316 patients who underwent LER, 3478 (80.6%) were treated for claudication, and 1342 (31.1%) received DCDs [34]. Median follow-up was 31 months, vital status was ascertained in 99.6% of patients, and there were 394 deaths. After weighting, DCDs were not associated with mortality (HR: 0.95; 95% CI: 0.83–1.09) or MALE (HR: 1.08; 95% CI: 0.90–1.30) but were associated with reduced unplanned index limb revascularization (3-year Kaplan-Meier: 21.5% vs. 24.6%; HR: 0.84; 95% CI:0.76–0.92).

Katsanos et al. [35] performed an updated systematic review and meta-analysis of RCTs to investigate the risk of major amputation associated using paclitaxel coated balloons in the lower limbs. In all, 21 RCTs with 3760 lower limbs were analysed (52% intermittent claudication and 48% CLI; median follow up 2 years). There were 87 major amputations of 2216 limbs in the paclitaxel arms (4.0% crude risk) compared with 41 major amputations in 1544 limbs in the control arms (2.7% crude risk). The risk of major amputation was significantly higher for paclitaxel coated balloons with a hazard ratio (HR) of 1.66 (95% CI 1.14–2.42; p = .008). The observed amputation risk was consistent for both femoropopliteal (p = .055) and infrapopliteal (p = .055) vessels. Number needed to harm was 35 for CLI. There was good evidence of a significant non-linear dose response relationship with accelerated risk per cumulative paclitaxel dose (p = .007). There was no evidence of publication bias (p = .80) and no significant statistical heterogeneity between studies ($I^2 = 0\%$, p = .77). There appears to be heightened risk of major amputation after use of paclitaxel coated balloons in the peripheral arteries. Downstream embolisation of cytotoxic paclitaxel particulate material would be the most likely explanation.

11.2.4 Special Issue

11.2.4.1 High-Pressure Intermittent Limb Compression

Oresanya et al. [36] conducted a systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of high-pressure intermittent limb compression (HPILC) in improving walking distance in patients with IC. Eight studies eligible for inclusion were identified. These studies had a combined total of 290 subjects, 172 of whom were randomized to HPILC. All studies identified an increase in walking distance for subjects receiving compression therapy. Several devices have been developed that perform HPILC. The most common devices are similar to the appliances used for the prevention of deep venous thrombosis but work at higher pressures. These devices rapidly and sequentially apply pressures of >100 mmHg to the calf, foot, or both. On meta-analysis, the mean difference of absolute claudication distance from baseline to follow-up among subjects receiving compression compared with controls was 125 m ($P < .01$). However, further studies are needed to better guide the use of HPILC in the treatment of claudication.

11.3 Conclusions for Clinical Practice

1. For patients with IC, modification of risk factors and secondary prevention of cardiovascular disease are the most important treatment options.
2. In a step-by-step concept, in patients with claudication a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms. When daily life activities are compromised despite exercise therapy, revascularization should be considered.
3. Endovascular procedures over open surgery are recommended for focal occlusive disease of the SFA (superficial femoral artery) not involving the origin at the femoral bifurcation.
4. In the common femoral segment, open common femoral endarterectomy will provide greater net benefit than endovascular intervention for the treatment of IC.
5. In the infrapopliteal segment, invasive intervention for the treatment of IC is of unclear benefit and may be harmful.
6. The higher risk of mortality and major amputation found in meta-analyses when using drug coated balloons and stents has not yet been confirmed so far in registry-based clinical studies.

11.4 Perioperative Management

11.4.1 Antithrombotic Therapy

11.4.1.1 Guidelines

The ESC/ESVS guidelines [1] recommend:

- Long-term SAPT (single antiplatelet therapy) is recommended in symptomatic patients. (Class I recommendation/Level of evidence A).
- Long-term SAPT is recommended in all patients who have undergone revascularization. (Class I recommendation/Level of evidence C).
- SAPT is recommended after infra-inguinal bypass surgery. (Class I recommendation/Level of evidence A).
- In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin. (Class IIb recommendation/Level of evidence B).
- Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass. (Class IIb recommendation/Level of evidence B).
- DAPT (Dual antiplatelet therapy) with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation. (Class IIa recommendation/Level of evidence C).
- DAPT with aspirin and clopidogrel may be considered in below-the-knee bypass with a prosthetic graft. (Class IIb recommendation/Level of evidence B).

11.4.1.2 Antithrombotic Therapy for PADs Patients Requiring Oral Anticoagulant

In patients with PADs and atrial fibrillation (AF), oral anticoagulation (OAC):

- is recommended when the CHA_2DS_2–VASc score is ≥2. (Class I recommendation/Level of evidence A),
- should be considered in all other patients. (Class IIa recommendation/Level of evidence B).
- [Note: the CHA_2DS_2–VASc score is calculated as follows: **C**ongestive heart failure history (1 point), **H**ypertension (1 point), **A**ge ≥ 75 years (2 points), **D**iabetes mellitus (1 point), **S**troke or TIA or arterial thromboembolic history (1 point), **V**ascular disease history (1 point), **A**ge 65–74 years (1 point), **S**ex category (1 point if female)].
- In patients with PADs who have an indication for OAC (e.g. AF or mechanical prosthetic valve), oral anticoagulants alone should be considered. (Class IIa recommendation/Level of evidence B).
- After endovascular revascularization, aspirin or clopidogrel should be considered in addition to OAC for at least 1 month if the bleeding risk is low compared

with the risk of stent/graft occlusion. (Class IIa recommendation/Level of evidence C).

- After endovascular revascularization, OAC alone should be considered if the bleeding risk is high compared with the risk of stent/graft occlusion. (Class IIa recommendation/Level of evidence C).
- OAC and SAPT may be considered beyond 1 month in high ischaemic risk patients or when there is another firm indication for long-term SAPT. (Class IIb recommendation/Level of evidence C).

11.4.1.3 Reviews

A Cochrane review evaluated whether antithrombotic treatment improves graft patency, limb salvage and survival in patients with chronic PAD undergoing infrainguinal bypass surgery [37]. A total of 14 trials were included in this review; 4970 patient results were analysed. Patients undergoing infrainguinal venous graft were more likely to benefit from treatment with VKA than platelet inhibitors. Patients receiving an artificial graft benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive. Randomised controlled trials with larger patient numbers are needed in the future to compare antithrombotic therapies with either placebo or antiplatelet therapies.

In a second Cochrane review, Bedenis et al. [38] determined the effects of antiplatelet agents for the prevention of thrombosis in people with lower limb atherosclerosis who were undergoing femoropopliteal or femorodistal bypass grafting. 16 studies with 5683 randomized participants were included. Antiplatelet therapy with aspirin or with aspirin plus dipyridamole had a beneficial effect on primary patency of peripheral bypass grafts compared to placebo or no treatment. This effect was not evident when evaluating venous grafts alone, but antiplatelet therapy did have a beneficial effect on patency in those who had prosthetic grafts.

11.4.1.4 Studies

In the VOYAGER PAD study, a double-blind trial, patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin [39]. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. A total of 6564 patients underwent randomization; 3286 were assigned to the rivaroxaban group, and 3278 were assigned to the placebo group. The primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan–Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P = 0.009).

Liang et al. [40] identified in the VQI database 7612 infrainguinal bypass grafts with intact 1-year follow-up information from 2003 to 2015. The majority of patients (71%) did not receive postoperative anticoagulation (AC). Warfarin was used as anticoagulant in 99.0%. Propensity-weighted analysis showed no significant association of AC with primary patency in the overall cohort (P = .8) but demonstrated a trend toward improvement of primary patency in those with a non-single-segment vein conduit to a below-knee popliteal target (P = 0.09). AC was associated with significantly improved secondary patency in those with prosthetic bypass grafts (P = .02) or prosthetic bypasses to an infrapopliteal target (P = .02). This study did not demonstrate a significant impact of therapeutic AC on primary patency for infrainguinal bypass grafts. Treatment with AC may benefit secondary patency in those with a prosthetic bypass, especially to an infrapopliteal target, but at an increased risk of postoperative wound complications.

Postoperative treatment and outcomes of patients undergoing peripheral bypass operations between January 2012 and December 2017 from a statewide multicenter quality improvement registry were examined by Obi et al. [41]. Among 9682 patients, 7685 patients received no anticoagulation, whereas 1379 received a vitamin K antagonist (VKA) and 618 received a direct oral anticoagulant (DOAC) postoperatively. Compared with patients receiving VKAs postoperatively, there was no difference in readmission for anticoagulation complications, bypass thrombectomy or thrombolysis, major amputation, or graft patency at 1 year among patients receiving DOACs. On multivariate logistic regression, patients receiving a DOAC (odds ratio, 0.743; P = .011) or no anticoagulation (odds ratio, 0.792; P = .001) were less likely to require transfusion within 30 days than patients taking VKAs. Approximately 70% of the surveyed surgeons reported that they “sometimes” or “always” use DOACs instead of VKAs for protection of a high-risk bypass.

In the 2003 to 2018 VQI database, Belkin et al. [42] identified 13,020 patients with infrainguinal lower extremity bypass operations. 52.2% were discharged on aspirin monotherapy and 47% on dual antiplatelet therapy (DAPT). The proportion of patients discharged on DAPT increased significantly over the years, from 10.6% in 2003 to 60.6% in 2018 (P < .001). The DAPT cohort was younger, had higher rates of medical and atherosclerotic comorbidities, and had higher risk bypass procedures (more distal targets, prior inflow bypass procedure, prosthetic conduit use). After controlling for these differences, DAPT therapy had no beneficial effect on overall bypass graft patency or major adverse limb events. However, on subgroup analysis, DAPT was associated with improved bypass graft patency in patients receiving prosthetic bypass conduits. The authors proposed an individualized approach because patients with low bleeding risk and active cardiovascular disease may benefit from DAPT to provide a reduction in overall cardiovascular complications and improved prosthetic bypass graft patency.

11.4.2 Statin Therapy

11.4.2.1 Guidelines

The European Society of Cardiology (ESC) and European Society for Vascular Surgery (ESVS) guidelines recommend [1]:

- In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by ≥50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). (Class I recommendation/Level of evidence C).

11.4.2.2 Studies

Suckow et al. [43] studied 2067 patients (67% with CLI) who underwent infrainguinal bypass from 2003 to 2011. Of these, 1537 (74%) were on statins perioperatively and at 1-year follow-up, and 530 received no statin. By application of the stratified propensity-score method, they matched 431 patients in the statin group with 431 patients who were never on a statin. Despite higher comorbidity burdens, long-term survival was better for patients taking statins in crude (risk ratio [RR], 0.7; P < .001), adjusted (hazard ratio, 0.7; P = .001), and propensity-matched analyses (hazard ratio, 0.7; P = .03). In subgroup analysis, a survival advantage was evident in patients on statins with CLI (5-year survival rate, 63% vs. 54%; log-rank, P = .01) but not claudication (5-year survival rate, 84% vs. 80%; log-rank, P = .59). Statin therapy was not associated with 1-year rates of major amputation or graft occlusion in CLI patients.

Stavroulakis et al. [44] came to a similar result in the CRITISCH registry. Statins were used in 445 individuals, 371 patients received no statins. Statin therapy in CLI patients was associated with an increased amputation-free survival and lower rates of mortality and major adverse cardiovascular and cerebral events (MACCEs) without improving, however, the salvage rates of the affected limb. Peters et al. [45] reported on 10,922 matched patients. Statin initiation was associated with lower all-cause mortality (chronic limb-threatening ischemia: hazard ratio [HR], 0.75 [95% CI, 0.68–0.84]; intermittent claudication: HR, 0.80 [95% CI, 0.70–0.92]), lower risk of major amputation in patients with chronic limb-threatening ischemia (HR, 0.73; 95% CI, 0.58–0.93) and lower risk of cardiovascular events (hazard ratio, 0.80; 95% CI, 0.70–0.92) in patients with intermittent claudication during 5 years of follow-up.

Arya et al. [46] identified incident peripheral artery disease (PAD) patients in the national Veterans Affairs data. The cohort consisted of 155,647 veterans with a median follow up of 5.9 years. More than a quarter of patients (N = 45,503, 28.0%) were not on any statin medication at the time of PAD identification. Of these, 28,351 were on antiplatelet medications but not on statins and served as the active comparator in the subsequent analyses. Incident amputation and mortality risk declined significantly with any statin use in comparison with the antiplatelet therapy-only group.

In adjusted Cox models, the high-intensity statin users were associated with lower amputation risk and mortality in comparison with antiplatelet therapy-only users. Low-to-moderate-intensity statins also had significant reductions in the risk of amputation and mortality in comparison with no statins (antiplatelet therapy only), but effect size was significantly weaker than the high-intensity statins ($P < 0.001$). The association of high-intensity statins with lower amputation and death risk remained significant and robust in propensity score-matched, sensitivity, and subgroup analyses. Statins, especially high-intensity formulations, are underused in patients with PAD. This is the first population-based study to show that high-intensity statin use at the time of PAD diagnosis is associated with a significant reduction in limb loss and mortality in comparison with low-to-moderate-intensity statin users, and patients treated only with antiplatelet medications but not with statins, as well. In this study, intensity of statin therapy was defined according to the 2013 AHA/ACC guidelines [47], the classification is shown in Table 11.2.

Moore et al. [48] examined in the Vascular Quality Initiative registry the outcomes of patients intolerant to statin and antiplatelet agent (APA) and compared them with patients who were compliant or noncompliant with these therapies. 105,628 patients were identified. Statin intolerance was noted in 2.3% at discharge and 2.1% at the 1-year follow-up, with 0.7% listed as intolerant at all stages. Patients who were compliant with statins showed a 91% survival at 5 years vs. 87% survival in noncompliant patients and 87% in intolerant patients at 5 years ($P < .001$). Noncompliance with statins was correlated with noncompliance with APA medications ($R = 0.16$, $P < .001$). Patients with statin intolerance had a similar survival curve as noncompliant patients across all registry cohorts.

Table 11.2 High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel). According to 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [47]

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C, on average, by approximately ≥50% Atorvastatin (40)–80 mg Rosuvastatin 20 (40) mg	Daily dose lowers LDL-C, on average, by approximately 30% to <50% Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Daily dose lowers LDL-C, on average, by <30% Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

BID indicates twice daily

11.4.3 Beta Blocker

11.4.3.1 Guidelines

The ESC/ESVS guidelines [1] note: Beta-blockers are not contraindicated in patients with LEAD (lower extremity artery disease), as they do not alter walking capacity in patients with mild to moderate LEAD. Nevertheless, they should be carefully prescribed to patients with CLTI.

11.4.3.2 Studies

Shannon et al. [49] assessed the impact of preoperative beta blockade on 30-day major adverse cardiac events (MACEs) and major adverse limb events (MALEs) in patients undergoing infrainguinal revascularization for CLI. A retrospective analysis of prospectively collected National Surgical Quality Improvement Program data was performed. In 11,785 patients who underwent lower extremity revascularization for critical limb ischemia, perioperative beta blockers were used in 62% who underwent open bypass and 65% who underwent an endovascular limb procedure. The risk of cardiac events was significantly higher (5.8% vs. 3.4%) in patients receiving beta blockers, but the risk of adverse limb events was not different. The authors suggested that beta blockers be carefully considered in patients undergoing lower extremity revascularizations because of their apparent adverse effect on cardiac events in the perioperative period.

Scali et al. [50] determined whether the initiation of β-blockers before major elective vascular surgery decreased postoperative cardiac events or mortality within the Society for Vascular Surgery-Vascular Quality Initiative (SVS-VQI). The study analyzed 13,291 patients (lower extremity bypass, LEB, 68%; aortofemoral bypass, AFB, 11%; and open AAA, 21%); of these, 67.7% (n = 8999) were receiving β-blockers at time of their index procedure. Specifically, 13.2% (n = 1753) were identified to have been started on a preoperative β-blocker, 54.5% (n = 7426) were on chronic β-blockers, and 32.3% (n = 4286) were on no preoperative β-blockers. Exclusive of high-risk open AAA patients, preoperative β-blockers did not decrease rates of MACEs or mortality after LEB, AFB, or open AAA. Importantly, exposure to prophylactic preoperative β-blockers increased the rates of some adverse events in several subgroups. Given these data, the SVS-VQI cannot support routine initiation of preoperative β-blockers before major elective vascular surgery in most patients.

11.4.4 Antihypertensive Therapy

11.4.4.1 Guidelines

The ESC/ESVS guidelines [1] recommend:

- In patients with PAD and hypertension, it is recommended to control blood pressure at <140/90 mmHg. (Class I recommendation/Level of evidence A).
- ACEIs (angiotensin-converting enzyme inhibitors) or ARBs (angiotensin-receptor blockers) should be considered as first-line therapy in patients with PAD and hypertension. (Class IIa recommendation/Level of evidence B).

11.4.4.2 Studies

Bodewes et al. [51] evaluated long-term outcomes of RAS (renin-angiotensin system) inhibitor use in patients with chronic limb threatening ischemia (CLTI) undergoing a vascular intervention in a single-center retrospective cohort study. Of 1161 patients following either an open or endovascular intervention for CLTI those discharged on a high dose RAS inhibitor experienced a 30% increase in long-term survival when compared with patients discharged on a low dose or no RAS inhibitor. No associations were found between RAS inhibitor use and major adverse limb event (HR, 0.95), major amputation (HR, 0.82), or reintervention (HR, 1.05). The study demonstrated that RAS inhibitor use in patients with CLTI was associated with fewer cardiovascular adverse events and improved long-term survival, although this benefit was only observed in those on a high-dose therapy. Therefore, physicians should strive to maintain patients on a high-dose RAS inhibitor, provided that such doses are tolerated.

Khan et al. [52] assessed the effect of ACE inhibitors/ARBs on limb salvage (LS) and survival in patients undergoing peripheral vascular intervention (PVI) for CLTI using the VQI registry. A total of 12,433 limbs (11,331 patients) were included. Postmatching survival analysis at 5 years showed improved overall survival, OS (81.8% vs. 79.9%; P = .01) and amputation-free survival, AFS (73% vs. 71.5%; P = .04) with ACE inhibitors/ARBs but no difference in limb salvage, LS (ACE inhibitors/ARBs, 88.3%; no ACE inhibitors/ARBs, 88.1%; P = .56). After adjustment for multiple variables in a Cox regression model, ACE inhibitors/ARBs were associated with improved OS (hazard ratio, 0.89; P = .03) and AFS (hazard ratio, 0.92; P = .04). LS rates remained unaffected. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may improve survival in chronic limb-threatening ischemia patients.

11.4.5 Diabetes/Glycaemic Control

11.4.5.1 Guidelines

The ESC/ESVS guidelines [1] recommend:

- In diabetic patients with PAD, strict glycaemic control is recommended. (Class I recommendation/Level of evidence C).

11.4.5.2 Studies

Singh et al. [53] performed a retrospective, observational study in the VQI registry to determine whether higher preoperative hemoglobin A1c (HbA1c) levels are associated with an increased risk of major adverse limb events, major adverse cardiovascular events, and mortality in diabetic patients undergoing infrainguinal lower extremity bypass (LEB). A total of 7727 surgeries among 7090 patients were included for analysis. After adjustment for clinical and demographic variables, patients with high HbA1c values (≥8%) were at an increased risk of adverse limb events (odds ratio [OR], 1.37) compared with those with a normal HbA1c (>6% to ≤7%). High HbA1c values were not associated with an increased risk of cardiovascular events (OR, 1.07) or mortality (OR, 1.57). Patients with low HbA1c values (≤6%) did not experience a significantly higher risk for any of the three outcomes. In a stratified analysis, the association of high HbA1c values with adverse limb events was only present in those presenting without critical limb ischemia. Poor preoperative glycemic control in diabetic individuals undergoing infrainguinal LEB, particularly in those without critical limb ischemia, is associated with an increased risk of in-hospital limb events.

In another retrospective analysis of prospectively collected Vascular Quality Initiative data, of the 27,988 patients (30,813 operations) undergoing infrainguinal bypass, 26% had uncontrolled diabetes [54]. Those with HbA1c >10% had an 81% increase in major adverse cardiac events and 31% increase in major adverse limb events (MALEs) within 30 days of revascularization compared with patients without diabetes. Compared with patients with an HbA1c 7% to 10%, those with an HbA1c >10% had more total complications (23% vs. 20%; P = .03), MALEs (20% vs. 17%; P = .002), and major limb amputations (3% vs. 2%; P = .01). Uncontrolled diabetes with an HbA1c value >10.0% was associated with significantly worse 30-day surgical outcomes. Patients with incrementally better glycemic control (HbA1c level of 7.0%–10.0%) did not suffer the same rate of complications, suggesting that preoperative attempts at improving diabetes management even slightly could lead to improved surgical outcomes in open infrainguinal bypass patients.

Arya, Binney et al. [55] reviewed national Veterans Health Administration data to identify 26,799 vascular patients with at least one PAD revascularization procedure from 2003 to 2014 and HbA1c measured within 6 months of the procedure. In the Cox model, incremental HbA1c levels of 6.1% to 7.0%, 7.1% to 8.0%, and > 8%

were associated with 26%, 53%, and 105% higher risk of amputation, respectively. Similarly, the risk of major adverse limb events (MALEs) also increased by 5%, 21%, and 33% with worsening HbA1c levels of 6.1% to 7.0%, 7.1% to 8.0%, and > 8%, respectively (vs. HbA1c ≤6.0%). The authors recommended that all patients with peripheral arterial disease who require revascularization be screened for diabetes and that those with poor glycemic control be treated to achieve a hemoglobin A1c level of <7.0%.

11.4.6 Preoperative Anemia/Blood Transfusion

There are no guideline recommendations on this issue.

11.4.6.1 Studies

In the NSQIP database, Bodewes et al. [56] identified 5081 patients undergoing bypass, of which 741 (15%) had severe (hematocrit, HCT levels ≤29%), 1317 (26%) moderate (29.1%–34%), 1516 (30%) mild (34.1%—39%), and 1507 (30%) no anemia (HCT > 39%). After adjustment for baseline conditions, mortality was higher in those with severe anemia (3.1%) and moderate anemia (3.0%) compared with those without anemia (0.7%). Severe anemia was independently associated with major amputation (6.9% vs. 3.3%; OR, 1.6; 95% CI, 1.01–2.6) compared with no anemia. Moreover, mortality associated with preoperative anemia was not different in patients receiving postoperative blood transfusions compared with those who did not, whereas MACE was significantly higher in patients with preoperative anemia and blood transfusions (interaction; P < .001). Mortality and major adverse events in CLTI patients undergoing infrainguinal bypass are inversely associated with preoperative HCT levels, with the highest event rates in the most severely anemic patients. This effect was not improved with blood transfusion.

The latter result is consistent with the findings of another study. Using the Vascular Study Group of New England's database (2003–2010), Tan et al. [57] examined 1880 consecutive infrainguinal lower extremity bypasses (LEB) performed for critical limb ischemia. Perioperative transfusion was categorized as 0 U, 1 to 2 U, and ≥ 3 U. In the study cohort and group frequency matched cohort, transfusion was associated with significantly higher perioperative wound infection (0 U:4.8% vs. 1 to 2 U: 6.5% vs. ≥3 U: 14.0%; p = 0.0004) and graft thrombosis at discharge (4.5% vs. 7.7% vs. 15.3%; p < 0.0001). At 1 year, there were no differences in infection or graft patency. The presumed benefits of blood replacement should be weighed carefully because of the increased risk of perioperative complications with transfusion.

11.4.7 Anaesthesia

There are no guideline recommendations on this issue.

11.4.7.1 Studies, Review

A Cochrane Review was performed by Barbosa et al. [58] to determine the rates of death and major complications associated with spinal and epidural anaesthesia as compared with other types of anaesthesia for lower-limb revascularization in patients aged 18 years or older who are affected by obstruction of lower-limb vessels. Four studies that compared neuraxial anaesthesia with general anaesthesia were included in this analysis. The total number of participants was 696, of whom 417 were allocated to neuraxial anaesthesia and 279 to general anaesthesia. Available evidence from included trials was insufficient to rule out clinically important differences for most clinical outcomes. Neuraxial anaesthesia may reduce pneumonia. No conclusions can be drawn with regard to mortality, myocardial infarction and rate of lower-limb amputation, or less common outcomes.

General endotracheal anesthesia (GETA), epidural anesthesia (EA), and spinal anesthesia (SA) are the three methods commonly used during lower extremity arterial bypass surgery. To examine and compare the safety of the three common types of anesthesia used, Singh et al. [59] queried the database of the Veterans Affairs (VA) National Surgical Quality Improvement Program (NSQIP). 14,788 patients (GETA, 9757 patients; SA, 2848 patients; EA, 2183 patients) were identified who underwent a lower extremity infrainguinal arterial bypass. The type of anesthesia significantly affected graft failure at 30 days. Compared with SA, the odds of graft failure were higher for GETA. There was no statistically significant difference in 30-day graft failure between EA and SA. Regarding cardiac events, defined as postoperative myocardial infarction or cardiac arrest, patients with normal functional status (activities of daily living independence) and no history of congestive heart failure or stroke did worse with GETA than with SA. There was no statistically significant difference between EA and SA in the incidence of cardiac events. GETA, when compared with SA and EA, was associated with more cases of postoperative pneumonia (odds ratio: 2.2 [95% CI, 1.1–4.4; P = .034]). Compared with SA, GETA was associated with an increased odds of returning to the operating room, as was EA. There was no significant difference in 30-day mortality among the three groups with univariate or multivariate analyses. Although GETA is the most common type of anesthesia used in infrainguinal bypasses, these results suggest that it is not the best strategy, because it is associated with significantly worse morbidity than regional techniques.

Ghanami et al. [60] also used the NSQIP database and examined the effects of regional versus general anesthesia for infrainguinal bypass procedures performed in the treatment of CLI. A total of 5462 patients were identified. There was no difference in rates of cardiac events, graft failure, postoperative pneumonia, or return to

the operative room. In contrast to previous reports, anesthetic type was not associated with postoperative complications or mortality in either unadjusted or multivariate analyses. These data suggested that anesthetic choice should be governed by local expertise and practice patterns.

A third study is that of the Vascular Quality Initiative (VQI) [61]. There were 16,052 patients identified to have a lower extremity bypass with 572 (3.5%) receiving regional (epidural/spinal) anesthesia (RA). Regional anesthesia was associated with lower rates of congestive heart failure and postoperative renal dysfunction and shorter hospitalizations. There was no survival advantage. This study suggested that regional anesthesia may have some benefits in patients undergoing lower extremity bypass.

Roberts et al. [62] conducted a population based comparative effectiveness study in Ontario, Canada. Residents aged 18 years and older who underwent lower limb revascularization surgery between 1 April 2002 and 31 March 2015 were identified. Of 20,988 patients, 6453 (30.7%) received neuraxial anaesthesia and 14,535 (69.3%) received general anaesthesia. The use of neuraxial anaesthesia declined by 17% over the study period. Death within 30 days occurred in 204 (3.2%) patients who received neuraxial anaesthesia and 646 (4.4%) patients who received general anaesthesia. After multivariable, multilevel adjustment, use of neuraxial anaesthesia compared with use of general anaesthesia was associated with decreased 30 day mortality. Use of neuraxial anaesthesia compared with use of general anaesthesia was also associated with decreased in-hospital cardiopulmonary and renal complications. These findings support the increased use of neuraxial anaesthesia in patients undergoing these surgeries.

Kikuchi et al. [63] reported on ultrasound-guided lower extremity nerve blockade (UGNB) for infragenicular bypass surgery in high risk patients with CLTI. After induction of sedation with dexmedetomidine in the operating room, ultrasound guided femoral nerve and sciatic nerve blockade, with or without obturator nerve blocks, was performed using levobupivacaine. Fifty-six pairs of CLTIs were matched and analyzed (55% dialysis dependent). The authors demonstrated a significantly lower rate of heart failure, lower catecholamine indices and infusion volumes, higher mean arterial pressure during induction, faster recovery of fluid and food intake, and decreased rates of delirium in patients treated with UGNB, whereas survival, patency, and limb salvage were similar in both groups. This study was commented by Vos et al. [64]. They thought the lower rate of heart failure and reduced rate of delirium found in this study is relevant for the population of frequently frail and older CLTI patients. However, the retrospective nature of the study poses a substantial risk of selection bias and confounding. An important limitation of the technique is that it cannot be recommended when a vein from the contralateral leg or upper extremities is required in composite venous bypasses.

11.4.8 Analgesia

There are no guideline recommendations on this issue.

11.4.8.1 Meta-Analysis

The aim of a systematic review and meta-analysis by Bosanquet et al. [65] was to evaluate the effects of using an intraoperatively placed perineural catheter (PNC) with a postoperative local anaesthetic infusion on immediate and long-term outcomes after lower limb amputation. Perineural catheters were placed alongside the transected sciatic nerve (for transfermoral amputations) or tibial nerve (for transtibial amputations). The review demonstrated that postoperative opioid consumption is approximately halved, without affecting immediate postoperative pain, mortality, long-term phantom limb or stump pain.

This meta-analysis was compiled again 6 years later based on 10 studies (731 patients) [66]. The message was that PNC use in amputees is associated with a significant reduction in post-operative pain scores and postoperative morphine requirements, although this latter finding is lost on sensitivity analysis of randomised trials only. There was no evidence of PNC effect on mortality, phantom limb pain, or chronic stump pain.

11.4.9 Enhanced Recovery After Surgery (ERAS)

There are no guideline recommendations on this issue.

11.4.9.1 Studies, Review

There were no articles reporting ERAS-like clinical pathways for lower extremity surgery included in the systematic review of enhanced recovery after surgery for vascular operations performed by McGinigle et al. [67]. Three articles did report merely on some key components of ERAS, nonopioid pain strategies and early postoperative mobilization.

Meanwhile, Witcher et al. [68] have described the implementation and early results of an enhanced recovery program (ERP) and barriers to its implementation for lower extremity bypass surgery. During 9 months, an ERP (n = 57) was successfully developed and implemented spanning preoperative, intraoperative, and postoperative phases. Early successes included 97% use of fascia iliaca block and multimodal analgesia administration in 81%. Barriers included only 47% of patients achieving day of surgery mobilization and 19% receiving celecoxib preoperatively.

ERP patients had decreased total and postoperative LOS compared with non-ERP patients. Variable and total costs for ERP patients were significantly reduced.

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Chapter 12
Chronic Limb-Threatening Ischemia (Critical Limb Ischemia)



12.1 Guidelines

12.1.1 Preliminary Remark

The term "critical limb ischaemia" (CLI) covers the clinical manifestations of pain at rest (Fontaine stage III) and ischaemic ulcer and gangrene (Fontaine stage IV) or the Rutherford categories 4–6. What is required—not least because of the significant increase in diabetes—is a more precise description of the extent of tissue loss and the presence and severity of infection. Perfusion is only one determinant of outcome; wound extent and the presence and severity of infection also greatly impact the threat to a limb. The Society for Vascular Surgery has taken this into account and developed an integrated lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) [1]. Particularly in patients with diabetes, limb threat is part of a broad disease spectrum. The "WIFI" classification is therefore given in Chap. 17, Diabetic Foot.

The ESC [2] guidelines use the term "chronic limb-threatening ischaemia" (CLTI). This entity includes clinical patterns with a threatened limb viability related to several factors. In contrast to the former term 'critical limb ischaemia', severe ischaemia is not the only underlying cause. Three issues must be considered with the former terminology of critical limb ischaemia. First, 'critical' implies that treatment is urgent to avoid limb loss, while some patients can keep their legs for long periods of time even in the absence of revascularization. Second, the increasing predominance of diabetes in these situations, present in 50–70% of cases, presents mostly as neuro-ischaemic diabetic foot ulcers. Third, the risk of amputation not only depends on the severity of ischaemia, but also the presence of a wound and infection. In this chapter, analogous to the ESC, we also use the term "chronic limb-threatening ischaemia" (CLTI) for the former term "critical limb ischaemia".

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12.1.2 European Society of Cardiology (ESC) in Cooperation with the European Society for Vascular Surgery (ESVS) [2]

12.1.2.1 Recommendations on Revascularization of Aorto-Iliac Occlusive Lesions (Apply for Patients with IC and CLTI)

- An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions. (Class I recommendation/Level of evidence C)
- In patients fit for surgery, aorto-(bi)femoral bypass should be considered in aorto-iliac occlusions. (Class IIa recommendation/Level of evidence B)
- An endovascular-first strategy should be considered in long and/or bilateral lesions in patients with severe comorbidities. (Class IIa recommendation/Level of evidence B)
- An endovascular-first strategy may be considered for aorto-iliac occlusive lesions if done by an experienced team and if it does not compromise subsequent surgical options. (Class IIb recommendation/Level of evidence B)
- Primary stent implantation rather than provisional stenting should be considered. (Class IIa recommendation/Level of evidence B)
- Open surgery should be considered in fit patients with aortic occlusion extending up to the renal arteries. (Class IIa recommendation/Evidence level C)
- In the case of ilio-femoral occlusive lesions, a hybrid procedure combining iliac stenting and femoral endarterectomy or bypass should be considered. (Class IIa recommendation/Level of evidence C).
- Extra-anatomical bypass may be indicated for patients with no other alternatives for revascularization. (Class IIb recommendation/Level of evidence C)

12.1.2.2 Recommendations on Revascularization of Femoro-Popliteal Occlusive Lesions (Apply to Patients with IC and CLTI)

- An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions. (Class I recommendation/Level of evidence C)
- Primary stent implantation should be considered in short (i.e. <25 cm) lesions. (Class IIa recommendation/Level of evidence A)
- Drug-eluting balloons may be considered in (i.e. <25 cm) short lesions. (Class IIb recommendation / Level of evidence A)
- Drug-eluting stents may be considered for short (i.e. <25 cm) lesions. (Class IIb recommendation/Level of evidence B)
- Drug-eluting balloons may be considered for the treatment of in-stent restenosis. (Class IIb recommendation/Level of evidence B)
- In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. >25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is >2 years. (Class I recommendation/Level of evidence B)

- The autologous saphenous vein is the conduit of choice for femoropopliteal bypass. (Class I recommendation/Level of evidence A)
- When above-the-knee bypass is indicated, the use of a prosthetic conduit should be considered in the absence of an autologous saphenous vein. (Class IIa recommendation/Level of evidence A)
- In patients unfit for surgery, endovascular therapy may be considered in long (i.e. >25 cm) femoro-popliteal lesions. (Class IIb recommendation/Level of evidence C)

12.1.2.3 Recommendations on Revascularization of Infra-Popliteal Occlusive Lesions (Apply to Patients with CLTI)

- In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage. (Class I recommendation/Level of evidence C)
- For revascularization of infra-popliteal arteries, bypass using the great saphenous vein is indicated. (Class I recommendation/Level of evidence A)
- For revascularization of infrapopliteal arteries, endovascular therapy should be considered. (Class IIa recommendation/Level of evidence B)

12.1.3 American College of Cardiology (ACC)/American Heart Association/AHA) [3]

These guidelines make the following recommendations for CLI:

- In patients with CLI, revascularization should be performed when possible to minimize tissue loss. (Class I recommendation/Level of evidence B-NR)
- An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI. (Class I recommendation/Level of evidence C-EO)

12.1.3.1 Endovascular Revascularization

- Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene. (Class I recommendation/Level of evidence B-R)
- A staged approach to endovascular procedures is reasonable in patients with ischaemic rest pain. (Class IIa recommendation / Level of evidence C-LD)
- Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene. (Class IIb recommendation/Level of evidence B-NR)

12.1.3.2 Surgical Revascularization

- When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e. tibial, pedal) should be constructed with suitable autogenous vein. (Class I recommendation/Level of evidence A)
- Surgical procedures are recommended to establish in-line blood flow to the foot in patients with non-healing wounds or gangrene. (Class I recommendation/Level of evidence C-LD)
- In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries. (Class IIa recommendation/Level of evidence B-NR)
- A staged approach to surgical procedures is reasonable in patients with ischaemic rest pain. (Class IIa recommendation/Level of evidence C-LD)

12.1.3.3 Wound Healing

- An interdisciplinary care team should evaluate and provide comprehensive care for patients with CLI and tissue loss to achieve complete wound healing and a functional foot. (Class I recommendation/Level of evidence B-NR)
- In patients with CLI, intermittent pneumatic compression (arterial pump) devices may be considered to augment wound healing and/or ameliorate severe ischaemic rest pain. (Class IIb recommendation/Level of evidence B-NR).
- In patients with CLI, the effectiveness of hyperbaric oxygen therapy for wound healing is unknown. (Class IIb recommendation/Level of evidence C-LD)
- Prostanoids are ***not*** indicated in patients with CLI. (No benefit/Level of evidence B-R)

(Note: R Randomized; NR Nonrandomized; LD Limited Data)

12.1.4 Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia—Joint Guidelines of the Society for Vascular Surgery, European Society for Vascular Surgery, and World Federation of Vascular Societies [4]

Strong recommendations of these guidelines include:

4.3 Treat all patients with CLTI with an antiplatelet agent. (Strong recommendation; level of evidence A, high).

4.7 Use moderate or high-intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI. (Strong recommendation; level of evidence A, high).

4.8 Control hypertension to target levels of <140 mm Hg systolic and < 90 mmHg diastolic in patients with CLTI. (Strong recommendation; level of evidence B, moderate)

4.10 Use metformin as the primary hypoglycemic agent in patients with type 2 DM and CLTI. (Strong recommendation; level of evidence A, high)

6.6 Use an integrated threatened limb classification system (such as WIFI) to stage all CLTI patients who are candidates for limb salvage. (Strong recommendation; level of evidence C, low).

6.11 Offer revascularization to all average-risk patients with advanced limb-threatening conditions (e.g., WIFI stage 4) and significant perfusion deficits (e.g., WIFI ischaemia grades 2 and 3). (Strong recommendation; level of evidence C, low)

6.17 Perform ultrasound vein mapping when available in all CLTI patients who are candidates for surgical bypass. (Strong recommendation; level of evidence C, low)

6.22 Correct inflow disease alone in CLTI patients with multilevel disease and low-grade ischemia (e.g., WIFI ischemia grade 1) or limited tissue loss (e.g., WIFI wound grade 0/1) and in any circumstance in which the risk-benefit of additional outflow reconstruction is high or initially unclear. (Strong recommendation; level of evidence C, low).

6.23 Re-stage the limb and repeat the hemodynamic assessment after performing inflow correction in CLTI patients with inflow and outflow disease. (Strong recommendation; level of evidence C, low).

6.25 Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (e.g., GLASS stage IA) aorto-iliac (AI) disease, depending on the history of prior intervention. (Strong recommendation; level of evidence B, moderate)

6.27 Perform open CFA [common femoral artery] endarterectomy with patch angioplasty, with or without extension into the PFA [profound femoral artery], in CLTI patients with hemodynamically significant (> 50% stenosis) disease of the common and deep femoral arteries. (Strong recommendation; level of evidence C, low).

6.32 In average-risk CLTI patients with infrainguinal disease, base decisions of endovascular intervention vs. open surgical bypass on the severity of limb threat (e.g., WIFI), the anatomic pattern of disease (e.g., GLASS), and the availability of autologous vein. (Strong recommendation; level of evidence C, low).

6.40 Use autologous vein as the preferred conduit for infrainguinal bypass surgery in CLTI. (Strong recommendation; level of evidence B, moderate)

6.42 Perform intraoperative imaging (angiography, duplex ultrasound or both) on completion of open bypass surgery for CLTI and correct significant technical defects if feasible during the index operation. (Strong recommendation; level of evidence C, low).

7.5. Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible. (Strong recommendation; level of evidence C, low)

7.6 Do not offer HBOT [hyperbaric oxygen therapy] to improve limb salvage in CLTI patients with severe, uncorrected ischemia (e.g., WIFI ischemia grade 2/3). (Strong recommendation; level of evidence B, moderate).
9.2 Offer primary amputation to CLTI patients who have pre-existing dysfunctional or unsalvageable limb, a poor functional status (e.g., bedridden), or a short life expectancy after shared decision-making with the patient and health care team. (Strong recommendation; level of evidence C, low)
9.6 Involve a multidisciplinary rehabilitation team from the time a decision to amputate has been made until successful completion of rehabilitation has been achieved. (Strong recommendation; level of evidence C, low).
9.7 Continue to observe CLTI patients who have undergone amputation at least yearly to monitor progression of disease in the contralateral limb and to maintain optimal medical therapy and risk factor management. (Strong recommendation; level of evidence C, low)
10.1 Continue best medical therapy for PAD, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization. (Strong recommendation; level of evidence A, high).
10.10 Offer intervention for duplex ultrasound-detected vein graft lesions with an associated peak systolic velocity (PSV) of >300 cm/s and a PSV ratio > 3.5 or grafts with low velocity (midgraft PSV < 45 cm/s) to maintain patency. (Strong recommendation; level of evidence B, moderate)
10.11 Maintain long-term surveillance after surgical or catheter-based revision of a vein graft, including DUS graft scanning where available, to detect recurrent graft- threatening lesions. (Strong recommendation; level of evidence B, moderate)
10.14 Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds. (Strong recommendation; level of evidence A, high).
10.14 Provide counseling on continued protection of the healed wound and foot to include appropriate shoes, insoles and monitoring of inflammation. (Strong recommendation; level of evidence A, high)

12.2 Suggested Objective Performance Goals (OPG) for Evaluating New Catheter-Based Treatments in Critical Limb Ischemia (CLI)

Conte et al. [5] developed a set of suggested objective performance goals (OPG) for evaluating new catheter-based treatments in critical limb ischemia (CLI), based on evidence from historical controls. A set of outcome variables as the basis for safety and efficacy targets was defined:

- Amputation was defined by major index limb loss at or proximal to the transtibial level.
- Major adverse cardiovascular event (MACE) included myocardial infarction and stroke in addition to death from any cause.

- RAO was defined as any reintervention or above ankle amputation of the index limb.
- RAS was defined as any reintervention, above ankle amputation of the index limb, or stenosis.
- Major reinterventions included the creation of a new surgical bypass graft, the use of thrombectomy or thrombolysis (ie, procedures done in the setting of lost primary-assisted patency), or a major surgical graft revision such as a jump graft or an interposition graft.
- Major adverse limb event (MALE): Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
- Primary efficacy endpoint of perioperative death or any major adverse limb event.

(a) Perioperative targets (30-day events) for overall CLI cohort

- MACE: 6.2% (death: 2.7% / myocardial infarction (MI) 3.1%/cerebrovascular accident (CVA) 1.0%). Safety objective performance goal (OPG): 8%
- MALE: 6.1%. Safety OPG: 8%
- Amputation 1.9%. Safety OPG: 3%

(b) Perioperative targets (30-day events) for clinical high risk (age ≥ 80 and tissue loss) subgroup

- MACE: 11.8% (death: 6.6%/MI 5.2%/CVA 2.2%). Safety OPG 18%
- MALE: 5.1%. Safety OPG: 10%
- Amputation 2.9%. Safety OPG: 7%

(c) Perioperative targets (30-day events) for anatomic high risk (infra-popliteal) subgroup

- MACE: 7.3% (death: 2.8%/MI 4.2%/CVA 1.2%). Safety OPG 10%
- MALE: 6.1%. Safety OPG: 9%
- Amputation 2.2%. Safety OPG: 4%

(d) Efficacy outcomes (1 year) for overall CLI cohort and suggested OPG for each endpoint. Rates reported as proportion free from adverse event.

- MALE and perioperative death: 76.9%. Efficacy OPG: 71%
- AFS (Amputation-free survival): 76.5%. Efficacy OPG: 71%
- RAS: 46.5%. Efficacy OPG: 39%
- RAO 61.3%. Efficacy OPG: 55%
- Limb salvage: 88.9%. Efficacy OPG: 84%
- Survival: 85.7%. Efficacy OPG: 80%

(e) Efficacy outcomes (1 year) for clinical high risk (age ≥ 80 and tissue loss) subgroup. Rates reported as proportion free from adverse event.

- MALE and perioperative death: 69.1%. Efficacy OPG: 61%
- AFS: 60.5%. Efficacy OPG: 53%
- RAS: 40.4%. Efficacy OPG: 29%

- RAO 62.8%. Efficacy OPG: 54%
- Limb salvage: 86.5%. Efficacy OPG: 80%
- Survival: 70.3%. Efficacy OPG: 63%

(f) Efficacy outcomes (1 year) for anatomic high risk (infra-popliteal) subgroup. Rates reported as proportion free from adverse event.

- MALE and perioperative death: 74.0%. Efficacy OPG: 67%
- AFS: 74.4%. Efficacy OPG: 68%
- RAS: 44.0%. Efficacy OPG: 36%
- RAO 58.3%. Efficacy OPG: 51%
- Limb salvage: 86.6%. Efficacy OPG: 81%
- Survival: 85.9%. Efficacy OPG: 80%

12.3 Results

12.3.1 Randomized Trials

12.3.1.1 BEST-CLI Clinical Trial-Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

Farber et al. [6] performed the Best Endovascular versus Best Surgical Therapy in Patients with CLTI (BEST-CLI) trial to determine whether endovascular revascularization was superior to surgical revascularization in patients with CLTI caused by infrainguinal peripheral artery disease who were judged to be suitable candidates for both approaches. In this international, randomized trial, 1830 patients with CLTI and infrainguinal peripheral artery disease were enrolled in two parallel-cohort trials. Patients who had a single segment of great saphenous vein that could be used for surgery were assigned to cohort 1. Patients who needed an alternative bypass conduit were assigned to cohort 2. The primary outcome was a composite of a major adverse limb event—which was defined as amputation above the ankle or a major limb reintervention (a new bypass graft or graft revision, thrombectomy, or thrombolysis)—or death from any cause. In cohort 1, after a median follow-up of 2.7 years, a primary-outcome event occurred in 302 of 709 patients (42.6%) in the surgical group and in 408 of 711 patients (57.4%) in the endovascular group (hazard ratio, 0.68; 95% confidence interval [CI], 0.59 to 0.79; $P < 0.001$). In cohort 2, a primary-outcome event occurred in 83 of 194 patients (42.8%) in the surgical group and in 95 of 199 patients (47.7%) in the endovascular group (hazard ratio, 0.79; 95% CI, 0.58 to 1.06; $P = 0.12$) after a median follow-up of 1.6 years. In patients with CLTI who had an adequate single segment of great saphenous vein for conduit and were considered to be suitable candidates for both endovascular intervention and surgical bypass, initial bypass surgery was associated with a lower incidence of major adverse limb events or death than initial endovascular intervention. In patients

without a suitable great saphenous vein, results associated with initial endovascular intervention were not significantly different from those associated with initial bypass surgery.

12.3.1.2 Bypass Versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-2

Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-2 was an open-label, pragmatic, multicentre, phase 3, randomised trial [7]. Eligible patients were those who presented with chronic limb-threatening ischaemia and who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. Participants were randomly assigned (1:1) to receive either vein bypass (vein bypass group) or best endovascular treatment (best endovascular treatment group) as their first revascularisation procedure. The primary outcome was amputation-free survival defined as time to major (above the ankle) amputation of the trial leg or death from any cause (whichever occurred first). 345 participants with CLTI were enrolled in the trial and randomly assigned: 172 (50%) to the vein bypass group and 173 (50%) to the best endovascular treatment group. 108 (63%) of 172 patients in the vein bypass group and 92 (53%) of 173 patients in the best endovascular treatment group had a major amputation or died (adjusted HR 1·35 [95% CI 1.02–1.80]; p = 0.037). The median amputation-free survival was 3·3 years [IQR 2.1–4.3] in the vein bypass group and 4.4 years [IQR 3.4–5.9] in the best endovascular group. The BASIL-2 trial showed that a vein bypass first revascularisation strategy led to a 35% increased risk of major amputation or death in patients with CLTI who required an infrapopliteal revascularisation procedure to restore limb perfusion compared with a best endovascular treatment first revascularisation strategy. This difference was mainly driven by fewer deaths in the best endovascular treatment first revascularisation group as limb-based outcomes were similar between the two groups.

12.3.2 Systematic Reviews/Meta-Analyses

12.3.2.1 WIFI Classification System

Van Reijen et al. [8] reviewed the available evidence regarding the value of the WIfI classification in patients presenting with CLTI to predict the 1 year major amputation risk and the benefit of revascularisation. There were 12 studies comprising 2669 patients, most of whom underwent endovascular or open revascularisation. Data for each WIfI stage from four studies (569 patients, 575 limbs) reporting on major amputation were pooled. The estimated risk of a major amputation after 1 year was 0% for WIfI stage I patients, 8% for stage II, 11% for stage III, and 38%

Table 12.1 Observed 1-year outcomes by Wound, Ischemia, and foot Infection (WIfI) composite score substratification in patients undergoing a first-time lower extremity revascularization for chronic limb-threatening ischemia (according to [9])

WIfI-Composite-Score	Limbs (n)	Limb salvage (%)	Freedom from RAS (%)	Survival (%)
Composite 1-3	336	96	58	85
Composite 4-6	557	89	54	79
Composite 7-9	100	67	43	78

RAS reintervention, amputation or stenosis
Limbs graded in all three WIfI components

for stage IV. Five studies comprising 757 patients and 786 limbs reported on AFS. The estimated 1 year AFS was 83% for patients classified as WIFI stage I, 76% for stage II, 75% for stage III, and 55% for stage IV. The likelihood of an amputation after 1 year in patients with CLTI increases with higher WIfI stages, which is important prognostic information. However, prospective evaluations are needed to determine its role in clinical practice.

Darling et al. [9] performed a retrospective record review of patients undergoing a lower extremity revascularization for CLTI. 1336 limbs were included, of which 992 had sufficient data to classify all three WIfI components (wound, ischemia, and foot infection). A WIfI composite score was calculated by summing the three individual WIfI component scores (e.g., a limb with a wound score of 3, an ischemia score of 2, and an infection score of 1 would have a WIfI composite score of 6), and the WIfI mean score was calculated by summing the three individual components and dividing by the number of individual WIfI components. In addition, for statistical purposes, a further subclassification was created within the WIfI composite scores, where limbs were stratified into low-risk (composite scores 1-3), moderate-risk (4-6), and high-risk groups (7-9). The study supported the ability of the SVS WIfI classification system to predict major amputation; however, the novel WIfI mean and WIfI composite scores predicted amputation, RAS events, and mortality more consistently than any other current WIfI scoring system (Table 12.1).

12.3.2.2 Conservative Treatment

A systematic review of the available literature was conducted to obtain best estimates of outcomes of conservative treatment in patients with CLTI [10]. Twenty-seven publications were included, consisting of 12 observational studies and 15 placebo arms from randomised clinical trials, totalling 1642 patients. Most studies included patients with nonreconstructable CLTI. The pooled 12 month all cause mortality rate in 14 studies comprising 1003 patients was 18%. The pooled major amputation rate from 14 studies comprising 755 patients was 27% after 1 year, and pooled AFS rate after 12 months in 11 studies with 970 patients was 60%. This review shows that conservative treatment outcomes in patients with chronic limb threatening ischemia are not dismal. Therefore, the conservative treatment option should be discussed with every patient in the decision making process.

The role of cilostazol therapy in patients with advanced PAD and critical limb ischemia (CLI) remains unclear. Desai et al. [11] reviewed ten studies that evaluated the effect of cilostazol vs standard antiplatelet therapy on limb-related and arterial patency-related outcomes. They found that patients who received cilostazol therapy along with open and/or endovascular intervention have overall improved outcomes. Specifically, patients who receive cilostazol have improved amputation-free survival, limb salvage rates, and decreased arterial restenosis rates. Additionally, patients who received cilostazol along with endovascular revascularization procedures also demonstrated higher freedom from TLR. There was no difference in all-cause mortality between patients who received and did not receive cilostazol therapy. This study included patients with both IC and CLI to help determine the effects of cilostazol therapy in a broader range of patients affected by symptomatic PAD. This inclusion criterion may have introduced confounding variables associated with disease severity, distribution of disease, and types of adjunct interventions offered.

12.3.2.3 Percutaneous Intervention Vs. Bypass Surgery for CLTI

Wang et al. [12] performed a meta-analysis of all available randomized controlled trials and observational clinical studies comparing percutaneous vascular interventions (PVI) vs bypass surgeries (BSX) in patients with CLI. Primary endpoints included overall survival, amputation-free survival, 30-day mortality, and major adverse cardiovascular and cerebrovascular events. They identified 45 cohorts and one randomized controlled trial in over 20,903 patients. In overall population, PVI reduced the risks of 30-day mortality (odds ratio [OR] 0.69), major adverse cardiovascular and cerebrovascular events (OR 0.42), and surgical site infection (OR 0.31), but increased the risks of long-term all-cause mortality (hazard ratio [HR] 1.16) and primary patency failure (HR 1.31). When compared with autogenous BSX, PVI was also associated with additional increased risks of long-term death or amputation (HR 1.41) and secondary patency failure (HR 1.51). In patients with infrapopliteal lesions, PVI had inferior primary patency (HR 1.39) compared with BSX. For patients in good physical condition with long life-expectancy, BSX may represent a better choice compared with PVI, particularly when autogenous bypass is available. Main outcomes of this review are given in Table 12.2.

Furthermore, a Cochrane review [13] assessed the effects of bypass surgery in patients with CLTI. Eleven trials reporting a total of 1486 participants were included. Six trials compared bypass surgery with PTA and one each compared with endarterectomy, thromboendarterectomy, thrombolysis, exercise and spinal cord stimulation. Comparing bypass surgery with PTA revealed a possible increase in early postinterventional non-thrombotic complications (OR 1.29, 95% CI 0.96 to 1.73; six studies; 1015 participants) with bypass surgery, but bypass surgery was associated with higher technical success rates. Analyses by different clinical severity of disease (intermittent claudication (IC) or CLI) revealed that peri-interventional complications occurred more frequently in participants with CLI undergoing bypass

Table 12.2 Percutaneous vascular interventions (PVI) vs. bypass surgeries in patients with CLI. Only the significant differences are presented. Hazard (HR) or Odds (OR) ratios >1 indicate an increased risk with PVI, HR and OR < 1 a lower risk compared to bypass surgery. (According to meta-analysis by [12])

Names of Outcomes	Effect Measure	Number of Studies (n)	Effect Estimate	Confidence Interval
Long-term outcomes				
– Overall survival	HR	19	1.16	1.05-1.27
– Matched/adjusted	HR	11	1.15	1.02-1.31
– Vein graft	HR	7	1.41	1.20-1.66
Amputation-free survival				
– Vein graft	HR	6	1.41	1.02-1.94
Primary patency				
– Overall	HR	10	1.31	1.08-1.58
– Matched/adjusted	HR	4	1.26	1.01-1.57
– Vein graft	HR	3	1.36	1.09-1.71
– Infrapopliteal	HR	4	1.39	1.10-1.75
Secondary patency				
– Vein graft	HR	3	1.51	1.17-1.95
30-day outcomes				
– Mortality overall	OR	14	0.56	0.33-0.95
MACCEs				
– Overall	OR	10	0.42	0.29-0.61
– CAD/MI	OR	10	0.52	0.31-0.87
Wound complications				
– Overall	OR	11	0.25	0.12-0.53
– Hemorrhage	OR	5	0.24	0.07-0.87
– Surgical site infections	OR	6	0.31	0.19-0.51
Infection	OR	5	0.14	0.03-0.63

HR Hazard Ratio, *OR* Odds Ratio, *MACCE* major adverse cardiovascular and cerebrovascular events, *CAD* coronary artery diseases, MI myocardial infarction

surgery than PTA. No differences in periprocedural mortality were identified. The primary patency rate at 1 year was higher after bypass surgery than after PTA, but this difference was not shown at 4 years. No differences in clinical improvement, amputation rates or mortality within the follow-up period between surgical and endovascular treatment were identified. This analysis has shown that PTA is associated with decreased peri-interventional complications in participants treated for CLI and shorter hospital stay compared with bypass surgery. Surgical treatment seems to confer improved patency rates up to 1 year. Endovascular treatment may be advisable in patients with significant comorbidity. No solid conclusions could be drawn regarding comparisons of bypass surgery with other treatments because of the paucity of available evidence.

12.3.2.4 Revascularization in Octogenarians

The aim of a systematic review and meta-analysis was to assess the clinical outcomes after revascularization in octogenarians with CLTI [14]. Twelve studies with a total of 17,118 patients were included. A 1 year mortality rate of 32% was found in octogenarians, which was significantly higher than in the non-octogenarians (17%). No significant difference in 1 year amputation rate was found (octogenarians 15%; non-octogenarians 12%). AFS was significantly lower in the octogenarian group. In a subgroup analysis differentiating between endovascular and surgical revascularization, amputation rates were comparable. For octogenarians, those treated conservatively had a mortality rate significantly higher than those treated by revascularizations. No significant difference in mortality rate was found between primary amputation and revascularization in octogenarians. As a consequence, the focus should be more on whether patient quality of life is improved by a therapeutic approach rather than increasing physical health and life expectancies of octogenarians.

12.3.2.5 Gender Differences in Outcome in Patients with Symptomatic PAD

A meta-analysis examined the effect of gender on all-cause mortality and major adverse cardiovascular events (MACE) in patients with symptomatic PAD [15]. For the primary end point of all cause mortality, 13 studies, incorporating 668,690 patients, were evaluated. Male gender was associated with a greater risk of all-cause mortality (HR, 1.13; $P < .001$) and MACE (HR, 1.10; 9; $P < .001$). In a stratified analysis, male gender was associated with a higher mortality risk for patients presenting with either critical limb ischemia or mixed clinical presentations but not for those with intermittent claudication. Elevated mortality risk was evident after revascularization (HR, 1.11), hospitalization (HR, 1.15), and amputation (HR, 1.09), although not in outpatient clinics, in men compared with women.

The long-term outcome of men and women after open surgery for CLTI was examined by Kotov et al. [16] in a propensity score matched cohort analysis comprising 6502 matched patients. Data of a German health insurance fund were used. In the matched cohort, the median follow up was 746 days for women and 871 days for men. Female sex was significantly associated with better overall survival (hazard ratio, HR, 0.80, log rank $p < .001$), AFS (HR 0.81, log rank $p < .0001$), and cardiovascular event free survival (HR 0.84, log rank $p < .001$) 5 years after the index treatment. These investigators also aimed to determine the sex disparities in long-term outcomes after endovascular revascularization of symptomatic peripheral arterial occlusive disease using health insurance claims data [17]. 50,051 patients (47.2% women) were identified and used to compose a matched cohort of 35,232 patients. Female patients exhibited better overall survival, amputation-free survival, and cardiovascular event-free survival at 5 years after treatment.

12.3.2.6 Infrainguinal Bypass Following Failed Endovascular Intervention

A systematic review and meta-analysis of all studies that compared primary infrainguinal bypass with bypass after failed endovascular intervention for PAD was performed by Hossain et al. [18] to determine whether bypass after failed endovascular intervention leads to inferior outcomes. Fifteen studies involving 11,886 patients met the inclusion criteria. No significant differences were found in 30-day mortality or 30-day amputation rates comparing primary bypass with bypass after failed endovascular intervention. However, 1 year amputation free survival was higher in the patients who had primary bypass (OR 1.30; 95% CI 1.10-1.52) compared with patients who had bypass after failed endovascular therapy. There was also worse 1 year primary patency (OR 1.65; 95% CI 1.04-2.62) for patients with prior failed endovascular intervention and there was a trend towards higher rates of early graft occlusion. The existing literature is limited by observational study design, inconsistent patient selection, and significant heterogeneity, yet suggests that bypass following failed endovascular intervention may result in suboptimal outcomes. Physicians who care for patients with peripheral arterial disease should consider the effect of endovascular treatment failure on future interventions.

12.3.2.7 Venous Arterialization for CLTI

In theory, venous arterialization allows reversal of blood flow through the capillaries, increases flow in existing collateral vessels, and stimulates angiogenesis. Yan et al. [19] systematically reviewed original venous arterialization studies for CLTI. Twelve studies included 442 patients that underwent treatment for 445 limbs (374 patients and 377 limbs underwent venous arterialization while remainder underwent traditional bypass and served as control subjects). Seven studies described superficial vein arterialization, 2 studies described open deep vein arterialization (DVA), 2 studies described hybrid DVA, 6 studies described percutaneous DVA, and 3 studies described a mix of venous arterialization techniques. The pooled 30-day mortality was 3.7%, 30-day morbidity was 15.5%, 30-day major adverse cardiovascular event was 5.2% and 30-day major adverse limb event was 16.7%. The pooled 1-year limb-salvage rate was 79.0% and 1-year survival rate was 85.7%. Venous arterialization has an acceptable 1-year limb salvage rate, however, this is based on low levels of evidence.

12.3.2.8 30-Day Readmission to the Hospital after Revascularization

A systematic review and meta-analysis aimed to determine the incidence of and risk factors for 30-day readmission after revascularization for PAD [20]. Fourteen publications reporting the outcomes of 526,008 patients were included. Reported

readmission rates ranged from 10.9% to 30.0% with a mean of 16.4%. The following risk factors had a significant association with readmission: female sex, black race, dependent functional status, critical limb ischemia, emergency admission, hypertension, heart failure, chronic pulmonary disease, diabetes, chronic kidney disease, dialysis dependence, smoking, postoperative bleeding, and postoperative sepsis. Approximately one in six patients undergoing revascularization for PAD are readmitted within 30 days of their procedure. The findings from this systematic review demonstrate a need for strategies to better filter out patients at high risk for readmission at the initial admission. An important limitation of the included studies was they were all based on data from the US healthcare system. It is, therefore, unclear as to how these results relate to patients in other settings.

Thirty-day readmission rates are used as a performance metric by the Centers for Medicare & Medicaid Services to judge the quality of hospital care and to penalize hospitals with higher-than-expected readmission rates for certain target conditions such as AMI, heart failure, and pneumonia. Kolte et al. [21] identified in the 2013 to 2014 Nationwide Readmissions Databases (USA) 60,998 index CLI hospitalizations (24.6% for rest pain, 37.2% for ulcer, and 38.2% for gangrene). The 30-day readmission rates for hospitalizations for rest pain, ulcer, and gangrene were 14.8%, 19.5%, and 25.0%, respectively (Table 12.3). Infections (23.5%), persistent or recurrent manifestations of peripheral artery disease (22.2%), cardiac conditions

Table 12.3 In-hospital outcomes of 60,998 patients with CLTI undergoing endovascular or surgical therapy and discharged alive after index hospitalization. Nationwide Readmissions Databases of the USA (according to [21])

Parameter	Rest pain (n = 15,007)	Ulcer (n = 22,706)	Gangrene (n = 23,285)
Age (years)	67.2 ± 11.3	70.3 ± 12.0	68.7 ± 12.1
Women, n (%)	6565 (43.7)	9402 (41.4)	8921 (38.3)
Charlson comorbidity index	2.3 ± 1.2	2.9 ± 1.3	3.1 ± 1.3
Revascularization			
– Endovascular only, n (%)	4829 (32.2)	13,018 (57.3)	13,838 (59.4)
– Surgery only, n (%)	7950 (53.0)	7831 (34.5)	7391 (31.7)
– Hybrid, n (%)	2228 (14.8)	1857 (8.2)	2056 (8.8)
Amputation, n (%)	205 (1.4)	2041 (9.0)	10,626 (45.6)
Major bleeding, n (%)	2513 (16.7)	4081 (18.0)	5850 (25.1)
Acute kidney injury, n (%)	922 (6.1)	2911 (12.8)	4114 (17.7)
Acute myocardial infarction, n (%)	267 (1.8)	510 (2.2)	627 (2.7)
Any complication, n (%)	6143 (40.9)	9608 (42.3)	12,105 (52.0)
Length of stay, days, n	5.4 ± 5.5	8.5 ± 8.8	13.6 ± 13.3
Discharge home (self-care), n (%)	9743 (64.9)	8987 (39.6)	6297 (27.1)
Discharge skilled nursing facility, n (%)	2075 (13.8)	6907 (30.4)	9694 (41.7)

(11.4%), procedural complications (11.0%), and endocrine issues (5.7%) were the most common reasons for readmission. Thirty-day readmissions for CLI contributed to more than $624 million in healthcare costs in 2013 to 2014. Adoption of 30-day readmission rate for CLI as a performance metric may provide hospitals an incentive to improve systems of care and to develop and implement strategies to lower CLI readmissions. Multidisciplinary CLI teams and wound teams may represent one such strategy.

12.3.2.9 Atherectomy for Peripheral Arterial Disease

A Cochrane Review evaluated the effectiveness of atherectomy for peripheral arterial disease compared to other established treatments [22]. Seven studies, with a total of 527 participants and 581 treated lesions were included. Six studies compared atherectomy versus balloon angioplasty (BA). No studies compared atherectomy with bypass surgery. The review showed that the evidence is very uncertain about the effect of atherectomy on patency, mortality and cardiovascular event rates compared to plain balloon angioplasty, with or without stenting. There were no clear differences in initial technical failure rates or target vessel revascularization rates, but there may be reduced dissection and bailout stenting after atherectomy although this is uncertain. The findings of this review agree with current widespread practice and established guidelines for balloon angioplasty in the routine treatment of people with peripheral arterial disease who are amenable to standard angioplasty.

12.3.2.10 Drug-Coated Balloon Angioplasty for the Treatment of CLTI

Safety and efficacy of drug-coated balloons (DCB) for the treatment of femoropopliteal or infrapopliteal lesions in patients with CLTI were investigated in a meta-analysis (26 studies, 12 retrospective, 14 prospective; 2108 patients) by Giannopoulos et al. [23]. The overall 12-month all-cause mortality and major amputation rates were 9% and 5%, respectively. A sensitivity analysis of the infrapopliteal lesions demonstrated no difference between DCB and balloon angioplasty in terms of primary patency, target lesion revascularization (TLR), major amputation, or mortality over 12 months. However, patients with infrapopliteal lesions undergoing DCB angioplasty did have a significantly lower risk for reocclusion (10% vs 25%, $p = 0.002$).

The risk of all-cause mortality after treatment with paclitaxel-coated devices vs uncoated controls in patients with chronic limb-threatening ischemia (CLTI) were identified in a second meta-analysis (11 randomised trials, 2213 patients, mean follow-up 25.6 months) by Dinh et al. [24]. There were 161 (18.6%) deaths among 866 subjects in the paclitaxel device group and 116 deaths among 584 (19.9%) subjects in the non-coated control group (RR 0.93, 95% CI 0.78 to 1.12, $p = 0.45$). This meta-analysis demonstrated that there is no increased risk of all-cause mortality in a predominately CLTI patient population treated with paclitaxel-coated vs uncoated

devices. With clear benefit and no suggestion of a link between the use of paclitaxel-coated devices and mortality, the authors recommended their continued use in this high-risk patient population.

12.3.3 Registries

12.3.3.1 Endovascular Vs. Open Revascularization

Using the NSQIP database, Mehaffey et al. [25] found a total of 13,294 lower extremity bypasses (LEBs) and infrainguinal endovascular interventions (IEI), with 8066 cases performed for CLI. Propensity matching identified 3848 cases (1924 per group). At 30 days, rates of MALEs were significantly lower in the LEB group (9.2% LEB vs IEI 12.2%; P = .003). Furthermore, there was no difference in 30-day MACE rate between the groups despite higher inherent risk with open surgical procedures. Therefore, this study supported the effectiveness and primacy of LEB for revascularization in CLI (Table 12.4).

In the Nationwide Readmissions Database, a total of 66,277 patients were identified between 2016 and 2018 who underwent endovascular revascularization (ER)

Table 12.4 Lower extremity bypass (LEB) for critical limb ischemia vs infrainguinal endovascular intervention (IEI). National Surgical Quality Improvement Program (NSQIP) database. Propensity-matched cohorts (according to [25])

Parameter	IEI	LEB	*P* value
Patients, n	1924	1924	
Age (years)	69 ± 12	69 ± 12	.42
Sex, male (%)	57.2	58.4	.47
ASA (%)			
– Class 2	10.6	2.2	.09
– Class 3	57.1	66.6	.22
– Class 4	23.0	30.9	.34
Functional status, independent (%)	83.6	84.6	.63
Wound clean (%)	96.1	92.7	.08
Revascularization suprageniculate (%)	70.3	71.9	
Revascularisation infrageniculate (%)	29.7	28.1	
MALE (%)	12.2	9.2	.003
– Untreated loss of patency (%)	1.7	2.7	.03
– Reintervention (%)	5.5	4.8	.38
– Amputation (%)	6.8	4.2	.0003
MACE, %	3.7	4.9	.07
– CVA or MI (%)	2.1	2.8	.14
– Mortality (%)	2.1	2.9	.15

MALE major adverse limb event, *MACE* major adverse cardiovascular event, *CVA* cerebrovascular accident, *MI* myocardial infarction

and surgical revascularization (SR) for CLI [26]. A total of 54,546 patients (82.3%) underwent ER and 11,731 (17.7%) underwent SR. After propensity score matching, 11,106 matched pairs were found. Endovascular revascularization was associated with an 18% higher risk of major amputation compared with SR (9.9% vs 8.4%; P = .001). Endovascular revascularization and SR had similar mortality rates (4.7% vs 4.4%; P = .39). However, the ER group had a 17% lower risk of in-hospital safety outcomes compared with the SR group (23.3% vs 26.8%; odds ratio, 0.83; P < .001). The results of this study suggest that ER was safer, without any difference in mortality, but ER was associated with an increased risk of major amputation compared with SR. However, the risk of major amputation was similar when both procedures were performed at high-volume centers.

Mathlouthi et al. [27] identified all patients who had undergone limb revascularization from January 2010 to December 2016 in the Vascular Quality Initiative Medicare-linked database. The aim of the study was to compare the midterm outcomes of the endovascular-first (EVF) and bypass-first (BF) strategies in patients with CLTI. The EVF approach was applied to 12,062 patients (70%) and the BF approach to 5166 patients (30%). At 2 years, the BF group had achieved greater rates of limb salvage (86.4% vs. 82.1%; P < 0.001), freedom from reintervention (72% vs. 68%; P < 0.001), AFS (66.9% vs. 56.3%; P < 0.001), and freedom from all-cause mortality (75.7% vs. 66.1%; P < 0.001). After adjusting for potential confounders, an effect of the treatment strategy on limb salvage, reintervention, AFS and all-cause mortality was not observed. The present study was the largest real-word analysis showing the noninferiority of the EVF approach in patients with CLTI.

Patients who underwent intervention for CLTI from 2015-2018 were identified by Latz et al. [28] using the American College of Surgeons National Quality Improvement Program (NSQIP) Vascular Surgery module. A total of 10,783 patients underwent an infrainguinal intervention for CLTI from 2015-2018. Of these, 6003 (55.7%) underwent LEB and 4780(44.3%) underwent infrainguinal endovascular intervention (IEI). Forty percent of the cohort was considered "high anatomic risk" by Objective Performance Goals (OPG) standards, and 13.6% were considered "high clinical risk." The IEI cohort vs. the LEB cohort experienced a myocardial infarction (MI)/Stroke rate of 1.8% vs. 3.6% (p < .001) and had a mortality rate of 2.0% vs. 1.7% (p = .22), which yielded a composite MACE of 3.4% vs. 4.8% (p = .001). The rate of reintervention for IEI vs LEB was 4.4% vs. 5.3% (p = .04), the loss of patency (without re-intervention) rate was 1.8% vs. 1.8% (p = 1.0), and the major amputation rate was 4.1% vs. 3.5% (p = 0.15), which resulted in a MALE rate of 9.1% vs. 8.8% (p = 0.50). Endovascular outcomes continue to demonstrate inferiority in major amputation and overall MALE. However, endovascular intervention has a significantly reduced incidence of MACE.

12.3.3.2 Revascularization with Paclitaxel-Coated Devices in Patients with CLTI

Smith et al. [29] retrospectively studied patients who underwent femoropopliteal artery (FPA) intervention for an indication of CLTI in the Vascular Quality Initiative peripheral vascular intervention database from 2016 to 2020. Data regarding the safety and efficacy of paclitaxel (PTX)-coated peripheral arterial devices were analyzed in propensity score matched patients. Demographics, comorbidities, indications, and procedural details were similar between 14,065 PTX and 14,065 non-PTX propensity-matched patients. Peripheral vascular intervention using a paclitaxel-coated device was associated with improved limb salvage, primary patency, and freedom from major adverse limb events at the 18-month follow-up compared with uncoated devices. This benefit was not associated with an increase in all-cause mortality out to 4.5 years. Peripheral vascular intervention using a paclitaxel-coated device in patients with chronic limb-threatening ischemia is associated with improved limb salvage and freedom from major adverse limb events.

12.3.3.3 Endovascular Revascularization in Patients with Impaired Ambulatory Capacity

The Global Vascular Guidelines recommend offering primary amputation to CLTI patients who have pre-existing dysfunctional or unsalvageable limb, a poor functional status (e.g., bedridden), or a short life expectancy after shared decision-making with the patient and health care team. Naazie et al. [30] evaluated the impact of impaired ambulatory capacity on the outcomes of peripheral vascular interventions (PVI) among patients with CLTI using the Vascular Quality Initiative database. Of the 49,807 patients studied, 28,469 (57.2%) were ambulatory, 15,148 (31.0%) were ambulatory with assistance, 5395 (10.8%) were wheelchair bound, and 525 (1.1%) were bedridden. After PVI, there was a two-fold increase in the odds of 30-day death in patients who were ambulatory with assistance (odds ratio [OR], 2.03; $P < .001$) and wheelchair-bound patients (OR, 2.09; $P < .001$), and a more than six-fold increase in bedridden patients (OR, 6.28; $P < .001$) compared with ambulatory patients. Among ambulatory patients, the risks of major amputation and death within 1 year were only 10% and 12%, respectively, whereas that of bedridden patients were as high as 30% and 38%, respectively. A stepwise decrease in amputation-free survival from 81% with full ambulatory capacity to less than 50% (47.7%) in bedridden patients was observed. These risks should be considered during shared decision-making regarding management options for non-ambulatory patients with CLTI.

12.3.3.4 Failed Femoropopliteal Covered Vs. Bare Metal Stents

DeCarlo et al. [31] sought to determine if patients with failed SFA covered stent (CS) were more likely to present with more severe ischemic symptoms than patients with failed SFA bare metal stent (BMS) in a retrospective review of data from the Vascular Quality Initiative. There were 3721 patients: 3338 with index BMS, 383 with index CS. At reintervention, acute limb ischemia (ALI) was the presenting symptom for 12.0% of the CS cohort vs 6.3% of the BMS cohort ($P < .001$). More patients with an index CS underwent major amputation at the time of reintervention (2.6% vs 1.0%; $P = .006$). This study demonstrates that patients with a failed SFA CS are almost twice as likely to present with ALI as patients with a failed SFA BMS. Patients with failed SFA CS are also more likely to present with more severe ischemia, more likely to require an urgent or emergent reintervention, and more likely to undergo an open bypass at the time of representation for failure. Concerns about CS and their use in femoropopliteal occlusive disease have been raised. First, the placement of a CS in the femoropopliteal segment could result in the coverage of important collaterals. Second, the mechanism of failure with these grafts is referred to as edge stenosis. The edge of the stiff CS causes intimal hyperplasia, leading to compromised inflow or outflow and subsequent stent thrombosis, resulting in a new, long-segment occlusion. The risks of CS placement should be considered in operative planning and preoperative discussion for SFA stenting.

12.3.3.5 Lower Extremity Bypass in Patients on Hemodialysis

Hemodialysis patients who underwent infrainguinal open operation using autogenous versus prosthetic conduits in the United States Renal Data System between January 2007 and December 2011 were studied by Arhuidese et al. [32]. There were 9739 (autogenous: 59%, prosthetic: 49%) infrainguinal open bypass operations performed in this cohort. Of these, 4717 (48%) were femoral-popliteal, 3321 (34%) were femoral-tibial, and 1701 (18%) were popliteal-tibial bypasses. Bypass operations were performed most commonly for critical limb ischemia (72%). Primary patency was 18% for both types of conduits at 5 years ($P = .16$). Comparing autogenous versus prosthetic conduits, primary-assisted patency was 23% vs 20% at 5 years ($P = .98$), while secondary patency was 30% for both conduits at 5 years ($P = .05$). Absolute all-cause mortality during the study period was 58% for patients who received autogenous bypasses versus 63% for patients who received prosthetic bypasses. Multivariable analyses demonstrated greater patency (adjusted hazard ratio [aHR]: 1.16; $P = .003$) and limb salvage (aHR: 1.12; $P = .03$) for autogenous compared to prosthetic bypasses. The data confirm the long-term benefits of autogenous conduits compared with prosthetic conduits in this high-risk population of patients, especially for the treatment of distal lesions.

12.3.3.6 High-Intensity Statin Therapy among Patients Undergoing Lower Extremity Bypass

He et al. [33] performed a retrospective cohort study using the IBM MarketScan database (2008 to 2017) to identify all insured adult patients with CLTI that underwent a LEB procedure, including those performed to above-knee and below-knee targets. A total of 25,907 patients who underwent LEB for CLTI were identified, of which 6696 (26%) were maintained on high-dose statins, 9297 (36%) were on low-dose statins, and 9914 (38%) had inconsistent pharmacy claims for statin therapy after surgery. Patients maintained on high intensity statins after LEB had a significantly lower risk-adjusted likelihood of requiring a reintervention or amputation as compared with patients on low-intensity and/or limited (ie, inconsistent) statin therapy. These findings were independent of the indication for revascularization, extent of LEB, or whether an autologous vein graft was used. The results of this study suggest that patients undergoing lower extremity bypass procedures for CLTI should be up-titrated and/or maintained on high-intensity statin therapy to achieve the best long-term outcomes.

12.3.3.7 Revascularization in Active Smokers

Active smokers undergoing lower extremity endovascular (LEE) revascularization or open lower extremity bypass (LEB) were identified in the NSQIP data set [34]. From 2011 to 2014, 4706 lower extremity revascularizations were performed in active smokers (37% of all revascularizations). In this group, 1497 were LEE revascularizations (55.6% for CLI, 13.4% for below-knee pathology) and 3209 were LEB (68.9% CLI, 34.7% below-knee). Analysis of 30-day outcome revealed that in active smokers, LEB for IC and CLI requires fewer reinterventions but is associated with a higher rate of postoperative wound complications compared with LEE revascularization. However, the risk for limb amputation is higher in actively smoking patients when treated by LEE revascularization compared with LEB for CLI. Importantly, cardiovascular complications are significantly higher in actively smoking patients with IC undergoing LEB compared with LEE. This additional cardiovascular risk should be carefully weighed when proposing LEB for actively smoking patients with non-limb-threatening IC. The authors suggested smoking cessation and avoiding open surgical bypass in claudicant patients who smoke.

12.3.4 Clinical Trials with Specific Questions

12.3.4.1 Drug-Coated Devices

IN.PACT DEEP was an independently adjudicated prospective, multicenter, randomized controlled trial that enrolled 358 subjects with below the knee CLI. Subjects were randomized 2:1 to DCB angioplasty or PTA. Freedom from clinically driven

target lesion revascularization through 5 years was 70.9% and 76.0% (log-rank p = 0.406), and the incidence of the safety composite endpoint was 59.8% and 57.5% (log-rank p = 0.309) in the DCB angioplasty and PTA groups, respectively [35]. The rate of major amputation was 15.4% for DCB angioplasty compared with 10.6% for PTA (log-rank p = 0.108). Additional analyses from this study showed no increase in all-cause mortality with DCB angioplasty (39.4%) compared with PTA (44.9%) (log-rank p = 0.727). Predictors of mortality included age, Rutherford category >4, and previous revascularization but not paclitaxel by dose tercile. No difference in clinical performance was found in patients with CLI treated with the IN.PACT Amphirion DCB or PTA, including major amputation and mortality.

In the PADI trial, adults with CLI (Rutherford category ≥4) and infrapopliteal lesions were randomized to receive DES with paclitaxel or PTA ± BMS ([36]. Seventy-four limbs (73 patients) were treated with DES and 66 limbs (64 patients) with PTA ± BMS. The 5-year major amputation rate was lower in the DES group (19.3% vs 34.0% for PTA ± BMS; p = 0.091). In addition, the 5-year amputation-free survival and event-free survival were significantly higher in the DES group (31.8% vs 20.4%, p = 0.043; and 26.2% vs 15.3%, p = 0.041, respectively). After 1 year, the cost difference per patient between DES and PTA ± BMS is €1.679 in favor of DES and €2.694 after 3 years. In this analysis, DES were cost-effective due to the higher hospital costs of amputation and rehabilitation in the PTA ± BMS group. For the PADI trial, the 10-year results were published [37]. Ten years after the first inclusion, 109/137 (79.6%) patients had died. There was no significant difference between mortality in the DES group compared with the PTA ± BMS group (Log-rank p value = 0.12). No specific dose-related mortality (HR 1.00, 95% CI 0.99-1.00, p = 0.99) or dose per weight mortality (HR 1.05, 95% CI 0.93-1.18, p = 0.46) relationships were identified. In conclusion, the 10-year survival of CLI patients treated below the knee (BTK) is poor. There were no significant differences between 10-year mortality in patients with CLI treated BTK with either paclitaxel-coated DES or PTA ± BMS.

The Zilver PTX RCT [38] was a prospective, multinational, randomized study comparing the safety and effectiveness of the polymer-free, paclitaxel-coated Zilver PTX DES to PTA and provisional BMS placement in patients with femoropopliteal PAD. There were 336 patients treated with the DES and 143 patients treated with percutaneous transluminal angioplasty (PTA) or BMS. There was no difference in all-cause mortality for the DES compared to PTA/BMS in the RCT (19.1% DES versus 17.1% PTA/BMS through 5 years, p = 0.60).

12.3.4.2 Tack Endovascular System for Post-Angioplasty Dissections

The Tack Endovascular System (4F; Intact Vascular) is specifically designed for post-PTA dissection repair. A prospective, single-arm, multicenter study evaluated the Tack Endovascular System for treating post-PTA dissections in the mid/distal popliteal, tibial, and peroneal arteries [39]. Of the 233 patients enrolled, 117 (50.2%) had Rutherford class 5 and 78 (33.5%) had Rutherford class 4. A total of 341

post-PTA dissections were treated. Each patient received at least one Tack implant, and 100% of the dissections resolved according to the angiographic core laboratory findings. The 6-month Tacked segment patency was 82.1% (247 of 301) and target limb salvage was 98.5% (202 of 205). The Kaplan-Meier freedom from clinically driven target lesion revascularization and amputation-free survival at 6 months was 92.0% and 95.7%, respectively. Using Tack implants to repair below-the-knee dissections is safe and effective, with high rates of patency, limb salvage, and freedom from major adverse limb events.

12.3.4.3 LimFlow System for Percutaneous Deep Vein Arterialization

The LimFlow System consists of arterial and venous catheters that allow ultrasonographic determination of crossover direction and location; an antegrade, over-the-wire valvulotome; and selfexpanding stent grafts specifically designed to divert blood flow from the tibial (donor) artery into the tibial and pedal (recipient) venous system. PROMISE I is a prospective, multicenter, single-arm, early feasibility study of the LimFlow percutaneous deep vein arterialization (pDVA) approach to treating no-option CLTI [40]. Of 32 enrolled patients, 31 (97%) were successfully treated with the LimFlow System at the time of the procedure, and two (6.3%) were lost to follow-up. The 30-day, 6-month, and 12-month AFS rates were 91%, 74%, and 70% respectively. The wound healing status of fully healed or healing was 67% at 6 months, and 75% at 12 months. Reintervention was performed in 16 patients (52%) with 14 (88%) of the maintenance reinterventions occurring within the first 3 months. These results suggest early safety and provide an initial assessment of the efficacy of the LimFlow pDVA System.

The PROMISE I study established the feasibility of transcatheter arterialization of the deep veins for the treatment of no-option CLTI. The PROMISE II study was performed to expand on this work to evaluate the effect of the procedure on amputation-free survival and limb salvage as compared with an objective performance goal [41]. 105 patients who had CLTI were enrolled. Of the patients enrolled, 33 (31.4%) were women. Transcatheter arterialization of the deep veins was performed successfully in 104 patients (99.0%). At 6 months, 66.1% of the patients had amputation-free survival. Limb salvage (avoidance of above-ankle amputation) was attained in 67 patients (76.0% by Kaplan-Meier analysis). Wounds were completely healed in 16 of 63 patients (25%) and were in the process of healing in 32 of 63 patients (51%). No unanticipated device-related adverse events were reported. Transcatheter arterialization of the deep veins was safe and could be performed successfully in patients CLTI and no conventional surgical or endovascular revascularization treatment options. The PROMISE II study was commented by McGinigle et al. [42]. These authors considered the trial design as inadequate for an unproven therapy. The presented 6-month outcomes (25% healing and 24% major amputation) reflect the natural history of disease; similar outcomes may be achieved with palliative wound care (absent the 37% reintervention rate). It is unclear which patients might benefit because data regarding the staging of wounds, ischemia, and

foot infection and hemodynamic measures (e.g., toe pressure and transcutaneous oxygen) before and after treatment were not provided. Thus, the present data are insufficient to determine a meaningful benefit for the technology evaluated in this study, and transcatheter deep-vein arterialization should not be considered as a standard treatment option for patients with advanced CLTI.

12.4 Conclusions for Clinical Practice

1. Offer revascularization to all average-risk patients with advanced limb-threatening conditions and significant perfusion deficits.
2. Use an endovascular-first approach for treatment of CLTI patients with moderate to severe aorto-iliac disease, depending on the history of prior intervention.
3. Perform open common femoral artery endarterectomy with patch angioplasty, with or without extension into the profound femoral artery, in CLTI patients with hemodynamically significant (> 50% stenosis) disease of the common and deep femoral arteries.
4. In average-risk CLTI patients with infrainguinal disease, base decisions of endovascular intervention vs. open surgical bypass on the severity of limb threat, the anatomic pattern of disease, and the availability of autologous vein.
5. The Society for Vascular Surgery's Objective Performance Goals (OPGs) represent a measure by which each practitioner should assess the long-term quality of his interventions in CLTI patients.
6. Thirty-day readmission rates are a performance metric to judge the quality of hospital care.
7. Hemodialysis patients with CLTI have a significantly higher risk of amputation compared to non-dialysis patients. Data confirm the long-term benefits of autogenous conduits compared with prosthetic conduits in this high-risk population.
8. Most current studies conclude that there is no increased risk of all-cause mortality in a predominately CLTI patient population treated with paclitaxel-coated vs uncoated devices.
9. Initial results demonstrate the safety and effectiveness of the Tack Endovascular System for the treatment of post-angioplasty dissections below the knee.
10. In selected patients with no-option CLTI, the LimFlow percutaneous deep vein arterialization may be a safe and effective treatment to prevent amputation and heal wounds.
11. The likelihood of an amputation after 1 year in patients with CLTI increases with higher WIfI stages, which is an important prognostic information.

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Chapter 13
Acute Limb Ischemia



13.1 Clinical Categories and Prognosis

Acute limb ischaemia (ALI) is caused by an abrupt decrease in arterial perfusion of the limb. Potential causes are artery disease progression, cardiac embolization, aortic dissection or embolization, graft thrombosis, thrombosis of a popliteal aneurysm or cyst, popliteal artery entrapment syndrome, trauma, phlegmasia cerulea dolens, ergotism, hypercoagulable states and iatrogenic complications related to vascular procedures. Limb viability is threatened and prompt management is needed for limb salvage. The emergency level and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficits. The clinical categories and prognosis according to Rutherford are presented in Table 13.1 [1].

Table 13.1 Clinical categories of acute limb ischaemia (ALI) (according to ESC guidelines, [1])

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 revascularized
III	Irreversible	Profound, anaesthetic	Profound, paralysis (rigor)	Major tissue loss, permanent nerve damage inevitable

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13.2 Guidelines

13.2.1 European Society of Cardiology (ESC) in Collaboration with the European Society for Vascular Surgery (ESVS) [1]

- In the case of neurological deficit, urgent revascularization is indicated (Class I recommendation / Level of evidence C).
- In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision (Class I recommendation / Level of Evidence C).
- Heparin and analgesics are indicated as soon as possible (Class I recommendation/Level of evidence C).

Different revascularization modalities can be applied, including percutaneous catheter–directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy) and surgical thrombectomy, bypass and/or arterial repair. The strategy will depend on the presence of a neurological deficit, ischaemia duration, its localization, comorbidities, type of conduit (artery or graft) and therapy-related risks and outcomes. Owing to reduced morbidity and mortality, endovascular therapy is often preferred, especially in patients with severe comorbidities. Thrombus extraction, thrombo-aspiration and surgical thrombectomy are indicated in the case of neurological deficit, while catheter-directed thrombolytic therapy is more appropriate in less severe cases without neurological deficit.

13.2.2 American College of Cardiology (ACC) /American Heart Association /AHA) [2]

Preliminary Note The guidelines distinguish between level A, level B-R (randomized), level B-NR (non-randomized), level C-LD (limited data) and level C-EO (expert opinion). All comments are referred only in abbreviated form. COR Class of Recommendation; LOE Level of Evidence.

13.2.2.1 Clinical Presentation of ALI

- Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy. (COR I; LOE C-EO).

Comment: Depending on local clinical expertise, the vascular specialist may be a vascular surgeon, interventional radiologist, cardiologist, or a general surgeon with specialized training and experience in treating PAD. If such expertise is not locally or rapidly available, there should be strong consideration of transfer of the patient to a facility with such resources.

- In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging. (COR I; LOE C-LD).

  Comment: ALI is a medical emergency and must be recognized rapidly. The time constraint is due to the period that skeletal muscle will tolerate ischemia—roughly 4–6 h. A rapid assessment of limb viability and ability to restore arterial blood flow should be performed by a clinician able to either complete the revascularization or triage the patient. The bedside assessment includes arterial and venous examination with a handheld continuous-wave Doppler because of the inaccuracy of pulse palpation. The loss of dopplerable arterial signal indicates that the limb is threatened. The absence of both arterial and venous Doppler signal indicates that the limb may be irreversibly damaged (nonsalvageable).

13.2.2.2 Medical Therapy for ALI

- In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated. (COR I; LOE C-EO).

13.2.2.3 Revascularization for ALI

- In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology and degree of ischemia). (COR I; LOE C-LD).

  Comment: For marginally or immediately threatened limbs (Category IIa and IIb ALI; Table 13.1), revascularization should be performed emergently (within 6 h). For viable limbs (Category I ALI), revascularization should be performed on an urgent basis (within 6–24 h). The revascularization strategy can range from catheter-directed thrombolysis to surgical thromboembolectomy. Available facilities and clinical expertise are factors that should be considered when determining the revascularization strategy. The technique that will provide the most rapid restoration of arterial flow with the least risk to the patient should be selected.
- Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb. (COR I; LOE A).
- Amputation should be performed as the first procedure in patients with a nonsalvageable limb. (COR I; LOE C-LD).

Comment: For patients with Category III ALI, amputation should be performed as the index procedure. Prolonged duration of ischemia is the most common factor in patients requiring amputation for treatment of ALI. The risks associated with reconstruction outweigh the potential benefit in a limb that is already insensate or immobile because of prolonged ischemia. Patients who have an insensate and immobile limb in the setting of prolonged ischemia (>6–8 h) are unlikely to have potential for limb salvage.

- Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization. (COR I; LOE C-LD).

  Comment: When compartment pressure is >30 mm Hg, there is capillary and venule compression that leads to malperfusion of the muscle; this is compartment syndrome. Fasciotomy is indicated when the compartment pressure increases. Measurement of intracompartment pressure is not always easily accessible. In such cases, evaluation for fasciotomy is prompted by development of increased pain, tense muscle, or nerve injury. Fasciotomy should be considered for patients with Category IIb ischemia for whom the time to revascularization is >4 h.
- In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis. (COR IIa; LOE B-NR).
- In patients with ALI due to embolism and with a salvageable leg, surgical thromboembolectomy can be effective. (COR IIa; LOE C-LD).
- The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown. (COR IIb LOE C-LD).

  Comment: The use of ultrasound-accelerated catheter delivery of thrombolytic agents has been published in case series and retrospective analyses. However, the single RCT comparing this technique to standard catheter-based thrombolytic therapy failed to demonstrate a difference in outcomes, including bleeding, despite a lower total amount of lytic delivered.

13.2.3 European Society for Vascular Surgery (ESVS) [3]

Not all recommendations are given if they overlap with the previous ones.

- Recommendation 2: For patients with acute limb ischemia and underlying malignant disease, active revascularization in selected patients should be considered, as the immediate postoperative outcome is comparable to patients without malignancy. (Recommendation class IIa; Level of evidence B).
- Recommendation 3: For patients presenting with a possible diagnosis of ALI, it is recommended that clinical assessment is performed urgently by a vascular specialist, who should be responsible for planning further investigation and management. (Recommendation class I; Level of evidence C).

- Recommendation 6: For patients presenting with ALI, computed tomography angiography is recommended as the first line modality for anatomical imaging. (Recommendation class I; Level of evidence B).
- Recommendation 7: For patients presenting with acute limb ischemia, duplex ultrasound or contrast-enhanced magnetic resonance angiography may be considered for alternative imaging before starting treatment, depending on availability and clinical assessment. (Recommendation class IIb; Level of evidence B).
- Recommendation 9: For patients with acute limb ischemia awaiting revascularization, heparin is recommended. (Recommendation class I; Level of evidence C).
- Recommendation 10: For patients with acute limb ischemia awaiting revascularization, supplemental oxygen is recommended. (Recommendation class I; Level of evidence C).
- Recommendation 11: For patients with acute limb ischemia awaiting revascularization, adequate analgesia and intravenous rehydration are recommended. (Recommendation class I; Level of evidence C).
- Recommendation 12: For patients with acute limb ischemia, treated by open surgery, prostacyclin analogues may be considered during and after revascularization. (Recommendation class IIb; Level of evidence B).
- Recommendation 13: It is recommended that patients diagnosed with acute limb ischaemia in a non-vascular centre be transferred to a vascular centre that offers the full range of open and endovascular interventions with an urgency that depends on the severity of the ischaemia. (Recommendation class I; Level of evidence B).
- Recommendation 14: It is recommended that patients with acute limb ischaemia should have access to treatment in a hybrid theatre, or operating theatre with C arm equipment, and by a clinical team able to offer a full range of open or endovascular interventions during a single procedure. (Recommendation class I; Level of evidence C).
- Recommendation 18: For patients undergoing open and endovascular surgery for acute limb ischaemia, completion angiography is recommended. (Recommendation class I; Level of evidence C).
- Recommendation 19: For patients with residual thrombus after open surgery for acute limb ischaemia, intra-operative local thrombolysis may be considered. (Recommendation class IIb; Level of evidence C).
- Recommendation 21: After open revascularisation for acute limb ischaemia, simultaneous endovascular treatment addressing inflow or outflow stenosis should be considered. (Recommendation class IIa; Level of evidence C).
- Recommendation 22: For patients with acute limb ischaemia, intravenous thrombolysis is ***not*** recommended. (Recommendation class III; Level of evidence A).
- Recommendation 23: For patients with acute onset claudication (Rutherford grade I) that does not threaten the limb, (percutaneous) catheter-directed thrombolysis is ***not*** **recommended**. (Recommendation class III; Level of evidence B).

- Recommendation 24: For patients with ALI Rutherford grade IIa, it is recommended that (percutaneous) catheter-based thrombolysis is considered as an alternative to surgery. (Recommendation class I; Level of evidence A).
- Recommendation 25: For patients with Rutherford grade IIb acute limb ischaemia, (percutaneous) catheter-directed thrombolysis may be considered if initiated promptly, and may be combined with percutaneous aspiration or thrombectomy. (Recommendation class IIb; Level of evidence B).
- Recommendation 33: For patients with acute limb ischaemia, aspiration and mechanical thrombectomy should be considered. (Recommendation class IIa; Level of evidence C).
- Recommendation 34: For patients with acute limb ischaemia secondary to thrombosis of a popliteal artery aneurysm, repair of the aneurysm with a saphenous vein bypass should be considered. (Recommendation class IIa; Level of evidence B).
- Recommendation 35: For patients with acute limb ischaemia secondary to popliteal artery aneurysm, pre-operative or intra-operative thrombolysis to improve runoff should be considered. (Recommendation class IIa; Level of evidence B).
- Recommendation 36: For patients with acute limb ischaemia secondary to popliteal artery aneurysm, stent grafting is ***not*** recommended as first line treatment. (Recommendation class III; Level of evidence B).
- Recommendation 37: For patients who have had revascularisation for acute limb ischaemia, clinical examination is recommended to diagnose post-reperfusion compartment syndrome. [Recommendation refers to the lower limb]. (Recommendation class I; Level of evidence B).
- Recommendation 39: For patients who have had revascularisation for acute limb ischaemia, routine prophylactic fasciotomy is ***not*** recommended, as it is associated with prolonged hospital stay, local infection, and development of late deep venous insufficiency. [Recommendation refers to the lower limb]. (Recommendation class III; Level of evidence C).
- Recommendation 42: When post-ischaemic compartment syndrome is diagnosed, fasciotomy should be considered as soon as possible, and always within 2 h. [Recommendation refers to the lower limb]. (Recommendation class IIa; Level of evidence C).

13.3 Results

13.3.1 Systematic Reviews/Meta-Analyses

13.3.1.1 Catheter Directed Thrombolysis

Catheter directed thrombolysis (CDT) is the first choice treatment in many centres for patients with marginally threatened ALI (sensory loss present; Rutherford IIA). A systematic literature review was performed by Doelare et al. [4] to investigate the

short and long term outcomes of CDT for patients with not immediately threatening limb ischaemia. Thirty-nine studies were included, comprising 1861 patients who received CDT for not immediately threatening ALI. Funnel plots showed an indication of publication bias, and heterogeneity was substantial. Data from 5 to 13 studies were included in the meta-analysis. The pooled treatment duration was 2 days, with an angiographic success rate of 80% and a 30 day freedom of amputation rate of 98%. The major bleeding rate was 5%, with a 30 day mortality rate of 3%. The amputation free survival rate was 71% at the 1 year and 63% at the 3 year follow up. Long term patency rates were retrieved from four studies: 48% at 1 year. Although CDT in the treatment of not immediately threatening ALI showed high angiographic success, the long term outcomes were relatively poor, with low patency and a substantial risk of major amputation. Further research is required to interpret the outcome of CDT in the context of potential confounders such as age and comorbidities.

13.3.1.2 Ultrasound-Accelerated Thrombolysis

Araujo et al. [5] assessed the safety and effectiveness of percutaneous thrombectomy or ultrasound-accelerated thrombolysis (USAT) for the initial management of ALI in adults. They included one RCT in this Cochrane review. This study had a total of 60 participants and compared USAT with standard treatment catheter-directed thrombolysis (CDT). There was insufficient evidence to assess the safety and effectiveness of USAT versus CDT alone for ALI for the evaluated outcomes: amputation rate, major bleeding, clinical success, and adverse effects.

13.3.1.3 Infusion Techniques for Peripheral Arterial Thrombolysis

The effects of infusion techniques during peripheral arterial thrombolysis for treatment of patients with ALI were compared by Broderick and Patel [6] in a Cochrane Review (9 studies/671 patients).Trials were grouped according to types of techniques assessed (e.g. intravenous and intra-arterial delivery of the agent, ‘high-’ and ‘low-dose’ regimens of the agent, continuous infusion and ‘forced infusion’ of the agent, use of adjunctive antiplatelet agents). There was insufficient evidence to show that any thrombolytic regimen provides a benefit over any other in terms of amputation-free survival, amputation, or 30-day mortality. The rate of cerebrovascular accident or major bleeding requiring surgery or blood transfusion did not clearly differ between regimens but may occur more frequently in high dose and IV regimens. This evidence was limited and of very low certainty. Minor bleeding may be more common with high-dose and IV regimens. In this context, thrombolysis may be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa) compared with surgery. Caution is advised for patients who do not have limb-threatening ischaemia (Rutherford grade I) because of risks of major haemorrhage, cerebrovascular accident, and death from thrombolysis.

13.3.1.4 Endovascular and Surgical Revascularization Techniques

Veenstra et al. [7] compared the safety and effectiveness of catheter-driven thrombolysis (CDT) with surgical revascularization and evaluated the various fibrinolytic agents, endovascular, and pharmacochemical approaches that aim for thrombectomy. Twenty-five studies, investigating a total of 4689 patients, were included for meta-analysis. No differences were found in limb salvage between thrombectomy and thrombolysis. More major vascular events were seen in the thrombolysis group (6.5% compared with 4.4% in the surgically treated group; P = .02). Comparable limb salvage was found for high- and low-dose recombinant tissue plasminogen activator (r-tPA). No significant differences were found in major vascular event between low r-tPA (14%) and high r-tPA (10.5%; P = .13). The 30-day limb salvage rate was 79.7% for r-tPA treatment and 60.4% for streptokinase (OR, 3.14; P = .01). AngioJet showed more limb salvage at 6 months compared with r-tPa (OR, 2.21; P = .01). Both CDT and surgery have comparable limb salvage rates in patients with ALI; however, CDT is associated with a higher risk of hemorrhagic complications. No conclusions can be drawn regarding the risk of hemorrhagic complications regarding thrombolytic therapy by means of r-tPA, streptokinase, or urokinase. Insufficient data are available to conclude the preference of using a hybrid approach, ultrasound-accelerated CDT, heated r-tPA. or novel endovascular (rheolytical) thrombectomy systems.

13.3.1.5 Outcomes after Acute Limb Ischemia in Patients with Cancer

Cancer results in a hypercoagulable state that is associated with both venous and arterial thromboses. In a systematic review and meta-analysis, Govsyeyev et al. [8] analyzed the available clinical data on cancer and its association with ALI and evaluated the outcomes in these patients after a diagnosis of ALI. Seven studies with 2899 patients were included in this review. 1195 (41%) had had a diagnosis of ALI before their cancer diagnosis, and 1704 (59%) had presented with ALI after a cancer diagnosis. Nearly three quarters of ALI events were among patients with cancer of the skin and soft tissue (19%), genitourinary (18%), lung (17%), and gastrointestinal (16%) systems. Major amputation was more likely in patients with a diagnosis of ALI after a cancer diagnosis (7.4% vs 4.6%; P < .01). The incidence of mortality at 1 year was significantly greater for patients with established cancer who had presented with ALI compared with the patients who had presented with ALI before a cancer diagnosis (50.6% vs 29.9%; P < .01). The occurrence of ALI in patients with cancer results in high mortality, regardless of whether it precedes or follows a cancer diagnosis. Because the occurrence of ALI could be a paraneoplastic phenomenon of a clinically silent cancer, an underlying cancer should be considered in otherwise healthy patients presenting with ALI, and a cancer risk assessment should be performed.

13.3.2 Studies/Registries

13.3.2.1 Acute Limb Ischemia among Patients with COVID-19 Infection

The aim of a review presented by Galyfos et al. [9] was to evaluate pooled data on patients with COVID-19 infection and ALI. In total, 34 studies (19 case reports and 15 case series/cohort studies) were found. These studies evaluated a total of 540 patients, out of which 199 were eligible for this analysis. Mean age of patients was 61.6 years and 78.4% of patients were male. Medical treatment was selected as first-line treatment for 41.8% of cases. Pooled mortality rate among 34 studies reached 31.4%. Pooled amputation rate among 34 studies reached 23.2%. Pooled clinical improvement rate among 28 studies reached 66.6%. Pooled reoperation rate among 29 studies reached 10.5%. Medical treatment was associated with a higher death risk compared with any intervention (odds ratio, 4.04; P = .045) although amputation risk was not different between the two strategies (odds ratio, 0.977; P = .986) (data from 31 studies). The message was that SARS-CoV-2 infection is associated with a high risk for thrombotic complications including ALI. COVID-19 associated ALI occurred in patients with a low incidence of comorbidities and was associated with high mortality and amputation risk. Conservative therapy seemed to have a higher mortality risk than any intervention.

Bellosta et al. [10] evaluated the data from 20 patients with ALI who were positive for COVID-19. Operative treatment was performed in 17 patients (85%). Revascularization was successful in 12 of the 17 (70.6%). Of the 20 patients, eight (40%) had died in the hospital. The patients who had died were significantly older (81 ± 10 years vs 71 ± 5 years; P = .008). Although successful revascularization was not significantly associated with the postoperative use of intravenous heparin (64.7% vs 83.3%; P = .622), no patient who had received intravenous heparin required reintervention. The use of continuous postoperative systemic heparin infusion was significantly associated with survival (0% vs 57.1%; P = .042).

Lou et al. [11] assessed endovascular and open surgical lower-extremity revascularization and amputation procedural volumes and outcomes before, during, and after the first North American COVID-19 pandemic surge, using data from the Society for Vascular Surgery Vascular Quality Initiative (VQI). The final cohort comprised 57,181 patients from 147 US and Canadian sites. Overall procedure volumes fell 35.2% during and 19.8% following the surge, compared with presurge months. Procedure volumes fell 71.1% for claudication ($p < 0.001$) and 15.9% for CLTI ($p < 0.001$) but remained unchanged for ALI when comparing surge to presurge months. Adjusted mortality was significantly higher among those with claudication (0.5% vs 0.1%; $p = 0.01$) and ALI (6.4% vs 4.4%; $p = 0.003$) when comparing postsurge with presurge period.

13.3.2.2 Endovascular-First Approach to Acute Limb Ischemia

Poursina et al. [12] performed a single-center, single-arm, retrospective cohort study of 60 consecutive patients with ALI from 2015 to 2018. The Rutherford class was I in 15 patients (25%), IIa in 23 (38%), IIb in 13 (22%), and III in 9 patients (15%).The endovascular-first approach procedures included catheter-directed thrombolysis only (n = 19; 32%), catheter-directed thrombolysis plus aspiration and/or rheolytic thrombectomy (n = 19; 32%), and aspiration and/or rheolytic thrombectomy (n = 16; 26%). Six patients (10%) underwent covered stent placement only. Technical success was achieved in 58 patients (97%), with open conversion required in two patients (3%). At 30 days postoperatively, 52 patients (87%) survived, and 53 (88%) had successful limb salvage. Five patients (8%) had required four-compartment fasciotomy. At 1 year, the Kaplan-Meier estimates were as follows: amputation-free survival 58%, limb salvage 74.3% and survival 73.3%. The current endovascular approaches to ALI have high technical success rates. Survival, limb salvage, perioperative complications, and length of stay were similar to those from previous reports of historical open cohorts.

Tsujimura et al. [13] compared the outcomes of endovascular therapy in 2398 cases of ALI with those in 74,171 patients with CLTI using data from a national Japanese registry of EVT between January 2015 and December 2018. Patients with ALI were older and had a higher prevalence of female sex, impaired mobility, and history of cerebrovascular disease, but a lower prevalence of cardiovascular risk factors and history of coronary artery disease. The proportion of in-hospital EVT-related complications in ALI was 6.1% and was significantly higher compared with those in chronic symptomatic PAD patients (2.0%, $P < 0.001$). Bedridden status, history of coronary artery disease, and a suprapopliteal lesion were identified as independent risk factors for in-hospital complications.

13.3.2.3 Open Surgical Intervention for ALI

Using the NSQIP database from 2012–2017, Gupta et al. [14] assessed the rate of reintervention for ALI after open surgical intervention. A total of 2878 ALI patients underwent open revascularization; 35.7% were transfers from another acute care hospital. A total of 13.8% required reoperation and 7.9% required readmission within 30 days. A total of 32% of reoperations were recurrent revascularization, representing 4.4% of all ALI patients. The 30-day all-cause mortality was 9.24%. 2135 (74.2%) patients underwent lower extremity revascularization and 707 (24.6%) underwent upper extremity revascularization. Patients with lower extremity ALI had significantly higher mortality rate (10.1% vs. 6.6%, $P = 0.03$), readmission rate (9.1% vs. 4.4%, $P < 0.01$), and reintervention rate (15.0% vs. 10.1%, $P < 0.01$) respectively, compared to upper extremity patients.

13.3.2.4 Endovascular Versus Surgical Revascularization for ALI

Kolte et al. [15] used the 2010 to 2014 National Inpatient Sample databases to identify hospitalizations with a primary diagnosis of ALI. Patients were propensity-score matched on the likelihood of undergoing endovascular versus surgical revascularization using a logistic regression model. The primary outcome was in-hospital mortality. Of 10,484 hospitalizations for ALI, endovascular revascularization was performed in 5008 (47.8%) and surgical revascularization in 5476 (52.2%). In the propensity-score matched cohort (n = 7746; 3873 per group), patients who underwent endovascular revascularization had significantly lower in-hospital mortality (2.8% versus 4.0%; P = 0.002), myocardial infarction, composite of death/myocardial infarction/stroke, acute kidney injury, fasciotomy, major bleeding, and transfusion, but higher vascular complications, compared with those undergoing surgical revascularization. Rates of any amputation were similar between the 2 groups. Median length of stay was shorter and hospital costs higher with endovascular versus surgical revascularization (Table 13.2). In patients with ALI, endovascular revascularization was associated with better in-hospital clinical outcomes compared with surgical revascularization.

In the National Inpatient Sample databases from 2005 to 2014, Holscher et al. [16] found a total of 116,451 admissions for ALI. 40,982 (35.2%) patients had an endovascular first approach. There was an increase in the proportion of ALI admissions treated by an endovascular-first approach over time, starting from 25.7% in 2005 and increasing to 41.6% in 2014 (per year: odds ratio, 1.07; P < .001). Independent predictors of endovascular-first management included younger age, male sex, renal insufficiency, and more recent calendar year of admission (P ≤ .02), whereas patients who underwent fasciotomy, those with Medicaid, and those admitted on a weekend were more likely to undergo open-first management (P ≤ .02).

Table 13.2 In-hospital outcomes of endovascular vs surgical revascularization for acute limb ischemia. Propensity score matched analysis. Data from the National Inpatient Sample databases 2010 to 2014 (according to [15])

Outcome	Endovascular n = 3873	Surgical n = 3873	P
Death, n (%)	108 (2.8)	156 (4.0)	0.003
Myocardial infarction, n (%)	74 (1.9)	104 (2.7)	0.023
Stroke, n (%)	56 (1.4)	73 (1.9)	0.13
Death/Myocardial infarction/Stroke, n (%)	202 (5.2)	292 (7.5)	<0.001
Any amputation, n (%)	182 (4.7)	197 (5.1)	0.43
Fasciotomy, n (%)	74 (1.9)	315 (8.9)	<0.001
Acute kidney injury, n (%)	406 (10.5)	462 (11.9)	0.044
Major bleeding, n (%)	648 (16.7)	812 (21.0)	<0.001
Intracranial haemorrhage, n (%)	27 (0.7)	13 (0.3)	0.030
Transfusion, n (%)	400 (10.3)	716 (18.5)	<0.001
Vascular complications, n (%)	53 (1.4)	26 (0.7)	0.003
Length of stay, days	4.0 (2.0 bis 7.0)	5.0 (3.0 bis 8.0)	<0.001

Endovascular-first management had higher mean hospital costs than open-first management ($29,719 vs $26,193; P < .001). The risk-adjusted odds of in-hospital major amputation was similar in both groups (adjusted odds ratio, 0.99; 95% CI, 0.85–1.15; P = .88). ALI patients treated with an endovascular-first approach had lower crude in-hospital mortality than those with an open-first approach (3.9% vs 6.4%; P < .001). After adjustment for patient, hospital, and admission factors, an endovascular-first approach was associated with 32% lower odds of in-hospital mortality compared with an open-first approach.

Yang et al. [17] compared the safety, feasibility, and outcomes of ALI after surgical embolectomy or catheter-directed therapy (CDT). Data from the Taiwan's National Health Insurance Database (NHID) between the years 2000 and 2015 were used. There was no significant difference in mortality risk between CDT (n = 905) and surgical intervention (n = 4559; 9.5% vs 10.68%). The risk of amputation was also comparable between the two groups. (13.59% vs 14.81%). Age (p < 0.001) and liver disease (p = 0.01) were associated with higher mortality risks. Heart failure (p = 0.03) and chronic or end-stage renal disease (p = 0.03) were associated with higher amputation risks. Prior antithrombotic agent use (p = 0.03) was associated with a reduced risk of amputation. Both surgical intervention and CDT were effective and feasible procedures for patients with ALI in Taiwan.

13.3.2.5 Thrombolytic Therapy for ALI

Acosta et al. [18] compared the effects of thrombolysis, complications, and outcomes of pharmaco-mechanical thrombolysis (PMT) first versus catheter-directed thrombolysis (CDT) first in a large cohort of patients with ALI. In this monocenter study, all consecutive endovascular thrombolytic/ thrombectomy events in patients with ALI performed between January first, 2009, and December 31st, 2018 (n = 347) were included. Presentation of Rutherford IIb ALI was more common in the PMT first group (36.2% vs. 22.5%, respectively, P = 0.027). Among the 58 patients receiving PMT first, 36 (62.1%) were terminated within a single session of therapy without need of CDT. The median duration of thrombolysis was shorter (P < 0.001) for the PMT first group (n = 58) compared to the CDT first group (n = 289) (4.0 vs. 23.0 h, respectively). There was no significant difference in amount of tissue plasminogen activator given, successful thrombolysis/thrombectomy (86.2% and 84.8%), major bleeding (15.5% and 18.7%), distal embolization (25.9% and 16.6%), major amputation or mortality at 30-days (13.8% and 7.7%) in the PMT first compared to the CDT first group, respectively. The proportion of new onset of renal impairment was higher in the PMT first compared to the CDT first group (10.3% vs. 3.8%, respectively), and the increased odds (odds ratio 3.57, 95% confidence interval 1.22–10.41) were maintained in the adjusted model. In conclusion, both PMT first and CDT first have high technical success rates, and PMT first appears to be a good treatment alternative in Rutherford IIb ALI. The found renal function deterioration in the PMT first group needs to be evaluated in a prospective, preferably randomized trial.

Doelare et al. [19] determined the relationship between deviating blood clotting tests, APTT and fibrinogen, and major bleeding, as well as its impact on patient relevant clinical outcomes after CDT. All consecutive patients treated with CDT for ALI in two Dutch hospitals between January 2004 and April 2021 were analysed retrospectively. Patients were treated with two dosing regimens (low dose: 50,000 IU/h; high dose: 100,000 IU/h) of urokinase and, after 2018, with a single low dose regimen of alteplase (rtPA) due to urokinase manufacturing problems. Of the 443 included cases, 277 underwent CDT with urokinase and 166 with rtPA. The incidence of major bleeding in the whole cohort was 7%. Patients with a fibrinogen levels <1.0 g/L developed more major bleeding than those in whom the fibrinogen level did not drop below 1.0 g/L (15% vs. 6%; p = .041). Systemic heparinisation during CDT or high (> 80 seconds) APTT were not significantly associated with major bleeding. Angiographic success (47% vs. 72%; p = .003) and 30 day amputation free survival (53% vs. 82%; p < .001) were lower for cases with major bleeding. Older age, cardiac history, high dose regimens (≥75,000 IU/hour urokinase), and fibrinogen values <1.0 g/L were independent predictors for major bleeding during CDT. In conclusion, high dose thrombolytic regimens and fibrinogen levels of ≤1.0 g/L were associated with more major bleeding during thrombolytic therapy. Major bleeding significantly worsened the clinical outcome.

Bath et al. [20] analyzed the trends, outcomes, and complications of thrombolytic therapy for ALI in the United States using the Nationwide Inpatient Sample (2003–2013). A total of 162,240 patients with acute limb ischemia were estimated: 33,615 patients (20.7%) underwent thrombolysis as the initial treatment. The utilization of thrombolysis increased significantly during the study period (16.8–24.2%, p < 0.0001). The most common group was thrombolysis and endovascular procedure (40.7%), followed by thrombolysis alone (34.1%), and thrombolysis and open surgery, T + OPEN (25.2%). Overall mortality was 4.9%; thrombolysis and endovascular procedure compared to thrombolysis alone and T + OPEN had a lower mortality rate (3.2% vs. 6.1% and 5.9%, p < 0001). The overall stroke rate was 1.9%; thrombolysis alone had the highest stroke rate (3.0%, p < 0.0001) with thrombolysis and endovascular procedure the lowest (1.2%) and T + OPEN 1.7%. The highest amputation rate was T + OPEN (11.6%, p < 0.001) compared to thrombolysis and endovascular procedure (5.1%) and thrombolysis alone (5.3%). T + OPEN had the highest incidence of cardiac (5.5%), respiratory (7.3%) and renal complications (12.5%), pneumonia (4.0%), and fasciotomy (16.8%) (all p < 0.0001). Thrombolysis remains an effective treatment for acute limb ischemia with increased utilization over time.

Using a Swedish database, Grip et al. [21] reported long-term outcomes after thrombolysis in 590 patients (689 limbs) with ALI. The aetiology of ischaemia was graft/stent/stent graft occlusion in 39.8%, arterial thrombosis in 27.7%, embolus in 25.1% and popliteal aneurysm in 7.4%. The mean follow-up was 59.4 months, during which 32.9% needed further re-interventions, 16.4% underwent amputation without re-intervention, and 50.7% had no re-intervention. The need for re-intervention during follow-up was 48.0% in the graft/stent occlusions group, 34.0% of the popliteal aneurysm group, 25.4% in the thrombosis group, and 16.3% in the embolus group (p < .001). The amputation rate was lower in the embolic group at 1

Table 13.3 Long-term outcome after thrombolysis for acute lower limb ischaemia. (According to [21])

Variable	Thrombosis	Embolus	Popliteal aneurysm	Graft/stent occlusion
Patients, n (%)	191 (27.7)	173 (25.1)	51 (7.4)	274 (39.8)
Age, years	72.6	***76.6***	70.1	***69.1***
Successful thrombolysis, %	***73.4***	86.7	78.4	85.8
Adjuvant revascularisation procedure, %	80.6	***67.1***	82.4	81.4
– Endovascular, %	84.4	87.1	33.3	77.1
– Open, %	7,1	***4.3***	***54.8***	9.0
– Hybrid, %	8.4	8.6	11.9	13.9
Major bleeding complications, %	13.7	8.7	21.6	15.0
Major amputation <30 days, %	13.6	***4.1***	***25.5***	10.9
Survival <30 days, %	93.7	93.6	98.0	97.4
Primary patency after 1 year, %	67.3	85.7	59.1	62.6
Amputation after 1 year, %	19.9	***8.1***	27.1	20.4
Survival after 1 year, %	83.2	81.5	96.1	85.8
Primary patency after 5 years, %	55.1	***83.3***	37.9	***43.3***
Amputation after 5 years, %	22.3	***11.1***	30.6	***40.1***
Survival after 5 years, %	54.1	49.6	***83.3***	50.5

Note: Significant differences highlighted

and 5 years (8.1% and 11.1%, respectively, p = .001). Survival was higher in the group with occluded popliteal aneurysms at 5 years (83.3%, p = 0.004). Amputation free survival was 72.1% and 45.2% at 1 and 5 years; lower in the occluded graft/stent group at 5 years (37.9%, p = .007). In conclusion, intra-arterial thrombolytic therapy achieves good medium and long-term clinical outcome, reducing the need of open surgical treatment in most patients (Table 13.3).

Ascher et al. [22] created a fast-track thrombolysis protocol for arteries (FTTP-A). The goal of the protocol is to re-establish patency during the first session of thrombolysis, thus decreasing costs and complications associated with prolonged periods of thrombolytic exposure. FTTP-A includes periadventitial lidocaine injection at the arterial puncture site under ultrasound guidance, contrast arteriography of the entire targeted segment, pharmacomechanical rheolytic thrombectomy of the occluded arterial segment, tissue plasminogen activator infusion along the occluded segment, balloon maceration of the thrombus, and (if deemed necessary) placement of a stent in an area of significant (≥30%) stenosis that is refractory to balloon angioplasty and thrombolysis. Primary FTTP-A (50 total interventions) was performed in 42 patients. The mean operative time was 148.9 ± 62.9 min (range, 83–313 minutes), and the mean volume of tissue plasminogen activator infused was 9.7 ± 4.0 mg (range, 2–20 mg). Of 42 patients with acute limb ischemia (ALI) who underwent FTTP-A, 34 (81%) patients had complete thrombus resolution in a single

session, with no intensive care unit stays, decreased use of tissue plasminogen activator, and decreased costs compared with procedures that required overnight thrombolytic infusion. There was no limb loss or mortality at 5 years.

13.3.3 Special Issues

13.3.3.1 ALI after Cardiac Surgery

In a retrospective analysis of single center prospectively collected registry data, Folkert et al. [23] investigated the outcomes of patients who suffered from ALI after open cardiac and thoracic aortic surgery. Between 2002 and 2012, there were 11,343 patients who underwent major open cardiac surgery, with 156 cases of ALI for an incidence of 1.4%. There were 105 operations performed for 156 cases of ALI. The most common operation performed for ALI was thrombectomy (43 [28%]), followed by fasciotomies (20 [13%]); percutaneous intervention (6 [4%]), endarterectomy (5 [3%]), and lower extremity bypass operations (4 [3%]) were less commonly performed. There were 21 major (13%) and six minor (4%) amputations performed on the index hospitalization, including two upper extremity amputations. ALI was associated with a significant reduction in long-term survival (hazard ratio, 3.72; 95% CI, 2.97–4.65; $P < .0001$). This study suggests that acute limb ischemia after open cardiac operations is associated with a significant risk of amputation and decreased long-term survival.

13.3.3.2 Management of Acute Limb Ischemia in Paediatric Patients

Wang et al. [24] reported the long-term morbidity associated with infants who develop ALI and are not offered initial surgical intervention A total of 25 (28% female) infant patients were diagnosed with ALI. The average age for this cohort was 3.5 ± 3.2 months (standard deviation). Most cases were secondary to iatrogenic injury (88%) from arterial cannulation. Injury sites were more concentrated to the lower extremities (84%) compared with the upper. Absence of Doppler signals was noted in 64% of infants, whereas limb cyanosis was observed in 60% at the time of presentation. Infants were initially treated with anticoagulation (80%) when possible. Two patients failed to respond to nonoperative management and required thrombolysis secondary to progression of thrombus burden while anticoagulated. There were no major (above-ankle) amputations at 30 days. Three deaths occurred within 30 days; all were unrelated to limb ischemia. In the 30-day survivors, overall duration of follow-up was 53.5 ± 38.5 months. One infant required above-knee amputation 6 weeks after diagnosis, resulting in an overall limb salvage rate of 96% on follow-up. In contrast to the adult population, ALI in infants can be managed

with anticoagulation alone with good results. Long-term follow-up continues to demonstrate excellent functional results and minimal disability.

The Healthcare Cost and Utilization Project State Inpatient Database (California, Iowa, and New York) between 2007 and 2013 was queried by Lim et al. [25]. A total of 1576 pediatric patients with ALI were identified among 6,122,535 pediatric admissions (26 per 100,000 admissions). Average age was 9.9 ± 7.1 years. There were 263 patients who underwent surgical revascularization. Overall, the amputation rate was low (<2%; n = 28), especially in the upper extremities. Infants demonstrated the highest limb preservation rate compared with older age groups. Mortality rate for patients with ALI was statistically different between groups (8.5% in infants, 4.2% in children, and 3.0% in adolescents; P < .01). Open surgical revascularization is not associated with improved major amputation or in-hospital mortality. Nonoperative management may be considered an initial treatment modality for most pediatric ALI.

13.4 Conclusions for Clinical Practice

1. Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.
2. For marginally or immediately threatened limbs (Category IIa and IIb ALI), revascularization should be performed emergently (within 6 h). For viable limbs (Category I ALI), revascularization should be performed on an urgent basis (within 6–24 h).
3. For patients with acute limb ischemia awaiting revascularization, heparin is recommended.
4. In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology and degree of ischemia).
5. Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb. An endovascular-first approach seems to be associated with lower odds of in-hospital mortality compared with an open-first approach.
6. ALI in infants can be managed with anticoagulation alone with good results.

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Chapter 14
Popliteal Artery Aneurysm

14.1 Guidelines

14.1.1 Society for Vascular Surgery

The Society for Vascular Surgery (SVS) clinical practice guidelines recommend [1]:

1. We recommend that patients who present with a popliteal artery aneurysm (PAA) are screened for both a contralateral PAA and an AAA. (Grade of recommendation 1, strong; quality of evidence B, moderate).
2. We recommend that patients with an asymptomatic PAA ≥ 20 mm in diameter should undergo repair to reduce the risk of thromboembolic complications and limb loss. (Grade of recommendation 1, strong; quality of evidence B, moderate).

   For selected patients at higher clinical risk, repair can be deferred until the PAA has become ≥30 mm, especially in the absence of thrombus. (Grade of recommendation 2, weak; quality of evidence C, low).
3. We suggest that for patients with a PAA < 20 mm, in the presence of thrombus and clinical suspicion of embolism or imaging evidence of poor distal runoff, repair should be considered to prevent thromboembolic complications and possible limb loss. (Grade of recommendation 2, weak; quality of evidence C, low).
4. For asymptomatic patients with a life expectancy of ≥5 years, we suggest open PAA repair, provided that an adequate saphenous vein is present. For patients with a diminished life expectancy, if intervention is indicated, endovascular repair should be considered. (Grade of recommendation 2, weak; quality of evidence C, low).
5. We recommend that intervention for thrombotic and/or embolic complications of PAA be stratified by the severity of ALI at presentation. We recommend that patients with mild to moderate ALI (Rutherford grade I and IIa) and severely obstructed tibiopedal arteries undergo thrombolysis or pharmacomechanical

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intervention to improve runoff status, with prompt transition to definitive PAA repair. We recommend that patients with severe ALI (Rutherford grade IIb) undergo prompt surgical or endovascular PAA repair, with the use of adjunctive surgical thromboembolectomy or pharmacomechanical intervention to maximize tibiopedal outflow. Nonviable limbs (Rutherford grade III) require amputation. (Grade of recommendation 1, strong; quality of evidence B, moderate).

6. We recommend that patients who undergo open or endovascular PAA repair should be followed up using clinical examination, ABI [ankle-brachial index] and Doppler ultrasound (DUS) at 3, 6 and 12 months during the first postoperative year and, if stable, annually thereafter. In addition to DUS evaluation of the repair, the aneurysm sac should be evaluated for evidence of enlargement. If abnormalities are found on clinical examination, ABI or DUS, appropriate clinical management according to the lower extremity endovascular or open bypass guidelines should be undertaken. (Grade of recommendation 1, strong; quality of evidence B, moderate). If compressive symptoms or symptomatic aneurysm sac expansion are noted, we suggest surgical decompression of the aneurysm sac. (Grade of recommendation 1, strong; quality of evidence C, low).
7. We suggest that patients with an asymptomatic PAA who are not offered repair should be monitored annually for changes in symptoms, pulse examination, extent of thrombus, patency of outflow arteries, and aneurysm diameter. (Grade of recommendation 2, weak; quality of evidence C, low).

14.2 Results

14.2.1 Meta-Analyses and Systematic Reviews

14.2.1.1 Open Vs. Endovascular Repair

A Cochrane review 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 [2]. A single RCT with a total of 30 PAAs met the inclusion criteria. At 4 years there was no clear benefit from either endovascular stent graft or surgery to primary or assisted primary patency (moderate-certainty evidence). As both operating time and hospital stay were reduced in the endovascular group (moderate-certainty evidence), it may represent a viable alternative to open repair of PAA.

Leake et al. [3] evaluated all available comparative studies of open repair of PAA (OPAR) vs endovascular repair (EPAR) by meta-analysis. A total of 14 studies were identified encompassing 4880 popliteal artery aneurysm repairs (OPAR, 3915; EPAR, 1210). OPAR patients were younger and more likely to have worse tibial runoff than EPAR patients. OPAR had higher odds of wound complications (OR, 5.182; $P < .001$) and lower odds of thrombotic complications (OR, 0.362; $P < .001$). OPAR had longer length of stay ($P < .001$) and fewer reinterventions ($P < .001$).

Primary patency was better for OPAR at 1 year and 3 years (relative risk, 0.607 [P = .01] and 0.580 [P = .006], respectively). There was no difference in secondary patency at 1 year and 3 years (0.770 [P = .458] and 0.642 [P = .073], respectively). The overall literature is lacking in quality, and the need for well-controlled studies is critically important. The current treatment strategy of the authors incorporates both techniques: if patients have favorable anatomy (two-vessel runoff or more with adequate landing zones of ≥15 mm of normal, non-aneurysmal artery), no available venous conduit, and high surgical morbidity risks (poor cardiopulmonary reserve), they undergo endovascular repair. Exceptions include patients with acute ischemia who need emergent revascularization or lytic therapy. All others are shifted toward OPAR.

To support the Society for Vascular Surgery guidelines, Beuschel et al. [4] conducted a systematic review and meta-analysis to summarize the best available evidence comparing the efficacy of OAR with EVAR in the treatment of PAAs, as well as the natural history of PAAs. Thirty-two original studies and 4 systematic reviews were identified. Meta-analysis showed that compared with the endovascular approach, open surgical repair was associated with higher primary patency at 1 year, lower occlusion rate at 30 days and fewer reinterventions, but a longer hospital stay and more wound complications. There was no statistically significant difference in primary patency at 3 years, secondary patency, mortality at the longest follow-up, mortality at 30 days, or amputation. The certainty in these estimates was, in general, low. These findings suggest that open PAA repair may be more durable than endovascular repair, albeit with a higher risk of complications and resource use.

Another meta-analysis [5] was based on 17 studies, incorporating 6887 PAA cases (1662 EVAR and 5225 OAR). Popliteal artery aneurysms ranged in mean diameter from 22.9 to 36.9 mm. Rates of primary patency were found to be significantly higher for patients treated with OAR compared to those treated with EVAR (HR = 1.60; 95% confidence interval [CI]: 1.12-2.30; P = .03). Operating time and length of stay were significantly shorter for patients treated with EVAR. Patients with EVAR experienced significantly higher rates of graft thrombosis and reintervention within 30 days compared to OAR patients. However, no significant differences were observed between both approaches with respect to amputation rates (OR = 1.01; 95% CI: 0.55-1.85; P = .98).

14.2.2 Registries

14.2.2.1 Popliteal Aneurysms with Screening Detected Abdominal Aortic Aneurysms

Cervin et al. [6] presented data on PAA prevalence in patients with screening-detected AAA from Uppsala county. A total of 19,820 65-year-old men (84.6%) accepted the invitation to screening between 2006 and 2017. AAA was found in 173 (0.9%), and subaneurysmal aortic dilatation (25-29 mm, SAA) in 149 subjects

(1.1% of those screened 2006–2013, eligible for this study). In the whole cohort, 14.2% of those examined had at least one PAA of any size, 3.0% were ≥ 15 mm and 2.2% ≥ 20 mm. There was no difference in PAA prevalence between AAA and SAA: 15.9% vs. 12.2% (p = .48). There was no difference in aortic diameter in those with or without PAA (p = .46), but there were significant correlations with common iliac artery (p < .001), common femoral artery (p < .001), and superficial femoral artery (p < .001) diameters. A high prevalence of PAA among subjects with screening detected AAA and SAA was found. PAA was not correlated with the aortic diameter in this cohort, where all had dilated aortas, while correlations with peripheral and iliac artery diameters were identified.

14.2.2.2 Vascunet Registry

Vascunet is an international collaboration of vascular registries. During 2012–2018, data from 10,764 PAA repairs were included [7]. The incidence was 10.4 cases/million inhabitants/year (2.4-19.3). The mean age was 71.3 years (66.8-75.3). Most patients, 93.3%, were men and 40.0% were active smokers. The operations were elective in 73.2% (60.0%-85.7%). The mean pre-operative PAA diameter was 32.1 mm (27.3-38.3 mm). Open surgery dominated in both elective (79.5%) and acute (83.2%) cases. A medial surgical approach was used in 77.7%, and posterior in 22.3%. Vein grafts were used in 63.8%. Early amputation and death were higher after acute presentation than after elective surgery (5.0% vs. 0.7%; 1.9% vs. 0.5%). This pattern remained 1 year after surgery (8.5% vs. 1.0%; 6.1% vs. 1.4%). Elective open compared with endovascular surgery had similar 1 year amputation rates (1.2% vs. 0.2%; p = .095) but superior patency (84.0% vs. 78.4%; p = .005). Veins had higher patency and lower amputation rates, at 1 year compared with synthetic grafts (86.8% vs. 72.3%; 1.8% vs. 5.2%; both p < .001). The posterior open approach had a lower amputation rate (0.0% vs. 1.6%, p = .009) than the medial approach. The authors concluded that the frequent use of endovascular repair and prosthetic grafts should be reconsidered based on these results.

14.2.2.3 POPART Registry

From June 2014 to August 2019, 794 cases of PAAs had been recorded in the POPART registry [8]. Of the 662 patients in the open surgical repair (OSR) group, 50.3% were symptomatic compared with 29.2% of the 106 patients in the endovascular repair (ER) group (P < .05). Emergency treatment because of acute ischemia, critical ischemia, or rupture was necessary for 149 patients (22.5%) in the OSR group and 11 patients (10.3%) in the ER group. The most frequent postoperative complications were impaired wound healing (OSR 7.1%; ER 2.8%; P > .05) and major bleeding (OSR 3.9%; ER 2.8%; P > .05). The in-hospital length of stay was significantly longer for the OSR group than for the ER group (median, 10 days vs median 7 days). The overall patency for the OSR and ER groups after 12 and

24 months was 83.2% and 44.7% (P < .005) and 74.2% and 29.1% (P < .005), respectively. The outcomes with a prosthetic graft vs an autologous vein were significantly poorer in the OSR group (primary patency, 71.4% vs 88.1% at 12 months). In this registry, patency rates after 12 and 24 months were low in the ER group compared to patients treated with open repair. However, despite its large number of patients, the POPART registry suffers from multiple drawbacks common to registries including high loss to follow-up and bias [9]. In addition, low rate of ER and low use of percutaneous access in ER may suggest operator inexperience with endovascular skills. To answer the question as to which treatment strategy is best for patients with PAA requires a randomized controlled trial (RCT) that would eliminate confounding and minimize selection bias.

14.2.2.4 Open PAA Repair in Men and Women

Using Vascular Quality Initiative data, Naazie et al. [10] investigated whether sex disparities exist for patients treated with open PAA repair. The study included 3807 adult patients, of whom 160 were women (4.2%). Women were more likely to undergo repair for symptomatic disease (77.5% vs 64.1%; P = .001). No difference was found between the women and men in primary patency (95.2% vs 90.8%; P = .230) and overall survival (94.3% vs 96.1%; P = .270). Amputation-free survival was lower for women than for men (91.4% vs 95.3%; P = .033). After adjustment for confounders, no differences were found between the women and men regarding the loss of primary patency and all-cause mortality. For symptomatic PAAs, the risk of major amputation was threefold greater for women (adjusted hazard ratio, 3.09; 95% confidence interval, 1.05-9.06; P = .040), and the risk of the composite end point of major amputation or death was twofold higher for women than for men (adjusted hazard ratio, 1.97; 95% confidence interval, 1.02-3.79; P = .043). Early recognition and treatment of PAAs in women at a smaller size cutoff before they become symptomatic might potentially lead to improved outcomes. Consideration should be given to sex-based guidelines for treating asymptomatic PAAs in women.

14.2.2.5 Open PAA Repair Using Vein and Prosthetic Conduits

In the 2003–2019 Vascular Quality Initiative database, a total of 1146 limbs in 1065 patients underwent elective open revascularization for PAA [11]. Vein was used in 921 limbs (80%), and prosthetic in 225 (20%). Patients in the prosthetic cohort had a shorter procedure time, were older, and had a higher prevalence of COPD. There was no significant difference in the rate of surgical site infection (2% vs. 2%; P = 0.946). There was an increased tendency toward more symptomatic patients in the vein cohort although not statistically significant (49% vein vs. 41% prosthetic; P = 0.096). On a mean follow-up of 13 ± 5 months, the incidence of MALE and MALE-free survival were comparable between the two groups. At multivariable analysis, outflow bypass targets to the infrapopliteal arteries (HR 2.05; 95%

confidence interval (CI), 1.16-3.65; P = 0.014) and symptomatic aneurysm (HR 1.81; 95% CI, 1.04-3.15; P = 0.037) were independently associated with loss of primary patency. Conduit type did not make a difference in MALE-free survival, or primary graft patency at 2-years. The study demonstrates that conventional open PAA repair with prosthetic conduit yields results comparable to those with vein conduit with regard to primary and secondary patency and MALEs at 2-years for targets to the popliteal artery. However, when the distal target was infrapopliteal, worse outcomes were observed with prosthetic conduit.

14.2.2.6 Open Vs Endovascular Repair of Symptomatic PAAs

Naazie et al. [12] aimed to study the comparative effectiveness of endovascular PAA repair (EPAR) versus open PAA repair (OPAR) in the treatment of patients presenting symptomatic. A total of 1375 patients of the VQI database were studied, of which 23.7% (n = 326) were treated with EPAR. Patients treated with OPAR were younger, less likely to have coronary artery disease (CAD) and chronic kidney disease (CKD), but more likely to be smokers and to present with acute lower extremity ischemia. OPAR treated patients had better 2-year AFS (84.5% vs. 72.5%, P < 0.001) and overall survival (86.2% vs. 74.7%, P < 0.001). Freedom from major amputation at 2 years was comparable between EPAR and OPAR (95.5% vs. 97.7%, P = 0.164) in the overall cohort. OPAR and EPAR had comparable adjusted risk of 2-year major amputation in the overall cohort. However, for patients presenting with acute limb ischemia OPAR was associated with 72% lower risk of 2-year major amputation compared to EPAR (aHR, 0.28; 95% CI, 0.10-0.83; P = 0.021). In this study of symptomatic popliteal aneurysms, OPAR was associated with significantly better amputation free and overall survival compared to EPAR.

14.2.2.7 Open Repair Vs Endovascular Repair in Patients with Acute Limb Ischemia

Satam et al. [13] compared the outcomes of urgent endovascular and open repair of PAAs for patients presenting with ALI in the Vascular Quality Initiative (VQI) database from 2010 to 2021. Urgent PAA repair for ALI constituted 10.5% (n = 571) of all PAAs. Of the urgent PAA repairs for ALI, 460 (80.6%) were open, and 111 (19.4%) were endovascular. The proportion of endovascular repair significantly increased from 16.7% in 2010 to 85.7% in 2021. Patients undergoing endovascular repair were older (71.2 ± 12.5 vs 68.0 ± 11.8; P = .011) than patients undergoing open repair. They were also more likely to have coronary artery disease (32.4% vs 21.7%; P = .006). Open PAA repair was associated with more bleeding complications (20.8% vs 2.7%; P < .001), longer postoperative length of stay (8.1 ± 9.3 days vs 4.9 ± 5.6 days; P < .001), and less likelihood of discharge to home (64.9% vs 70.3%; P = .051). The perioperative major amputation rate was 7.5% with no difference between the two treatment strategies. Patients undergoing endovascular repair

had significantly higher inpatient (1.1% vs 0%; P < .001) and 30-day (6.3% vs 0.4%; P < .001) mortality than open repair. The 1-year major amputation rate was 15% for both groups, and there was no difference between the two, but 1-year minor amputation was significantly higher in the endovascular group (4.8% vs 1.3%; P = .048). However, patients receiving endovascular repair had significantly higher 1-year (16.5% vs 8.4%; P = .02) mortality compared with open repair. Patients undergoing endovascular revascularization had significantly higher reintervention rate (28.6% vs 2%; P < .001) with no significant difference in secondary patency compared with open revascularization. Endovascular repair is associated with decreased complications and hospital length of stay. The increased perioperative mortality seen in this group may be related to patient selection and baseline comorbidities.

14.2.3 Studies

14.2.3.1 PAA Growth Rates

In a population-based retrospective cohort study from two centres, Jergovic et al. [14] presented treatment trends in 241 patients diagnosed with PAA. Treatment was indicated at the occurrence of emergent symptoms or considered at a PAA threshold of >2 cm. The PAAs were divided into small (≤15 mm) and large (>15 mm) aneurysms. The mean surveillance follow-up was 5.1 years. Most of the 241 identified patients (397 limbs) with a diagnosis of PAAs had bilateral aneurysms (n = 156). Most patients were treated within the study period (163 of 241; 68%). No differences were found in the mean diameters between the elective and emergent groups (30.1 mm vs 32.2 mm; P = .39). Growth was recorded in 110 PAAs and on multivariate analysis was associated with a larger index diameter and a concurrent abdominal aortic aneurysm (odds ratio, 2.553; P = .046). The study has shown that most patients receiving monitoring for PAAs will require elective repair, usually within 1 year.

14.2.3.2 Open Surgery for Acute Ischemia Due to Thrombosed PAA

Jungi et al. [15] analyzed peri-operative, as well as long-term outcomes of patients undergoing urgent open surgery for ALI due to thrombosed PAA, assessing limb salvage and mortality. Fifty-one patients (92% male), median age 75 years were identified. Twenty patients (39%) presented with category IIa acute limb ischemia, 20 (39%) with category IIb, and 11 (22%) with category III. Four patients (8%) underwent primary major amputation. Forty-seven (92%) underwent bypass surgery, 43/47 (91%) using great saphenous vein. One vessel runoff was present in 27/47 patients (57%). Thirty day mortality was 4% (n = 2). Four patients needed major amputation within 30 days, resulting in an overall 30-day major amputation

rate of 16% (8/51). No further major amputations were necessary during a median follow up of 41 months (range 4 -114 months) resulting in an estimated 4-year limb salvage of 84%. The one year primary assisted and secondary bypass patency rates were 90% and 95%, respectively. Rapid open surgical revascularisation in patients with acute limb ischaemia due to a thrombosed popliteal artery aneurysm results in good long-term limb salvage rates, especially in Rutherford category IIa and IIb acute ischaemia.

14.2.3.3 Open PAA Repair with Prosthetic Grafts

In a single-center, retrospective cohort study 82 patients had undergone open surgical repair with prosthetic grafts for 104 PAAs [16]. Of the 104 PAAs, 72 (68%) had been asymptomatic, 8% had had acute ischemia. A medial approach was used for 35 PAAs (34%) and a posterior approach for 69 (65%). No perioperative deaths occurred. The median follow-up was 34.6 months (IQR, 8.5-62.7 months). Of the 82 patients, 13 (16%) had been lost to follow-up, 16 (20%) had died during follow-up of unrelated causes, and 19 (23%) had undergone reintervention. The primary and secondary patency at 3 years was 80% and 91%, respectively, after PAA repair with the presence of at least two distal running vessels. In contrast, primary and secondary patency had decreased to 71% and 77%, respectively, for patients with only one tibial vessel, although neither difference was statistically significant. Open surgical repair of PAAs with prosthetic grafts is safe and feasible, with good mid-term results and satisfactory primary and secondary patency at 3 years. A posterior approach was preferred when anatomically feasible because it requires one incision instead of two, results in complete interruption and excision of the aneurysm, requires shorter reconstruction, and includes saphenous vein sparing, with good perioperative and mid-term outcomes.

14.2.3.4 Open Vs. Endovascular PAA Repair

Based on Swedish population-based registry data, factors affecting the outcome after open surgical (OSR) and endovascular (ER) repair of PAAs were identified by Cervin et al. [17]. Seventy-seven legs treated by ER were matched, by indication, with 154 legs treated with OSR. Patients in the ER group were older (73 vs. 68 years, $p = .001$), had more lung disease ($p = .012$), and were treated with dual antiplatelet therapy or anticoagulants more often ($p < .001$). The hazard ratio (HR) for occlusion was 2.69 for ER, but 3.03 for poor outflow. For permanent occlusion, the HR after ER was 2.47 but 4.68 for poor outflow. Larger stent graft diameter reduced the risk (HR 0.71 [0.54-0.93], $p = .014$). In Cox regression analysis adjusted for indication and stent graft diameter, elongation increased the risk (HR 1.020 per degree [1.002-1.033], $p = .030$). PAAs treated for acute ischaemia had a median stent graft diameter of 6.5 mm, with those for elective procedures being 8 mm ($p < .001$). In conclusion, patency is better and the need for reintervention is less frequent after

Table 14.1 Re-interventions and complications in 212 patients with popliteal artery aneurysm, treated by endovascular (ER) or open surgical repair (OSR). Matched comparison within a population-based cohort (according to [17])

Parameter	OSR (n = 154)	ER (n = 77)	*P*
Permanent occlusion, n (%)			
– 30 days	5/154 (3.2)	8/76 (10.5)	.034
– 1 year	13/144 (9.0)	21/68 (30.9)	< .001
– 3 years	18/102 (17.6)	22/50 (44.0)	.001
Reintervention (thrombolysis), n			
– 30 days	0	5	.038
– 1 year	3	14	< .001
– 3 years	4	16	< .001
Conversion/new bypass, n			
– 30 days	2	2	.60
– 1 year	4	9	.012
– 3 years	4	11	< .001
Major amputation, n (%)			
– 30 days	3/154 (1.9)	4/77 (5.2)	.23
– 1 year	6/149 (4.0)	4/75 (5.3)	.74
– 3 years	6/117 (5.1)	4/51 (7.8)	.49
Death, n (%)			
– 30 days	0/141 (0)	1/71 (1.4)	.34
– 1 year	3/141 (2.1)	8/71 (11.3)	.008
– 3 years	13/141 (9.2)	17/71 (23.9)	.006

OSR than ER. The potential benefit of a minimally invasive treatment for elderly and frail patients should be weighed against the increased risk of complications and re-interventions. Patients with slender, elongated popliteal arteries, and/or with acute ischaemia, have higher risk of occlusion after ER, which should be considered in surgical decision making (Table 14.1).

In a retrospective monocenter study, Ge et al. [18] compared the outcomes after OSR (n = 151) and ER (n = 35) of PAAs. Seventy-seven patients (41%) were asymptomatic. Overall, 57 (31%) patients underwent catheter-directed thrombolysis (CDT) and/or embolectomy before or during PAA repair. For OSR, an autologous vein was used in 100 patients, and an ePTFE graft in 51 patients. The peri-operative mortality rate was 0.5%. Peri-operative complications occurred in 7 OSR patients and 2 ER patients (P = 0.67). The peri-operative morbidity was 4.8%. During follow-up, 18 patients had a type II endoleak (14 in the OSR group and 4 in the ER group). Patients who underwent the posterior approach for OSR developed less type II endoleaks compared to those with medial approach. The average follow-up time was 61.7 ± 45.5 months. The estimated primary graft patency rates in the OSR autologous-vein group at 1, 3, and 5 years were 100%, 97.3%, and 95.7%, respectively, after the initial procedure; the corresponding rates in the OSR prosthetic graft group were 88.9%, 86.3%, and 79.2%, respectively, and the ER group's primary graft patency rates were 91.4%, 88.3%, and 84.1%, respectively. In this study, the

results of OSR and ER of PAAs were equivalent. In OSR, autologous vein grafts had better graft patency and the posterior approach was less likely to lead to type II endoleaks and sac enlargements.

From 1998 to 2017, in a single-center retrospective cohort study 29 patients with 33 PAAs had undergone open repair (OR) and 35 patients with 40 PAAs had undergone endovascular repair (ER) [19]. Overall, the presence of symptoms was similar between the two groups. However, the OR group had a significantly higher number of patients who had presented with acute ischemia (P = .01). The length of stay was significantly shorter for the ER cohort (mean, 1.8 days; range, 1-11 days) than for the OR group (mean, 5.4 days; range, 2-13 days; P < .0001). No significant difference was found in the primary or secondary patency rates between the two groups. In the ER group, good runoff (two or more vessels) was a positive predictor for primary patency at 1 year (odds ratio, 3.36; 95% confidence interval, 1.0-11.25). However, it was not in the OR group. Postoperative single and/or dual antiplatelet therapy did not affect primary patency in either cohort. The results of this study have demonstrated that ER of PAAs has patency rates similar to that of OR of PAAs with no limb loss during follow-up and a decreased LOS when used in a similar population of patients. Good runoff was a positive predictor of primary patency in the ER cohort and overall. Thus, ER of PAAs is a safe and durable option for patients with PAAs who have good runoff, producing outcomes similar to those after OR.

14.2.3.5 Endovascular Repair

A retrospective review of medical records for all patients diagnosed with a PAA and treated with endovascular popliteal aneurysm repair (EPAR) at the University of Pittsburgh Medical Center from January 2006 to December 2018 has been presented by Zaghloul et al. [20]. 117 limbs from 101 patients with a mean follow-up of 55.6 months (range, 0.43-158 months) were included. The average age was 73 ± 9.3 years. Thirty-two patients (29.1%) were symptomatic (claudication, rest pain, tissue loss, or rupture). The median arterial length covered was 100 mm, with an average length of stent overlap of 25 mm. The majority of limbs (62.8%) had a three-vessel runoff, 20.2% had a two-vessel runoff, and 17% has a one-vessel runoff. The Kaplan-Meier estimates of graft occlusion at 1 and 3 years were 6.3% and 16.2%, respectively. The 1- and 3-year primary patency rates were 88.2% and 72.6%, and the 1- and 3-year major adverse limb event-free survival (MALE-FS) rates were 82% and 57.4%. On multivariable Cox regression, aneurysm size, one-vessel runoff, and coverage below the knee were associated with a lower 3-year MALE-FS. EPAR is a safe and effective way to treat popliteal artery aneurysms. Factors associated with poor MALE-FS after EPAR include single-vessel tibial runoff and coverage below the knee.

14.2.4 Special Issues

14.2.4.1 Thrombolysis for Acute Thrombosed Popliteal Artery Aneurysms

A systematic review to summarize outcomes of acute thrombosed popliteal artery aneurysms (PAAs) treated with thrombolysis or thrombectomy followed by bypass was performed by Kropman et al. [21]. 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% (P = 0.026), 54% (P = 0.164) and 45% (P = 0.249) in the 'thrombectomy' group. No distinction could be made regarding secondary patency and limb-salvage rates between the groups owing to insufficient data. Preoperative and intra-operative 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. [22] investigated outcomes of preoperative or intraoperative intra-arterial urokinase thrombolysis in the treatment of PAA thrombosis with acute ischemia Rutherford grade IB to IIA in terms of limb salvage and midterm patency. Eighty-six patients were treated including intraoperative thrombolysis (group A: 47 cases) or preoperative thrombolysis (group B: 39 cases) followed by acute (<24 h) or elective surgery. The 2-year primary patency was 61.7% for group A and 43.6% for group B (hazard ratio [HR] 1.85; 95% CI: 0.96 to 3.54; p = 0.06). The 2-year secondary patency was 70.2% for group A and 53% for group B (p = 0.08). One-month amputation rate was 18% in group A and 29% in group B (p < 0.001), and 12-month amputation rate was 19% in group A and 44% in B (p = 0.05). The results suggest that the immediate surgery with intraoperative thrombolysis improved the outcome of patients with acute leg ischemia due to PAA thrombosis in terms of limb salvage.

Dragas et al. [23] reported on a total of 156 patients with Rutherford grade IIa and IIb acute ischemia resulting from PAA thrombosis admitted between 1 January 2011 and 1 January 2017. The patients were divided into two groups, those who underwent additional treatment with intra-operative intra-arterial thrombolysis (20 patients), and those who did not (136 patients). After a median follow up of 55 months, the estimated MALE rate was significantly lower in the thrombolysis group (30% vs. 65%, p < .001). Also, patients in the thrombolysis group had a significantly lower mortality rate (20% vs. 42.65%). There were no cases of major

(intracranial and gastrointestinal) bleeding in either group. The data suggest that intra-operative thrombolysis in the treatment of selected patients with ALI due to PAA thrombosis has long term MALE and overall survival benefits, without a significant risk of major, life-threatening bleeding complications.

14.3 Conclusions for Clinical Practice

1. Patients with an asymptomatic PAA ≥ 20 mm in diameter should undergo repair to reduce the risk of thromboembolic complications and limb loss.
2. Open PAA repair may be more durable than endovascular repair, albeit with a higher risk of complications and resource use.
3. If patients have favorable anatomy (two-vessel runoff or more with adequate landing zones of >15 mm of normal, non-aneurysmal artery) endovascular repair may be considered.
4. In patients with acute limb ischemia resulting from PAA thrombosis, immediate intervention combined with intraoperative thrombolysis is recommended.
5. Patients with slender, elongated popliteal arteries, and/or with acute ischemia, have higher risk of occlusion after endovascular repair, which should be considered in surgical decision making.
6. In open popliteal aneurysm repair, a posterior approach may be preferred to a medial approach when anatomically feasible because it requires one incision instead of two, results in complete interruption and excision of the aneurysm, requires shorter reconstruction, and includes saphenous vein sparing, with good perioperative and mid-term outcomes.

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Chapter 15
Popliteal Entrapment Syndrome



15.1 Guidelines

Guidelines for the treatment of popliteal entrapment syndrome (PES) are not available.

15.2 Definitions

PES describes a group of conditions in which there is compression of the popliteal artery, popliteal vein, or tibial nerve (singly or in combination) in the popliteal fossa by surrounding musculoskeletal structures, causing vascular and neurogenic symptoms. Popliteal artery entrapment syndrome (PAES) is by far the most common entrapment and is responsible for a significant proportion of intermittent claudication (IC) in young patients. The description of Insua et al. [1] is still valid today, according to which the numerous anatomical variants that can lead to compression of the popliteal artery in the popliteal fossa can basically be divided into two types: In type 1, in which the medial head of the gastrocnemius, in its development, originates on the medial condyle of the femur and passes between the popliteal artery and vein. As a result, the popliteal artery passes medially across the posterior aspect of the medial gastrocnemius, then passes deep (anterior) to this muscle, coursing laterally to go deep to the soleus in its usual manner in company with the vein, and in a type 2, in which the artery shows a normal course but is compressed by an anomalous origin of the gastrocnemius or plantaris muscles. Therapy has two approaches: Correction of the anomaly and repair of any damage that has occurred to the artery [1]. If the basic problem is one of an abnormal course of the artery around the medial head of the gastrocnemius, this muscle should be divided so as to

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restore the artery to its proper course. If the artery is constricted by an aberrant origin of the gastrocnemius or the plantaris muscle, this muscle should be divided so as to release the artery.

The anatomical variants that can lead to compression of the popliteal artery must be distinguished from functional PAES, where no abnormalities, no anatomical trap are discovered and in which entrapment of the artery occurs as a result of hypertrophy of the gastrocnemius muscle, especially in intensively trained young athletes [2].

A case report and literature review [3] answered the following questions:
What is popliteal artery entrapment syndrome (PAES)?

- PAES is a frequent cause of intermittent claudication in an otherwise healthy, often athletic cohort, with potentially severe adverse sequelae and can represent a diagnostic challenge.

Why is PAES missed?

- The median delay before diagnosis of PAES has been reported as 12 months (range, 4 h to 120 months). The diagnosis may be missed due to young patient age, often a lack of atherosclerotic risk factors and difficultly in distinguishing from other causes of lower-limb pain. Furthermore, unless popliteal artery occlusion has occurred, distal pulses will be normal on physical examination.

Tips for ultrasound diagnosis of popliteal artery entrapment syndrome:

- Lie the patient prone with their feet off the end of the bed and pressed against a wall.
- Assess the popliteal artery for normal triphasic flow.
- Use a lower-frequency curvilinear probe in the popliteal fossa while asking the patient to plantar flex. It is crucial to examine the popliteal artery proximal to the sural artery branch.
- The diagnostic sonographic finding is absolute obstruction of flow within the popliteal artery.
- A dampened, low-velocity arterial waveform is considered equivocal.
- Coexisting popliteal vein entrapment may be assessed for by squeezing the calf to look for normal augmentation of venous flow.

15.3 Results

15.3.1 Systematic Review

A systematic review of PES has been performed by Sinha et al. [4]. Forty-four articles were included in the final analysis, of these, 30 studies were on popliteal artery entrapment syndrome (PAES). Intermittent claudication (IC) was the most common presenting symptom in 22 studies. Eleven studies described a median

proportion of 11% of limbs presenting with acute ischemia. A median proportion of 38.25% of patients diagnosed with bilateral PAES was described in 26 studies. No relationship was found between duration of symptoms and the presence of irreversible arterial injury. Each study used a median of three diagnostic tests (range, 1–6). Arteriography was used in 28 of 30 studies to diagnose PAES, with an estimated mean sensitivity of 97% (range, 85–100%). Surgical treatment for PAES was described in 28 of 30 studies. An exclusively posterior approach to the popliteal fossa was used in five studies. Three studies described using the medial approach more frequently than the posterior approach. After musculotendinous division to release the entrapment, only one study described reattachment of the gastrocnemius muscle. Twenty-three studies described arterial reconstructive procedures, with a median failure rate of 27.5%. The proportion of patients asymptomatic after surgery was reported in only 12 of 30 studies, with a median value of 77% (range, 70%–100%). In 3 of 4 studies on popliteal vein entrapment (PVES), the most common presenting symptom was limb swelling. The four PVES case series described decompressive surgery (fasciotomy with or without musculotendinous section), and two of the four described popliteal vein reconstruction.

15.3.2 Case Series

From a Japanese nationwide clinical registry, data for patients who underwent surgical treatment for PAES between 2013 and 2018, including 58 limbs from 41 institutes, were retrieved and evaluated by Fujimura et al. [5]. The mean patient age was 36 ± 19 years, 78% were male, and the incidence of PAES was 0.24 limbs/centre/year, reflecting a clinical setting where PAES cases are not centralised. The most frequent arterial symptom was intermittent claudication (90%). Computed tomography was performed in 57 limbs (98%) for the diagnosis, however active manoeuvres such as dorsiflexion and plantarflexion during the examination were performed in only 13 limbs (22%), and occlusion of the popliteal artery was present in 38 limbs (66%) at diagnosis. Myotomy alone was performed in only seven limbs (12%), the other limbs were revascularised. Mean follow up was 26 ± 20 months. Surgical treatment was effective as it relieved symptoms in >96% of limbs, with 5 year primary and secondary patency rates of 72% and 93%, respectively. This retrospective study showed that surgical treatment was acceptable even in a clinical setting where PAES cases are not centralised. However, the low incidence of active manoeuvres performed during the examination and the high incidence of occlusion at diagnosis suggests there may be a possibility of delayed or underdiagnosis of PAES in Japan, and increased awareness for PAES is warranted.

A retrospective study of all patients that underwent surgery in the Department of Vascular Surgery, Strasbourg for popliteal artery entrapment syndrome between January 2003 and December 2009 was performed by Lejay et al. [6]. Eighteen patients (25 limbs; 17 men [94%] and one woman [6%]) underwent surgery for PAES. Presentation was bilateral in seven patients (39%). In four limbs the popliteal

artery was compressed and undamaged (16%), and treatment consisted of musculotendinous division alone. In 16 limbs the popliteal artery was damaged with lesions limited to the popliteal artery (64%) where treatment consisted of venous interposition. In the five limbs with the lesions extended beyond the popliteal artery, treatment consisted of below knee bypasses. There was no loss to follow up. Mean follow up was 82 months. Five-year patency was 84%. Graft occlusion occurred in four limbs in three patients respectively. No patient required amputation following graft occlusion. In patients that underwent musculo-tendinous division alone no late stenosis of the popliteal artery was seen. The best surgical approach was a posterior S-shaped incision in the popliteal fossa, which enables complete exposure of the popliteal artery and its surrounding structures. Ideally, if the condition is recognized early and the vessel remains undamaged, simple release of the popliteal artery can be performed. When the artery is damaged, revascularization can be carried out using the posterior approach, affording good access to the artery and other structures of the popliteal fossa, facilitating both confirmation of the diagnosis and popliteal artery release.

15.3.2.1 PAES in Children

Clinical and surgical experience of PAES in children was reported by Settembre et al. [7]. Data from 79 children (106 limbs, 27 bilateral PAES) were collected and analysed. Of 79 children, 54 (68%) were male. The mean age of onset was 15 years (range 7–17 years). The most common symptoms on admission were claudication in 68 cases (64.2%) and ALI in 17 cases (18%); one patient presented with critical limb ischaemia (0.9%). In four cases (4%), symptoms were not reported. The treatment was surgical in the majority of cases (n = 96, 90.6%). In 41 cases (38.7%), only section of the musculo-tendinous structures was necessary. In the remaining 60 cases (56.6%), revascularisation was also required. In one patient, medical treatment was performed; in three the treatment was not reported, and one patient declined any surgery. Complications occurred in four children (4%), but in all of the cases the patients obtained full recovery during long-term follow-up. A PAES diagnosis can be difficult, since children may ignore the symptoms. As a result, the diagnosis is often delayed. ALI in paediatric patients is rare but may lead to limb loss and lifelong complications. Symptomatic PAES in children must be considered a severe condition needing urgent investigation in order to avoid any delays in treatment.

15.3.3 Functional PAES and Chronic Exertional Compartment Syndrome (CECS)

15.3.3.1 Reviews

A review of diagnosis and management of functional PAES extracted data from six studies, from which the number of patients, demographic information, preoperative workup, treatment details, follow-up imaging, and results of treatment were obtained

[8]. A total of 133 patients were studied. Mean age was 26 years; 57% were female, and noninvasive testing revealed bilateral findings in 39%. Treatment involved surgical myotomy/myomectomy (98; five studies) and botulinum toxin injection (35; two studies). At a mean follow-up of 25 months, a total of three patients had recurrent symptoms, four had abnormal duplex ultrasounds, and six patients had residual symptoms. Thirteen of the 16 limbs that received one set of botulinum A toxin injections experienced "mild" to "significant" improvement of symptoms upon subjective assessment for 4 months. None of the 35 patients who received botulinum toxin injections were reported to have experienced complications. In conclusion, based on the review, FPAES can be treated successfully with surgical myotomy at first or a test of botulinum injections, with surgery reserved for patients with recurrent symptoms.

Although the exact mechanism has not been fully elucidated, the pathology of chronic exertional compartment syndrome (CECS) is thought to arise from transient muscular ischemia and progressive neurovascular dysfunction due to the increased intramuscular pressures experienced during endurance exercise. Campano et al. [9] performed a systematic review of the published literature to characterize the at-risk demographic, operative indications, surgical techniques, functional outcomes, and reoperation and complication rates after operative management of CECS of the lower leg. Twenty-four primary studies with 1596 patients met the inclusion criteria. The mean age was 26.6 years (standard deviation, 8.9 years), and the majority of patients were male patients (70%). The total study population mostly comprised military service members (54%) and athletes (29%). Of the athletes, 83% were recreational; 9% were college level; and 8% were either national, international, or professional. The most commonly involved compartment was the anterior compartment (51%), followed by lateral (33%), deep posterior (13%), and superficial posterior (3%). The cumulative posterior involvement rate was 16%. Of the entire population included, 1495 (94%) underwent eventual surgical management, including compartment-specific open fasciotomy (86%), fasciotomy with partial fasciectomy (12%), and endoscopic fasciotomy (<2%). Primary operative management of lower-extremity CECS was successful in approximately two-thirds of all young athletic patients, and 84% were satisfied with their surgical outcomes at short- to mid-term follow-up.

15.3.3.2 Diagnostic Approach of Functional Popliteal Artery Entrapment Syndrome

Morgan et al. [10] described their diagnostic imaging protocol in a cohort of patients undergoing release for functional popliteal artery entrapment syndrome (FPAES). There were a total of 63 patients with an average age of 32.4 years; 63.4% were female. Fifty-four patients underwent ABI with plantar and dorsiflexion and 33 underwent ABI with exercise demonstrating some overlap of the protocols. Forty-six patients underwent venous duplex examinations, 28 underwent PA duplex examinations, and 26 underwent MRA. Regarding treatment pathways, of the 63 patients, 12 patients underwent entrapment release for FPAES and 51 underwent

alternative treatments for atypical claudication with chronic exertional compartment syndrome (CECS). Entrapment release was performed via either the medial or posterior approach. Of the 51 patients evaluated for CECS, 18 were diagnosed with CECS and underwent fasciectomy; the remaining 33 patients opted for conservative management consisting of activity modification and physical therapy. Exercise with an ankle-brachial index in the functional popliteal artery entrapment syndrome (FPAES) cohort demonstrated a statistically significant difference of −14 mm Hg in systolic blood pressure. Arterial Doppler ultrasound examination showed a trend toward statistical significance with plantarflexion, but requires further study. Magnetic resonance angiography with plantarflexion was positive in 6 of 11 patients with FPAES. Because different provocative maneuvers and testing modalities yield widely different diagnostic yields for diagnosing FPAES, the authors recommended using a combination of exercise ankle-brachial index, plantarflexion Doppler ultrasound examination, venous ultrasound examination, and plantarflexion magnetic resonance angiography for the diagnosis of FPAES.

The importance of patient position when defining normal versus pathological functionality in the diagnosis of PAES with duplex ultrasound was investigated by Barrett et al. [11]. To reduce false positive rates (from asymptomatic compression) and scanning time, the recommended ultrasound protocol assesses potential PAES candidates only in the erect position (i.e., scanning supine may not be required), paying particular attention to changes (diameter, peak systolic velocities (PSV), waveform, and occlusions) on plantarflexion (but still assesses dorsiflexion), in the distal below knee popliteal artery. There is no need to complete ankle brachial pressure index testing, but exercise is important.

15.3.3.3 Studies

Functional popliteal artery entrapment syndrome (FPAES) is an uncommon overuse injury in young physically active adults manifest by neuromuscular symptoms (gastric/soleus cramping, plantar paresthesias). It is commonly confused with chronic recurrent exertional compartment syndrome (CRECS). Turnipseed [12] evaluated the diagnostic testing, mechanism of injury, and treatment differences between FPAES and CRECS. Between 1987 and 2007, 854 patients (557 women, 297 men; mean age, 28.5 years) were surgically treated for the diagnosis of CRECS or FPAES, or both. Compartment pressures were measured in all patients who had anterior lateral or posterior superficial calf symptoms (normal pressure < 15 mm Hg). Noninvasive stress positional plethysmography was routine. Stress positional magnetic resonance imaging (MRI) or angiography (MRA) was performed on patients with positive plethysmography result and symptoms consistent with FPAES. Of the 854 patients, 757 (95%) had elevated compartment pressures (>25 mm Hg), and fasciectomy was performed for CRECS under local anesthesia (anterior lateral, 508; posterior superficial, 191; distal deep posterior, 101). MRA/MRI demonstrated normal musculotendinous anatomy and lateral neurovascular compression with plantar flexion in 43 patients. All patients had normal compartment pressures. Under general anesthesia, all had excision of the soleal band, with relief from symptoms.

In conclusion, FPAES and CRECS occur in the same population with similar symptoms but require different treatment.

Popliteal artery entrapment syndrome (PAES) is still underdiagnosed, yet it may significantly interfere with lifestyle, especially among young sportspeople, with symptoms like intermittent claudication. In a population of 327 consecutive explored symptomatic sportspersons, PAES was confirmed in 35 patients on 61 pathologic limbs [13]. In this center, when sportspersons are referred for chronic leg pain during exercise, they systematically receive color duplex ultrasonography (CDUS) with dynamic manoeuvres specific to the search for a PAES. When patients were suspected of PAES after CDUS, the diagnosis was confirmed by computed tomography angiography (CTA) or magnetic resonance angiography (MRA), with the foot in the neutral position and dynamic plantar flexion of the ankle during resistive exercises to demonstrate vascular (arterial compression, stenosis, occlusion or aneurysm, deviated course) and extravascular (abnormal muscle position or muscular hypertrophy) abnormalities linked to this disease. The median time with the symptoms before diagnosis was 34 months (range, 3–180 months). The mean age of patients was 30.5 years (range, 17–52 years) with 83% of males. The proportion of patients diagnosed with bilateral PAES was 74%. The main sports practiced were running (15 patients, 43%), soccer (nine patients, 26%), rugby (two patients), and athletics (two patients). Among 21 patients, intra-compartmental pressure measurements (ICP) found 18 (86%) to have an associated chronic exertional compartment syndrome (CECS). Of the 35 patients with a confirmed PAES on 61 legs, 21 finally underwent surgery on 37 legs: three patients were operated only for PAES (five legs), eight patients were operated for PAES and CECS (15 legs) and 10 persons were treated only for CECS (17 legs). Among the patients followed up after PAES surgery, 80% were able to resume sport at a level comparable to that before the onset of pain. PAES could be sought earlier in young sportspeople who experience unexplained leg pain during exercise to diagnose the disease and avoid complications in a timely manner. Compartmental pressures should systematically be measured in the search for an associated CECS.

Lavingia et al. [14] reported on the surgical management of functional popliteal entrapment syndrome in 36 athletes (56 limbs). Of the patients, 27 (75%) had bilateral symptoms and evidence of entrapment; however, only 20 of the 36 (56%) underwent bilateral surgical treatment for symptom resolution. The mean amount of gastrocnemius muscle removed was 7.6 cm^3. Nine percent of limbs underwent a bypass along with debulking owing to arterial occlusion at presentation. Postoperatively, there were no nerve or vascular complications noted, although two patients had wound/seroma complications (6%). At follow-up, more than three-fourths of athletes limited by FPAES demonstrated full return to prior competitive levels with fasciotomy and surgical debulking of the anterolateral quadrant of the medial gastrocnemius muscle. Provocative CTA protocols can help to guide the location of muscle debulking to alleviate the functional entrapment that occurs in these athletes with exercise.

Deveze et al. [15] described a cohort of 38 patients who underwent surgery for PAES. Among them, 36 (94.7%) were functional PAES. The mean age at the time of surgery was 24.7 ± 9 years. Clinical presentation was bilateral in 30 patients

(81.1%). The most frequent symptom was intermittent claudication with calf cramp during exercise. Surgical procedures were performed through direct posterior popliteal approaches in ventral prone position. Surgery always consisted of a complete popliteal artery examination after neurovascular fibers of the popliteal region were recognized and dissected free. In case of muscular or tendon abnormalities causing compression of the popliteal vessel these were sectioned. All patients also had systematic gastrocnemius muscles fascia incisions, especially when no abnormality was found. The mean time of follow-up was 2.3 months +/− 1.2 months. After surgery, D-scan showed no signs of remaining popliteal artery compression in 92.5% of the cases. Twelve patients (33.3%) were able to resume sport, 18 (50%) partially, and 6 (16.6%) did not resume sport yet.

15.3.3.4 Botulinum Toxin as a Treatment for FPAES

Botulinum toxin A (BoNT-A) has been proposed as an alternative approach to reduce the volume and/or tonus of gastrocnemius muscles in patients with FPAES. Isner-Horobeti [16] reported the case of a patient with bilateral FPAES who was treated by intramuscular injection of BoNT-A in the gastrocnemius muscles after unsuccessful surgical intervention. The disappearance of exercise-induced pain and the improvement in physical performance were maintained in the short and medium term. Neither adverse effects nor motor deficit of the gastrocnemius muscles was reported.

Hislop et al. [17] reported a larger cohort of patients suffering from functional PAES. Twenty-seven patients met diagnostic criteria confirming the presence of functional PAES and agreed to go ahead with ultrasound-guided BTX-A injection at the level of artery occlusion. Two occlusion sites per calf were consistently identified: the deep proximal medial gastrocnemius muscle belly in the intercondylar fossa adjacent to the popliteal artery and the plantaris muscle belly immediately overlying the popliteal artery at the level of the proximal tibial metaphysis. Each of these sites was then targeted and injected under ultrasound guidance. No patients reported being worse off after the intervention; 59% of patients were categorized as having a good response (i.e., initial improvement that was maintained at 12 months), 22% a mixed response (i.e., an initial improvement that subsequently reduced over 12 months) and 19% a poor response (i.e., no difference) to treatment. The authors concluded that ultrasound-guided BTX-A injection represents a viable alternative to surgery in the treatment of functional PAES.

15.4 Conclusions for Clinical Practice

1. Popliteal artery entrapment (PAES) is by far the most common entrapment and is responsible for a significant proportion of intermittent claudication (IC) in young patients.

2. Therapy has two approaches: Correction of the anomaly and repair of any damage that has occurred to the artery. If the basic problem is one of an abnormal course of the artery around the medial head of the gastrocnemius, this muscle should be divided so as to restore the artery to its proper course. If the artery is constricted by an aberrant origin of the gastrocnemius or the plantaris muscle, this muscle should be divided to release the artery.
3. The anatomical variants that can lead to compression of the popliteal artery must be distinguished from functional PAES (FPAES), where no abnormalities, no anatomical trap are discovered and in which entrapment of the artery occurs as a result of hypertrophy of the gastrocnemius muscle, especially in intensively trained young athletes.
4. In FPAES, surgery always consists of a complete popliteal artery examination after neurovascular fibers of the popliteal region were recognized and dissected free. Muscular or tendon abnormalities causing compression of the popliteal vessel should be sectioned and gastrocnemius muscles fascia incisions should be performed.
5. In case of suspicion of FPAES, compartmental pressures should systematically be measured in the search for an associated chronic exertional compartment syndrome (CECS).
6. CECS and FPAES occur in the same population with similar symptoms but require different treatment. Patients with CECS show elevated compartment pressures (>25 mm Hg), and fasciectomy is the treatment of choice.

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Chapter 16
Vascular Access for Haemodialysis



16.1 Guidelines

16.1.1 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

The ESVS recommends, among others [1]:

Clinical decision-making

- Recommendation 1: Referral of chronic kidney disease patients to the nephrologist and/or surgeon for preparing vascular access is recommended when they reach stage 4 of chronic kidney disease (glomerular filtration rate < 30 ml/min/1.73 m^2), especially in cases of rapidly progressing nephropathy. Class I recommendation; Level of evidence C
- Recommendation 2: A permanent vascular access should be created 3–6 months before the expected start of haemodialysis treatment. Class I recommendation; Level of evidence B
- Recommendation 3: An autogenous arteriovenous (AV) fistula is recommended as the primary option for vascular access. Class I recommendation; Level of evidence A
- Recommendation 4: The radiocephalic arteriovenous fistula is recommended as the preferred vascular access. Class I recommendation; Level of evidence B
- Recommendation 5: When vessel suitability is adequate, the non-dominant extremity should be considered as the preferred location for vascular access. Class IIa recommendation; Level of evidence C
- Recommendation 6: A lower extremity vascular access should be considered only when upper extremity access is impossible. Class IIa recommendation; Level of evidence C

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- Recommendation 7: Tunnelled cuffed central venous catheters as a long-standing haemodialysis modality should be considered when the creation of arteriovenous fistulas or grafts is impossible or in patients with limited life expectancy. Class IIa recommendation; Level of evidence B

Pre-operative imaging

- Recommendation 8: Pre-operative ultrasonography of bilateral upper extremity arteries and veins is recommended in all patients when planning the creation of a vascular access. Class I recommendation; Level of evidence A
- Recommendation 9: Duplex ultrasound is recommended as the first line imaging modality in suspected vascular access dysfunction. Class I recommendation; Level of evidence B
- Recommendation 10: Computed tomographic angiography may be considered in patients with inconclusive ultrasonographic or angiographic results concerning the degree of central venous stenosis. Class IIb recommendation; Level of evidence C
- Recommendation 11: Contrast enhanced magnetic resonance angiography is ***not*** recommended in patients with end stage renal disease, because of the potential risk of gadolinium associated nephrogenic systemic fibrosis. Class III recommendation; Level of evidence C
- Recommendation 12: In vascular access dysfunction digital subtraction angiography should be performed only when subsequent intervention is anticipated. Class I recommendation; Level of evidence C

Technical aspects

- Recommendation 15: Broad spectrum antibiotics should be given prior to insertion of an arteriovenous graft including prophylaxis for Staphylococcus aureus. Class I recommendation; Level of evidence A
- Recommendation 17: Patients should be examined prior to surgery with a tourniquet in a warm room and the proposed site of an arteriovenous fistula should be marked pre-operatively. Class I recommendation; Level of evidence C
- Recommendation 18: Regional anaesthesia should be considered in preference to local anaesthesia for vascular access surgery because of a possible improvement in access patency rate. Class IIa recommendation; Level of evidence B
- Recommendation 19: In adults when the inner radial arterial diameter is less than 2.0 mm and/or the cephalic venous diameter is less than 2.0 mm by ultrasound measurement an alternative site for access should be considered. Class IIa recommendation; Level of evidence B
- Recommendation 20: If there is an indwelling central venous catheter or pacemaker the vascular access should be created in the opposite arm because of the risk of central venous stenosis and reduced access patency. Class I recommendation; Level of evidence C
- Recommendation 21: When the upper arm cephalic vein is unavailable, a basilic vein transposition arteriovenous fistula should be considered in preference to an

arteriovenous graft because of its improved patency and the reduced risk of infection. Class IIa recommendation; Level of evidence A

- Recommendation 22: When lower limb vascular access is necessary a femoral vein transposition should be considered in preference to an arteriovenous graft. Class IIa recommendation; Level of evidence B
- Recommendation 23: When an arteriovenous fistula cannot be created, a biological graft should be considered in preference to a synthetic graft in the presence of infection. Class IIa recommendation; Level of evidence C
- Recommendation 24: The implantation of a self-sealing arteriovenous graft is recommended for patients who have difficult central venous access and who require early cannulation for haemodialysis. Class I recommendation; Level of evidence C
- Recommendation 27: In patients with early peri-operative (<30 days) autogenous arteriovenous fistula infection and absence of haemorrhage or pseudoaneurysm, appropriate antibiotic therapy is recommended. Class I recommendation; Level of evidence C
- Recommendation 28: Early peri-operative (<30 days) arteriovenous graft infection with systemic sepsis, purulent discharge, perigraft abscess or haemorrhage should be treated by total graft removal. Class I recommendation; Level of evidence C
- Recommendation 29: For early autogenous arteriovenous fistula infection in the presence of systemic signs, bleeding and involvement of the anastomosis, fistula ligation should be performed. Class I recommendation; Level of evidence C
- Recommendation 30: For early limb threatening vascular access induced ischaemia and for all cases of early ischaemic monomelic neuropathy in the absence of steal, the access should be ligated urgently. Class I recommendation; Level of evidence C
- Recommendation 31: For vascular access salvage after early thrombosis, thrombectomy and revision (if needed) should be performed as soon as possible. Class I recommendation; Level of evidence C
- Recommendation 33: Establishing vascular access training programs is recommended in order to supervise adequate numbers (>25) of autogenous fistulas for each trainee. Class I recommendation; Level of evidence C

Surveillance of vascular access

- Recommendation 34: Arteriovenous fistulas should be considered for cannulation 4–6 weeks after creation, and standard arteriovenous grafts after 2–4 weeks. Class IIa recommendation; Level of evidence B
- Recommendation 38: Structured post-operative hand exercise training should be considered, to increase arteriovenous fistula maturation. Class IIa recommendation; Level of evidence B
- Recommendation 39: Long-term anti-thrombotic therapy should **not** be used to prolong vascular access patency in haemodialysis patients. Class III recommendation; Level of evidence C

- Recommendation 45: It is recommended that vascular access surveillance is performed by flow measurement of arteriovenous grafts monthly and arteriovenous fistulas every 3 months. Class I recommendation; Level of evidence B
- Recommendation 46: When arteriovenous fistula blood flow measurements during dialysis indicate the presence of a vascular access stenosis based on an access blood flow <500 ml/min, angiographic assessment of the access should be considered. Class IIa recommendation; Level of evidence B

Late vascular access complications

- Recommendation 52: Surgical revision of vascular access aneurysms is recommended if cannulation sites and access diameter can be preserved. Class I recommendation; Level of evidence C
- Recommendation 53: Surgical revision of pseudoaneurysms in arteriovenous grafts is recommended when the aneurysm: limits the availability of cannulation sites or is associated with pain, poor scar formation, spontaneous bleeding and rapid expansion. Class I recommendation; Level of evidence C
- Recommendation 54: Stent graft exclusion of vascular access aneurysms may be considered in selected patients. Class IIb recommendation; Level of evidence C
- Recommendation 60: Balloon angioplasty is recommended as primary treatment for inflow arterial stenosis of any type of vascular access. Class I recommendation; Level of evidence C
- Recommendation 61: Surgical proximal relocation of the vascular access anastomosis should be considered in juxta-anastomotic stenosis in the forearm. Class IIa recommendation; Level of evidence C
- Recommendation 62: Balloon angioplasty is recommended for the treatment of venous outflow stenosis. Class I recommendation; Level of evidence C
- Recommendation 63: Endovascular treatment with stent grafts should be considered for the treatment of cephalic arch stenosis. Class IIa recommendation; Level of evidence B
- Recommendation 66: After creation of a vascular access, evaluation of persistent arm oedema by fistulography or computed tomographic angiography is recommended to evaluate ipsilateral central venous outflow. Class I recommendation; Level of evidence C
- Recommendation 67: Balloon angioplasty as primary treatment of symptomatic central venous outflow disease is recommended, with repeat interventions if indicated. Class I recommendation; Level of evidence C
- Recommendation 68: The use of stent grafts may be considered for the treatment of central vein stenosis. Class IIb recommendation; Level of evidence C
- Recommendation 69: Stenting or repeat balloon angioplasty should be considered if there is significant elastic recoil of the central vein after balloon angioplasty or if the stenosis recurs within 3 months. Class IIa recommendation; Level of evidence C
- Recommendation 70: In patients with symptomatic vascular access induced extremity ischaemia with arterial inflow stenosis balloon angioplasty should be considered. Class IIa recommendation; Level of evidence C

16.2 Results

16.2.1 Meta-Analyses and Systematic Reviews

16.2.1.1 Medical Adjuvant Treatment to Increase Patency of Arteriovenous Fistulae

In a Cochrane Review, various medical therapies were compared to placebo to measure the effect on the patency of arteriovenous fistula (AVF) and prosthetic arteriovenous graft (AVG) for haemodialysis [2]. Thirteen studies with 2080 participants were included. Medical adjuvant treatments used in the included trials were aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel, sulphinpyrazone and glyceryl trinitrate (GTN) patch. The meta-analyses of three studies for ticlopidine, which all used the same dose of treatment but with a short follow-up of only 1 month, suggest ticlopidine may have a beneficial effect as an adjuvant treatment to increase the patency of AVFs and AVGs in the short term. There was insufficient evidence to determine if there was a difference in graft patency between placebo and other treatments.

16.2.1.2 Percutaneous Endovascular Arteriovenous Fistula

The first approved by the US Food and Drug Administration, percutaneous AVF (pAVF) systems were introduced in 2018 and include the Ellipsys (Medtronic,Minneapolis, MN) and EverlinQ devices (BD, Murray Hill, NJ). The 6F EverlinQ has been replaced by the second generation, 4F WavelinQ (BD) in 2019, making Ellipsys and WavelinQ the two devices currently commercially available. Bontinis et al. [3] performed a systematic review, followed by both aggregated data and individual participant data (IPD) meta-analyses, to assess the short-term and midterm safety and effectiveness of pAVF creation. Eighteen studies with 1863 patients were included. The overall pAVF, primary patency, secondary patency, functional cannulation and abandonment rates were 54.01%, 87.27%, 79.94%, and 15.58%, respectively. The overall pAVF, technical success, maturation, reintervention per person-years and mean time to maturation rates were 97.08%, 82.13%, 0.80, and 58 days, respectively. Secondary patency and pAVF abandonment rates where the only end points were WavelinQ and Ellipsys displayed statistically significant differences of 81.36% versus 92.12% and 32.54% versus 11.13%. An IPD meta-analysis of hazard ratios for primary and secondary patency between pAVF and surgical AVF (sAVF) were 1.27 (95% CI, 0.61–2.67) and 1.25 (95% CI, 0.87–1.80), favoring sAVF. Statistically significant difference between pAVF and sAVF were solely depicted for steal syndrome relative risk of 5.91 (95% CI, 1.12–31.12) and wound infections relative risk of 4.19 (95% CI, 1.04–16.88). Percutaneous AVFs could potentially provide a viable alternative for a medical condition where surgery has failed to produce consistent results. Although this review

suggests no improved outcomes regarding patency and overall AVF usability, and despite the small number of included studies in the comparative analysis, pAVF displayed a significant risk decrease regarding steal syndrome and infection occurrence compared with sAVF. Additionally, the minimally invasive nature of the procedure, along with the addition of available anatomic options (eg, deep vein AVF), enhances the arsenal of physicians treating end-stage renal disease. Nevertheless, high reintervention and abandonment rates should be kept in mind.

16.2.1.3 Brachiobasilic Arteriovenous Fistulas Vs. Arteriovenous Grafts

It is unclear what the optimal upper extremity hemodialysis access is for patients without a suitable cephalic vein for AVFs. The objective of a systematic review and meta-analysis was to compare the outcomes for upper extremity transposed brachiobasilic AVFs (BBAVFs) and AVGs [4]. Twenty-three studies examining 2799 patients were identified and included in the study. The 1-year primary patency rates (OR = 1.68, p = 0.001) and 2-year primary patency rates (OR = 2.33, p < 0.001) were significantly better for BBAVFs than AVGs. Compared to AVGs, the 1-year secondary patency rates (OR = 1.45, p = 0.022) and 2-year secondary patency rates (OR = 1.93, p < 0.001) were also significantly higher for BBAVFs. This analysis supports the preferential placement of BBAVFs over AVGs in patients who have exhausted radiocephalic and brachiocephalic AVF options.

16.2.1.4 Tapered and Non-tapered Prosthetic Grafts

It is unclear whether tapered AVGs are superior to non-tapered AVGs when it comes to preventing upper extremity ischemic steal syndrome. Jasty et al. [5] evaluated the outcomes of tapered and non-tapered AVGs using systematic review and meta-analysis. Five studies involving 4397 patients met the inclusion criteria. There were no significant differences for the risk of ischemic steal syndrome (pooled OR 0.92, p = 0.89) between the tapered and non-tapered upper extremity AVG. The primary patency (OR 1.33, p = 0.12%) and secondary patency at 1-year (OR 1.49, p = 0.17%), and rate of infection (OR 0.62, p = 0.19) were also similar between the tapered and non-tapered AVG. This meta-analysis does not support the routine use of tapered graft over non-tapered graft to prevent ischemic steal syndrome in upper extremity dialysis access.

16.2.1.5 Regional Anaesthesia Vs. Local Anaesthesia for AV Fistula Creation

Gao et al. [6] conducted a systematic review and meta-analysis to synthesize evidence from seven randomized controlled trials (565 patients) and one observational study (408 patients) with the aim of evaluating the safety and efficacy of regional (RA) versus local anesthesia (LA) for AV-fistula creation. Pooled data showed that

RA was associated with higher primary patency rates than LA (OR, 1.88; P = 0.003) and improved local blood flow compared with LA. Moreover, operation duration and the use of pain medication was significantly reduced with RA versus LA. Brachial plexus block can contribute to vessel dilation and reduced vasospasm via sympathectomy-like effects, increasing fistula blood flow, reducing fistula maturation time, and improving the success rates of vascular access procedures.

To study the effects of RA versus LA on longer-term AVF patency, Aitken et al. [7] performed an observer-blinded randomized controlled trial. 126 patients undergoing primary radiocephalic or brachiocephalic AVF creation were randomly assigned to receive RA (brachial plexus block) or LA. At 12 months, higher primary patency among patients receiving regional versus local anesthesia (79% versus 59%; OR 2.7; P = 0.02) was found as well as higher functional patency (68% versus 49% patients; OR, 2.1; P = 0.008). The results also proved RA is cost-effective in AVF creation. Regional anesthesia resulted in net savings of £195.10 (US$237.36) per patient at 1 year, and an incremental cost-effectiveness ratio of approximately £12,900 (US$15,694.20) per quality-adjusted life years over a 5-year time horizon.

16.2.1.6 Arteriovenous Fistulae Aneurysms

Aneurysm formation is a complication of vascular access AVF characterised by an enlargement of all three layers of the vessel wall with a diameter of more than 18 mm and has a prevalence of more than 40% in the dialysis population. Baláž et al. [8] performed a systematic review and meta-analysis evaluating the surgical options for the treatment of aneurysmal AVF. Thirteen full text articles were included in the meta-analysis. The total number of patients was 597. Aneurysms were located in the upper arm in 289 (59%) cases and the smallest diameter of a treated aneurysm was 15 mm. The most frequent indication for treatment was bleeding prevention in 513 (86%) cases. Aneurysmorrhaphy was the surgical method of choice in all 13 studies. The pooled primary patency at 12 months was 82% (12 studies). The 12-month primary patency rates were similar for aneurysmorrhaphy with external prosthetic reinforcement (85%, two studies) and aneurysmorrhaphy performed using a stapler (74%, four studies) and without a stapler (82%, six studies). In the studies included none described covered stent graft implantation. The authors believed that all symptomatic aneurysmal arteriovenous access fistulae should be treated surgically by aneurysmorrhaphy without external reinforcement (because prosthetic reinforcement has a potential risk of infection). Aneurysmorrhaphy performed with or without a stapler device seems to be the preferred option.

16.2.1.7 DCB Angioplasty Vs. PBA Angioplasty for Hemodialysis Dysfunction

A meta-analysis presented by Liu et al. [9] compared the safety and efficacy of drug-coated balloon angioplasty (DCB) and plain balloon angioplasty (PBA) in treating hemodialysis access dysfunction. A total of 18 randomized controlled trials

including 877 and 875 patients in the DCB and PBA groups, respectively, were included. Drug-eluting balloon angioplasty was superior to plain balloon angioplasty during short-term follow-up regarding target lesion patency, circuit patency, and target lesion revascularization rates with a similar mortality profile. Using drug-eluting balloon in treating hemodialysis access dysfunction may reduce the requirement of reintervention and its related healthcare cost compared with plain balloon angioplasty in the short-term.

Paclitaxel-coated balloon (PCB) angioplasty and PBA for hemodialysis (HD) access stenosis or occlusion was also investigated by Chen et al. [10]. A total of 16 studies were included in this meta-analysis, 12 randomized controlled trials and 4 cohort studies involving 1086 patients who underwent endovascular treatment for HD access stenosis or occlusion. This meta-analysis showed a significant improvement of short-term and midterm primary patency of HD access after treatment with PCB angioplasty. This favorable outcome was observed in both AVF and central venous stenosis (CVS). There was no association between paclitaxel and all-cause mortality in HD patients at 6-, 12-, and 24-month follow-up in this analysis. However, there was a trend suggesting that PCB angioplasty might increase the risk of 24- month mortality compared with PBA if the sample size is large enough. Further studies on long-term mortality are needed to investigate the safety of PCB angioplasty in patients with ESRD.

Han et al. [11] also compared the efficacy and safety of DCB and PB angioplasty in treating arteriovenous access stenosis in a systematic review and meta-analysis of randomized controlled trials. Sixteen eligible trials, including 1682 lesions, were included in the quantitative analysis for the efficacy and safety of paclitaxel coated DCBs. DCBs were associated with a lower risk of loss of target lesion patency at 6 months (HR 0.53, 95% CI 0.42–0.66) and 12 months (HR 0.60, 95% CI 0.47–0.76), and were also associated with improved six- and 12-month circuit patency. Overall quality of evidence was moderate to low. Procedural complications were rare, and the risk of death up to 12 months was similar between the two groups. In conclusion, this meta-analysis demonstrated an advantage of DCB angioplasty over PB angioplasty in treating arteriovenous dialysis access stenosis.

Tripsianis et al. [12] compared the effectiveness of all first-line endovascular modalities for the treatment of AVF-related stenosis using a network meta-analysis (NMA). Eleven randomized controlled trials were included, with 814 patients, 395 of whom had undergone PBA. The network meta-analysis showed that DCBA at 6 months was significantly more effective than PBA (odds ratio, 0.39; 95% confidence interval, 0.18–0.81) and ranked as the best treatment option, although the difference was not statistically significant compared with cutting balloon angioplasty (odds ratio, 0.65; 95% confidence interval, 0.20–2.12). The differences among the three treatments at 1 year were not statistically significant. Additional conventional pairwise metaanalyses did not find significant differences at 1 year. For patients with failing autogenous AVFs with outflow vein stenosis, DCBA was significantly superior to PBA, with an improved 6-month failure rate. However, the effectiveness of DCBA in the long term deserves further investigation.

16.2.1.8 Distal Revascularization and Interval Ligation (DRIL)

Distal revascularization and interval ligation (DRIL) is one form of treatment of vascular access-induced ischemia. This intervention preserves the AVF while relieving or reversing ischemia symptoms. The procedure involves ligation of the artery immediately distal to the arteriovenous anastomosis site followed by an arterial bypass (artery to artery). This is conducted using a conduit (vein, artery, and prosthetic material) and anastomosis 5–10 cm proximal to the arteriovenous anastomosis from the artery to the distal part of the artery and beyond the ligation site. Kordzadeh and Parsa [13] examined the efficacy of the procedure through a systematic review. In twenty-two studies 459 individuals were subjected to DRIL. Time to ischemia was 196 days. Ischemia grade 3/4 (52%) was the most common presentation. The overall success (grades 1–4) was 81% during a mean and median follow-up of 22.2 months and 18 months, respectively. The conduit of choice was the great saphenous vein (n = 300/459 [65%]), and bypass thrombosis was highest in the polytetrafluoroethylene group (n = 19/44 [43%]). DRIL is an effective modality (grade of recommendation B, level of evidence III/IIb) in the treatment of vascular access-induced ischemia in upper limb AVF and could be successful in 81% of cases.

16.2.1.9 AV Fistula Closure in Renal Transplant Recipients

Ligating an AVF after successful renal transplantation remains a matter of debate. Zheng et al. [14] performed a meta-analysis to evaluate the cardiac effects and allograft function after AVF closure, as well as to assist in deciding whether to preserve or ligate the AVF. 10 studies were included in this meta-analysis. Kidney transplant recipients with occluded AVF had lower left ventricular mass index and left ventricular end-diastolic diameter values compared with patients with patent AVF. Patients with occluded AVF also had lower serum creatinine levels versus those with patent AVF. No difference was seen regarding ejection fraction between the groups. The meta-analysis showed that AVF closure improves cardiac morphology and is associated with better kidney graft function. Therefore, AVF closure may be considered in patients with well-functioning allografts.

Rao et al. [15] presented the first randomized controlled trial looking at the effects of arteriovenous fistula ligation on cardiac magnetic resonance imaging–derived left ventricular mass in kidney transplant recipients. Fifty-four participants completed the study: 27 in the AVF ligation group and 27 in the control group. The primary end point showed a mean decrease of 22.1 g in LVM in the AVF ligation group compared with no significant change in the control group ($P < 0.001$). Significant decreases in LV end-diastolic volumes, LV end-systolic volumes, cardiac output, cardiac index, atrial volumes, and NT-proBNP were also seen in the AVF closure group ($P < 0.01$). No significant changes were observed in LV ejection fraction ($P = 0.93$) and pulmonary artery velocity ($P = 0.07$). These results have

significant implications for the management of cardiovascular risk after kidney transplantation, given that a single intervention, undertaken as a day procedure, has the potential to provide substantial cardiovascular benefits.

16.2.2 Clinical Trials and Registries

16.2.2.1 Hemodialysis Access Type and Mortality

Hicks et al. [16] analyzed the effects of age and initial dialysis access type on all-cause mortality. The study included 507,791 patients (63.4 ± 0.02 years; 56.5% male; 40.9% mortality; follow-up, 1.57 ± 1.36 years). Increasing age was a significant predictor of overall mortality (adjusted hazard ratio [aHR], 1.03; P < .001). Compared with patients with hemodialysis catheters (HCs, n = 418,932), overall risk-adjusted mortality was lowest in patients with AVFs (n = 71,316; aHR, 0.63; P < .001) followed by AVGs (n = 17,543; aHR, 0.83; P < .001). AVF was superior to both HC and AVG for all age groups (P < .001). However, there was a significant change in the relative efficacy of AVG at ages 48 years and 89 years based on spline modeling; there were no significant differences comparing adjusted mortality with AVG vs HC for patients aged 18 to 48 years or for patients >89 years, but AVG was superior to HC for patients 49 to 89 years of age (aHR, 0.811; P < .001). The mortality benefit of AVF was consistently superior to that of AVG and HC for patients of all ages (all, P < .001). AVF is superior to AVG and HC regardless of the patient's age, including in octogenarians. In contrast, the mortality benefit of AVG over HC may not apply to younger (18–48 years) or older (>89 years) age groups. All patients 18 to 48 years should receive AVF for dialysis access whenever possible.

Malas et al. [17] performed a retrospective analysis of the cohort of patients in the United States Renal Data System (USRDS) database who initiated dialysis between January 1, 2006, and December 31, 2010. Patients who initiated dialysis using AVF vs arteriovenous graft (AVG) vs HC were compared. 71,452 (14.0%) patients initiated HD with AVF, 17562 (3.4%) initiated with AVG, and 420,986 (82.5%) initiated with HC. Survival at 1 year was 78% in the HC group compared with 84% for the AVG group and 89% for the AVF group (Wilcoxon P < .001). Five-year survival in the HC group was 45% compared with 48% in the AVG group and 55% in the AVF group (Wilcoxon P < .001). A Cox proportional hazard model showed a 35% reduction in mortality rate in the AVF group compared with the HC group (P < .001) and an 18% reduction in mortality rate in the AVG group compared with the HC group (P < .001). Initiating HD with an AVF provides 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 aim of a study presented by Locham et al. [18] was to use a large national renal database to report the incidence and risk factors of sepsis in patients with

end-stage renal disease (ESRD) initiating HD access using AVF, AVG, or HC in the United States. All patients with ESRD initiating HD access (AVF, AVG, HC) between January 1, 2006, and December 31, 2014, in United States Renal Data System were included. A total of 870,571 patients were identified, of whom, 29.8% (n = 259,686) developed sepsis. HC (31.2%) and AVG (30.6%) were associated with a higher number of septic cases compared with AVF (22.9%; P < .001). The incident rate of sepsis was 12.66 episodes per 100 person-years. It was the highest among HC vs AVG vs AVF (13.86 vs 11.49 vs 8.03 per 100 person-years). Compared with patients with no sepsis, sepsis was associated with a three-fold increase the odds of mortality (odds ratio, 3.16; 95% CI, 3.11–3.21; P < .001). Additionally, in patients who developed sepsis, AVF use was associated with significantly lower mortality compared with AVG and HC (73.7% vs 78.7% vs 78.0%; P < .001). After adjusting for significant covariates, compared with AVF, mortality at 1 year after sepsis was 21% higher in AVG (HR, 1.21; 95% CI, 1.15–1.28; P < .001) and nearly doubled in HC (HR, 1.94; 95% CI, 1.88–2.00; P < .001). Sepsis risk in HD patients is clearly related to access type and is associated with dramatic increase in mortality. Initiating HD access with AVF to meet the National Kidney Foundation Kidney Disease Outcomes Quality recommendations should be implemented to reduce the incidence of sepsis and improve survival in patients with ESRD.

16.2.2.2 Permanent Vascular Access Type for Elderly Patients

There is inadequate evidence regarding the first permanent vascular access type and risk of mortality or hospitalization among the elderly population undergoing hemodialysis. Lyu et al. [19] emulated a randomized controlled trial using observational data to compare the effect of AVF versus AVG creation on the risks of mortality, hospitalization, and sepsis among elderly patients receiving HD. Elderly patients registered in the US Renal Data System were enclosed. Inclusion criteria were initiation of HD between 2013 and 2014, age $\geq$ 67 years at HD initiation, no AVF/AVG created before HD initiation, and a first AVF/AVG created within 6 months after HD initiation. A total of 19,867 patients were included for the analyses, with 80.1% receiving an AVF and 19.9% an AVG. In unweighted analysis, AVF creation was associated with significantly lower risks of mortality and hospitalization, especially within 6 months after vascular access creation. In inverse probability of treatment weighting analysis, AVF creation was associated with lower incidences of mortality and hospitalization within 6 months after creation for mortality and all-cause hospitalization, respectively), but not between 6 months and 3 years after access creation. No association between AVF creation and mortality, sepsis, or all-cause, cardiovascular disease-related, or infection-related hospitalization was found in instrumental variable analyses. However, AVF creation was associated with a lower risk of access-related hospitalization not due to infection. Using observational data to emulate a target randomized controlled trial, the type of initial arteriovenous access created was not associated with the risks of mortality, sepsis, or all-cause,

cardiovascular disease-related, or infection-related hospitalization among elderly patients who initiated HD with a catheter and had an AVF/AVG created within 6 months.

16.2.2.3 Hemodialysis Access in Diabetic Patients

A retrospective study evaluated the effect of diabetes on outcomes of autogenous fistulas and prosthetic grafts for hemodialysis access in a large population-based cohort of patients [20]. The United States Renal Database System (2007–2014) was used. The study of 381,622 patients comprised 303,307 (79.5%) autogenous fistulas and 78,315 (20.5%) prosthetic grafts placed in 231,134 (60.6%) diabetic patients and 150,488 (39.4%) nondiabetic patients. There was decrease in maturation for diabetics compared to nondiabetics who received autogenous fistulas and prosthetic grafts. Comparing diabetics vs nondiabetics, primary patency at 5 years was 19.4% vs 23.5% ($P < .001$) for autogenous fistulas and 9.1% vs 11.2% ($P < .001$) for prosthetic grafts. In this population-based cohort of hemodialysis patients, diabetes mellitus was associated with a decrease in patient survival, access maturation, and primary fistula patency. In contrast, there was no association between diabetes and prosthetic graft patency and severe prosthetic graft infection warranting excision. Further details are given in Table 16.1.

16.2.2.4 Brachiobasilic AV Fistula—One-Stage Vs. Two-Stage

The brachiobasilic arteriovenous fistula (BBAVF) can be created successfully using either a one-stage or a two-stage procedure [21]. For the one-stage procedure, the transposition of the basilic vein and arteriovenous anastomosis are performed during the same procedure. In the two-stage approach, a first procedure is typically used to create the arteriovenous anastomosis through an incision at the antecubital fossa. This is followed by a second procedure later to elevate or to transpose the arterialized vein. A new arteriovenous anastomosis may or may not be required. The

Table 16.1 Kaplan-Meier estimates of primary patency, secondary patency and survival for diabetic and non-diabetic patients who received autogenous AV fistulas or prosthetic grafts (according to [20])

Outcome	AV fistula/diabetic	AV fistula/non-diabetic	Graft/diabetic	Graft/non-diabetic
Primary patency (%)				
– 1 year	40.5	46.0	30.3	31.6
– 3 years	26.8	31.8	13.6	16.0
Secondary patency (%)				
– 1 year	60.8	64.2	58.3	59.4
– 3 years	51.9	55.8	43.7	45.5
Patient survival, %				
– 1 year	83.2	83.7	76.9	75.8
– 3 years	58.5	62.2	49.7	51.1

theoretical advantages of the one-stage procedure include the shorter time between the fistula creation and cannulation for dialysis and the requirement for only one procedure. The downside of this approach is the use of an extended incision if the fistula fails to mature and the risk of injuring the unarterialized basilic vein during surgery. In comparison, the two-stage procedure leaves the patient with a smaller antecubital incision if the fistula fails. In addition, the mobilization of the larger arterialized vein may be technically easier in the two-stage approach. Tan et al. [21] identified 2648 patients who had received BBAVFs within the Vascular Quality Initiative data set (2010–2016) and compared those created using the one-stage and two-stage technique. There were 1234 (47%) one-stage and 1414 (53%) two-stage BBAVFs in the study cohort. Patients undergoing one-stage BBAVFs had larger vein diameters (4.1 vs 3.4 mm; P < .001) and the procedure was more often performed in an inpatient setting (21% vs. 13%; p < 0.001) compared with patients undergoing a two-stage procedure. The 12-month primary patency rate was higher for the one-stage BBAVF (49.1% vs 40.4%; P = .005), although the secondary patency rate was comparable (80.0% vs 77.9%; P = .54). In multivariable analysis, although loss of primary patency at 12 months and 3-month wound infection were similar between the two approaches, the risk of 3-month arm swelling was significantly lower for two-stage BBAVFs (aHR, 0.35; 95% CI, 0.16–0.77; P = .009). Both types of BBAVF approaches should be considered standard of care. Most surgeons in the VQI favored a two-stage procedure for patients with a smaller basilic vein and those with a history of failed access.

16.2.2.5 End-to-Side or Side-to-Side Arteriovenous Anastomosis for AVF

ElKassaby et al. [22] compared the results of both surgical techniques, end-to-side (ETS) or side-to-side (STS) anastomosis between artery and vein for creation an AVF in a randomized prospective controlled setting with 50 patients each. Primary and secondary patency rates at 12 months were 76% ETS vs. 78% STS (P = 0.381) and 84% ETS vs. 86% STS (P = 0.225), respectively. The ability of the access to withstand 6 consecutive full dialysis sessions within a period of 30 days was defined as functional maturation of AVF. This parameter showed the most significant difference between the two groups of the study population, with clear favour for the ETS technique (70% vs. 34%, P = 0.0001). This was also reflected in the results of maximum flow achieved during the first three dialysis sessions. Considering these results, the authors recommended the ETS technique when creating AVF.

16.2.2.6 Surgical Vs Percutaneous AV Fistulas

In a single-center retrospective study, Harika et al. [23] compared the first 107 patients who had undergone percutaneous arteriovenous fistula (p-AVF) creation with the Ellipsys system from May 2017 to May 2018 with an equal number of consecutive patients who had undergone surgical arteriovenous fistulas (s-AVFs). The p-AVFs showed superior maturation rates at 6 weeks (65% vs 50%; P = .01).

The primary patency rates were greater for the s-AVFs at 12 months (86% vs 61%; P < .01). However, primary patency was comparable between the two groups at 24 months (52% vs 55%; P = .48). No significant difference was found in the secondary patency rates at 12 (90% vs 91%) and 24 (88% vs 91%) months. At the 2-year follow-up point, the rate of percutaneous reintervention was similar; however, the s-AVFs had required more frequent surgical revision (36% vs 17%; P = .01). Issues with wound healing and infection were also more frequent with s-AVFs (9% vs 0.9%; P < .01). These data support the conclusion that p-AVFs have results comparable, and in some respects superior, to those of s-AVFs.

Shahverdyan et al. [24] compared the Ellipsys percutaneous AVF (n = 89) with a proximal forearm Gracz-type surgical AVF (n = 69) in a retrospective study of prospectively collected clinical data. The Gracz-type AVF is a proximal forearm arteriovenous fistula involving an end-to-side anastomosis between a perforating branch of the cephalic or median antecubital vein and the brachial or proximal radial artery. Technical success was 100% for both groups. Average procedure times were 14 min for percutaneous AVFs and 74 min for surgical AVFs (P < 0.001). Proximal radial artery (PRA) was used in all percutaneous AVF cases. Inflow for surgical AVFs included radial (30%), ulnar (12%), and brachial (58%) arteries. Outflow veins for both groups were the cephalic and/or basilic veins. Access flow volumes, times to maturation, and overall numbers of interventions per patient-year were not significantly different. Cumulative incidence of primary patency failure at 12 months was lower for surgical AVF (47% vs 64%, P = 0.1), but secondary patency failure was not different between groups (20% vs 12%, P = 0.3). PRA surgical AVFs had similar primary patency (65% vs 64%, P = 0.8) but higher secondary patency failure rates than percutaneous AVFs at 12 months (34% vs 12%, P = 0.04). When a distal radial artery AVF is not feasible, percutaneous AVF might offer an appropriate procedure for creating a safe and functional access, maintaining further proximal forearm surgical AVF creation options.

Mordhorst et al. [25] compared autogenous arteriovenous access created with the EverlinQ endoAVF system with accesses created by conventional surgical technique with respect to functional and patency related outcomes. A total of 369 accesses were created during the study period, including 61 endovascular accesses, 171 radiocephalic accesses, and 137 brachiocephalic accesses (median follow-up, 17 months; range, 1–71 months). Maturation failure at the end of follow-up was 27% ± 6%, 27% ± 5%, and 18% ± 4% for endovascular, radiocephalic, and brachiocephalic accesses, respectively (P = .049 for brachiocephalic vs endovascular accesses). Primary patencies at 12 and 24 months were 42% ± 5% and 32% ± 7% for endovascular accesses, 43% ± 4% and 24% ± 4% for radiocephalic accesses, and 42% ± 4% and 29% ± 4% for brachiocephalic accesses (P = .906). Secondary patencies at 12 and 24 months were 68% ± 6% and 60% ± 7% for endovascular accesses, 75% ± 3% and 67% ± 4% for radiocephalic accesses, and 91% ± 3% and 81% ± 4% for brachiocephalic accesses (P = .006 for brachiocephalic vs endovascular accesses). There were no statistically significant differences in ischemic steal. Endovascular arteriovenous accesses were comparable to radiocephalic fistulas

with respect to maturation and patency; however, they were inferior to brachiocephalic accesses. EndoAVF should not be seen as a replacement for surgically created dialysis access. Rather, it is another option which can be used in attempts to preserve more proximal creation.

16.2.2.7 Early Cannulation Arteriovenous Grafts

Tawfik et al. [26] recruited 477 hemodialysis patients indicated for vascular access creation and compared outcomes with standard AV grafts (PTFE) (n = 236) with those using early cannulation grafts (ACUSEAL, n = 241) in a single center randomized controlled trial. Primary patency rate was 65.7% and 68.0% (P = .58) at 6 months and 53.8% and 56.4% (P = .57) at 12 months in the standard AVG (sAVG) and early cannulation AVG (eAVG) groups, respectively. Primary assisted patency rate was 70.8% and 69.7% (P = .8) in patients with sAVG and eAVG at 6 months, whereas the reported rates at 12 months were 59.3% and 61.0% (P = .71) respectively. Patients in the eAVG group experienced significantly earlier cannulation when compared with patients in the sAVG group (median, 3.0 days; range, 1.0–9.0 days vs 19.0 days; range, 15.0–22.0 days; P < .001). Early cannulation grafts had comparable 12-month outcomes to standard grafts with the added advantage of earlier time to first cannulation.

In a retrospective cohort study, too, eighteen-month patency and infection rates were similar between 148 standard (sAVG) and 62 immediate-access arteriovenous grafts (IAAVG), but immediate-access grafts had fewer secondary procedures and allowed earlier cannulation and tunneled catheter removal, thereby significantly decreasing catheter-related complications [27]. Primary patency was similar at both 1 year (sAVG, 39.4%; IAAVG, 56.7%; P = .4) and 18 months (sAVG, 29.0%; IAAVG, 43.7%; P = .4). Overall survival was 48% at 24 months. IAAVG patients required fewer overall additional procedures to maintain patency (mean number of procedures, 0.99 for sAVGs vs 0.61 for IAAVGs; P = .025). There was no difference in occurrence of steal syndrome (sAVG, 6.8%; IAAVG, 8.1%; P = .74) or graft infection (sAVG, 19.0%; IAAVG, 12.0%; P = .276). Seventy-five percent of all grafts were successfully cannulated, with shorter median time to first cannulation in the IAAVG group (6 days; interquartile range [IQR], 1–19 days) compared with the sAVG group (31 days; IQR, 26–47 days; P < .01). Catheter-related complications occurred less frequently in the IAAVG group (16.4% vs 2.9%; P < .045).

Mohapatra et al. [28] constructed a Markov state-transition model in which patients initially received either an IAAVG or an sAVG and a tunneled dialysis catheter (TDC) until graft usability; patients were followed through multiple subsequent access procedures for a 60-month time horizon. IAAVG placement was a dominant strategy under both real-world ($1201.16 less expensive and 0.03 QALY more effective) and ideal ($1457.97 less expensive and 0.03 QALY more effective) conditions. The mean catheter time was lower with IAAVG (3.9 vs 8.7 months; P < .0001), as was the mean number of access-related infections (0.55 vs 0.74; P < .0001).

Median survival in the model was 29 months. Overall mortality was similar between groups (76.3% vs 76.7% at 5 years; P = .33). The Markov decision analysis model supported the hypothesis that IAAVGs come with added initial cost but are ultimately cost-saving and more effective.

16.2.2.8 Heparin-Bonded PTFE Arteriovenous Grafts

Heparin-bonded polytetrafluoroethylene grafts were marketed to improve hemodialysis access outcomes but are twice the cost of standard polytetrafluoroethylene. The "Propaten Randomized Investigation on Cost-benefit and Efficacy" trial was designed as a multicenter, single-blinded, prospective randomized controlled trial to examine efficacy and cost-effectiveness of heparin-bonded polytetrafluoroethylene (HB-PTFE) versus standard polytetrafluoroethylene (S-PTFE) hemodialysis access grafts [29]. Planned sample size was 200 with 1-year primary patency as the primary endpoint. One hundred and five patients were enrolled at the time of interim analysis. One-year primary patency was 34.9% in the heparin-bonded-polytetrafluoroethylene group vs 32.7% in the standard-polytetrafluoroethylene group (P = .884). At interim analysis, a meta-analysis was also performed. Summary rate ratio from the meta-analysis (1209 patients) was 0.87 favoring heparin-bonded polytetrafluoroethylene (P = .33). Posterior hazard ratio from Cox regression was 0.90 (credible interval 0.70–1.13) favoring heparin-bonded polytetrafluoroethylene, which was not significant. Bayesian posterior probability of the a priori hypothesized 20% better patency with heparin-bonded polytetrafluoroethylene was 24%. Sample size to detect superiority with the small observed effect size would require about 3800 subjects. There was no meaningful difference in patency and the trial was stopped for futility.

16.2.2.9 Distal Revascularization and Interval Ligation (DRIL)

A total of 66 patients who had undergone DRIL for hand ischemia were presented by Weaver et al. [30]. An arm vein conduit was used in 40 patients and a great saphenous vein (GSV) conduit in 26 patients. No significant differences in comorbidities were found between the two groups, except for diabetes mellitus (arm vein group, 78%; GSV group, 50% GSV; P = .02). At 12 and 24 months after DRIL, 86.9% and 82.0% of patients with an arm vein conduit had access patency compared with 93.8% and 76.9% of those with a GSV conduit, respectively. All but one patient had symptom resolution. The incidence of wound complications was significantly greater in the GSV group than in the arm vein group (46% vs 11%; P = .003). DRIL bypass had remained patent in all but one patient in each group, with a median follow-up of 18 months in the arm vein conduit group and 15 months in the GSV conduit group. In this series, symptom resolution and access salvage were similar but distinctly fewer wound complications had occurred in the arm vein group.

Additionally, the use of an arm vein conduit avoids the need for general anaesthesia. If an ipsilateral arm vein is available, it should be the conduit of choice when performing DRIL.

16.2.2.10 Paclitaxel-Assisted Balloon Angioplasty of AVF

The Paclitaxel-assisted balloon Angioplasty of Venous stenosis in hEmodialysis access (PAVE) trial is a large-scale randomized controlled trial designed to test the efficacy of paclitaxel-coated balloons in angioplasty of AVFs [31]. 212 patients from 20 UK centers were randomized into the trial (106 paclitaxel-coated balloon and 106 standard balloon). The primary endpoint was time to loss of clinically driven target lesion primary patency. Primary analysis showed no significant evidence for a difference in time to end of target lesion primary patency between groups: hazard ratio 1.18 with a 95% confidence interval of 0.78–1.79. At 6 months, the target lesion primary patency (TLPP) was 71.7% in the paclitaxel-coated balloon group, compared with 84.5% in the standard balloon group. By 12 months, these figures were 52.5% and 58.8%, respectively. The study demonstrated no evidence that paclitaxel-coated balloons provide benefit, following standard care high-pressure balloon angioplasty, in the treatment of arteriovenous fistulas. Hence, in view of the benefit suggested by other trials, the role of paclitaxel-coated angioplasty balloons remains uncertain.

The aim of a small single-center, parallel group, randomized controlled trial was to evaluate the effect of drug-coated balloons in the treatment of arteriovenous fistula stenosis [32]. A total of 39 patients with primary or recurrent stenosis in a failing native arteriovenous fistulas were randomized to drug-coated balloon (n = 19) or standard balloon angioplasty (n = 20). Follow-up was 1 year. Primary outcome measure was target lesion revascularization. A total of 88.9% (16/18) in the drug-coated balloon group was revascularized or occluded within 1 year, compared to 22.2% (4/18) of the stenoses in the balloon angioplasty group (relative risk for drug-coated balloon 7.09). Mean time-to-target lesion revascularization was 110 and 193 days after the drug-coated balloon and balloon angioplasty, respectively ($p = 0.06$). The target lesion revascularization-free survival after drug-coated balloon-treatment was clearly worse. The reason for this remains unknown, but it may be due to differences in the biological response to paclitaxel in the venous arteriovenous fistula-wall compared to its antiproliferative effect in the arterial wall after drug-coated balloon treatment of atherosclerotic occlusive lesions.

In another prospective, single-centre, single-blinded, 1:1 randomized, clinical trial a total of 42 patients with primary or restenotic lesions in native upper extremity arteriovenous (AV) fistulas or at the graft-venous anastomosis were included [33]. Patients were randomized to angioplasty with POBA or DEB. This trial detected no significant differences between DEB and standard POBA in the treatment of dysfunctional hemodialysis circuits.

The aim of a retrospective, monocentric study [34] was to evaluate the acute and mid-term results of treatment of AV access stenosis and occlusion using plain cutting balloon (CB) and drug-coated balloon (DCB) angioplasty compared to standard treatment using plain-old balloon angioplasty (POBA). One hundred and eighty-four patients met the inclusion criteria. POBA as stand alone or combined with DCB angioplasty was performed in 71 patients (38.6%), CB in 54 patients (29.3%), and in 59 patients (32.1%), both CB and DCB were used. Primary patency rate at 12 months was 31.6% for the POBA/DCB-group, 52.3% for the CB-group, and 64.8% for the CB/DCB-group, respectively. In total, 80 patients (51.6%) had a TLR including endovascular or surgical revision, or a shunt replacement. All-cause mortality at 12 months was 7.2% in the DCB group and 9.1% in the group of patients treated without a DCB ($p = 0.747$). In conclusion, the use of CB seems to be crucial for a better outcome. The combination of CB and DCB achieved the best patency results at mid-term.

16.2.2.11 Drug Coated Balloons for the Treatment of Stent Graft Stenosis

Clinical trials have evaluated the use of DCBs in dialysis arteriovenous (AV) fistulas, with conflicting results. However, these clinical trials excluded stent graft stenosis. Therefore, Hsieh et al. [35] investigated the efficacy of DCBs for stent graft stenosis of dysfunctional hemodialysis vascular access compared with conventional angioplasty in a prospective, single blinded, randomized controlled study. 40 patients were randomized 1:1 to the DCB group (n = 20) and control group (n = 20). The study was concluded when all participants had completed at least 6 months of follow up. None of the patients died during the study period, although three accesses were abandoned before the end of follow up. All interventions for stent graft stenosis achieved anatomical and clinical success. No major or minor complications occurred in either group of patients. Thirty-six participants completed follow up angiography. The DCB group had a superior mean late luminal loss at 6 months compared with the control group (1.82 mm ± 1.83 mm vs 3.63 mm ± 1.08 mm, respectively, p = .001. The DCB group had a superior six-month target lesion primary patency compared with the control group [hazard ratio (HR) 0.23, 95% confidence interval (CI) 0.07–0.71; p = .005). Additionally, the DCB group had a numerically higher six-month access circuit primary patency rate than the control group, although the difference was not statistically significant (HR 0.54, 95% CI 0.26–1.11, p = .095). Treatment of stent graft stenosis with drug coated balloons provided less late luminal loss and potentially superior target lesion patency compared with conventional balloons. The results warrant further validation with a larger number of patients.

16.2.2.12 Covered Stent Versus Angioplasty for AVF Stenosis

In the Arteriovenous (AV) Stent Graft in the Treatment of Venous Outflow Stenosis in AV Fistula Access Circuits (AVeNEW) study, patients with AVF stenosis of 50% or more and evidence of AVF dysfunction underwent treatment with PTA followed

by randomization of 142 patients to include a covered stent or 138 patients with PTA alone [36]. Safety was statistically non-inferior between groups, whereas target lesion primary patency (TLPP) was statistically superior for the covered-stent group at 6 and 12 months, with benefit observed through 2 years. Although access circuit primary patency (ACPP) did not show improvement statistically, patients treated with the covered stent received fewer interventions to maintain AVF patency, had prolonged time between interventions, and had cumulative AVF patency comparable to that in the PTA group (>90%).

16.2.2.13 Anticoagulation Therapy and Hemodialysis Access Patency

Kumpfbeck et al. [37] identified in the Vascular Quality Initiative (VQI) database a total of 27,757 patients who underwent hemodialysis access creation, with the majority undergoing AVF creation (78.8%). 12.9% of patients were on postoperative anticoagulation (AC) therapy. The wound infection rate was 2.3 vs 3.8% in the no AC and AC cohorts, respectively ($P < 0.001$). At 6 months follow-up, patency was 85.7 vs 84.3% in the no AC and AC cohorts, respectively ($P = 0.044$). Expectedly, grafts had lower patency rates compared to AVF; those within the no AC cohort had a patency of 83.0% compared to 81.2% in those on AC ($P = 0.106$). On multivariable analysis, anticoagulation use was associated with a higher risk of wound infections (odds ratio [OR] 1.513, 95% confidence interval [CI] 1.160–1.973, $P = 0.002$). Anticoagulation therapy was associated with a higher rate of wound infections but did not affect short-term access patency within 6-months.

16.3 Conclusions for Clinical Practice

1. An autogenous arteriovenous (AV) fistula is recommended as the primary option for hemodialysis vascular access. The radiocephalic arteriovenous fistula is recommended as the preferred vascular access.
2. When the upper arm cephalic vein is unavailable, a basilic vein transposition arteriovenous fistula should be considered in preference to an arteriovenous graft because of its improved patency and the reduced risk of infection.
3. When a distal radial artery AVF is not feasible, percutaneous AVF might offer an appropriate procedure for creating a safe and functional access, maintaining further proximal forearm surgical AVF creation options.
4. Regional anaesthesia should be considered in preference to local anaesthesia for vascular access surgery.
5. DRIL is an effective modality (grade of recommendation B, level of evidence III/IIb) in the treatment of vascular access-induced ischemia in upper limb AVF.
6. Symptomatic aneurysmal arteriovenous access fistulae should be treated surgically by aneurysmorrhaphy without external reinforcement. Aneurysmorrhaphy performed with or without a stapler device seems to be the preferred option.

7. AVF closure may be considered in patients with well-functioning allografts.
8. Early cannulation grafts have comparable 12-month outcomes to standard grafts with the added advantage of earlier time to first cannulation.
9. Balloon angioplasty is recommended for the treatment of venous outflow stenosis. The role of paclitaxel-coated balloon angioplasty and covered stents is uncertain.

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Chapter 17
The Diabetic Foot

17.1 Guidelines

17.1.1 Society for Vascular Surgery

The Society for Vascular Surgery (SVS), in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine, made specific practice recommendations for the treatment of diabetic foot [1]. The level of evidence to support the recommendations is divided into three categories: A (high quality), B (moderate quality), and C (low quality). Recommendations are categorized as strong (Grade 1) or weak (Grade 2). Key statements include:

1. **Prevention of diabetic foot ulceration**
    - We recommend that patients with diabetes undergo annual interval foot inspections by physicians or advanced practice providers with training in foot care (Grade 1C).
    - We recommend that foot examination include testing for peripheral neuropathy using the Semmes-Weinstein test (Grade 1B).
    - We recommend education of the patients and their families about preventive foot care (Grade 1C).
    - We suggest against the routine use of specialized therapeutic footwear in average-risk diabetic patients (Grade 2C).
    - 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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- We suggest adequate glycaemic control (haemoglobin A1c < 7% with strategies to minimise hypoglycaemia) to reduce the incidence of diabetic foot ulcers (DFUs) and infections, with subsequent risk of amputation (Grade 2B).
- We recommend against prophylactic arterial revascularization to prevent DFU (Grade 1C).

2. **Off-loading DFUs**

- In patients with plantar DFU, we recommend offloading with a total contact cast (TCC) or irremovable fixed ankle walking boot (Grade 1B).
- In patients with DFU requiring frequent dressing changes, we suggest offloading 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).
- 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).
- 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)**

- 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).
- 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).
- 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 or if the plain film is not useful (Grade 1B).
- 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).
- 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).
- 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**

- 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).
- 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).
- We suggest that treatment of DFIs should follow the most current guidelines published by the Infectious Diseases Society of America (IDSA) (Ungraded).
- 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).
- We recommend sharp débridement of all devitalized tissue and surrounding callus material from diabetic foot ulcerations at 1- to 4-week intervals (Grade 1B).
- 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).
- 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).
- 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).
- 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**

- We suggest that patients with diabetes have ankle-brachial index (ABI) measurements performed when they reach 50 years of age (Grade 2C).
- 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 (e.g., coronary, cerebral, or renal) have an annual vascular examination of the lower extremities and feet including ABI and toe pressures (Grade 2C).

- 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).
- In patients with DFU who have PAD, we recommend revascularization by either surgical bypass or endovascular therapy (Grade 1B). 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.

17.1.2 International Working Group on the Diabetic Foot (IWGDF)

17.1.2.1 Recommendations on the Diagnosis and Management of Foot Infections in Persons with Diabetes [2]

Quality of evidence is rated as ‘high’, ‘moderate’ or ‘low’. Strength of each recommendation is assessed as ‘strong’ or ‘weak’.

- Classification/diagnosis
  - Diabetic foot infection must be diagnosed clinically, based on the presence of local or systemic signs or symptoms of inflammation (strong; low).
  - Assess the severity of any DFI using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification scheme (strong; moderate).
- Osteomyelitis
  - 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 (strong; high).

  - Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (weak; moderate).
  - 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 (strong; moderate).
  - 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 (strong; weak).
  - 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 (strong; moderate).
  - Obtain plain X-rays of the foot in all cases of non-superficial diabetic foot infection (strong; low).
  - Use MRI when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (strong; moderate).
  - 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 (weak; moderate).

- Assessing severity
  - 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 (strong; moderate).
  - At initial evaluation, assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (strong; low).

- Microbiological considerations
  - Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the causative microorganisms and their antibiotic sensitivity (strong; high).
  - Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (strong; low).
  - 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 (strong; low).

- Surgical treatment
  - Consult a surgical specialist in selected cases of moderate, and all cases of severe diabetic foot infection (weak; low).

  - Perform urgent surgical interventions in cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (strong; low).
  - 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 (strong; low).

- Antimicrobial therapy
  - While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected wounds with antimicrobial therapy (strong; low).
  - 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 (strong; moderate).
  - A course of antibiotic therapy of 1–2 weeks is usually adequate for most mild and moderate infections (strong; high).
  - Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (strong; low).
  - Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome (strong; high).
  - 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 (strong; moderate).
  - We suggest not using any adjunctive treatments for diabetic foot infection (weak; low).
  - 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 (strong; low).

17.1.3 International Working Group on the Diabetic Foot (IWGDF)

17.1.3.1 Guidance on Use of Interventions to Enhance the Healing of Chronic Ulcers of the Foot in Diabetes [3]

- Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing (strong; low).
- In general, remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contraindications such as severe ischemia into account (strong; low).

- Select dressing principally on the basis of exudate control, comfort and cost (strong; low).
- Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection (strong; moderate).
- Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomized trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use (weak; moderate).
- Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remain to be established (weak; moderate).
- Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care (strong; low).
- Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care (strong; low).
- Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care (strong; low).

17.1.4 International Working Group on the Diabetic Foot (IWGDF 2019 Update) [4, 5]

17.1.4.1 Guidelines on Diagnosis, Prognosis, and Management of Peripheral Artery Disease in Patients with Foot Ulcers and Diabetes [4]

- Examine the feet of all patients with diabetes annually for the presence of peripheral artery disease (PAD), even in the absence of foot ulceration. At a minimum, this should include taking a relevant history and palpating foot pulses (strong; low).
- Clinically examine (by relevant history and palpation of foot pulses) all patients with diabetes and foot ulceration for the presence of PAD (strong; low).
- As clinical examination does not reliably exclude PAD in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement. No single modality has been shown to be optimal, and there is no definite threshold value above which PAD can reliably be excluded. However, PAD is a less likely diagnosis in the presence of ABI, 0.9–1.3; TBI, $\geq$0.75; and triphasic pedal Doppler waveforms (strong; low).

- Perform at least one of the following bedside tests in a patient with a diabetic foot ulcer and PAD, any of which increases the pretest probability of healing by at least 25%: a skin perfusion pressure of ≥40 mmHg, a toe pressure of ≥30 mmHg, or a transcutaneous oxygen pressure (TcPO2) of ≥25 mmHg (strong; moderate).
- Use the Wound, Ischaemia, and foot Infection (WIfI) classification system as a means to stratify amputation risk and revascularization benefit in a patient with a diabetic foot ulcer and PAD (strong; moderate).
- Always consider urgent vascular imaging, and revascularization, in a patient with a diabetic foot ulcer and an ankle pressure of <50 mmHg, ABI of <0.5, a toe pressure of <30 mmHg, or a TcPO2 of <25 mmHg (strong; low).
- Always consider vascular imaging in patients with a diabetic foot ulcer, irrespective of the results of bedside tests, when the ulcer is not healing within 4–6 weeks despite good standard of care (strong; low).
- Always consider revascularization in a patient with a diabetic foot ulcer and PAD, irrespective of the results of bedside tests, when the ulcer is not healing within 4–6 weeks despite optimal management (strong; low).
- Do not assume diabetic microangiopathy, when present, is the cause of poor healing in patients with a diabetic foot ulcer; therefore, always consider other possibilities for poor healing (strong; low).
- Use any of the following modalities to obtain anatomical information when considering revascularizing a patient's lower extremity: colour duplex ultrasound, computed tomographic angiography, magnetic resonance angiography, or intra-arterial digital subtraction angiography. Evaluate the entire lower extremity arterial circulation with detailed visualization of below-the-knee and pedal arteries, in an anteroposterior and lateral plane (strong; low).
- When performing revascularization in a patient with a diabetic foot ulcer, aim to restore direct blood flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the ulcer. After the procedure, evaluate its effectiveness with an objective measurement of perfusion (strong; low).
- As evidence is inadequate to establish whether an endovascular, open, or hybrid revascularization technique is superior, make decisions based on individual factors, such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities, and local expertise (strong; low).
- Any centre treating patients with a diabetic foot ulcer should have expertise in, and rapid access to facilities necessary to diagnose and treat, PAD, including both endovascular techniques and bypass surgery (strong; low).
- Ensure that after a revascularization procedure in a patient with a diabetic foot ulcer, the patient is treated by a multidisciplinary team as part of a comprehensive care plan (strong; low).
- Urgently assess and treat patients with signs or symptoms of PAD and a diabetic foot infection, as they are at particularly high risk for major limb amputation (strong; moderate).

- Avoid revascularization in patients in whom, from the patient's perspective, the risk-benefit ratio for the probability of success of the procedure is unfavourable (strong; low).
- Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia, and treatment with a statin drug as well as low-dose clopidogrel or aspirin (strong; low).

17.1.4.2 Guidelines on Offloading Foot Ulcers in Persons with Diabetes [5]

1. (a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a nonremovable knee-high offloading device with an appropriate foot-device interface as the first choice of offloading treatment to promote healing of the ulcer (strong; high).

   (b) When using a nonremovable knee-high offloading device to heal a neuropathic plantar forefoot or midfoot ulcer in a person with diabetes, use either a total contact cast or nonremovable knee-high walker, with the choice dependent on the resources available, technician skills, patient preferences, and extent of foot deformity present (strong; moderate).
2. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a nonremovable knee-high offloading device is contraindicated or not tolerated, consider using a removable knee-high offloading device with an appropriate foot-device interface as the second choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to wear the device at all times (weak; low).
3. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a knee-high offloading device is contraindicated or not tolerated, use a removable ankle-high offloading device as the third choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to wear the device at all times (strong; low).
4. (a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, do not use, and instruct the patient not to use, conventional or standard therapeutic footwear as offloading treatment to promote healing of the ulcer, unless none of the abovementioned offloading devices is available (strong; moderate).

   (b) In that case, consider using felted foam in combination with appropriately fitting conventional or standard therapeutic footwear as the fourth choice of offloading treatment to promote healing of the ulcer (weak; low).
5. In a person with diabetes and a neuropathic plantar metatarsal head ulcer, consider using Achilles tendon lengthening, metatarsal head resection(s), or joint

arthroplasty to promote healing of the ulcer, if non-surgical offloading treatment fails (weak; low).

6. In a person with diabetes and a neuropathic plantar or apex digital ulcer, consider using digital flexor tenotomy to promote healing of the ulcer, if non-surgical offloading treatment fails (weak; low).
7. (a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with either mild infection or mild ischaemia, consider using a nonremovable knee-high offloading device to promote healing of the ulcer (weak; low).

   (b) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both mild infection and mild ischaemia or with either moderate infection or moderate ischaemia, consider using a removable knee-high offloading device to promote healing of the ulcer (weak; low).

   (c) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both moderate infection and moderate ischaemia or with either severe infection or severe ischaemia, primarily address the infection and/or ischaemia, and consider using a removable offloading intervention based on the patient's functioning, ambulatory status, and activity level, to promote healing of the ulcer (weak; low).
8. In a person with diabetes and a neuropathic plantar heel ulcer, consider using a knee-high offloading device or other offloading intervention that effectively reduces plantar pressure on the heel and is tolerated by the patient, to promote healing of the ulcer (weak; low).
9. In a person with diabetes and a nonplantar foot ulcer, use a removable ankle-high offloading device, footwear modifications, toe spacers, or orthoses, depending on the type and location of the foot ulcer, to promote healing of the ulcer (strong; low).

17.1.5 Guidelines on the Classification of Foot Ulcers in People with Diabetes (IWGDF 2023 Update) [6]

- In a person with diabetes and a foot ulcer, use the SINBAD system for communication between healthcare professionals about the characteristics of an ulcer, and clearly state the presence or absence of each of the composing variables (Strength of recommendation: Strong; Certainty of evidence: Low)
- In a person with diabetes and a foot ulcer, when re-sources exist in addition to an appropriate level of expertise and it is considered feasible, consider using the WIfI system for communication about the characteristics of an ulcer between healthcare professionals, but with characterization of each of the composing variables (Conditional; Low)

SINBAD system for grading foot ulcers

Category	Definition	Score
Site	- Forefoot - Midfoot and hindfoot	0 1
Ischemia	- Pedal blood flow intact: at least one palpable pulse - Clinical evidence of reduced pedal flow	0 1
Neuropathy	- Protective sensation intact - Protective sensation lost	0 1
Bacterial infection	- None - Present	0 1
Area ulcer	- Ulcer <1 cm^2 - Ulcer ≥1 cm^2	0 1
Depth	- Ulcer confined to skin and subcutaneous tissue - Ulcer reaching muscle, tendon or deeper	0 1

Total possible score 0–6

17.1.6 WIfI Classification System

For patients with a threatened lower extremity because of ischemia, wound and infection, the Society for Vascular Surgery has proposed the threatened limb classification system. The primary purpose of this classification is to provide more precise description of the disease burden to allow accurate outcomes assessments and comparisons between similar groups of patients and alternative therapies [7]. The classification system is based simply on grading each of the three major factors (Wound, Ischemia, and foot Infection [WIfI]). It is based on a scale from 0 to 3, where 0 represents none, 1 mild, 2 moderate, and 3 severe.

1. Wound Grades
   - 0 = No ulcer/No gangrene
   - 1 = Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx/No gangrene
   - 2 = Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement/Gangrenous changes limited to digits
   - 3 = Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement/Extensive gangrene involving forefoot and/or midfoot; full thickness heel necrosis ± calcaneal involvement
2. Ischemia
   - 0 = ABI ≥ 0.80/Ankle systolic pressure > 100 mmHg/Tp, $TcPO_2 \geq 60$ mmHg
   - 1 = ABI 0.6–0.79/Ankle systolic pressure 70–100 mmHg/Tp, $TcPO_2$ 40–59 mmHg
   - 2 = ABI 0.4–0.59/Ankle systolic pressure 50–70 mmHg/Tp, $TcPO_2$ 30–39 mmHg

- 3 = ABI ≤ 0.39/Ankle systolic pressure < 50 mmHg/Tp, $TcPO_2$ < 30 mmHg

ABI, Ankle-brachial index; TP, toe pressure; $TcPO_2$, transcutaneous oximetry.

3. Clinical manifestation of infection

- 0 = No symptoms or signs of infection
- 1 = Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs)
- 2 = Local infection with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis)
- 3 = Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following:
  - Temperature > 38° or < 36 °C
  - Heart rate > 90 beats/min
  - Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg
  - White blood cell count >12,000 or < 4000 cu/mm or 10% immature (band) forms

$PACO_2$, Partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome.

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 available evidence was reviewed by van Reijen et al. [8] regarding the value of the WIfI classification in patients presenting with CLTI to predict the one-year major amputation risk and the benefit of revascularization. In this systematic review, 12 studies comprising 2669 patients, most of whom underwent endovascular or open revascularization were included. Overall study quality was moderate. All but one were retrospective studies, including a variety of subpopulations of patients with CLTI, such as only haemodialysis dependent, diabetic or non-diabetic patients. Estimated one year major amputation rates from four studies comprising 569 patients were 0%, 8% (95% CI 3–21%), 11% (95% CI 6–18%) and 38% (95% CI 21–58%), for WIfI stages I-IV, respectively. This review showed that the likelihood of a major amputation after 1 year in patients with CLTI does increase with higher clinical WIfI stages, especially in stage IV, which is important prognostic information. Similarly, the higher the WIfI stage, the lower AFS and limb salvage rates after 1 year. However, sufficient evidence was not found to support the use of the WIfI classification to predict the benefit of revascularization.

17.2 Systematic Reviews and Studies

17.2.1 Classification

A systematic review aimed to gather all the available evidence around the existing systems that were used to classify foot ulcers in people with diabetes [9]. 28 systems addressed in 149 studies were found. Overall, the certainty of the evidence for each classification was low or very low, with 19 (68%) of the classifications being assessed by ≤3 studies. The most frequently validated system was the one from Meggitt-Wagner, but the articles validating this system focused mainly on the association between the different grades and amputation. Clinical outcomes were not standardized but included ulcer-free survival, ulcer healing, hospitalisation, limb amputation, mortality, and cost. Despite the limitations, this systematic review provided sufficient evidence to support recommendations on the use of six particular systems in specific clinical scenarios.

Meggitt-Wagner classification of foot ulcers

Grade	Description
0	Pre-or post-ulcerative site
1	Superficial ulcer
2	Ulcer penetrating to tendon or joint capsule
3	Lesion involving deeper tissues
4	Forefoot gangrene
5	Whole foot gangrene involving more than two thirds of the foot

17.2.2 Epidemiology and Prognosis

Nascimento de Aquino et al. [10] analyzed the incidence, prevalence, and risk factors associated with diabetic foot in people with type 2 Diabetes Mellitus. The meta-analysis showed that the prevalence of diabetic foot was 14% in a hospital setting and 5% in a community setting. The overall prevalence and incidence were 9% and 4%, respectively. Significant risk factors included time of DM (odds ratio [OR] =1.46, confidence interval [CI], 0.36–2.57, P = 0.009), smoking (OR = 1.46, CI, 1.16–1.85, P < .001), glycated hemoglobin (OR = 0.96, CI, 0.50; 1.42, P < .001), peripheral arterial disease (OR = 3.38, CI, 2.07; 5.53, P < .001) and peripheral neuropathy (OR = 5.88, CI, 2.39–14.45, P < .001). Multidisciplinary monitoring, educational strategies, periodic foot examination for alterations, and early identification of risk factors are essential to prevent ulceration and reduce the disease burden.

Chen et al. [11] conducted a systematic review and meta-analysis of all available studies to assess the long-term survival rates of DFU in a global view. 34 studies, with 124,376 participants were identified representing 16 countries, among whom there were 51,386 deaths. Of these, 27 studies with 21,171 patients were included in the Kaplan-Meier-based meta-analysis. The estimated Kaplan-Meier-based survival rates were 86.9% at 1 year, 66.9% at 3 years, 50.9% at 5 years and 23.1% at 10 years. Cardiovascular disease and infection were the most common causes of death, accounting for 46.6% and 24.8%, respectively. Patients with older age (per 1 year, hazard ratio [HR] 1.054, 95% CI 1.045–1.063), peripheral artery disease (HR 1.882, 95% CI 1.592–2.225), chronic kidney disease (HR 1.535, 95% CI 1.227–1.919), end-stage renal disease (HR 3.586, 95% CI 1.333–9.643), amputation (HR 2.415, 95% CI 1.323–4.408) and history of cardiovascular disease (HR 1.449, 95% CI 1.276–1.645) had higher mortality risk. This meta-analysis found that the overall mortality of DFU was high, with nearly 50% mortality within 5 years. Cardiovascular disease and infection were the two leading causes of death.

Meloni et al. [12] aimed to evaluate the pattern of diabetes-related complications and co-morbidities in patients with DFUs, comparing neuropathic and ischemic patients. Furthermore, the characteristics of neuropathic and ischemic/neuro-ischemic DFUs were reported and compared, as well as the long-term outcomes. One thousand, one hundred and ninety-eight subjects were included in this cohort study; 386 (32.2%) neuropathic and 812 (67.8%) ischemic DFUs. Neuropathic patients were younger and reported less cases of nephropathy, ischemic heart disease, cerebrovascular disease, heart failure and end-stage-renal-disease than ischemic patients; they also showed less cases of large (>5 cm^2) (10.3 vs. 22.9%, $p = 0.0007$), infected (40.4 vs. 55.7%, $p = 0.0005$) and deep to the bone (22.3 vs. 39.2, $p = 0.0002$) ulcers, as well less multiple ulcerations (21.8 vs. 32.8%, $p = 0.006$) than patients with ischemic DFUs. The outcomes for neuropathic and ischemic DFUs were limb salvage (98.4 vs. 82.3%, $p < 0.0001$), healing (97.3 vs. 79.6%, $p < 0.0001$), healing time (34.9 vs. 35.6 weeks, $p = 0.8$), major amputation (0.5 vs. 6.6%, $p = 0.0001$), death (1.1 vs. 11%, $p < 0.0001$) respectively. Ischemic DFUs patients showed more severe clinical and ulcers features as well worse outcomes than neuropathic DFUs patients.

17.2.3 Topical Therapy

17.2.3.1 Dressings and Topical Agents Containing Hyaluronic Acid

It has been suggested that the application of hyaluronic acid to chronic wounds may promote healing, and the mechanism may be due to its ability to maintain a moist wound environment which helps cell migration in the wound bed. A Cochrane review evaluated the effects of hyaluronic acid (and its derivatives) on the healing of chronic wounds [13]. 12 trials (13 articles) were included in a qualitative synthesis. Overall, the included trials involved 1108 participants (mean age 69.60 years)

presenting 178 pressure ulcers, 54 diabetic foot ulcers, and 896 leg ulcers. There is currently insufficient evidence to determine the effectiveness of hyaluronic acid dressings in the healing of pressure ulcers or foot ulcers in people with diabetes. Practitioners may, therefore, consider other issues such as cost and symptom management when choosing between dressings. However, evidence was found that hyaluronic acid probably improves complete ulcer healing and may slightly decrease pain and increase change in ulcer size when compared with neutral vehicle.

17.2.3.2 Hyperbaric Oxygen Therapy

Health Quality Ontario performed a review of the clinical and economic literature for the effectiveness and cost-effectiveness of hyperbaric oxygen therapy (HBOT) for the treatment of diabetic foot ulcers [14]. Seven randomized controlled trials and one nonrandomized controlled trial met the inclusion criteria. Comparing standard wound care plus HBOT with standard wound care alone, mixed results for major amputation rates (GRADE quality of evidence: low), a significant difference in favour of standard wound care plus HBOT on ulcers healed (GRADE quality of evidence: low), and no difference in terms of adverse events (GRADE quality of evidence: moderate) were found. There is a large degree of uncertainty associated with the evaluation of the cost-effectiveness of standard wound care plus HBOT. However, results appear to suggest that this treatment results in lower costs and better outcomes than standard wound care alone. There is a substantial daily burden of care and emotional weight associated with living with diabetic foot ulcers, both of which are compounded by concern regarding possible amputation. Patients feel that HBOT is an effective treatment and reported that they were satisfied with how their ulcers healed and that this improved their quality of life.

An overview of systematic reviews evaluating the effects of HBOT in people with diabetic foot ulcers has been elaborated by Wenhui et al. [15]. There were 9 systematic reviews (SRs) that included patients with diabetic foot, 1 included patients with ischemic diabetic foot, and 1 included patients with a non-ischemic diabetic foot. There were 10 SRs that reported the ulcer healing rate. Of these, 3 showed no difference in the ulcer healing rate between the HBOT and standard treatment; 6 showed that the HBOT increased the ulcer healing rate. 10 SRs reported major amputations. No significant difference in the risk of major amputations between the HBOT and standard treatment was demonstrated in 3 SRs, while 6 other SRs showed that HBOT reduced the risk of major amputations. A total of 10 SRs reported the minor amputations. There were 7 SRs that showed no difference in the risk of minor amputations between HBOT and standard treatment, while 2 SRs demonstrated that HBOT reduced the risk of minor amputations. This overview highlights that there is limited clinical evidence to support the routine use of HBOT in the treatment of DFUs, especially in patients with non-ischemic diabetic foot ulcers. However, HBOT may have a role in promoting ulcer healing and reducing amputation rate in patients with ischemic DFUs.

17.2.3.3 Negative Pressure Wound Therapy

Wynn and Freeman [16] investigated the current state of knowledge on negative pressure wound therapy (NPWT) used to treat diabetic foot ulceration (DFU). The search yielded seven studies for inclusion in the qualitative analysis. All the included studies reported that NPWT led to better clinical outcomes when compared to standard treatment. However, the studies had numerous methodological flaws such as the absence of validated tools for the measurement of outcomes such as wound area and depth; a lack of statistical power calculations to determine adequate sample sizes or the significance of outcome measures. Due to these flaws in methodology, it remains unclear as to whether NPWT has the potential to reduce amputation incidences, increase the rate of granulation formation, heal wounds faster or offer greater quality of life for patients with DFU.

Following this review, Seidel et al. [17] published the German randomized DiaFu study. 368 patients were randomized, and 345 participants (in 40 study sites) were included in the modified intention to-treat (ITT) population. Adult patients suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for NPWT were allowed to be included. The primary outcome was wound closure (100% epithelialisation of the wound, no drainage, no suture material and no need for wound dressing or adjuvants) within the maximum study treatment period of 16 weeks. NPWT was compared with standard moist wound care (SMWC) according to local standards and guidelines. NPWT was not superior to SMWC in diabetic foot wounds in German clinical practice. Overall, wound closure rate was low. Documentation deficits and deviations from treatment guidelines negatively impacted the outcome wound closure.

17.2.3.4 Growth Factor Therapy in Healing Diabetes-Related Foot Ulcers

Thanigaimani et al. [18] presented a network meta-analysis of randomized controlled trials to examine the relative efficacy of growth factor therapies in healing diabetes-related foot ulcers (DFU). A total of 31 RCTs involving 2174 participants were included. Only 13 of the trials (n = 924) reported on the aetiology of the ulcers (85.4% neuropathic and 14.6% ischaemic). Epidermal growth factor (RR 3.83), plasma-rich protein (PRP) (RR 3.36) and platelet-derived growth factor (PDGF) (RR 2.47) significantly improved the likelihood of complete ulcer healing compared to control. Sub-analyses suggested that PRP (3 trials - RR 9.69) and PDGF (6 trials - RR 2.22) significantly improved the likelihood of wound closure amongst trial mainly recruiting participants with neuropathic ulcers. Eleven trials had a low risk of bias, 9 had some concerns and 11 had a high risk of bias. Sub-analysis of trials with a low risk of bias suggested that none of the growth factors significantly improved ulcer healing compared with control. This network meta-analysis found low-quality evidence that Epidermal growth factor, PRP and PDGF therapy improved DFU healing likelihood compared with control.

17.2.4 Free Tissue Transfer in Diabetic Foot Ulcers

Bhat et al. [19] performed an updated systematic review and meta-analysis investigating the flap characteristics, concurrent revascularisation rates, complications, and outcomes associated with free tissue transfer in diabetic foot ulcers. 67 studies encompassing 1846 patients and 1871 free flaps were included. A median of 18 patients [IQR 9, 37] per study, with a median age of 58.5 years, were followed up for a median of 15 months. Most studies had serious risk of bias (n = 47 studies, 70%); sixteen (24%) had moderate risk of bias; and four (6%) had low risk of bias. Peripheral artery disease was a major comorbidity in this cohort of patients. Up to 75% of patients underwent a revascularisation procedure prior to their free flap surgery. The time between revascularisation and free tissue transfer ranged between 0 and 20 days, with median time of 8 days (n = 9 studies). The pooled complete flap survival, major amputation, and ambulation rates were 88% (85–92%, n = 49 studies), 10% (7–14%, n = 50 studies), and 87% (80–92%, n = 36 studies), respectively. Mortality at individual study follow up was 6% (3–10%, n = 26 studies). In conclusion, data to date suggest that free tissue transfer may be a useful adjunct in the treatment of complex, chronic diabetic foot ulcers. Overall low quality evidence suggests that this technique demonstrates a high success rate with low donor site morbidity and recipient site complications over a relatively short follow up period. Early and ongoing involvement of plastic surgeons in the multidisciplinary foot team for patients with large diabetic foot ulcers may be an important paradigm shift in the management of these patients.

17.2.5 Effectiveness of Revascularisation for the Ulcerated Foot

A systematic review aimed to determine, in people with diabetes and tissue loss, if direct revascularisation is superior to indirect revascularisation and if endovascular revascularisation is superior to open revascularisation for the outcomes of wound healing, minor or major amputation, and adverse events including mortality [20]. 26 studies met the inclusion criteria for the comparison of direct angiosome revascularisation (DR) and indirect revascularisation (IR), and 11 studies met the inclusion criteria for the comparison of endovascular and open revascularisation. One study was included in both comparisons. Of the included studies, 35 were observational (31 retrospective and 4 prospective cohorts) and 1 was a randomised controlled trial. Cohort study quality was variable and generally low. For studies of DR and IR, results were variable, and it is uncertain if one technique is superior to the other for healing, prevention of minor or major amputation, or mortality. However, the majority of studies reported that a greater proportion of participants receiving DR healed compared with IR, and that IR with collaterals may have similar outcomes to DR for wound healing. For patients with diabetes, infrainguinal PAD, and an adequate great saphenous vein available for use as a bypass conduit who were deemed suitable for

either surgical procedure, an open revascularisation first approach was superior to endovascular therapy to prevent a major adverse limb event or death (Hazard Ratio: 0.72; 95% CI 0.61–0.86). For other studies of open and endovascular approaches, there was generally no difference in outcomes between the interventions. In conclusion, data from one high quality randomised controlled trial supports the use of open over endovascular revascularisation to prevent a major limb event and death in people with diabetes, infrainguinal disease and tissue loss who have an adequate great saphenous vein available and who are deemed suitable for either approach.

17.2.6 Amputation Technique

Cheun et al. [21] compared outcomes between primary lower extremity above-ankle amputations (primary amputation [PA]) and staged ankle guillotine amputations followed by interval formalization to an above-ankle amputation (staged amputation [SA]) for nonsalvageable infected diabetic foot disease. The interval between stages in the SA cohort ranged from 1 to 14 days, with an average of 4 days. Sixty-one patients underwent SA, and 55 patients underwent PA. There were no 30-day mortalities, and the rates of major cardiovascular complications were equivalent (2% vs 4%; staged vs primary; P = .6). However, staged amputation had superior short-term technical outcomes compared with primary amputation in terms of average length of stay, 30-day unplanned conversion to a higher level amputation (2% vs 13%; P = .026), and 30-day readmission rate (7% vs 27%; P = .0047). In the setting of infected diabetic foot disease, a staged lower extremity amputation achieves quality outcomes superior to a one-stage amputation, despite the former cohort's greater illness acuity level. In patients presenting with two or more SIRS criteria or poorly controlled diabetes mellitus, a SA is recommended.

17.2.7 Offloading Interventions

The aim of a systematic review was to investigate the effectiveness of offloading interventions to heal diabetic foot ulcers [22]. 165 studies were available. Six included studies were meta-analyses, 26 randomised controlled trials, 13 other controlled studies, and 120 non-controlled studies. Strong evidence supports the use of non-removable knee-high offloading devices (either Total Contact Casts (TCCs) or non-removable walker) as the first-choice offloading intervention for healing plantar neuropathic forefoot and midfoot ulcers. Removable offloading devices, either knee-high or ankle-high, are preferred as second choice over other offloading interventions. The evidence bases to support any other offloading intervention is still weak and more high-quality controlled studies are needed in these areas.

The objective of another study was to gather all empirical evidence on adherence to foot offloading and find out what is known about measurements, to describe the

proportion of participants who adhere to foot offloading, factors influencing adherence and interventions to reduce non-adherence [23]. Twenty-four trials were identified from 1001 citations. Only 25% of the included studies used objective methods to quantify adherence. The proportion of adherent participants (≥80% of daily steps/time) ranged from 28% to 60%. Psychosocial factors were the most common influencers of adherence. It emerged that suboptimal levels of adherence to offloading resulted from a mix of physical and psychosocial factors such as high BMI, shoe weight, aesthetics, discomfort, imbalance, daily activity limitations, lack of motivation or knowledge, culture, and emotions. Offloading treatment is the core of diabetic foot management, and enhanced adherence to foot offloading is therefore crucial in preventing and treating diabetic foot disease.

17.2.8 Diabetic Peripheral Neuropathy

17.2.8.1 Nerve Decompression

In a systematic review and meta-analysis, Tu et al. [24] included a total of 12 studies encompassing 1825 patients with diabetic peripheral neuropathy (one randomized controlled trial, 11 observational studies; 7 of them were classified as upper-extremity nerve decompression and 4 of them were classified as lower-extremity nerve decompression). The review demonstrated the efficacy of surgical decompression procedures especially for carpal tunnel syndrome, but more data are needed to elucidate the role of surgical procedures for diabetic peripheral neuropathy.

Liao et al. [25] reported on a total of 306 patients with painful diabetic lower-extremity neuropathy who underwent surgical nerve decompression adopting Dellon [26] triple procedures, including decompression of the common peroneal nerve below the fibula head, neurolysis of the posterior tibial nerve and its calcaneal and medial and lateral plantar branches at the ankle and decompression of the deep peroneal nerve over the dorsum of the foot. Decompression was performed using a microscope under epidural anesthesia. The results of this study supported the efficacy of decompression of multiple lower-extremity peripheral nerves in patients with painful diabetic neuropathy who presented with a positive Tinel sign. The authors speculated that in the early stage, nerve thickening may play a fundamental role in the pathophysiology of painful diabetic neuropathy, with a manifestation of focal pain. As such, it would be conceivable that entrapment of affected nerves at sites of anatomic narrowness may occur, which could be treated through surgical decompression.

Neurolysis for diabetic patients with lower extremity (LE) nerve compression remains controversial. Ten clinical series (875 diabetic patients and 1053 LEs) with a mean clinical relevance score of 70% and a mean methodologic quality score of 50% were included in a systematic review with meta-analysis by Baltodano et al. [27]. Regarding the method to diagnose nerve compression, 7 studies for a total of 762 patients relied on a positive Tinel sign to diagnose nerve compression. On the

other hand, 3 studies for a total of 113 patients based the diagnosis of nerve compression on electrodiagnostic studies. All the 1053 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 >3 points on visual analog scale occurred in 91% of patients; sensibility improved in 69%. Pooled data analysis showed that the postoperative incidence of amputations (0.2%) after a pooled follow-up period of 19.9 ± 14.8 months was significantly reduced compared to the expected incidence of postoperative amputations (10–15%). All the patients in the study population had an ankle-brachial index >0.7, making ischemia an unlikely cause of amputation. Hence, the reduced postoperative incidence of amputations is likely due to the gain of protective sensation with a subsequent lower incidence of ulceration, infection, and soft-tissue necrosis.

To estimate the incremental cost-effectiveness of lower extremity nerve decompression over a 10-year period, a Markov model was developed by Rinkel et al. [28] to simulate the onset and progression of diabetic foot disease in patients with diabetes and neuropathy who underwent lower extremity nerve decompression surgery, compared to a group undergoing current nonsurgical care. The results suggested that lower extremity nerve decompression surgery is superior in relieving neuropathy symptoms and avoiding lower extremity complications, thereby saving life-years and improving quality of life, at lower costs. Both Dutch and U.S. health technology assessment criteria suggested that lower extremity nerve decompression surgery is a cost-effective strategy compared to the current care of diabetic subjects with neuropathy.

Sarmiento et al. [29] determined whether tibial neurolysis performed as a surgical intervention for patients with diabetic neuropathy and superimposed tibial nerve compression in the prevention of the diabetic foot is cost-effective when compared with the current prevention programme. The primary outcome was the long-term trends concerning the development of ulcers and amputations with each strategy. The secondary outcome measures were quality adjusted life years (QALYs), incremental cost-effectiveness and net monetary benefits of the optimal strategy. When compared with standard prevention, for a patient population of 10,000, surgery prevented a simulated total of 1447 ulcers and 409 amputations over a period of 5 years. Survival was 73% for those receiving medical prevention compared with 95% for those undergoing surgery. The results indicated that a surgical intervention that decreases the incidence of diabetic foot ulcers and lower extremity amputations is a cost-effective strategy for patients with diabetes plus sensory neuropathy identified by symptoms and neurosensory testing. In this model, surgery also generated greater economic benefits.

17.2.9 Achilles 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. Shortening of the Achilles tendon can result in plantarflexion at the ankle and increased plantar forefoot pressures during gait. Achilles tendon lengthening (ATL), gastrocnemius recession (GR) procedures and selective plantar fascia release (SPFR) have been proposed for the management of diabetic foot ulcers. A systematic review and meta-analysis investigated the effectiveness of these surgical procedures in the management of diabetic foot ulcers [30]. Eleven studies (614 participants) were included in the review, with a median sample size of 29 participants. Meta-analysis of two randomized-controlled trials found that there was no statistically significant difference between Achilles tendon lengthening or gastrocnemius recession and total contact casting for time to healing of diabetic foot ulcers and the rate of ulcers healed. The rate of ulcer recurrence was significantly lower following Achilles tendon lengthening or gastrocnemius recession than total contact casting (RR, 0.45; 95% CI, 0.28 to 0.72; $P < 0.001$). Conversely, surgery can expose patients to greater complications and adverse events. The development of transfer ulcers, particularly under the heel, were the most common complications following ATL or GR procedures. Transfer ulcers may occur due to pressure being transferred elsewhere under the foot as a result of changes to foot function and/or overcorrection. As SPFR does not affect ankle joint range of motion, it may reduce the risk of heel ulcers. This review found that ATL and GR appear to be effective surgical treatments in healing diabetic foot ulcers when an equinus deformity is present. Therefore, these surgical procedures may provide viable treatment options for the management and prevention of diabetic foot ulcers. At present, ATL appears to be the procedure of choice as it is relatively quick and easy to perform.

17.2.9.1 Percutaneous Flexor Tenotomies

There is a high prevalence of digital deformities in diabetic patients, particularly claw toe, which can result in ulceration, often located at the tip of the toe. A systematic review was carried out by Calvo-Wright et al. [31] to assess the effectiveness of flexor tenotomies in healing and preventing diabetic foot ulcers located on the apex of the toe. The secondary objective was to evaluate the safety and efficacy of flexor tenotomies in preventing and healing diabetic foot ulcers associated with digital deformities. 11 studies were included for analysis. Among the total of 770 tenotomies, 387 had a curative indication, and 388 were prophylactic; six studies included both indications, two evaluated only prophylactic tenotomies, and three evaluated only the curative indication. Satisfactory results were found, with a healing rate of

92% to 100% and a mean healing time of 2–4 weeks. Few mild complications were observed, and the recurrence rate was very low. Transfer lesions were the most prevalent, but simultaneous tenotomy of all toes can eliminate this risk. Flexor tenotomies are a simple, effective, and safe procedure for the treatment and management of DFUs located at the apex of the toes and should be considered part of the standard of care for diabetic feet.

17.3 Conclusions for Clinical Practice

1. Patients with diabetes should undergo annual interval foot inspections by physicians or advanced practice providers with training in foot care. Foot examination should include testing for peripheral neuropathy using the Semmes-Weinstein test.
2. Patients with diabetes should have ankle-brachial index (ABI) measurements performed when they reach 50 years of age.
3. As clinical examination does not reliably exclude peripheral arterial disease (PAD) in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement.
4. Always consider revascularization in a patient with a diabetic foot ulcer and PAD, irrespective of the results of bedside tests, when the ulcer is not healing within 4–6 weeks despite optimal management.
5. Diabetic foot infection (DFI) must be diagnosed clinically, based on the presence of local or systemic signs or symptoms of inflammation. 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.
6. For treating diabetic foot ulcers, hydrogels are more efficacious than basic wound contact dressings, and non-adherent dressings are more cost-effective than hydrofiber dressings. Ultimately, dressing choice should be tailored to the wound and the patient.
7. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a nonremovable knee-high offloading device with an appropriate foot-device interface as the first choice of offloading treatment to promote healing of the ulcer.
8. Study results support the efficacy of decompression of multiple lower-extremity peripheral nerves in patients with painful diabetic neuropathy who present with a positive Tinel sign.
9. Achilles tendon lengthening (ATL) and gastrocnemius recession (GR) procedures appear to be effective surgical treatments in healing diabetic foot ulcers when an equinus deformity is present.

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Chapter 18
Chronic Venous Disease and Varicose Veins



18.1 Guideline Recommendations

18.1.1 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) on the Management of Chronic Venous Disease of the Lower Limbs [1]

18.1.1.1 Classification and Diagnostic Workup

Recommendation 1

For patients with chronic venous disease, the use of the CEAP (Clinical, Etiological, Anatomical, Pathophysiological) classification (Tables 18.1 and 18.2) is recommended for clinical audit and research. (Recommendation class I/Level of evidence C).

Recommendation 2

For patients with chronic venous disease, grading of clinical severity and evaluation of treatment success using the revised Venous Clinical Severity Score (r-VCSS) and the Villalta scale for post-thrombotic syndrome should be considered for clinical audit and research. (Recommendation class IIa/Level of evidence C).

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Table 18.1 2020 update of the CEAP (Clinical—Etiology—Anatomy—Pathophysiology) classification system (according to [24]). Clinical classifications (C)

C class	Description
C0	No visible or palpable signs of venous disease
C1	Teleangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed
C6	Active venous ulcer
C6r	Recurrent active venous ulcer

Table 18.2 2020 update of the CEAP (Clinical – Etiology – Anatomy - Pathophysiology) classification system (according to [24]). Summary of etiologic (E), anatomic (A), and pathophysiologic (P) classification

Grade	Description
E class	
Ep	Primary
Es	Secondary
Esi	Secondary—intravenous
Ese	Secondary—extravenous
Ec	Congenital
En	No cause identified
A class	
As	Superficial
Ad	Deep
Ap	Perforator
An	No venous anatomic location identified
P class	
Pr	Reflux
Po	Obstruction
Pr, o	Reflux and obstruction
Pn	No pathophysiology identified

Recommendation 3

For diagnosis and treatment planning in patients with suspected or clinically evident chronic venous disease, full lower limb venous duplex ultrasound is recommended as the primary imaging modality (Recommendation class I/Level of evidence B).

Recommendation 4

For patients with suspected supra-inguinal venous obstruction, in addition to full leg duplex assessment, ultrasound of the abdominal and pelvic veins should be considered, as part of the initial assessment. (Recommendation class IIa / Level of evidence C).

Recommendation 5

When an intervention is contemplated in patients with suspected supra-inguinal venous obstruction, cross sectional imaging by magnetic resonance venography or computed tomography is recommended in addition to duplex ultrasound assessment. (Recommendation class I/Level of evidence C).

18.1.1.2 Conservative Management

Recommendation 9

For patients with symptomatic chronic venous disease, elastic compression stockings, exerting a pressure of at least 15 mmHg at the ankle, are recommended to reduce venous symptoms. (Recommendation class I/Level of evidence B).

Recommendation 10

For patients with chronic venous disease and oedema (CEAP clinical class 3), compression treatment, using below knee elastic compression stockings, inelastic bandages or adjustable compression garments, exerting a pressure of 20–40 mmHg at the ankle, is recommended to reduce oedema. (Recommendation class I/Level of evidence B).

Recommendation 11

For patients with chronic venous disease and lipodermatosclerosis and/or atrophie blanche (CEAP clinical class C4b), using below knee elastic compression stockings, exerting a pressure of 20–40 mmHg at the ankle, is recommended to reduce skin induration. (Recommendation class I/Level of evidence B).

Recommendation 12

For patients with post-thrombotic syndrome, below knee elastic compression stockings, exerting a pressure of 20–40 mmHg at the ankle, should be considered to reduce severity. (Recommendation class IIa/Level of evidence B).

Note
Contraindications to compression treatment (according to [1]):

- Severe lower extremity atherosclerotic disease with ABI < 0.6 and/or ankle pressure < 60 mmHg
- Extra-anatomic or superficially tunnelled arterial bypass at the site of intended compression
- Severe heart failure, NYHA Class IV
- Heart failure NYHA Class III and routine application of compression devices without clinical and haemodynamic monitoring
- Confirmed allergy to compression material
- Severe diabetic neuropathy with sensory loss or microangiopathy with the risk of skin necrosis

NYHA Class IV: fatigue, palpitations, dyspnoea and/or angina at rest; NYHA Class III: ordinary physical activity causes undue fatigue, palpitations, dyspnoea and/or angina—comfortable at rest.

Recommendation 13

For patients with post-thrombotic syndrome, adjuvant intermittent pneumatic compression may be considered to reduce its severity. (Recommendation class IIb / Level of evidence B).

Recommendation 14

For patients with symptomatic chronic venous disease, who are not undergoing interventional treatment, are awaiting intervention, or have persisting symptoms and/or oedema after intervention, medical treatment with venoactive drugs should be considered to reduce venous symptoms and oedema, based on the available evidence for each individual drug. (Recommendation class IIa/Level of evidence A).

18.1.1.3 Interventions for Superficial Venous Incompetence

Recommendation 15

For patients with superficial venous incompetence presenting with symptomatic varicose veins (CEAP clinical class C2S), interventional treatment is recommended. (Recommendation class I/Level of evidence B).

Recommendation 17

For patients with superficial venous incompetence, presenting with skin changes as a result of chronic venous disease (CEAP clinical class C4 - C6), interventional treatment of venous incompetence is recommended. (Recommendation class I/ Level of evidence C).

Recommendation 18

For patients with superficial venous incompetence, undergoing treatment using endovenous techniques with or without phlebectomies, the procedures should be performed in the outpatient setting where possible. (Recommendation class I/Level of evidence C).

Recommendation 19

For patients with superficial venous incompetence treated by endovenous thermal ablation, ultrasound guided tumescent anaesthesia is recommended. (Recommendation class I/Level of evidence C).

Recommendation 20

For patients with superficial venous incompetence treated under tumescent anaesthesia, buffered solutions should be considered to reduce peri-procedural pain. (Recommendation class IIa/Level of evidence B).

Recommendation 21

For patients with superficial venous incompetence undergoing high ligation/stripping (HL/S), ultrasound guided tumescent anaesthesia may be considered, as an alternative to general or regional anaesthesia. (Recommendation class IIb / Level of evidence C).

18.1.1.4 Compression after Treatment/Thrombosis Prophylaxis

Recommendation 22

For patients with superficial venous incompetence undergoing ultrasound guided foam sclerotherapy (UGFS) or endovenous thermal ablation of a saphenous trunk, postprocedural compression treatment should be considered. (Recommendation class IIa/Level of evidence A).

Recommendation 23

For patients with superficial venous incompetence undergoing stripping and/or extensive phlebectomies, immediate postprocedural compression treatment is recommended. (Recommendation class I/Level of evidence A).

Recommendation 26

For patients with superficial venous incompetence undergoing intervention, individualised thromboprophylaxis strategies should be considered. (Recommendation class IIa/Level of evidence B).

18.1.1.5 Techniques for Saphenous Ablation

Recommendation 28

For patients with great saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended as first choice treatment, in preference to high ligation/stripping and ultrasound guided foam sclerotherapy. (Recommendation class I/Level of evidence A).

Recommendation 29

For patients with saphenous trunk incompetence undergoing thermal ablation, the selection of the device should be left to the discretion of the treating physician. (Recommendation class I/Level of evidence B).

Recommendation 30

For patients with great saphenous vein incompetence requiring treatment, cyanoacrylate adhesive closure should be considered when a non-thermal non-tumescent technique is preferred. (Recommendation class IIa/Level of evidence A).

Recommendation 31

For patients with saphenous trunk incompetence undergoing treatment, ultrasound guided foam sclerotherapy may be considered for treating saphenous trunks with a diameter less than 6 mm. (Recommendation class IIb/Level of evidence B).

Recommendation 32

For patients with superficial venous incompetence treated with foam sclerotherapy, the procedure should be performed under ultrasound guidance. (Recommendation class I/Level of evidence C).

Recommendation 33

For patients with great saphenous vein incompetence requiring treatment, catheter directed foam sclerotherapy with or without the use of peri-venous tumescent solution may be considered. (Recommendation class IIb/Level of evidence B).

Recommendation 34

For patients with great saphenous vein incompetence requiring treatment, mechanochemical ablation may be considered when a non-thermal non-tumescent technique is preferred. (Recommendation class IIb/Level of evidence A).

Recommendation 35

For patients with great saphenous vein incompetence requiring treatment, high ligation/stripping should be considered, if endovenous thermal ablation options are not available. (Recommendation class IIa/Level of evidence A).

Recommendation 36

For patients with chronic venous disease requiring treatment of varicose tributaries, ambulatory phlebectomy, ultrasound guided foam sclerotherapy or a combination of both are recommended. (Recommendation class I/Level of evidence B).

Recommendation 37

For patients with chronic venous disease requiring treatment of incompetent perforating veins, endovenous ablation, division or ligation should be considered. (Recommendation class IIa/Level of evidence C).

Recommendation 40

For patients with reticular veins, where treatment is planned, sclerotherapy is recommended, as the first choice treatment. (Recommendation class I/Level of evidence A).

Recommendation 41

For patients with telangiectasias, where treatment is planned, sclerotherapy should be considered. (Recommendation class IIa/Level of evidence A).

Recommendation 42

For patients with telangiectasias, where treatment is planned, transcutaneous laser should be considered. (Recommendation class IIa/Level of evidence B).

Recommendation 43

For patients with small saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended in preference to surgery or foam sclerotherapy. (Recommendation class I/Level of evidence A).

Recommendation 44

For patients with small saphenous vein incompetence requiring treatment, endovenous non-thermal non-tumescent ablation methods may be considered. (Recommendation class IIb/Level of evidence B).

Recommendation 45

For patients with small saphenous vein incompetence treated by endovenous thermal ablation, care should be taken to avoid injury to the sural nerve if cannulation is carried out below midcalf level. (Recommendation class I/Level of evidence B).

Recommendation 55

For patients with symptomatic recurrent varicose veins due to saphenous trunk incompetence, endovenous thermal ablation or ultrasound guided foam sclerotherapy with or without phlebectomy should be considered. (Recommendation class IIa/Level of evidence B).

Table 18.3 Summary of techniques available for treating saphenous trunk incompetence (according to [1])

Technique	Published follow-up	Reflux abolition	Quality of life improvement	Tumescence needed
EVTA	≥5 years	+++	+++	Yes
HLS	≥5 years	+++	+++	Yes, or alternative anaesthesia technique
CAC	3–5 years	+++	+++	No
UGFS	≥5 years	+/++	++/+++	No
CDFS	1 year	++	++	Yes/no
MOCA	3 years	++	+++	No

EVTA Endovenous thermal ablation, *HLS* High ligation and stripping, *CAC* Cyanoacrylate adhesive closure, *UGFS* Ultrasound guided foam sclerotherapy, *CDFS* Catheter directed foam sclerotherapy, *MOCA* Mechanochemical ablation
+++ very good effect
++ good effect
+ some effect

Recommendation 56

For patients with symptomatic recurrent varicose veins requiring treatment, where endovenous ablation is possible, re-exploration of the groin or popliteal fossa is ***not*** recommended. (Recommendation class III/Level of evidence B).

Recommendation 57

For patients with symptomatic recurrent varicose veins without truncal incompetence, ultrasound guided foam sclerotherapy and/or ambulatory phlebectomy should be considered. (Recommendation class IIa/Level of evidence C).

Note
A summary of the techniques available for treating saphenous trunk incompetence is given in Table 18.3.

18.2 Results

18.2.1 Meta-Analyses

18.2.1.1 Interventions for Great Saphenous Vein Incompetence

A Cochrane review [2] assessed the effects of endovenous laser ablation (EVLA), radiofrequency ablation (RFA), endovenous steam ablation (EVSA), ultrasound-guided foam sclerotherapy (UGFS), cyanoacrylate glue, mechanochemical ablation

(MOCA) and high ligation and stripping (HL/S) for the treatment of varicosities of the great saphenous vein (GSV). 24 RCTs with 5135 participants were included. Duration of follow-up ranged from 5 weeks to 8 years. The main results were:

- EVLA versus RFA: Technical success was comparable up to 5 years (moderate-certainty evidence); over 5 years, there was no evidence of a difference (low-certainty evidence). One study reported recurrence, showing no clear difference at 3 years (low-certainty evidence), but a benefit for RFA may be seen at 5 years (low-certainty evidence).
- EVLA versus UGFS: Technical success may be better in EVLA participants up to 5 years (low-certainty evidence), and over 5 years (low-certainty evidence). There was no clear difference in recurrence up to 3 years and at 5 years.
- EVLA versus HL/S: Technical success may be better in EVLA participants up to 5 years (low-certainty evidence). No clear difference in technical success was seen at 5 years and beyond (low-certainty evidence). Recurrence was comparable within 3 years and at 5 years (moderate-certainty evidence).
- RFA versus MOCA: There was no clear difference in technical success (low-certainty evidence), or recurrence (low-certainty evidence). Long-term data are not available.
- RFA versus HL/S: No clear difference in technical success was detected up to 5 years (low-certainty evidence); over 5 years, there was no evidence of a difference (low-certainty evidence). No clear difference in recurrence was detected up to 3 years (moderate-certainty evidence); but a possible long-term benefit for RFA was seen (low-certainty evidence).
- UGFS versus HL/S: Meta-analysis showed a possible benefit for HL/S compared with UGFS in technical success up to 5 years (low-certainty evidence), and over 5 years (moderate-certainty evidence). No clear difference was detected in recurrence up to 3 years (low-certainty evidence), and after 5 years (low-certainty evidence).

Technical success was comparable between most modalities. EVLA may offer improved technical success compared to UGFS or HL/S. HL/S may have improved technical success compared to UGFS. No evidence of a difference was detected in recurrence, except for a possible long-term benefit for RFA compared to EVLA or HL/S.

Another Cochrane review determined the effects of superficial endovenous ablation on the healing and recurrence of venous leg ulcers and the quality of life of people with venous ulcer disease [3]. Randomized controlled trials (RCTs) comparing endovenous ablative techniques with compression versus compression therapy alone for the treatment of venous leg ulcers (VLUs) were eligible for inclusion. There was a total of 506 participants with an active VLU, with mean durations of 3.1 months ± 1.1 months in the EVRA trial and 60.5 months ± 96.4 months in the VUERT trial. There is high-certainty evidence that combined endovenous ablation and compression compared with compression therapy alone, or compression with deferred endovenous treatment, improves time to complete ulcer healing. There is moderate-certainty evidence that the proportion of ulcers healed at 90 days is

probably higher with combined endovenous ablation and compression compared with compression therapy alone or compression with deferred endovenous treatment. The addition of endovenous ablation to compression is probably cost-effective at 1 year. Endovenous ablation of superficial venous incompetence in combination with compression improves leg ulcer healing when compared with compression alone. This conclusion is based on high-certainty evidence.

A systematic review [4] summarizes the evidence to develop and support forthcoming updated SVS/AVF/American Vein and Lymphatic Society clinical practice guideline recommendations on the management of varicose veins. HL/S was associated with higher anatomic closure rates at 30 days and 5 years when compared with RFA and UGFS (moderate certainty), while no significant difference was seen when compared with EVLA at 5 years. UGFS was associated with an increased risk of recurrence compared with HL/S. EVLA was associated with lower anatomic closure rates at 30 days than cyanoacrylate closure (CAC) and higher rates at one and 5 years when compared with UGFS. Thermal interventions were associated with lower generic quality of life scores and an increased risk of adverse events when compared with CAC or n-butyl cyanoacrylate (low certainty). Thermal interventions were associated with a lower risk of recurrent incompetence when compared with UGFS and an increased risk of recurrent incompetence than CAC.

A systematic review and meta-analysis on RCTs or follow-up studies of RCTs with a minimum follow-up of 5 years was presented by Hamann et al. [5] to compare long-term outcomes, such as technical success, recurrent reflux at the groin, venous clinical severity score (VCSS), and quality of life of the different treatments for incompetent great saphenous veins (GSVs). Three RCTs and 10 follow-up studies of RCTs were included of which 12 were pooled in the meta-analysis. In total, 611 legs were treated with EVLA, 549 with HL + S, 121 with UGFS, and 114 with HL + EVLA. UGFS had significantly lower pooled anatomical success rates than HL + S, EVLA, and EVLA with high ligation: 34% versus 83%, 88%, and 88% respectively; $p \leq .001$. The pooled recurrent reflux rate at the saphenofemoral junction (SFJ) was significantly lower for HL + S than UGFS (12% vs. 29%; $p \leq .001$) and EVLA (12% vs. 22%; $p = .038$). VCSS scores were pooled for EVLA and HL + S, which showed similar improvements. Based on this meta-analysis EVLA and HL + S are the preferred treatment options for GSV incompetence, both with superior long-term results than UGFS (Table 18.4). For the moment pooled data was only available for EVLA, but other forms of EVTA may appear to be equally effective at long term.

Aherne et al. [6] compared the outcomes of both concomitant and staged superficial varicose tributary (SVT) interventions as an adjunct to endovenous truncal ablation in the management of symptomatic venous incompetence. Fifteen studies (6915 limbs) were included in this systematic review for analysis. Meta-analysis established that concomitant treatment strategies (6.3%) were associated with significantly fewer reported reinterventions than those undergoing a staged approach (36.1%). Additionally, 12 studies reporting the lower limb thrombotic outcomes of 5735 limbs identified deep venous thrombosis (DVT) rates of 1.8% in the concomitant and 2.8% in the staged group with no difference between groups regarding

Table 18.4 Five year results of treatment options for great saphenous vein incompetence. Only RCTs or follow-up studies of RCTs are included (according to [5])

Comparison	Pooled proportion of anatomical success	*P*	Pooled proportion of recurrent reflux at the saphenofemoral junction/groin	*P*
EVLA vs. HL + S	0.88 vs. 0.83	.170	0.22 vs. 0.12	**.038**
EVLA vs. HL + EVLA	0.88 v. 0.88	.500	0.22 vs. 0.24	.404
EVLA vs. UGFS	0.88 vs. 0.34	**<.001**	0.22 vs. 0.29	.133
HL + S vs. HL+ EVLA	0.83 vs. 0.88	.409	0.12 vs. 0.24	.058
HL + S vs. UGFS	0.83 vs. 0.34	**<.001**	0.12 vs. 0.29	**< .001**
HL+ EVLA vs. UGFS	0.88 vs. 0.34	**<.001**	0.24 vs. 0.29	.269

EVLA endovenous laser ablation, *HL* high ligation, *S* stripping, *UGFS* ultrasound guided foam sclerotherapy

DVT, endovenous heat induced thrombosis (EHIT), or other procedural complications. In this analysis, truncal ablation alone was sufficient therapy for 63.9% of those assessed. While meta-analysis suggested that concomitant intervention offers significantly lower rates of re-intervention, this benefit was not reflected by the randomised trial subgroup analysis, which identified no difference in re-intervention.

18.2.1.2 Thromboprophylaxis for Endovenous Varicose Vein Interventions

The primary objective of a systematic review and meta-analysis was to elucidate the rate of venous thromboembolism (VTE) after endovenous interventions for varicose veins in the presence of pharmacological and mechanical thromboprophylaxis versus mechanical thromboprophylaxis alone [7]. There were 221 trials included in the review (47 randomized trial arms, 105 prospective cohort studies, and 69 retrospective studies). In randomized trial arms, the rate of deep venous thrombosis with additional pharmacological thromboprophylaxis was 0.52% versus 2.26% with mechanical thromboprophylaxis alone. The rate of pulmonary embolism in randomized trial arms with additional pharmacological thromboprophylaxis was 0.45% versus 0.23% for mechanical measures alone. The rate of endovenous heat-induced thrombosis (EHIT) grade III to IV was 0.35% versus 0.88%. There was 1 VTE-related mortality and 1 instance of major bleeding, with low rates of minor bleeding. The rate of VTE after endovenous varicose vein intervention may be higher than previously anticipated and carries a small but significant morbidity and mortality. There is evidence that additional pharmacological thromboprophylaxis reduces the rate of DVT and it is recommended that anticoagulant agents are considered for endovenous varicose vein procedures.

18.2.1.3 Compression Therapy Following Endovenous Thermal Ablation

Ma et al. [8] conducted a systematic review and meta-analysis of RCTs to evaluate the benefit of compression therapy with elastic stockings on clinical and patients self-reported outcomes following endovenous thermal ablation (EVTA) for varicose veins. Six RCTs with 1045 subjects were included. Overall, postoperative compression therapy significantly reduced the mean pain in the first 10 days post-EVTA, and the time to return to normal activities. In terms of the bruising score, the venous clinical severity score, complications, quality of life at 2 weeks and 6 months, and the saphenous vein occlusion rate, there were no significant differences between the compression and control groups.

A second meta-analysis was conducted by Hu et al. [9] to compare the outcomes of endovenous thermal ablation of primary varicose veins with or without post-procedural compression therapy. A total of seven randomized controlled trials (RCTs) comprising 1146 patients were included. Wearing compression stockings was correlated with lower post-operative pain scores. No difference was observed between wearing compression stockings or not in quality of life, target vein occlusion rates, or time to return to work. The conclusion was that given the discomfort and difficulty of applying compression stockings, they are probably unnecessary after endovenous thermal ablation.

18.2.1.4 Thermal Versus Non-thermal Endovenous Ablation

Shahzad et al. [10] conducted a meta-analysis of randomized controlled trials to compare effectiveness and complications of thermal vs. non-thermal endovenous ablation techniques for treatment of superficial venous incompetence (endovenous thermal ablation: laser or radiofrequency / non-thermal ablation: MOCA or CAC). Eight randomized controlled trials met the selection criteria. These comprised a total of 1956 patients, of whom 1042 underwent endovenous thermal ablation and 915 underwent endovenous non-thermal ablation. There was no statistically significant difference in occlusion rate at all time points. Relative risk at 4 weeks and 1 to 2 years was 0.99 (95% CI 0.96–1.02) and 0.95 (95% CI 0.88–1.01), respectively. Non-thermal ablation was tolerated better and had less risk of nerve injury. There was no statistically significant difference in risk of endothermal heat induced thrombosis (EHIT). There was improvement in quality of life scores post-procedure but there was no statistically significant difference in thermal vs. non-thermal ablation. The quality of evidence assessed using GRADE methodology showed high quality for occlusion rate at 4 weeks and 1 to 2 years, moderate quality for nerve injury and peri-procedural pain, and low quality for EHIT. This study showed that there is no statistically significant difference in vein occlusion rate between thermal and glue ablation of truncal varicose veins. Although the occlusion rate using MOCA, considered in isolation, is statistically significantly worse than for thermal ablation, improvement in quality of life after both thermal and non-thermal endovenous ablation is similar. In the early post-operative period, non-thermal endovenous ablation demonstrates the advantages of causes less pain and less risk of nerve injury.

18.2.1.5 Mechanochemical Ablation Versus Endothermal Ablation

A meta-analysis compared the clinical and technical outcomes after MOCA and EVTA [11]. Four RCTs were included in the meta-analysis comprising 654 patients. The anatomical occlusion rate at 1 year was lower after MOCA than EVTA (risk ratio 0.85, 95 per cent c.i. 0.78 to 0.91; $P < 0.001$). No significant differences were detected in procedural pain (mean difference − 3.25, −14.25 to 7.74; $P = 0.560$) or postprocedural pain (mean difference − 0.63, −2.15 to 0.89; $P = 0.420$). There were no significant differences in Aberdeen Varicose Vein Questionnaire score at 1 year (mean difference 0.06, −0.50 to 0.62; $P = 0.830$) or in incidence of venous thromboembolism (risk ratio 0.72, 95 per cent c.i. 0.14 to 3.61; $P = 0.690$). The rate of successful anatomical occlusion after MOCA is significantly lower than that after EVTA, but there is no difference in procedural and postprocedural pain between the two interventions. Long-term data are required to assess the impact of the reduced vein occlusion rate on clinical outcomes such as quality of life and reintervention.

18.2.1.6 Cyanoacrylate Ablation (CA)

Cyanoacrylate ablation (CA) consists of delivery of cyanoacrylate adhesive to the vein, which induces an inflammatory reaction of the vein wall to the foreign body. It is a non-thermal, non-tumescent endovenous ablation technique. In a meta-analysis three comparative studies, two randomized controlled trials and one observational study comprising 1057 participants were included for effectiveness assessment purposes [12]. Available evidence allowed comparison of CA with radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) but not with other treatments. The analysis showed that whereas all three treatments reduced disease severity, none was significantly better than any other in terms of effectiveness. In terms of safety, however, CA devices gave rise to fewer adverse events and less severity at 12 months of follow-up than did EVLA or RFA. Other important advantages of CA over EVLA or RFA were linked to quality of care; patients reported less pain during intervention with CA than with RFA or EVLA devices and registered shorter intervention and recovery times. Furthermore, tumescent anesthesia and compression bandages were not necessary, making this technique more comfortable for the patients than endothermal techniques.

The aim of a network meta-analysis was to compare VenaSeal closure system (cyanoacrylate embolization, CAE) with EVLA, RFA, mechanochemical ablation, sclerotherapy, and surgery for management of chronic venous insufficiency [13]. The findings from this study suggested CAE to be a promising therapeutic option in terms of superior outcomes as assessed by anatomic success (complete closure of treated vein), reduction of pain score, and lesser chance of occurrence of adverse events (including hyperpigmentation, bruising, pruritus, skin irritation, rash, phlebitis, paresthesia, wound infection, thrombophlebitis, DVT, groin infection, and PE) in patients treated with CVI compared with other interventions (EVLA, RFA,

MOCA, sclerotherapy, and surgery). The existing evidence is robust to demonstrate the safety and effectiveness of CAE (VenaSeal system) in treating these patients.

One cohort study and three randomized controlled trials, including a total of 1457 participants were included in a meta-analysis by Guo et al. [14] to analyze the efficacy of cyanoacrylate ablation (CA) in comparison with endovenous thermal ablation (ETA) for the treatment of incompetent saphenous veins. There was no statistical difference in closure rates between CA and ETA after pooled analysis. Similar symptom alleviation was observed. However, the CA group showed a lower ecchymosis rate than RFA and a significantly lower incidence of adverse events, such as ecchymosis, phlebitis, and paresthesia, than EVLA. Compared with ETA, patients receiving CA treatment exhibited lower pain scores without needing compression stocking, returned to normal life sooner, and had significantly better quality of care. CA had better overall outcomes than ETA and offered superior clinical benefits in the treatment of incompetent saphenous veins.

18.2.1.7 Mechanochemical Ablation, Cyanoacrylate Ablation, and Thermal Ablation

A meta-analysis and systematic review of comparative trials aimed to assess the efficacy of endovenous nonthermal (including MOCA and CA) and thermal (EVLA and RFA) ablative procedures in the management of lower limb superficial venous incompetence [15]. Six studies describing the outcomes of 1236 participants and 1256 truncal ablations were included for analysis. Nonthermal techniques (NTA) were as effective as standard thermal ablation (TA) in the first year and, in some studies, may be associated with less procedural pain. These data suggested that NTA offers an alternative and safe means to treat superficial venous disease. There is, however, a need for further powered trials with larger numbers of patients and longer follow-up to definitively examine this hypothesis.

A Health Technology Assessment on nonthermal endovenous procedures for varicose veins was developed by a multidisciplinary team from Ontario Health [16]. 19 primary studies reported in 25 publications comparing either MOCA or CAC with at least one other invasive treatment for symptomatic varicose veins were included. No studies compared MOCA with CAC. This report concluded: Cyanoacrylate adhesive closure (CAC) and MOCA produced similar patient-important outcomes, and slightly shorter recovery compared with thermal ablation. CAC yielded similar anatomical outcomes as thermal endovenous ablation, but the technical outcomes of MOCA were slightly poorer. Compared with surgical vein stripping, all endovenous treatments were more effective and less expensive. With respect to the most cost-effective strategy, EVLA is most likely to be cost-effective. For people with varicose veins, the CAC procedure was seen as a positive treatment method that reduced their symptoms and improved their quality of life.

18.2.2 Randomized Trials

18.2.2.1 Radiofrequency (RF) Thermal Ablations with Three RF Devices

The randomized Radiofrequency (3RF) study compared three radiofrequency devices, Venefit (Closurefast), Radiofrequency Induced Thermal Therapy (RFITT), and Endovenous Radiofrequency (EVRF) for treatment of incompetent great saphenous veins [17]. The 3RF long term study showed better closure rates and better patient reported varicose veins scores 72 months after treatment with Venefit and RFITT compared with EVRF. Failure of GSV closure on 72 month DUS was 16%, 21%, and 37% for Venefit, RFITT, and EVRF, respectively. When all technical failures were compared (including DUS results from re-treated participants), failure rates were eight of 57 (14%), 11 of 64 (17%), and 26 of 59 (44%) after Venefit, RFITT, and EVRF, respectively ($p < .001$). However, no differences were demonstrated between the three groups when quality of life (QoL) scores were compared using the EQ-5D or AVVQ tools.

18.2.2.2 Compression after Radiofrequency Ablation

In the randomized COMETA trial [18], patients with saphenous vein reflux undergoing treatment with endothermal ablation (with or without concurrent phlebectomies) were randomized to receive either 7 days of compression stockings or no stockings. In total, 206 patients were randomized, 49% of them to the compression group. The median pain score in the compression group using a visual analog scale was significantly lower on days 2–5, compared to the no compression group. Those having concurrent phlebectomies and compression stockings also had significantly better pain scores on days 1–3, day 5, and day 7. Improvement in the median venous clinical severity score was noted at 6-month follow-up, but this was not significant. No difference in the generic- or disease-specific quality of life was observed and the time to return to activities was similar. These results indicate that wearing compression stockings after endothermal ablation is advantageous in the first few days after treatment and is especially beneficial for those having concurrent phlebectomies.

18.2.2.3 Long-Term Outcomes of Laser Ablation, Foam Sclerotherapy, and Surgery

In a randomized, controlled trial involving 798 participants with primary varicose veins at 11 centers in the United Kingdom, Brittenden et al. [19] compared the outcomes of laser ablation, foam sclerotherapy, and surgery. Initial results from this CLASS trial had been published in 2014, and now the 5-year results have been

presented. Quality-of-life questionnaires were completed by 595 (75%) of the 798 trial participants. There were significant differences between the treatments with respect to disease-specific quality of life. Aberdeen Varicose Vein Questionnaire scores were better among participants treated with laser ablation or surgery than among those treated with foam sclerotherapy. Laser ablation was similar to surgery with respect to quality of life and of the three treatments had the highest chance of being cost-effective.

18.2.2.4 RFA Vs. EVLA

In a comparative prospective monthly altering-treatment cohort study of 311 patients (346 treated legs), each leg with incompetence of the GSV was treated with either RFA (158 patients, 175 legs) or EVLA (153 patients, 171 legs) [20]. The total primary obliteration rate after 36 and 60 months was 96.2% with RFA and 96.7% with EVLA. There was no difference in postoperative pain scores after both treatments during the first 14 days. The median time for return to work was 1 day after both treatments. No severe adverse events were observed. In conclusion, RFA and EVLA had similarly high GSV obliteration rates in the long term, and the treatments were equally effective clinically. Both treatments were associated with similar minimal postprocedural pain scores and short recovery times (Table 18.5).

18.2.2.5 Mechanochemical (MOCA) and Endovenous Thermal Ablation

The MARADONA trial is a multicenter prospective randomized controlled trial comparing MOCA (n = 105) with RFA (n = 104) to treat great saphenous vein incompetence [21]. Overall median pain scores during the first 14 days were lower after MOCA (0.2 vs 0.5 after RFA; P = .010), although the absolute difference was small. At 30 days, similar complication numbers and HRQoL scores were observed. Hyperpigmentation was reported in seven patients in the MOCA group and two patients in the RFA group (P = .038). In the MOCA group, there were four complete failures (3.8%) compared with none in the RFA group (P = .045), although in one patient at 1 year, the vein showed occlusion. Median 30-day Venous Clinical Severity Score (VCSS) was significantly lower at 30 days after MOCA (1.0 vs 2.0 in the RFA group; P = .001). At 1 and 2 years, anatomic success rate was lower after MOCA (83.5% and 80.0%) compared with RFA (94.2% and 88.3%; P = .025 and .066) because of partial recanalizations. Similar clinical success rates (MOCA, 88.7% and 93.0%; RFA, 93.2% and 90.4%; P = .315 and .699) were observed. The study suggests that MOCA is a good alternative for treatment of great saphenous vein incompetence at 2 years of follow-up, although partial recanalization is more frequent than after RFA.

Table 18.5 Prospective comparative cohort study evaluating incompetent great saphenous vein closure using RFA or EVLA (Varico 2 study). According to Lawson et al. [20]

Parameter	RFA	EVLA	*P* value
Cohort (n)	158 patients/175 legs	153 patients/172 legs	
CEAP class (n)			
– C2	40	35	
– C3	115	116	
– C4	18	18	
– C5	2	3	
Postoperative pain medication in first 14 days (%)			
– No medication	76.1	73.4	
– 1-5 units	17.8	20.3	
Postoperative complications (%)			
– Bruising	14.9	18.7	.39
– Temporary paresthesia	1.8	2.3	.72
– Permanent paresthesia	0.5	2.9	.21
– Deep venous thrombosis	0	0.6 (n = 1/crural vein)	
Persistent obliteration (%)			
– At 36 months / 60 months	96.2/96.2	96.7/96.7	
VCSS			
– Preoperative	3.75	4.04	
– At 12 months	1.98	1.96	
– At 60 months	1.77	2.13	
AVVQ scores (mean)			
– Preoperative	11.45	12.97	.13
– At 1 year	5.00	4.98	.96
– At 5 years	5.20	5.98	.48

VCSS Venous Clinical Severity Score, *AVVQ* Aberdeen Varicose Vein Questionnaire

18.2.2.6 Mechanochemical Ablation Vs Cyanoacrylate Adhesive

The MOCCA trial [22] was a prospective multicenter randomized clinical trial comparing MOCA with cyanoacrylate adhesive injection (CAE) for the treatment of primary truncal saphenous veins incompetence. All interventions (MOCA n = 83, CAE n = 84) were performed under ultrasonography guidance using local anesthesia. A total of 73 patients (47%) underwent adjunctive treatment of varicosities. The primary outcome of this study was pain score after truncal ablations as measured by VAS. Maximum and average pain score were low and similar between the MOCA and CAE groups. There was no statistically significant difference between treatment groups in pain experienced in the 10 days postoperatively, return to normal activities or work, ecchymosis score, and occlusion rates. The median clinical and QoL scores significantly improved in both groups after treatment with no difference between the groups. The duration of procedure was significantly longer in patients treated with CAE (17 vs 21 minutes; P < .001). This study found no difference in

outcomes following MOCA or CAE. This would suggest that the main determinant as to which interventions to use would be surgeon and patient preference and the cost-effectiveness of each technique.

18.2.2.7 Isolated Ambulatory Phlebectomy Versus Saphenous Thermal Ablation

Ambulatory selective varices ablation under local anaesthesia (ASVAL) is a method, in which the incompetent tributaries are treated by means of phlebectomy, with preservation of the saphenous trunk. The aim of the SAPTAP Trial was to determine whether single ambulatory phlebectomy with or without delayed endovenous truncal ablation (SAP) is non-inferior to thermal endovenous ablation with concomitant phlebectomy (TAP), and whether SAP is a cost-effective alternative to TAP [23]. Some 464 patients received the allocated treatment (SAP 227, TAP 237). Follow-up visits were scheduled at 3 months, 9 months (SAP group only), and 12 months after the initial treatment. VEINES-QOL scores were 52.7 (95% c.i. 51.9 to 53.9) for SAP and 53.8 (53.3 to 55.1) for TAP; VEINES-Sym scores were 53.5 (52.6 to 54.4) and 54.2 (54.0 to 55.6) respectively. Fifty-eight patients (25.6 per cent) in the SAP group received additional truncal ablation. Treatment with SAP was less costly than treatment with TAP. One year after treatment, participants who underwent SAP had non-inferior health-related quality of life compared with those who had TAP. Treatment with SAP was a cost-effective alternative to TAP at 12 months. Treating patients with SAP instead of TAP has several advantages. First, only 25.6% of those in the SAP group required additional treatment 9 months after ambulatory phlebectomy. Additional truncal treatment was not required in 73.5% of the patients as they had no symptoms (with or without truncal reflux) at 9-month follow-up. Thus, three-quarters of the patients were relieved of symptoms after one instead of two treatments. Second, the GSV/AASV was spared in these 73.5% of patients by being treated with SAP. Sparing the saphenous trunk may result in abolishment of reflux, owing to reduction of blood volume in the trunk after isolated phlebectomy. Therefore, it is given the opportunity to regain its function as one of the main veins of the superficial venous system.

18.3 Conclusions for Clinical Practice

1. For patients with superficial venous incompetence presenting with symptomatic varicose veins (CEAP clinical class C2S), interventional treatment is recommended.
2. For patients with great saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended as first choice treatment, in preference to high ligation/stripping and ultrasound guided foam sclerotherapy.

3. For patients with great saphenous vein incompetence requiring treatment, cyanoacrylate adhesive closure should be considered when a non-thermal non-tumescent technique is preferred.
4. For patients with great saphenous vein incompetence requiring treatment, mechanochemical ablation may be considered when a non-thermal non-tumescent technique is preferred.
5. No difference in outcomes following mechanochemical ablation or cyanoacrylate adhesive closure has been found. This suggests that the main determinant as to which interventions to use would be surgeon and patient preference and the cost-effectiveness of each technique.
6. For patients with saphenous trunk incompetence undergoing treatment, ultrasound guided foam sclerotherapy may be considered for treating saphenous trunks with a diameter less than 6 mm.
7. Endovenous ablation of superficial venous incompetence in combination with compression improves leg ulcer healing when compared with compression alone.
8. Wearing compression stockings after endothermal ablation is advantageous in the first few days after treatment and is especially beneficial for those having concurrent phlebectomies.

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Chapter 19
Deep Vein Thrombosis of the Lower Limb and Post-Thrombotic Syndrome



19.1 Guidelines

19.1.1 European Society of Cardiology

The "European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function" have published a joint consensus document on diagnosis and management of acute deep vein thrombosis [1].

19.1.1.1 Consensus Statement: Diagnosis

- Clinical prediction rule (two-level modified Wells score, Table 19.1) is recommended to stratify patients with suspected lower limb deep vein thrombosis (DVT).
- ELISA D-dimer measurement is recommended in 'unlikely' clinical probability patients to exclude DVT.
- Venous US is recommended as first line imaging method for DVT diagnosis.
- Venous CT scan should be reserved to selected patients only.
- Venous US should be proposed also in case of confirmed pulmonary embolism (PE), for initial reference venous imaging, useful in case of DVT recurrence suspicion or further stratification in selected patients.
- Venous US may be considered for further stratification in selected patients with concomitant suspected PE.

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Table 19.1 The Wells score for clinical assessment of deep-vein thrombosis [1, 26]

Clinical variable	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	+1
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (non varicose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	-2
Three-level Wells score – Low <1 – Intermediate 1–2 – High >2	
Two-level Wells score: – DVT unlikely: Score ≤ 1 – DVT likely: Score ≥ 2	

19.1.1.2 Consensus Statement: Initial and Long-Term Management

- Patients with proximal DVT should be anticoagulated for at least 3-months.
- Patients with isolated distal DVT at high-risk of recurrence should be anticoagulated, as for proximal DVT; for those at low risk of recurrence shorter treatment (4–6 weeks), even at lower anticoagulant doses, or ultrasound surveillance may be considered.
- In the absence of contraindications, DOACs should be preferred as first-line anticoagulant therapy in non-cancer patients with proximal DVT.
- Adjuvant catheter-directed thrombolysis (CDT) may be considered in selected patients with ilio-common femoral DVT, symptoms <14 days, and life expectancy >1 year if performed in experienced centres.
- Primary acute DVT stenting or mechanical thrombus removal alone are not recommended.
- Vena cava filters may be considered if anticoagulation is contraindicated, their use in addition to anticoagulation is not recommended.
- Compression therapy associated with early mobilization and walking exercise should be considered to relieve acute venous symptoms.

19.1.1.3 Consensus Statement: Extended Management

- Decision to discontinue or not anticoagulation should be individually tailored, balancing risk of recurrence against bleeding risk, taking into account patients' preferences and compliance.
- In the absence of contraindications, DOACs should be preferred as first line anticoagulant therapy in non-cancer patients. Currently low-dose apixaban and rivaroxaban have shown their benefit in this setting.
- When VKAs are proposed, they should be administered at conventional intensity regimen (INR 2–3).
- Aspirin may be considered for extended treatment if anticoagulation is contraindicated.
- Endovascular recanalization may be considered in patients with chronic venous occlusion class CEAP 4–6.
- Regular (at least yearly) assessment of compliance and benefit/risk balance should be performed in patients on extended treatment.
- At anticoagulation discontinuation, venous US should be performed to establish a baseline comparative exam in case of recurrence.

19.1.1.4 Consensus Statement: DVT Management in Special Situations

- In case of upper extremities DVT (UEDVT) suspicion, venous US is the first choice imaging test.
- Treatment of UEDVT is similar to that of lower limb DVT with regard to anticoagulation.
- LMWH are recommended for acute treatment of cerebral vein thrombosis.
- LMWH are recommended for acute treatment of splanchnic vein thrombosis.
- LMWH are recommended for initial and long-term treatment in cancer patients.
- In cancer patients, after 6 months, decision of continuation and, if so, the mode of anticoagulation should be based on individual evaluation of the benefit-risk ratio, tolerability, patients' preference, and cancer activity.
- During pregnancy, venous US is recommended as first line DVT imaging test.
- During pregnancy, LMWH is recommended for initial and long-term treatment.
- Anticoagulant treatment should be continued for at least 6 weeks after delivery with a total of 3-months treatment.

19.1.1.5 Venous Occlusion Recanalization

The following comments are made in this guideline:

- Endovascular techniques are available for selected patients with post-thrombotic syndrome (PTS). Case series and prospective cohort trials suggest that at least some subgroups of PTS patients (CEAP classes 4–6) may benefit from addition

of endovascular therapy into overall management strategy. In patients with moderate-to-severe PTS and iliac vein obstruction, endovascular stent placement may be used to restore vein patency.
- In selected infrequent cases, surgical vein bypass may be an option to relieve venous hypertension.

19.1.2 The Postthrombotic Syndrome—A Scientific Statement from the American Heart Association [2]

19.1.2.1 Recommendations for Thrombolysis and Endovascular Approaches to Acute DVT for the Prevention of Postthrombotic Syndrome (PTS)

- Catheter-directed thrombolysis (CDT) and pharmacomechanical catheter-directed thrombolysis (PCDT), in experienced centers, may be considered in select patients with acute (≤14 days) symptomatic, extensive proximal DVT who have good functional capacity, ≥1-year life expectancy, and low expected bleeding risk (Class IIb; Level of Evidence B).
- Systemic anticoagulation should be provided before, during, and after CDT and PCDT (Class I, Level of Evidence C).
- Balloon angioplasty with or without stenting of underlying anatomic venous lesions may be considered after CDT and PCDT as a means to prevent rethrombosis and subsequent PTS (Class IIb; Level of Evidence B).
- When a patient is not a candidate for percutaneous CDT or PCDT, surgical thrombectomy, in experienced centers, might be considered in select patients with acute (≤14 days) symptomatic, extensive proximal DVT who have good functional capacity and ≥ 1-year life expectancy (Class IIb; Level of Evidence B).
- Systemic thrombolysis is ***not*** recommended for the treatment of DVT (Class III; Level of Evidence A).

19.1.2.2 Recommendations for the Use of Graduated Elastic Compression Stockings (ECS) and Intermittent Compression to Treat PTS

- A trial of ECS may be considered in patients with PTS who have no contraindications (e.g., arterial insufficiency) (Class IIb; Level of Evidence C).
- For patients with moderate or severe PTS and significant edema, a trial of an intermittent compression device is reasonable (Class IIb; Level of Evidence C).

19.1.2.3 Recommendations for Exercise Training to Treat PTS

- In patients with PTS, a supervised exercise training program consisting of leg strength training and aerobic activity for at least 6 months is reasonable for patients who are able to tolerate it (Class IIa; Level of Evidence B).

19.1.2.4 Recommendations for Venous Ulcer Management

- Compression should be used to treat venous ulcers in preference to primary dressing alone, noncompression bandage, or no compression (Class I; Level of Evidence A).
- Multicomponent compression systems are more effective than single-component systems (Class I; Level of Evidence B).
- Pentoxifylline can be useful for treating venous ulcers on its own or with compression (Class IIa; Level of Evidence A).
- Neovalve reconstruction may be considered in patients with refractory postthrombotic venous ulcers (Class IIb; Level of Evidence C).

19.1.2.5 Recommendations for Endovascular and Surgical Treatment of PTS

- For the severely symptomatic patient with iliac vein or vena cava occlusion, surgery (e.g., femoro-femoral or femoro-caval bypass) (Class IIb; Level of Evidence C) or percutaneous endovenous recanalization (e.g., stent, balloon angioplasty) (Class IIb; Level of Evidence B) may be considered.
- For severely symptomatic patients with postthrombotic occlusion of their common femoral vein, iliac vein, and vena cava, combined operative and endovenous disobliteration may be considered (Class IIb; Level of Evidence C).
- For severely symptomatic patients with PTS, segmental vein valve transfer or venous transposition may be considered (Class IIb; Level of Evidence C).

The endovascular, surgical and hybrid approaches to the treatment of PTS as recommended in this guideline are summarized in Table 19.2. It is emphasized that experience with these procedures is limited and only the most severely affected patients are considered for treatment. Outcomes of these procedures are highly dependent on operator (surgical) expertise, and if not available locally, referral to a center with expertise is recommended.

Table 19.2 Endovascular, surgical and hybrid approaches to the treatment of post-thrombotic syndrome (PTS) (according to [2])

Indication	Approach
	Endovascular approaches
Iliocaval/iliofemoral obstruction	Venoplasty and stenting
Correction of superficial reflux	Endovenous thermal ablation
	Surgical approaches
Infrainguinal venous obstruction	– Saphenopopliteal bypass – Saphenotibial bypass
Iliofemoral obstruction	– Femoro-femoral bypass – Femoroiliac bypass – Iliocaval bypass – Femoro-caval bypass
Correction of reflux	– Segmental vein valve transfer via axillofemoral/popliteal transplant or venous transposition – Ligation of femoral vein
	Hybrid approaches
Femoral and iliac vein reconstruction	– Surgical endophlebectomy of common femoral vein with patch angioplasty and endoluminal balloon venoplasty and stenting of iliac veins and vena cava – Adjunctive arteriovenous fistula to maintain patency – Surgical disobliteration of common femoral vein to more effectively drain infrainguinal venous system and provide inflow to recanalized iliac veins

19.1.3 CHEST Guideline for Antithrombotic Management of Venous Thromboembolism [3]

The guidelines recommend among others:

- In patients with superficial venous thrombosis (SVT) of the lower limb at increased risk of clot progression to DVT or PE, we suggest the use of anticoagulation for 45 days over no anticoagulation (weak recommendation, moderate certainty evidence).
- In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over other anticoagulant treatment regimens such as (prophylactic- or therapeutic-dose) LMWH (weak recommendation, low-certainty evidence).
- In patients with acute DVT of the leg we suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate-certainty evidence).
- In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence).

- In patients with acute DVT of the leg, we suggest against using compression stockings routinely to prevent PTS (weak recommendation, low-certainty evidence).
- In patients with acute DVT of the leg, we recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (strong recommendation, moderate-certainty evidence).
- In patients with acute proximal DVT of the leg and a contraindication to anticoagulation, we recommend the use of an IVC filter (strong recommendation, moderate-certainty evidence).
- In patients with acute VTE who do not have a contraindication we recommend a 3-month treatment phase of anticoagulation (strong recommendation, moderate-certainty evidence).

19.1.4 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) on the Management of Chronic Venous Diseases of the Lower Limbs [4]. They Recommend

19.1.4.1 Recommendation 58

For patients with iliac vein outflow obstruction and severe symptoms/signs, endovascular treatment should be considered, as the first choice treatment. (Recommendation class IIa/Level of evidence B).

19.1.4.2 Recommendation 59

For patients with iliac vein outflow obstruction undergoing endovascular treatment, the use of intravascular ultrasound should be considered to guide treatment. (Recommendation class IIa/ Level of evidence C).

19.1.4.3 Recommendation 60

For patients with iliac vein outflow obstruction suffering from a recalcitrant venous ulcer, severe post-thrombotic syndrome, or disabling venous claudication, surgical or hybrid deep venous reconstruction may be considered when endovascular options alone are not appropriate. (Recommendation class IIb/ Level of evidence C).

19.1.4.4 Recommendation 61

For patients with iliac vein outflow obstruction, without severe symptoms, neither endovascular nor surgical interventions are recommended. (Recommendation class III/ Level of evidence C).

19.1.4.5 Recommendation 62

For patients undergoing either endovascular or surgical reconstruction of iliac vein outflow obstruction, duplex ultrasound surveillance is recommended 1 day and 2 weeks after the intervention, and at regular intervals thereafter. (Recommendation class I/Level of evidence C).

19.1.4.6 Recommendation 63

For patients with iliac vein outflow obstruction, management by a multidisciplinary team is recommended. (Recommendation class I/Level of evidence C).

19.1.4.7 Recommendation 64

For patients with extensive axial deep venous incompetence and severe persistent symptoms and signs, where previous management has failed, surgical repair of valvular incompetence may be considered in specialised centres. (Recommendation class IIb/ Level of evidence B).

19.1.5 European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines on the Management of Venous Thrombosis

This guideline notes on **thrombus removal strategies** [5]:

19.1.5.1 Recommendation 34

In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered. (Recommendation class IIa; Level of evidence A).

19.1.5.2 Recommendation 35

For patients with deep vein thrombosis limited to femoral, popliteal, or calf veins, early thrombus removal is ***not*** recommended. (Recommendation class III; Level of evidence B).

19.1.5.3 Recommendation 36

For patients with deep vein thrombosis treated by early thrombus removal, with or without stenting, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician. (Recommendation class I; Level of evidence C).

19.1.5.4 Recommendation 38

For patients with calf deep vein thrombosis, a decision to anticoagulate based on symptoms, risk factors for progression, and bleeding risk should be considered. (Recommendation class IIa; Level of evidence C).

19.1.5.5 Recommendation 39

For patients with symptomatic calf deep vein thrombosis requiring anticoagulant treatment, three months of therapy is recommended over shorter durations. (Recommendation class I; Level of evidence A).

19.1.5.6 Recommendation 40

For patients with calf deep vein thrombosis requiring anticoagulation, direct oral anticoagulants are recommended over low molecular weight heparin followed by vitamin K antagonists. (Recommendation class I; Level of evidence C).

19.1.5.7 Recommendation 41

For patients with symptomatic calf deep vein thrombosis and active cancer, anticoagulation beyond 3 months should be considered. (Recommendation class IIa; Level of evidence C).

19.1.5.8 Recommendation 42

For patients with symptomatic calf deep vein thrombosis not receiving anticoagulation, clinical re-assessment and repeat whole leg ultrasound after 1 week is recommended. (Recommendation class I; Level of evidence B).

19.2 Results

19.2.1 Deep Vein Thrombosis

19.2.1.1 Meta-Analyses/Systematic Reviews

Thrombolytic Clot Removal Strategies

A Cochrane review assessed the effects of thrombolytic clot removal strategies and anticoagulation compared to anticoagulation alone for the management of people with acute deep vein thrombosis (DVT) of the lower limb [6]. The review included a total of 19 RCTs, with 1943 participants. The review found moderate-certainty evidence that thrombolysis effectively dissolved the clot so that complete clot breakdown occurred more often with thrombolysis than with standard anticoagulant therapy. Those receiving thrombolysis had more bleeding complications than with standard anticoagulation (6.7% versus 2.2%). Most bleeding episodes occurred in the older studies. Six trials (1393 participants) continued for over 6 months and found that slightly fewer people developed PTS when treated with thrombolysis; 50% compared with 53% in the standard anticoagulation treatment group. Two trials (211 participants) that continued for over 5 years showed that fewer people developed PTS when treated with thrombolysis. Use of strict eligibility criteria appears to have improved the safety of this treatment, which is effective delivered directly to the clot by catheter or via the bloodstream from another vein. There was no evidence that the position of the clot within the leg made it more or less likely for people to get PTS. Evidence suggests that systemic administration of thrombolytics and catheter-directed thrombolysis (CDT) have similar effectiveness.

Catheter-Based Intervention for Acute Proximal Deep Vein Thrombosis

A meta-analysis of randomized controlled trials assessing the efficacy of lytic catheter-based interventions (LCBI) in proximal acute DVT for the prevention of PTS was undertaken by Javed et al. [7]. Included articles were randomized controlled trials that studied the use of LCBIs with additional anticoagulation vs anticoagulation alone. Three trials were included in the final meta-analysis, comprising 987 patients. Patients undergoing LCBIs had a reduced risk of PTS (relative risk [RR], 0.84; 95% confidence interval [CI], 0.74-0.95; P = .006) and a lower risk of

developing moderate to severe PTS (RR, 0.75; 95% CI, 0.58-0.97; P = .03). LBCIs increased the risk of having a major bleed (RR, 2.03; 95% CI, 1.08-3.82; P = .03). In the iliofemoral DVT subgroup analysis, there was a trend toward decreasing the risk of developing PTS and moderate to severe PTS (P = .12 and P = .05, respectively). There was no significant difference in quality-of-life score (as measured by the Venous Insufficiency Epidemiological and Economic Study—Quality of Life/Symptoms) between the two groups (P = .51). LCBIs in acute lower limb DVTs are likely to reduce the development of PTS and moderate to severe PTS as measured by the Villalta score; however, the magnitudes of risk reduction are not as large as previously thought. The decreases in PTS development are accompanied by a small but significant increase in major bleeding complications. Hence, in light of the modest risk reduction, patient selection is paramount.

Catheter-Based Intervention with Percutaneous Mechanical Thrombectomy

Li et al. [8] conducted a meta-analysis to investigate the effectiveness and safety of adjuvant percutaneous mechanical thrombectomy (PMT) during catheter-directed thrombolysis (CDT) compared with CDT alone in the treatment of acute iliofemoral DVT. The meta-analysis included 20 eligible studies with a total of 1686 patients. The rates of venous patency and thigh detumescence of the adjuvant PMT group were higher than those of the CDT alone group. Compared with CDT alone, the adjuvant PMT group experienced fewer incidences of major bleeding complications (odds ratio, 0.45; 95% CI, 0.26-0.77) and occurrences of post-thrombotic syndrome within 2 years of the procedure (odds ratio, 0.55; 95% CI, 0.33-0.92). Furthermore, the duration of thrombolytic therapy was shorter, and the total dose of administered thrombolytics was lower with adjuvant PMT. Adjuvant PMT during CDT is associated with improved clinical outcomes and a lower incidence of major bleeding complications. The studies investigated were, however, single-center cohort studies, and future randomized controlled trials are needed to substantiate these findings.

19.2.1.2 Randomized Trials

Pharmacomechanical Catheter-Directed Thrombolysis Vs. Anticoagulation

In the ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) trial 692 patients with acute proximal deep-vein thrombosis were randomly assigned to receive either anticoagulation alone (control group) or anticoagulation plus pharmacomechanical thrombolysis (catheter-mediated or device-mediated intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting) [9]. Between 6 and 24 months, there was no significant between-group difference in the percentage of patients with the post-thrombotic syndrome (47% in the pharmacomechanical-thrombolysis group and 48% in the control group; P = 0.56).

Pharmacomechanical thrombolysis led to more major bleeding events within 10 days (1.7% vs. 0.3% of patients, P = 0.049), but no significant difference in recurrent venous thromboembolism was seen over the 24-month follow-up period (12% in the pharmacomechanical-thrombolysis group and 8% in the control group, P = 0.09). Among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding.

Elastic Compression Stockings to Prevent Post-Thrombotic Syndrome

Yang et al. [10] evaluated the effectiveness of elastic compression stockings (ECS) in prevention of PTS in patients suffering from proximal DVT who did not undergo thrombus removal procedures. Two hundred thirty-two patients were included in this randomized trial. One hundred thirteen patients were in the ECS group and 119 in the control group. For the ECS group, kneelength ECS producing a pressure of 30 to 40 mmHg were used during the day for at least 6 days a week. Stockings were routinely replaced per 6 months or earlier if the stockings were torn or the leg circumference changed. Patients in the ECS group were instructed to wear ECS for 24 months. Compliance with ECS was recorded. Eightyfive patients (75.2%) reported using the ECS at least 6 days a week. The incidence of PTS was 42.0% in the ECS group and 57.8% in the control group at 24 months (P = .024). ECS can prevent the postthrombotic syndrome in patients with iliofemoral venous thrombosis and femoral popliteal venous thrombosis who do not undergo thrombus removal procedures.

19.2.1.3 Studies and Registries

Catheter-Directed Thrombolysis for Proximal Deep Venous Thrombosis

In the National Inpatient Sample (NIS) from 2005 to 2013, Tang et al. [11] identified a total of 138,049 patients who were discharged with a principal diagnosis of proximal and caval DVT. 7097 of these patients received CDT (5.1%). From this group, 2854 (40.2%) were treated with CDT alone, 2311 (32.6%) received adjunctive angioplasty alone, and 1932 (27.2%) received adjunctive angioplasty and stent. The primary outcome was a composite end point of all-cause mortality, gastrointestinal bleed, or intracranial hemorrhage. Adjunctive stenting had a significantly lower rate of primary composite outcome compared with CDT alone (2.7% vs 3.8%; P = .04). Stent placement was associated with a similar length of stay compared with angioplasty and CDT alone groups and higher in-hospital charges (Table 19.3). Rate of adjunctive stenting increased from January 2005 to December 2013. One in four patients undergoing CDT is treated with adjunctive stent

Table 19.3 Weighted outcomes of patients undergoing catheter-directed thrombolysis (CDT), adjunctive angioplasty, and stent placement for proximal deep venous thrombosis (according to [11])

Parameter	CDT alone (n = 2857.17)	CDT + angioplasty (n = 2348.49)	CDT + angioplasty + stenting (n = 1923.57)
Primary composite outcome: Death, ICH, and GI bleeding	107.3 (3.8)	63.4 (2.7)	51.3 (2.7)
Died during hospitalization	37.8 (1.3)	15.5 (0.7)	16.8 (0.9)
GI bleeding	52.8 (1.9)	34.1 (1.5)	23.2 (1.2)
ICH	21.3 (0.7)	17.6 (0.8)	14.8 (0.8)
Blood transfusion	311.8 (10.9)	225.3 (9.6)	210.8 (11.0)
Hematoma	72.6 (2.5)	51.3 (2.2)	57.1 (3.0)
Procedure-related Hemorrhage	36.8 (1.3)	28.2 (1.2)	20.0 (1.0)
Length of stay, days	7.1 (0.5-13.6)	6.9 (1-12.9)	6.80 (1.5-12.1)
Charges, $	80,441.63 ± 74,024.98	98,089.82 ± 72,921.94	115,164.01 ± 76,985.31
IVC filter	935.3 (32.7)	840.9 (35.8)	697.0 (36.2)

Categorical variables are presented as number (%)
ICH intracranial hemorrhage, *GI* gastrointestinal, *IVC* inferior vena cava

placement in the United States. Adjunctive stenting does not adversely affect the acute safety outcomes of CDT; in fact, it showed improvement in the primary composite outcome, which was mainly driven by all-cause mortality. The results suggest that future studies can consider the consistent use of intravascular ultrasound (IVUS), which would likely improve appropriate use of stents and help with understanding completeness of thrombus removal. In this study, only 2.1% of all CDT cases used IVUS to determine the need for stenting of the residual outflow venous stenosis. 61% of those patients who had IVUS received a stent as opposed to only 27% of those who did not have IVUS, suggesting the poor sensitivity of venography alone in detecting significant residual venous stenosis.

Using the National Inpatient Sample database between January 2005 and December 2013, Brailovsky et al. [12] identified 31,124 cancer patients with lower extremity proximal or caval DVT. 1290 (4%) patients were treated with CDT. Comparative outcomes as assessed in two matched groups of 1287 patients showed that there was no significant difference in in-hospital mortality of patients undergoing CDT plus anticoagulation compared with those treated with anticoagulation alone (2.6% vs 1.9%; P = .23). However, the bleeding complications and resource utilization were significantly higher in the CDT group compared with anticoagulation alone (Table 19.4). Therefore, in patients with cancer the upfront risk of bleeding complications and higher resource utilization must be carefully weighed against a potential reduction of PTS, and it would be prudent to screen high-risk

Table 19.4 Matched outcomes of cancer patients with and without undergoing catheter-directed thrombolysis (CDT) for proximal or venacaval deep venous thrombosis (DVT). According to Brailovsky et al. [12]

Parameter	Anticoagulation, No CDT (n = 1287)	CDT group (n = 1287)	*P*
Death, n (%)	25 (1.9)	33 (2.6)	.23
Blood transfusion, n (%)	168 (13.1)	239 (18.6)	<.001
Gastrointestinal bleed, n (%)	30 (2.3)	28 (2.2)	.89
Intracranial hemorrhage, n (%)	5 (0.4)	17 (1.3)	.02
Procedure-related hemorrhage, n (%)	4 (0.3)	13 (1.0)	.049
Procedure-related hematoma, n (%)	5 (0.4)	31 (2.4)	<.001
IVC filter placed, n (%)	336 (26.1)	434 (33.7)	<.001
Peripheral angioplasty, n (%)	37 (2.9)	765 (59.4)	<.001
Peripheral stent, n (%)	14 (1.1)	386 (30.0)	< .001
Acute kidney injury, n (%)	108 (8.4)	160 (12.4)	<.01
Length of stay, days	4.0 (2.0-7.0)	6.0 (4.0-10.0)	<.001
Hospital charges, US $, Median (interquartile range)	22,320 (11,482-41,005)	81,535 (50,968-127,045)	< .001

cancer patients for brain metastases before initiating CDT therapy. Furthermore, adjunctive percutaneous mechanical thrombectomy may be a reasonable approach in cancer patients to decrease both duration of therapy and thrombolytic dose.

In a retrospective monocentre study, Pouncey et al. [13] compared the outcomes of patients with iliofemoral deep venous thrombosis (DVT) treated with additional AngioJet pharmacomechanical thrombectomy (PCDT) vs. catheter directed lysis (CDT) alone. A total of 151 limbs were treated, 70 limbs with PCDT and 81 limbs with CDT alone. The primary outcome, as assessed by the 6 month and 12 month Villalta scores showed no statistically significant difference between the two groups. At 1 year, 22.2% of PCDT cases vs. 24.7% of CDT cases were observed to have PTS (p = .74), with 9.5% vs. 4.1% of all cases classified as moderate to severe (p = .30). This study was not significantly powered to show a difference in major and minor bleeding, but there was a trend towards reduced bleeding in the PCDT cohort (6.3% vs 17.1%). Use of PCDT resulted in a reduction in lysis duration (40 h vs 53 h; p < .001) and reduction in lytic dose (49 mg vs 57 mg; p = .011) vs. CDT. In conclusion, PCDT and CDT had similar long-term outcomes, but PCDT was associated with a reduction in both treatment time and lytic dose.

Midterm outcome of pharmacomechanical catheter-directed thrombolysis (PCDT) combined with stenting for treatment of iliac vein compression syndrome (May-Thurner syndrome) was assessed by Jiang et al. [14] in a retrospective study. PCDT combined with stenting in the treatment of 46 patients with iliac vein compression syndrome and acute iliofemoral deep venous thrombosis resulted in 100% technical success and no 30-day mortality. There was a significant reduction in

Venous Registry Index (9.82 ± 1.74 to 1.15 ± 1.02; P < .05) after the procedure. The 6-, 12-, and 24-month primary patency rates were 97.8%, 95.7%, and 91.1%, respectively. Only one patient developed mild post-thrombotic syndrome (PTS) and none developed severe PTS. Pharmacomechanical catheter-directed thrombolysis combined with stenting to treat patients with acute proximal deep venous thrombosis caused by iliac vein compression syndrome was feasible with excellent patency and no severe PTS at 24 months.

Outcomes of iliac vein stenting after catheter-directed thrombolysis for acute iliofemoral thrombosis were reported by Avgerinos et al. [15]. In 77 stented limbs of 73 patients with acute iliofemoral deep venous thrombosis (DVT), 3-year primary patency and secondary patency were 75% and 82%, respectively. DVT recurred perioperatively in nine (12.3%) patients. Four of them (six limbs) had incomplete thrombolysis (<50%); the rest recurred despite successful lysis (>50%). None of these recurrences had progressed to phlegmasia or limb-threatening venous congestion. Twelve stents extended below the inguinal ligament; three (25%) thrombosed. The overall rate of PTS (Villalta score ≥ 5) in the stented cohort at 2 and 5 years was 12.0% and 14.4%. Stent placement below the inguinal ligament did not affect the patency but was associated with a higher PTS rate. A strategy of complete thrombus removal for acute iliofemoral DVT is recommended. Stent extension into the contralateral iliac vein or below the inguinal ligament appears to be an acceptable adjunct to thrombolysis and iliac vein stenting for DVT.

19.2.2 Postthrombotic Syndrome

19.2.2.1 Systematic Reviews

Risk of Post-Thrombotic Syndrome after Isolated Distal Deep Vein Thrombosis

Isolated distal DVT (IDDVT), also referred to as calf vein DVT, in which thrombosis occurs below the level of the knee, is considered an altogether more benign clinical entity. A systematic review and meta-analysis aimed to define the risk of PTS after IDDVT, with the secondary aim of reporting PTS severity [16]. The results showed a post-thrombotic rate of 17% (95% CI 11–26%) (seven studies, 217 cases, 1105 participants). Heterogeneity was high. Three studies (302 participants) reported the severity of post-thrombotic syndrome: 78% were mild (Villalta score 5–9); 11% were moderate (Villalta score 10–14), and 11% were severe (Villalta score ≥ 15). This meta-analysis is the first to report the pooled risk of post-thrombotic syndrome across studies after isolated distal deep vein thrombosis. It demonstrates that post-thrombotic syndrome affects around one in five people and one in 50 will progress to severe post-thrombotic syndrome.

Venous Stenting for Lower Extremity Occlusive Disease

Williams and Dillavou [17] reviewed the efficacy and safety of venous stenting for lower extremity occlusive disease. 3812 stented limbs from 23 published studies and two national presentations were included in this systematic review. Dedicated venous stents were used in 740 patients, and standard stents were used in 3072 patients. The overall major complication rate was <1%. Median symptomatic improvement and ulcer healing were seen in 79% and 71% of the standard stented limbs, respectively. For standard stents, the median primary, assisted primary, and secondary patency rates were 71%, 89%, and 91%, respectively, with a median study follow-up of 23.5 months. Dedicated venous stents had an overall primary patency of 78.8% at 12 months, with lower patency (73%) seen in post-thrombotic vs compressive (96%) disease. Iliocaval venous stenting appears to be a safe and effective treatment of chronic venous disease.

Antithrombotic Management after Venous Stenting

Notten et al. [18] performed a systematic review to assess the available evidence on postinterventional antithrombotic management after venous stenting of the (post) thrombotic iliofemoral tract. 64 (56 original) studies were selected. Overall, a mean primary patency rate of 82.3% was seen 1 year after the intervention, which decreased to 73.3% after 2 years. In the majority (43 of 56 studies, 77%), treatment was based on use of vitamin K antagonists, either with (18%) or without (59%) use of antiplatelet drugs. Only two studies (4%) directly assessed the effect of antithrombotic therapy on treatment outcomes. The impact of postinterventional antithrombotic therapy on stent patency remains unknown because of limited and insufficient data available in current literature. Further clinical research should more clearly address the role of antithrombotic therapy for preservation of long-term patency following venous stenting.

19.2.2.2 Clinical Trials

Accelerated Thrombolysis for Post-Thrombotic Syndrome

The aim of the prospective ACCESS PTS study (Accelerated Thrombolysis for Post-Thrombotic Syndrome Using the AcousticPulse Thrombolysis Ekosonic Endovascular System) was to evaluate the effectiveness of combined percutaneous transluminal venoplasty (PTV) and ultrasound-accelerated thrombolysis (USAT) to improve PTS-related symptoms and venous disease–related QOL in subjects with PTS in the presence of chronic veno-occlusive disease [19]. The primary efficacy outcome was a reduction of ≥4 points in the Villalta score 30 days after procedure. The primary safety outcomes were major bleeding episodes within 72 hours and symptomatic pulmonary embolism during the index hospitalization. A total of 82

limbs (78 patients) were treated. The primary end point was met in 64.6% (51/79). Iliofemoral venous stenting was performed in 42 patients, with similar improvements seen in all outcomes, regardless of stenting status. One patient developed severe bleeding within 72 h of the intervention and died at 32 days after procedure (1.3% mortality rate). At 1 year, 77.3% (51/66) of limbs continued with a Villalta reduction ≥4. At 365 days, >90% of segments had patency with ultrasound flow present. For patients experiencing PTS from chronic venous obstruction, combined percutaneous transluminal venoplasty and ultrasound-accelerated thrombolysis interventions resulted in improvement in clinical PTS, as measured by the Villalta scale and Venous Clinical Severity Score as well as durable venous patency. ACCESS PTS intervention also resulted in significant improvement in quality of life.

Venous Stent Patency

A multicentre study assessed primary stent patency predictive factors in three groups of patients with history of lower limb (LL) vein thrombosis: non-thrombotic iliac vein lesion (NIVL), acute deep vein thrombosis (aDVT), and PTS [20]. 377 patients were included: 134 NIVL, 55 aDVT, and 188 PTS. Primary patency was statistically significantly higher in the NIVL group (99.3%) compared with the PTS group (68.6%) ($p < .001$) and the aDVT group (83.6%) ($p = .002$). PTS patients received a statistically significantly greater number of stents ($p < .001$) and had more stents below the inguinal ligament ($p < .001$). Median follow up was 28.8 months. Discontinuation of anticoagulation therapy at the last assessment was 93.2% for NIVL, 25.0% for aDVT, and 70.3% for the PTS group ($p < .001$). The only predictor of worse primary patency in the aDVT group was long term anticoagulation before stenting. No anticoagulation or antiplatelet treatment regimen was associated with improved stent patency in this study. The study showed that the primary patency of venous stents depended on the indication for stenting; and in acute venous thrombosis requiring stenting, patients with long term anticoagulation before stenting had lower primary patency. The best anticoagulant treatment regimen after venous stenting has not yet been established. PTS patients on indefinite anticoagulation (VKA or DOACs) before the procedure should continue anticoagulation after the procedure. If there is no indication for indefinite anticoagulation, post-operative anticoagulation should be prescribed. The optimal duration is not known, guidelines recommend that anticoagulant treatment should be continued for at least 6 months after intervention.

In a retrospective multi-center study, 698 patients treated by stenting for PTS in 15 French centers were analyzed [21]. Technical success, defined as successful recanalization and stent deployment restoring rapid anterograde flow in the targeted vessel, was obtained in 668 (95.7%) patients with a complication rate of 3.9%. No procedural-related death occurred during or within 1 month after the intervention. After a mean follow-up of 21.0 months, primary patency, primary assisted patency, and secondary patency were achieved in 537 (80.4%), 566 (84.7%), and 616 (92.2%)

of the 668 patients, respectively. The mean improvements of Villalta and Chronic Venous Insufficiency Questionnaire in 20 questions (CIVIQ-20) scores were 7.0 ± 4.7 points (p < .0001) and 19.1 ± 14.8 points (p < .0001), respectively. Venous patency was strongly correlated to the severity of post-thrombotic lesions in the thigh.

Symptoms of chronic venous insufficiency secondary to obstructive iliofemoral disease are often bilateral. The impact of iliofemoral stenting of the more symptomatic lower extremity on clinical outcomes in the less affected contralateral extremity is not clear. Jayaraj et al. [22] evaluated the impact of stenting on contralateral leg symptoms in 304 patients. In this contralateral group, at 12 months, the VAS pain score improved from 5 to 0 (P < .0001), the grade of swelling went from 3 to 1 (P < .0001), and VCSS went from 5 to 3 (P < .0001) after stenting of the ipsilateral side. During the median follow-up of 20 months, 15 contralateral limbs underwent stenting. Median time to stenting of the contralateral limb after ipsilateral stenting was 9 months. Patients with bilateral obstructive iliofemoral venous lesions often experience improvement of the contralateral limb symptoms (95%) after stenting of the worse ipsilateral limb. Only 15 of 304 (5%) symptomatic contralateral limbs had to undergo stenting during the follow-up period because of a worsening clinical picture. Based on this, a staged approach to iliofemoral stenting in patients with bilateral symptoms focusing initially on the more symptomatic limb is suggested.

Venous Stent Configuration

From the Swiss and Arnsberg Venous Stent Registries, Moeri et al. [23] analyzed 150 patients with post-thrombotic syndrome (mean age, 44 +/− 16 years; 48% women) with laser-cut (n = 101) or braided nitinol (n = 49) stents placed into the common femoral vein across the inguinal ligament. The primary study outcomes were the primary and secondary patency rates at 12 months. The 1-year primary patency rate was 67.3% for patients with laser-cut nitinol stents and 86.7% for patients with braided nitinol stents used to cross the inguinal ligament. Stent fractures were observed in four patients (4%) with laser-cut stents but did not occur in patients with braided stents. Braided nitinol stents might be less prone to fracture and reocclusion at the inguinal ligament compared with laser-cut nitinol stents.

Jayaraj et al. [24] evaluated the clinical and stent related outcomes following use of composite stenting (combination of a Wallstent body and a Z stent top) in the management of symptomatic chronic obstructive iliofemoral venous disease. Of the 545 limbs that underwent stenting, 183 were in men and 362 were in women. Post-thrombotic syndrome was seen in 441 limbs and nonthrombotic iliac vein lesions/May-Thurner syndrome in 104 limbs. At 24 months, visual analog scale pain score went from 5 to 2 (P < .0001), grade of swelling went from 3 to 1 (P < .0001), and Venous Clinical Severity Score went from 6 to 4 (P < .0001). Ulcers were present in 67 limbs and had healed in 49 limbs (73%) over a median follow-up of 26 months. Cumulative primary, primary-assisted, and secondary patencies at 60 months were 70%, 99% and 91%, respectively. One hundred eleven limbs (20%) underwent

reintervention, including for in-stent restenosis in 44 limbs, stent compression in 2 limbs, in-stent restenosis and stent compression in 48 limbs, and stent occlusion in 17 limbs. Use of a composite stent configuration of Wallstent and Z stent in patients requiring iliac vein stenting resulted in improved outcomes compared to published data from use of Wallstents alone. A composite stent configuration resulted in less need for contralateral iliac vein stenting and less contralateral deep vein thrombosis than the use of Wallstents alone.

Robertson et al. [25] evaluated the association between stent length and patency in patients treated for iliofemoral venous outflow obstruction. A total of 108 patients (58.3% female) had had 6-month duplex ultrasound scans available for review. Their mean age was 55.6 +/− 17.2 years. Overall, the 6-month patency was 89.9%. Of the 108 patients, 56 (51.9%) had had a total stented length of ≤100 mm with a 6-month patency of 92.9%. The remaining 52 patients (48.1%) had had a total stented length > 100 mm with a 6-month patency of 86.5%. The rate of patency did not differ significantly between the two groups (P = .222). Stent patency at 6 months for patients with nonthrombotic iliac vein lesions (NIVLs) was 98% (40 of 41). Stent patency for patients with post-thrombotic venous stenoses (PTs) was 84% (32 of 38). Patency for patients with acute DVT who had undergone stenting after thrombectomy was 86% (25 of 29). Overall, 10 patients with thrombotic disease, including PT and acute DVT, had developed stent thrombosis. The total stented length was not predictive of the loss of patency. The findings from the present study suggest that the length of stent coverage does not differ in the likelihood of stent thrombosis for patients with NIVLs and PTs. Interventionalists should treat affected venous segments identified on IVUS and effectively stent from normal to normal venous areas.

19.3 Conclusions for Clinical Practice

1. Patients with proximal DVT should be anticoagulated for at least 3-months.
2. In the absence of contraindications, DOACs should be preferred as first-line anticoagulant therapy in non-cancer patients with proximal DVT.
3. Catheter-directed thrombolysis (CDT) and pharmacomechanical catheter-directed thrombolysis (PCDT), in experienced centers, may be considered in select patients with acute (≤14 days) symptomatic, extensive proximal DVT who have good functional capacity, ≥1-year life expectancy, and low expected bleeding risk.
4. Balloon angioplasty with or without stenting of underlying anatomic venous lesions may be considered after CDT and PCDT as a means to prevent rethrombosis and subsequent PTS.
5. In patients with PTS, a composite stent configuration resulted in less need for contralateral iliac vein stenting and less contralateral deep vein thrombosis than the use of Wallstents alone.

6. A staged approach to iliofemoral stenting in patients with PTS and bilateral symptoms focusing initially on the more symptomatic limb is suggested.
7. For patients with deep vein thrombosis treated by early thrombus removal, with or without stenting, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician.

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Chapter 20
Vena Cava Filter



20.1 Guidelines

20.1.1 Society of Interventional Radiology Clinical Practice Guideline

The Society of Interventional Radiology developed in collaboration with other societies clinical practice guidelines for the use of inferior vena cava (IVC) filters in the treatment of patients with or at substantial risk of venous thromboembolic disease [1]. They recommend:

20.1.1.1 Acute Pulmonary Embolism

- In patients with acute pulmonary embolism (PE) with a contraindication to anticoagulation therapy, we suggest an IVC filter be considered based on various clinical risk factors, as outlined in the rationale. (Strength of recommendation: limited)

Benefits and Harms
The panel judged that the benefits associated with IVC filter placement (reduction in short-term PE recurrence and possibly a reduction in mortality from acute PE) outweigh the potential harms (bleeding, vascular injury, device migration, and increased risk of recurrent DVT) in most patients.

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20.1.1.2 Acute Deep Vein Thrombosis (DVT)

- In patients with acute DVT without PE and with a contraindication to anticoagulation therapy, we suggest that an IVC filter be considered based on various clinical risk factors, as outlined in the rationale. (Strength of recommendation: consensus)

20.1.1.3 Anticoagulation for Venous Thromboembolism (VTE)

- In patients undergoing anticoagulation for acute VTE (DVT, PE) in whom a contraindication to anticoagulation develops, we suggest that an IVC filter be considered in the setting of ongoing significant clinical risk for PE. (Strength of recommendation: consensus statement)
- In patients receiving extended anticoagulation after acute treatment for VTE in whom a contraindication to anticoagulation develops, we suggest that an IVC filter ***not*** be placed, with rare exceptions. (Strength of recommendation: consensus statement)

20.1.1.4 Recurrent Venous Thromboembolism

- In patients who are receiving therapeutic anticoagulation for VTE (DVT, PE) who experience a recurrent VTE, we suggest that a filter ***not*** be placed, with few exceptions. Reasons for anticoagulation failure should always be addressed. (Strength of recommendation: consensus statement)

20.1.1.5 Routine IVC Filter Placement

- In patients with acute VTE (DVT, PE) who are being treated with therapeutic anticoagulation, we recommend ***against*** routine placement of an IVC filter. (Strength of recommendation: moderate)

20.1.1.6 Trauma Patients without Known Venous Thromboembolism

- In trauma patients without known acute VTE, we recommend ***against*** the routine placement of IVC filters for primary VTE prophylaxis. (Strength of recommendation: moderate)

20.1.1.7 Major Surgery in Patients without Known VTE

- In patients without known acute VTE who are undergoing major surgery, we suggest ***against*** routine placement of IVC filters. (Strength of recommendation: consensus statement)

20.1.1.8 Indwelling IVC Filters with no Anticoagulation Indication

- In patients who have indwelling IVC filters with no other indication for anticoagulation, we cannot recommend for or against anticoagulation. (Strength of recommendation: consensus statement)

20.1.1.9 Indwelling IVC Filters with Mitigated PE Risk

- In patients with indwelling retrievable/convertible IVC filters whose risk of PE has been mitigated or who are no longer at risk for PE, we suggest filters be routinely removed/converted unless risk outweighs benefit. (Strength of recommendation: consensus statement)
- In patients with indwelling permanent IVC filters whose risk of PE has been mitigated or who are no longer at risk for PE, we suggest ***against*** routine removal of filters. (Strength of recommendation: consensus statement)

20.1.1.10 Complications and Indwelling IVC Filters

- In patients with complications attributed to indwelling IVC filters, we suggest filter removal be considered after weighing filter- versus procedure-related risks and the likelihood that filter removal will alleviate the complications. (Strength of recommendation: consensus statement)

20.1.1.11 Structured Follow-Up

- In patients who have an IVC filter, we suggest the use of a structured follow-up program to increase retrieval rates and detect complications. (Strength of recommendation: limited)

20.1.1.12 Planned Filter Removal

- In patients who are having an IVC filter removed or converted, we suggest against routine preprocedural imaging of the filter and the use of laboratory studies except in select situations. (Strength of recommendation: consensus statement)

20.1.1.13 Filter Removal without Standard Snare Techniques

- In patients undergoing filter retrieval/conversion whose filter could not be removed/converted by using standard techniques, we suggest attempted removal with advanced techniques, if appropriate and if the expertise is available, after reevaluation of risks and benefits. (Strength of recommendation: consensus)

20.1.1.14 Filter Placement Technique

- In patients undergoing IVC filter placement, we cannot recommend for or against any specific placement technique. (Strength of recommendation: consensus statement)

20.1.2 International Clinical Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer

These guidelines [2] comment on IVC filters:

- In the initial treatment of VTE, inferior vena cava filters may be considered when anticoagulant treatment is contraindicated or, in the case of pulmonary embolism, when recurrence occurs under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended, and anticoagulation should be resumed when safe (guidance, based on evidence of very low quality and an unknown balance between desirable and undesirable effects).
- Prophylaxis of VTE in patients with cancer who have undergone surgery: inferior vena cava filters are not recommended for routine prophylaxis. (Grade 1 A recommendation).

20.1.3 NICE (National Institute for Health and Care Excellence)

The NICE guidelines for venous thromboembolic disease recommend [3]:

- Do not offer an inferior vena caval (IVC) filter to people with proximal DVT or PE unless:
  - It is part of a prospective clinical trial **or**
  - anticoagulation is contraindicated or a PE has occurred during anticoagulation treatment.
- Consider an IVC filter for people with proximal DVT or PE when anticoagulation treatment is contraindicated. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established.
- Consider an IVC filter for people with proximal DVT or PE who have a PE while taking anticoagulation treatment only after taking the steps outlined in the recommendation on treatment failure.
- Before fitting an IVC filter, ensure that there is a strategy in place for it to be removed at the earliest possible opportunity. Document the strategy and review it if the clinical situation changes.

20.1.4 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism [4]

20.1.4.1 Recommendations for Vena Cava Filter

- IVC filters should be considered in patients with acute pulmonary embolism and absolute contraindications to anticoagulation. (Recommendation class IIa / Level of evidence C)
- IVC filters should be considered in cases of pulmonary embolism recurrence despite therapeutic anticoagulation. (Recommendation class IIa/Level of evidence C)
- Routine use of IVC filters is ***not*** recommended. (Recommendation class III/ Level of evidence A)

20.2 Results

20.2.1 Meta-Analyses and Systematic Reviews

A Cochrane review assessed the evidence for the effectiveness and safety of vena caval filters (VCFs) in preventing pulmonary embolism (PE) [5]. Six studies involving 1388 participants were included. The six studies were clinically heterogeneous and the authors were unable to carry out meta-analysis. Two of the six identified studies were relevant for current clinical settings. One showed no evidence of a benefit of retrievable filters in acute PE for the outcomes of PE, death, DVT and bleeding during the initial 3 months in people who can receive anticoagulation (moderate-certainty evidence). The other study did not show any benefit for prophylactic filter insertion in people who sustained multiple traumatic injuries, with respect to symptomatic PE, mortality, or lower extremity venous thrombosis (moderate-certainty evidence). No firm conclusions regarding filter efficacy in the prevention of PE could be drawn from the remaining four RCTs identified in this review. With the paucity of evidence for groups of people for whom filters are potentially beneficial and for the use of retrievable filters data suggest the current accepted indication for filters is a contraindication to anticoagulation.

Liu et al. [6] performed a meta-analysis of randomized trials to investigate the effect of IVC filters on PE-related mortality and complications. Seven articles with 1274 patients were included. They found no significant difference in mortality related to PE between the IVC filter and control groups within 3 months (P = .11) nor during the entire follow-up period with low heterogeneity. However, the use of IVC filters decreased the new occurrence of PE without increasing deep vein thrombosis or major bleeding.

In a meta-analysis of 10 studies (two of which were randomized controlled trials), Shariff et al. [7] investigated the prophylactic IVC filter placement among patients with major trauma. The use of prophylactic IVC filters was associated with a reduced risk of symptomatic PE among subjects with major trauma (RR: 0.27, CI 0.12–0.58, P value <0.05), the evidence was further reinforced by a trial sequential analysis. However, the use of IVC filters was not associated with a decreased risk of fatal PE among subjects with major trauma.

20.2.2 Randomized Trials

Data from the French multicentre randomised PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) trial were first published by Decousus et al. [8]. In this trial, 400 patients with proximal deep-vein thrombosis who were at risk for pulmonary embolism were assigned to receive a vena caval filter (200 patients) or no filter (200 patients), and to receive low-molecular-weight heparin (enoxaparin, 195 patients) or unfractionated heparin (205 patients). At day 12, two

patients assigned to receive filters (1.1%), as compared with nine patients assigned to receive no filters (4.8%), had had symptomatic or asymptomatic pulmonary embolism (odds ratio, 0.22; 95% confidence interval, 0.05–0.90). At 2 years, 37 patients assigned to the filter group (20.8%), as compared with 21 patients assigned to the no-filter group (11.6%), had had recurrent deep-vein thrombosis. The initial beneficial effect of vena caval filters for the prevention of pulmonary embolism was counterbalanced by an excess of recurrent deep-vein thrombosis, without any difference in mortality. An 8-year follow-up was performed to assess the very long-term effect [9]. At 8 years, vena cava filters reduced the risk of pulmonary embolism but increased that of deep-vein thrombosis and had no effect on survival. Although their use may be beneficial in patients at high risk of pulmonary embolism, systematic use in the general population with venous thromboembolism was not recommended.

In the PREPIC2-study [10], the efficacy and safety of retrievable vena cava filters plus anticoagulation vs anticoagulation alone for preventing pulmonary embolism recurrence in patients presenting with acute pulmonary embolism and a high risk of recurrence was evaluated. In the filter group, the filter was successfully inserted in 193 patients and was retrieved as planned in 153 of the 164 patients in whom retrieval was attempted. By 3 months, recurrent pulmonary embolism had occurred in 6 patients (3.0%; all fatal) in the filter group and in 3 patients (1.5%; 2 fatal) in the control group (relative risk with filter, 2.00 [95% CI, 0.51–7.89]; P = .50). Results were similar at 6 months. No difference was observed between the 2 groups regarding the other outcomes. Filter thrombosis occurred in 3 patients. These findings do not support the use of this type of filter in patients who can be treated with anticoagulation.

In a multicenter, randomized, controlled trial, Ho et al. [11] assessed whether insertion of a retrievable vena cava filter within 72 hours after admission for trauma would result in a lower incidence of pulmonary embolism than no filter in patients, who had a contraindication to anticoagulant agents. 240 patients were enrolled and underwent randomization. Of the 122 patients assigned to the vena cava filter group, 89% had the filter inserted within 24 h after enrollment. Early placement of a vena cava filter did not result in a significantly lower incidence of symptomatic pulmonary embolism or death than no placement of a filter (13.9% in the vena cava filter group and 14.4% in the control group; P = 0.98). Among the 46 patients in the vena cava filter group and the 34 patients in the control group who did not receive prophylactic anticoagulation within 7 days after injury, pulmonary embolism developed in none of those in the vena cava filter group and in 5 (14.7%) in the control group, including 1 patient who died (relative risk of pulmonary embolism, 0; 95% CI, 0.00 to 0.55). Except in the case of one patient, all filters were removed before day 232. An entrapped thrombus was found in the filter in 6 patients. In conclusion, early placement of a vena cava filter after major trauma did not result in a lower incidence of symptomatic pulmonary embolism or death at 90 days (the primary composite end point) than no placement of a filter.

20.2.3 Studies and Registries

20.2.3.1 Updated Trends in Inferior Vena Cava Filter Use in the United States

Using the Nationwide Inpatient Sample (NIS), Olanipekun et al. [12] analyzed IVCF placements from 2010 to 2019 stratified by indications to evaluate the impact of the FDA guidelines on the temporal trends in IVCF utilization for VTE treatment. A total of 823,717 IVCFs were placed over the study period, of which 644,663 (78.3%) were for VTE treatment and 179,054 (21.7%) were for prophylaxis indications. The median age for both categories of patients was 68 years. The total number of IVCFs placed for all indications decreased from 129,616 in 2010 to 58,465 in 2019, with an aggregate decline rate of −8.4%. The decline rate was higher between 2014 and 2019 than between 2010 and 2014 (−11.6% vs −7.2%). From 2010 to 2019, IVCF placement for VTE treatment and prophylaxis trended downward at rates of −7.9% and −10.2%, respectively. Inferior vena cava filters (IVCF) are associated with medical complications. The 2010 and 2014 FDA safety warnings appeared to have synergistically contributed to a significant decline in IVCF utilization rates from 2010–2019 in the US. IVC filter placements in patients without venous thromboembolism (VTE) declined at a higher rate than VTE.

20.2.3.2 IVC Filters in Severely Injured Patients

To analyze state and nationwide temporal trends in VCF placement and PE occurrence from 2003 to 2015, a retrospective trauma cohort study was conducted by Cook et al. [13]. Data from the Pennsylvania Trauma Outcome Study (PTOS), the National Trauma Data Bank (NTDB), and the National (Nationwide) Inpatient Sample (NIS) databases were used. Of patients receiving a filter (11,405 in the PTOS, 71029 in the NTDB, and 189,957 in the NIS), most were prophylactic VCFs (93.6% in the PTOS, 93.5% in the NTDB, and 93.3% in the NIS). Unadjusted and adjusted temporal trends for the PTOS and NTDB showed initial increases in filter placement followed by significant declines (unadjusted reductions in VCF placement rates, 76.8% in the PTOS and 53.3% in the NTDB). The NIS demonstrated a similar unadjusted trend, with a slight increase and modest decline (22.2%) in VCF placement rates over time; however, adjusted trends showed a slight but significant increase in filter rates. Adjusted PE rates for the PTOS and NTDB showed significant initial increases followed by slight decreases, with limited variation during the declining filter use periods. The NIS showed an initial increase in PE rates followed by a period of stagnation. Despite a precipitous decline of VCF use in trauma, PE rates remained unchanged during this period. Taking this association into consideration, VCFs may have limited utility in influencing rates of PE.

Gilligan et al. [14] performed a retrospective study using data from the National Trauma Data Bank (2005–2014). In total, 65,482 VCFs were placed by 448 centers.

Twenty centers (4.3%) placed no VCFs. The greatest predictors of VCF placement were deep vein thrombosis, spinal cord paralysis, and major procedure. The strongest negative predictor of VCF placement was admission during the year 2014. PE occurred in 7.5% of patients with a VCF and in 0.4% of patients who did not receive a VCF. Substantial variation in practice in VCF placement was seen.

Sabharwal et al. [15] determined the prevalence and variation of inferior vena cava filter (IVCF) use in the spine trauma population and evaluated patient and facility level factors associated with their use. Of the 120,920 patients identified with spinal injuries, 2.4% received prophylactic IVCF. Of the 13,273 patients with operatively treated spinal injuries, 8.2% received prophylactic IVCF. Of the 7770 patients with spinal cord injury (SCI), 10.8% received prophylactic IVCF. The interquartile ranges of placement rates among centers demonstrated greater than ten-fold variation. Based on multivariate logistic regression, ISS score > 12 demonstrated the strongest association with prophylactic IVCF (adjusted OR = 4.908). Even in the subpopulations perceived to be at highest risk for VTE (operatively treated spinal injuries, SCI), prophylactic IVCF use is relatively uncommon (8.2% and 10.8% respectively) but wide variation in their use was observed among centers.

20.2.3.3 IVC Filter Placement in Patients with Catheter-Based Thrombolysis

Akhtar et al. [16] investigated the contemporary trends and comparative effectiveness of adjunctive inferior vena cava filter (IVCF) placement in patients undergoing catheter-directed thrombolysis (CDT) for treatment of proximal lower extremity or caval deep vein thrombosis. The National Inpatient Sample database was used. Of the 7119 patients treated with CDT, 2421 (34%) received IVCFs. There was no significant difference in in-hospital mortality (0.7% vs 1.0%; p = 0.20), procedure-related hemorrhage (1.4% vs. 1.0%; p = 0.23), or intracranial hemorrhage (0.7% vs. 0.6%; p = 0.70) between the IVCF (n = 2259) and no-IVCF (n = 2259) groups, respectively. This nationwide observational study suggests that one-third of all patients undergoing CDT receive IVCFs. IVCF use was not associated with a decrease in in-hospital mortality but was associated with higher inpatient charges and longer length of stay (Table 20.1).

20.2.3.4 Stenting across Inferior Vena Cava Filters

A subset of patients presenting with acute or chronic iliocaval obstruction will have an indwelling inferior vena cava (IVC) filter in place. Endovascular techniques have been described for removing IVC filters before stenting. However, removal failures can result in catastrophic complications. Stenting across indwelling IVC filters has been proposed as an alternative to complex removal. The purpose of a study

Table 20.1 Outcome of patients undergoing catheter-directed thrombolysis with or without inferior vena cava filter placement. Propensity score matched comparison (according to [16])

Parameter	No IVC filter (n = 2259)	IVC filter (n = 2259)	P
Death, n (%)	23 (1.0)	15 (0.7)	0.20
Blood transfusion, n (%)	237 (10.5)	255 (11.3)	0.37
Gastrointestinal bleeding, n (%)	44 (1.9)	32 (1.4)	0.17
Intracranial haemorrhage, n (%)	13 (0.6)	15 (0.7)	0.70
Haematoma, n (%)	47 (2.1)	76 (3.4)	0.009
Procedure-related haemorrhage, n (%)	23 (1.0)	32 (1.4)	0.23
Charges, US $	92,881 ± 80,194	104,049 ± 75,572	< 0.001
Peripheral angioplasty, n (%)	1329 (58.8)	1394 (61.7)	0.048
Peripheral stent, n (%)	634 (28.1)	673 (29.8)	0.20
Procedure-related renal failure, n (%)	8 (0.4)	4 (0.2)	0.25
Acute renal failure, n (%)	188 (8.3)	195 (8.6)	0.71
Transient ischemic attack, n (%)	2 (0.1)	1 (0.04)	0.57
Embolic stroke, n (%)	2 (0.1)	2 (0.1)	0.99
Procedure-related cardiac complications, n (%)	5 (0.2)	5 (0.2)	0.98

presented by Cherfan et al. [17] was to evaluate whether stenting across an indwelling IVC filter is a safe and effective alternative to removal. A total of 224 consecutive patients were identified, of whom 71 were found to have undergone iliocaval stenting (age, 48 ± 18 years; 47.9% male). Of the 71 patients, 15 had had stents placed across an indwelling IVC filter (overstented group) and 56 had not had an IVC filter present (non-overstented group). For 71 patients who had undergone iliocaval stenting, the primary patency at 30 months was 85.6% for the group with stenting across an inferior vena cava (IVC) filter and 86.1% for the non-overstented group (P = .78). No adverse events were related to IVC filter crushing, and no differences were found in survival at 30 months of follow-up. Stenting across IVC filters can be a safe and durable alternative to complex removal of chronic and/or older generation permanent IVC filters. However, it should not yet be recommended as the reference standard approach owing to the lack of long-term data. The establishment of a registry in addition to multicenter retrospective studies would be crucial to determining the comparative effectiveness and long-term outcomes of this technique.

20.2.3.5 Prophylactic IVC Filter Prior to Bariatric Surgery

Reddy et al. [18] used the National Inpatient Sample database to identify obese patients who underwent bariatric surgery from January 2005 to September 2015. Using propensity score matching, outcomes associated with patients receiving prophylactic IVCFs prior to their bariatric surgery were compared with those among patients who did not receive IVCFs. A total of 258,480 patients underwent bariatric

surgery, of whom 1047 (0.41%) had prophylactic IVCFs implanted. Patients with prophylactic IVCFs compared with those without IVCFs had a significantly higher rate of the combined endpoint of in-hospital mortality or pulmonary embolism (1.4% vs. 0.4%; $p = 0.019$). Additionally, prophylactic IVCFs were associated with higher rates of lower extremity or caval deep vein thrombosis (1.8% vs. 0.3%; $p < 0.01$), length of stay (median 3 days vs. 2 days; $p < 0.01$), and hospital charges (median $63,000 vs. $37,000; $p < 0.01$). Prophylactic IVCF implantation prior to bariatric surgery was associated with worse clinical outcomes and increased health care resource utilization.

20.2.3.6 Filter Retrieval and Temporary IVC Filters

Retrieval of vena cava filters is important for safety as complications increase with longer dwell times. Mohapatra et al. [19] reviewed Florida state inpatient and ambulatory surgery databases from 2004 to 2014 and searched for patients undergoing inpatient or outpatient IVC filter placement. Each patient was longitudinally tracked to the time of inpatient or outpatient filter retrieval. During the period, 131,791 IVC filter placements were identified, with a 50% increase from 2004 to 2010 and a 24% decline from 2010 to 2014. Mean follow-up after filter placement was 17.3 ± 25.5 months. Only 8637 filters (6.6%) were retrieved. The annual retrieval rate trended upward, from 3.4% in 2004 to 8.5% in 2013 ($P < .001$). Retrieval rates were highest in younger patients (34.0% in patients younger than 20 years) and lowest in Medicare patients (2.5%). Filter retrieval rates were overall significantly lower than the 30–60% retrieval rates reported in single center studies. The estimated retrieval rate of 6.6% lag rates described in the literature and points to publication bias in single-center studies. Significant improvements are needed on a national scale to continue to reduce the number of IVC filters that are placed and to enhance filter retrieval rates in patients who no longer have an appropriate indication for an indwelling IVC filter.

Brown et al. [20] examined retrieval rates for vena cava filters (VCFs) in a national cohort. Of 54,766 patients receiving a VCF, 36.9% had pulmonary embolism, 43.9% had deep vein thrombosis only, and 19.2% had no apparent venous thromboembolism present. Over the 1 year of follow-up, the cumulative incidence of VCF retrieval was 18.4%. Retrieval increased over time from a low of 14.0% in 2010 up to ≈24% in 2014. Initiation of anticoagulation was poorly correlated with retrieval, with anticoagulation preceding retrieval by a median of 51 days while those without retrieval had a median of 278 days of exposure to anticoagulation. Despite safety warnings for indwelling VCFs, most remained in place and were poorly correlated with initiation of anticoagulation. Retrieval rates were strongly dependent on age, with older patients less likely to have retrieval. The US Food and Drug Administration has suggested that VCFs be removed once clinically appropriate to avoid complications. These warnings were in response to many reports of VCF failures including device fractures and penetration of the vena cava that were associated with indwell time. In order to maximize the net clinical benefit of VCFs, patients should be initiated on anticoagulation once contraindications have abated and VCFs should be removed.

Medicare patients aged ≥65 years with index VTE claims between 2015 and 2018 were followed by Williams et al. [21] through 2019 to identify IVCF placements and retrievals. Of 516,978 patients with VTE diagnoses, 5864 (1.1%) had IVCFs placed, and 1884 (32.1%) of those underwent retrieval procedures. Of those with IVCFs placed, the median time to IVCF placement from the index VTE diagnosis was 24 days (IQR, 1–192 days), whereas the median time to IVCF retrieval from placement was 103 days (IQR, 58–170 days) among those with IVCFs retrieved. Placement and retrieval rates varied significantly by demographics, comorbidity burden, and geographic region. In this large real-world cohort of Medicare beneficiaries with index VTE diagnoses, approximately 1 in 91 patients with VTE (1.1%) underwent IVCF placement, and of those, approximately 1 in 3 (32.1%) underwent retrieval procedures. The results indicate inequality in the placement and retrieval of IVCFs in Medicare patients with VTE.

20.2.3.7 Inferior Vena Cava Filter Thrombosis

Using data from the Society for Vascular Surgery Vascular Quality Initiative (VQI) from 2013 to 2019, King et al. [22] aimed to describe the contemporary rate of IVC thrombosis after IVCF placement and its associated risk factors. Of 5780 cases with 2 years of follow-up available, 78 (1.3%) had developed IVCF thrombosis. Five independent factors were associated with IVCF thrombosis: new/propagated deep vein thrombosis at follow-up, internal jugular venous access, venous thromboembolism on admission, a temporary IVCF placed, and the lack of antiplatelet therapy at follow-up. In a subgroup analysis of those who had received an IVCF for VTE, similar factors were predictive of IVCF thrombosis, including a lack of follow-up antiplatelet therapy (hazard ratio, 4.4; P = .002). The rate of IVCF thrombosis remained low in a contemporary database. The results from the present study suggest that antiplatelet therapy should be administered after IVCF placement to decrease the risk of IVCF thrombosis.

20.2.3.8 Effect of Filter Placement Position

A single center study examined the relationship between the position of the IVC filter in the vena cava and the short- and long-term complications [23]. The hypothesis was that IVC filters placed more caudally to the lowest renal vein would have a greater risk of IVC thrombosis. The final cohort consisted of 1230 patients. Most filters were placed immediately (<20 mm) inferior to the caudal renal vein (group B, n = 787; 64.0%), followed by >20 mm inferior to this level (group C, n = 265; 21.5%). Placement superior the caudal renal vein was the least common placement position (group A, n = 178; 14.5%). Short-term DVT and PE occurred in 4.2% and 2.0% of all patients, respectively, and long-term DVT and PE occurred in 10.6% and 3.0%, respectively. Although a pattern of increasing thrombosis with more

inferior placement was found, the difference between groups was not statistically significant (group A, 1.5%; group B, 1.8%; group C, 2.5%; P = .638). No cases of device-related mortality occurred. All-cause mortality after a mean follow-up of 2.6 ± 2.3 years was 41.3% and did not vary significantly between the groups (P = .051). Multivariate logistic regression revealed that placement position did not predict for short- or long-term deep vein thrombosis, pulmonary embolism, IVC thrombosis, or all-cause mortality after adjustment for the baseline patient characteristics. Complications of inferior vena cava filter placement are rare and the placement position relative to the renal veins did not affect the outcomes in this study.

20.3 Conclusions for Clinical Practice

1. In the initial treatment of VTE, inferior vena cava filters may be considered when anticoagulant treatment is contraindicated or, in the case of pulmonary embolism, when recurrence occurs under optimal anticoagulation.
2. In patients with acute VTE (DVT, PE) who are being treated with therapeutic anticoagulation, routine placement of an IVC filter is not indicated.
3. IVC filters should be considered in cases of pulmonary embolism recurrence despite therapeutic anticoagulation.
4. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established. Patients should be initiated on anticoagulation once contraindications have abated and VCFs should be removed.

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Chapter 21
Venous Leg Ulcers



21.1 Guidelines

21.1.1 Society for Vascular Surgery and the American Venous Forum

The clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum recommend for the management of venous leg ulcers among others [1]:

- We suggest use of a standard definition of venous ulcer as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension. (Best practice)
- We recommend that for all patients with suspected leg ulcers fitting the definition of venous leg ulcer, clinical evaluation for evidence of chronic venous disease be performed. (Best practice)
- We recommend identification of medical conditions that affect ulcer healing and other non-venous causes of ulcers. (Best practice)
- We suggest against routine culture of venous leg ulcers and only to obtain wound culture specimens when clinical evidence of infection is present. (Grade 2 recommendation; Level of evidence C)
- We recommend wound biopsy for leg ulcers that do not improve with standard wound and compression therapy after 4–6 weeks of treatment and for all ulcers with atypical features. (Grade 1 recommendation; Level of evidence C)
- We suggest laboratory evaluation for thrombophilia for patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers. (Grade 2 recommendation; Level of evidence C)

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- We recommend arterial pulse examination and measurement of ankle-brachial index on all patients with venous leg ulcer. (Grade 1 recommendation; Level of evidence B)
- We recommend comprehensive venous duplex ultrasound examination of the lower extremity in all patients with suspected venous leg ulcer. (Grade 1 recommendation; Level of evidence B)
- We suggest selective computed tomography venography, magnetic resonance venography, contrast venography, and/or intravascular ultrasound in patients with suspected venous leg ulceration if additional advanced venous diagnosis is required for thrombotic or nonthrombotic iliac vein obstruction or for operative planning before open or endovenous interventions. (Grade 2 recommendation; Level of evidence C)
- We recommend that all patients with venous leg ulcer be classified on the basis of venous disease classification assessment, including clinical CEAP, revised Venous Clinical Severity Score, and venous disease-specific quality of life assessment. (Best practice)

21.1.1.1 Wound Care

- We suggest that venous leg ulcers be cleansed initially and at each dressing change with a neutral, nonirritating, nontoxic solution, performed with a minimum of chemical or mechanical trauma. (Grade 2 recommendation; Level of evidence C)
- We recommend that venous leg ulcers receive thorough débridement at their initial evaluation to remove obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells. (Grade 1 recommendation; Level of evidence B). We suggest that additional maintenance débridement be performed to maintain the appearance and readiness of the wound bed for healing. (Grade 2 recommendation; Level of evidence B)
- We recommend that local anaesthesia (topical or local injection) be administered to minimize discomfort associated with surgical venous leg ulcer débridement. In selected cases, regional block or general anesthesia may be required. (Grade 1 recommendation; Level of evidence B)
- We recommend that surgical débridement be performed for venous leg ulcers with slough, nonviable tissue, or eschar. Serial wound assessment is important in determining the need for repeated débridement. (Grade 1 recommendation; Level of evidence B)
- We suggest hydrosurgical débridement as an alternative to standard surgical débridement of venous leg ulcers. (Grade 2 recommendation; Level of evidence B)
- We suggest ***against*** ultrasonic débridement over surgical débridement in the treatment of venous leg ulcers. (Grade 2 recommendation; Level of evidence C)
- We suggest enzymatic débridement of venous leg ulcers when no clinician trained in surgical débridement is available to débride the wound. (Grade 2 recommendation; Level of evidence C)

- We do not suggest enzymatic débridement over surgical débridement. (Grade 2 recommendation; Level of evidence C)
- We suggest that larval therapy for venous leg ulcers can be used as an alternative to surgical débridement. (Grade 2 recommendation; Level of evidence B)

21.1.1.2 Primary Wound Dressing

- We suggest applying a topical dressing that will manage venous leg ulcer exudate and maintain a moist, warm wound bed. (Grade 2 recommendation; Level of evidence C)
- We suggest selection of a primary wound dressing that will absorb wound exudate produced by the ulcer (alginates, foams) and protect the periulcer skin. (Grade 2 recommendation; Level of evidence B)
- We recommend ***against*** the routine use of topical antimicrobial-containing dressings in the treatment of noninfected venous leg ulcers. (Grade 2 recommendation; Level of evidence A)

21.1.1.3 Split-Thickness Skin Grafting

- We suggest ***against*** split-thickness skin grafting as primary therapy in treatment of venous leg ulcers. (Grade 2 recommendation; Level of evidence B)
- We suggest split-thickness skin grafting with continued compression for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4–6 weeks. (Grade 2 recommendation; Level of evidence B)

21.1.1.4 Cellular Therapy

- We suggest the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) to increase the chances for healing in patients with difficult to heal venous leg ulcers in addition to compression therapy in patients who have failed to show signs of healing after standard therapy for 4–6 weeks. (Grade 2 recommendation; Level of evidence A)

21.1.1.5 Tissue Matrices, Human Tissues, or Other Skin Substitutes

- We suggest the use of a porcine small intestinal submucosa tissue construct in addition to compression therapy for the treatment of venous leg ulcers that have failed to show signs of healing after standard therapy for 4–6 weeks. (Grade 2 recommendation; Level of evidence B)

21.1.1.6 Negative Pressure Therapy

- We suggest ***against*** routine primary use of negative pressure wound therapy for venous leg ulcers. (Grade 2 recommendation; Level of evidence C)

21.1.1.7 Compression

- In a patient with a venous leg ulcer, we recommend compression therapy over no compression therapy to increase venous leg ulcer healing rate. (Grade 1 recommendation; Level of evidence A)
- In a patient with a healed venous leg ulcer, we suggest compression therapy to decrease the risk of ulcer recurrence. (Grade 2 recommendation; Level of evidence B)
- We suggest the use of multicomponent compression bandage over single-component bandages for the treatment of venous leg ulcers. (Grade 2 recommendation; Level of evidence B)
- In a patient with a venous leg ulcer and underlying arterial disease, we do not suggest compression bandages or stockings if the ankle-brachial index is 0.5 or less or if absolute ankle pressure is less than 60 mm Hg. (Grade 2 recommendation; Level of evidence C)
- We suggest use of intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy. (Grade 2 recommendation; Level of evidence C)

21.1.2 European Society for Vascular Surgery

The European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs [2] recommend:

21.1.2.1 Recommendation 67

For patients with active venous leg ulceration without infection, the use of local or systemic antibiotics to improve ulcer healing is ***not*** recommended. (Class III recommendation; Level of evidence B).

21.1.2.2 Recommendation 68

For patients with active leg ulceration, objective arterial assessment is recommended. (Class I recommendation; Level of evidence C).

21.1.2.3 Recommendation 69

For patients with active venous leg ulceration, compression therapy is recommended to improve ulcer healing (Class I recommendation; Level of evidence A).

21.1.2.4 Recommendation 70

For patients with active venous leg ulceration, multilayer or inelastic bandages or adjustable compression garments, exerting a target pressure of at least 40 mmHg at the ankle, are recommended to improve ulcer healing. (Class I recommendation; Level of evidence A).

21.1.2.5 Recommendation 71

For patients with active venous leg ulceration, superimposed elastic compression stockings exerting a target pressure up to 40 mmHg at the ankle should be considered for small and recent onset ulcers. (Class IIa recommendation; Level of evidence B).

21.1.2.6 Recommendation 72

For patients with active venous leg ulceration, with ankle pressure less than 60 mmHg, toe pressure less than 30 mmHg, or ankle brachial index lower than 0.6, sustained compression therapy is ***not*** recommended. (Class III recommendation; Level of evidence C).

21.1.2.7 Recommendation 73

For patients with active venous leg ulceration, intermittent pneumatic compression should be considered when other compression options are not available, cannot be used, or have failed to promote ulcer healing. (Class IIa recommendation; Level of evidence B).

21.1.2.8 Recommendation 74

For patients with a mixed ulcer caused by coexisting arterial and venous disease, modified compression therapy under close clinical supervision, with a compression pressure less than 40 mmHg may be considered, provided the ankle pressure is higher than 60 mmHg. (Class IIb recommendation; Level of evidence C).

21.1.2.9 Recommendation 75

For patients with healed venous leg ulceration, long term compression therapy should be considered to reduce the risk of ulcer recurrence. (Class IIa recommendation; Level of evidence B).

21.1.2.10 Recommendation 76

For patients with active venous leg ulceration and superficial venous incompetence, early endovenous ablation is recommended to accelerate ulcer healing. (Class I recommendation; Level of evidence B).

21.1.2.11 Recommendation 77

For patients with superficial venous incompetence and healed venous leg ulceration, treatment of the incompetent veins is recommended to reduce the risk of ulcer recurrence. (Class I recommendation; Level of evidence A).

21.1.2.12 Recommendation 78

For patients with active venous leg ulceration, ablation of the sub-ulcer venous plexus using ultrasound guided foam sclerotherapy should be considered as part of the treatment strategy. (Class IIa recommendation; Level of evidence C).

21.1.2.13 Recommendation 79

For patients with superficial venous incompetence and active or healed venous leg ulceration, treatment of incompetent superficial veins is recommended, even in the presence of deep venous incompetence. (Class I recommendation; Level of evidence A).

21.1.2.14 Recommendation 80

For patients with active venous leg ulceration as a result of superficial venous incompetence and perforating vein incompetence close to the ulcer, concomitant treatment of both truncal reflux and incompetent perforators may be considered. (Class IIb recommendation; Level of evidence C).

21.1.2.15 Recommendation 81

For patients with active or healed venous leg ulceration and iliac vein outflow obstruction, venous stenting should be considered. (Class IIa recommendation; Level of evidence B).

21.1.2.16 Recommendation 82

For patients with active venous leg ulceration, micronized purified flavonoid fraction, hydroxyethylrutosides, pentoxifylline, or sulodexide should be considered, as an adjunct to compression and local wound care to improve ulcer healing. (Class IIa recommendation; Level of evidence A).

21.2 Results

21.2.1 Randomized Studies

21.2.1.1 Early Endovenous Ablation in Venous Ulceration

Although compression therapy improves venous ulcer healing, it does not treat the underlying causes of venous hypertension. Gohel et al. [3] performed the Early Venous Reflux Ablation (EVRA) trial to evaluate the role of early endovenous treatment of superficial venous reflux as an adjunct to compression therapy in patients with venous leg ulcers. In this trial, 450 patients with venous leg ulcers were randomly assigned to receive compression therapy and undergo early endovenous ablation of superficial venous reflux within 2 weeks after randomization (early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred until after the ulcer was healed or until 6 months after randomization if the ulcer was unhealed (deferred-intervention group). The time to ulcer healing was shorter in the early-intervention group than in the deferred intervention group; more patients had healed ulcers with early

intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI],1.13 to 1.68; P = 0.001). The median time to ulcer healing was 56 days in the early-intervention group and 82 days in the deferred-intervention group. The rate of ulcer healing at 24 weeks was 85.6% in the early-intervention group and 76.3% in the deferred-intervention group. The median ulcer-free time during the first year after trial enrollment was 306 days in the early-intervention group and 278 days in the deferred-intervention group (P = 0.002). Early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. Gohel et al. [4] performed an health economic evaluation of the EVRA trial and estimated costs and quality-adjusted life years (QALYs) from the perspective of the UK National Health Service and Personal Social Services over a 3-year time horizon. Early intervention accelerated the healing of venous leg ulcers and reduced the overall incidence of ulcer recurrence. At 3 years, early intervention was 91.6% likely to be cost-effective at a willingness to pay £20,000 ($26,283) per quality-adjusted life year and 90.8% likely at a threshold of £35,000 ($45,995) per quality-adjusted life year.

21.2.2 Meta-Analyses

21.2.2.1 Compression Bandages or Stockings for Treating Venous Leg Ulcers

In a Cochrane review, Shi et al. [5] assessed the effects of using compression bandages or stockings, compared with no compression, on the healing of venous leg ulcers in any setting and population. 14 studies (1391 participants) were included in the review. There is moderate-certainty evidence that there is probably a shorter time to complete healing of venous leg ulcers in people wearing compression bandages or stockings compared with those not wearing compression over a 12-month follow-up (five studies with 733 participants); and that people treated with compression bandages or stockings probably have more completely healed venous leg ulcers during follow-up to 12 months than people not using compression (10 studies with 1215 participants). Moderate-certainty evidence suggests that the use of compression bandages or stockings probably reduces pain compared with no compression (five studies with 859 participants and 69 ulcers in other participants). If using compression bandages or stockings, people with venous leg ulcers probably experience complete wound healing more quickly, and more people have wounds completely healed.

21.2.2.2 Dressings and Topical Agents for Treating Venous Leg Ulcers

Norman et al. [6] assessed the effects of dressings and topical agents for healing venous leg ulcers in any care setting. 78 RCTs (7014 participants) were included in this Cochrane review. The two most highly-ranked treatments both had more than

50% probability of being the best (sucralfate and silver dressings). However, the data for sucralfate was from one small study, which means that this finding should be interpreted with caution. When exploring the data for silver and sucralfate compared with widely-used dressing classes, there was some evidence that silver dressings may increase the probability of venous leg ulcer healing, compared with nonadherent dressings: RR 2.43, 95% CI 1.58 to 3.74 (moderate-certainty evidence in the context of a low-certainty network). For all other combinations it was unclear whether the intervention increased the probability of healing.

The effects of hydrogel wound dressings on the healing of venous leg ulcers in any care setting were assessed by Ribeiro et al. [7] in a Cochrane review. Four RCTs (10 articles) were included in a qualitative analysis. Overall, 272 participants were randomized, in sample sizes ranging from 20 to 156 participants. No studies provided evidence for the outcomes: recurrence of ulcer, health-related quality of life, pain and costs. There is inconclusive evidence to determine the effectiveness of hydrogel dressings compared with gauze and saline, alginate dressing, manuka honey or hydrocolloid on venous leg ulcer healing. Practitioners may, therefore, consider other characteristics such as costs and symptom management when choosing between dressings.

21.2.2.3 Growth Factors for Treating Chronic Venous Leg Ulcers

Lee et al. [8] evaluated the impact of growth factor treatments of venous leg ulcers in comparison to control for complete wound healing, percent reduction in wound area, time to wound healing, and adverse events. Of 13 studies with a total of 991 patients randomized to either a growth factor group or a control group, 960 patients were included in the final analysis of this review and meta-analysis. There was a significant difference between any growth factor and placebo in complete wound healing (P = 0.04). Any growth factor compared to placebo significantly increased the likelihood of percent wound reduction by 48.80% (P = <0.00001). There was no difference in overall adverse event rates. This meta-analysis suggested that growth factors have a beneficial effect in complete wound healing of venous leg ulcers. Growth factors may also increase percent reduction in wound area. The suggestion of benefit for growth factors identified in this review was of low quality of evidence. Publication bias was strongly suspected, and trials generally had small sample sizes, with only three trials randomizing 100 patients or more.

The weak evidence regarding the benefit of growth factors for treatment of venous leg ulcers is confirmed by Carvalho et al. [9]. They included 802 patients from 10 studies in a meta-analysis, 472 in the intervention group (application of growth factors) and 330 as control. The relative risk for the complete healing outcome was 1.06 [95% CI 0.92–1.22], p = 0.41. Participants who received Platelet-Rich Plasma and Epidermal Growth Factor showed a slight tendency to achieve complete healing, but without statistical relevance. Most of the studies were classified as moderate risk of bias.

21.2.2.4 Wound Cleansing for Treating Venous Leg Ulcers

McLain et al. [10] assessed the effects of wound cleansing, wound cleansing solutions and wound cleansing techniques for treating venous leg ulcers. Four studies with a total of 254 participants were included in this Cochrane review. All studies included comparisons between different types of cleansing solutions, and three of these reported complete wound healing or change in ulcer size over time, or both. Studies that compared cleansing with no cleansing were not identified. From the four studies identified, there is insufficient evidence to demonstrate whether the use of polyhexamethylene biguanide (PHMB) solution compared with saline solution; aqueous oxygen peroxide compared with sterile water; propyl betaine and polihexanide compared with a saline solution; or octenidine dihydrochloride/phenoxyethanol (OHP) compared with Ringer's solution makes any difference in the treatment of venous leg ulcers. Evidence from three of the studies is of very low certainty, due to study limitations and imprecision. One study did not present data for the primary or secondary outcomes. Further well-designed studies that address important clinical, quality of life and economic outcomes may be important, based on the clinical and patient priority of this uncertainty.

21.2.2.5 Medication

The clinical efficacy of sulodexide in patients with chronic venous disease was analyzed by Pompilio et al. [11] in a systematic review with meta-analysis. Randomized trials were not available. However, the network meta-analysis suggested that sulodexide has the highest probability (48%) of being the most effective adjuvant treatment in increasing the healing rate of venous ulcers followed by pentoxifylline (37%) and MPFF (16%). Sulodexide was at least as effective as pentoxifylline and more effective than micronized purified flavonoid fraction (MPFF) in improving the rate of ulcer healing in patients with chronic venous disease. The authors therefore recommended sulodexide as adjuvant therapy for chronic venous ulcers, with the caveat that the evidence is limited.

Phlebotonics represent a heterogeneous group of medications used to treat chronic venous insufficiency (CVI). Most of these drugs are natural flavonoids extracted from plants. Synthetic products with flavonoid-like properties are also used to treat venous disorders. In the Anatomical Therapeutic Chemical (ATC) system, phlebotonics are classified as vasoprotective agents. A Cochrane review [12] assessed the efficacy and safety of phlebotonics administered orally or topically for treatment of signs and symptoms of lower extremity CVI. In total, 69 RCTs of oral phlebotonics were included, but only 56 studies (7690 participants, mean age 50 years) provided quantifiable data for the efficacy analysis. These studies used different phlebotonics (28 on rutosides, 11 on hidrosmine and diosmine, 10 on calcium dobesilate, two on Centella asiatica, two on aminaftone, two on French maritime pine bark extract and one on grape seed extract). No studies evaluating topical phlebotonics, chromocarbe, naftazone or disodium flavodate fulfilled the inclusion

criteria. Moderate-certainty evidence suggested that phlebotonics probably reduce oedema slightly in the lower legs, compared with placebo; and probably reduce ankle circumference. Moderate-certainty evidence showed that phlebotonics probably make little or no difference in QoL compared with placebo; and similarly, may have little or no effect on ulcer healing. Thirty-seven studies reported on adverse events. Pooled data suggested that phlebotonics probably increase adverse events slightly, compared to placebo. Gastrointestinal disorders were the most frequently reported adverse events.

21.3 Conclusions for Clinical Practice

1. Arterial pulse examination and measurement of ankle-brachial index on all patients with venous leg ulcer is recommended.
2. For patients with active venous leg ulceration, multilayer or inelastic bandages or adjustable compression garments, exerting a target pressure of at least 40 mmHg at the ankle, are recommended to improve ulcer healing.
3. For patients with healed venous leg ulceration, long term compression therapy should be considered to reduce the risk of ulcer recurrence.
4. For local wound care, selection of a primary wound dressing that will absorb wound exudate produced by the ulcer (alginates, foams) and protect the periulcer skin is recommended.
5. For patients with active venous leg ulceration and superficial venous incompetence, early endovenous ablation is recommended to accelerate ulcer healing.
6. For patients with active or healed venous leg ulceration and iliac vein outflow obstruction, venous stenting should be considered.
7. For patients with active venous leg ulceration, micronized purified flavonoid fraction, hydroxyethylrutosides, pentoxifylline, or sulodexide should be considered, as an adjunct to compression and local wound care to improve ulcer healing.

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