SECTION 49

Peripheral arterial diseases

This section is supplementary data to the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, developed in collaboration with the European Society for Vascular Surgery (ESVS).

The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS)

Authors/Task Force Members: Victor Aboyans (ESC Chairperson) (France), Jean-Baptiste Ricco (ESVS Co-Chairperson) (France), Marie-Louise EL Bartelink (The Netherlands), Martin Björck (Sweden), Marianne Brodmann (Austria), Tina Cohnert (Austria), Jean-Philippe Collet (France), Martin Czerny (Germany), Marco De Carlo (Italy), Sebastian Debus (Germany), Christine Espinola-Klein (Germany), Thomas Kahan (Sweden), Serge Kownator (France), Lucia Mazzolai (Switzerland), A. Ross Naylor (UK), Marco Roffi (Switzerland), Joachim Röther (Germany), Muriel Sprynger (Belgium), Michal Tendera (Poland), Gunnar Tepe (Germany), Maarit Venermo (Finland), Charalambos Vlachopoulos (Greece), Ileana Desormais (France)

Contents

Chapter 49.1 Introduction

In 2011, the European Society of Cardiology (ESC) published its first 'Guidelines on the Diagnosis and Management of Peripheral Arterial Diseases'.[1] This publication filled an important gap within the ESC Guidelines documents compendium. Meanwhile, the European Society for Vascular Surgery (ESVS) released on a regular basis several guidelines documents on the management of specific localizations of arterial diseases.

Both societies emphasized the need for a multidisciplinary management of these patients. When the decision was made to update these guidelines, it appeared obvious that the combination of efforts from both societies would provide the most comprehensive single document, providing updated guidelines on peripheral arterial diseases (PADs) for clinicians.

It is of the outmost importance that every cardiologist should be sensitive in regard to the diagnosis and management of patients with PADs, as many of them are seen and managed for concomitant cardiac conditions. In the 2011 ESC Guidelines, a specific chapter was dedicated to patients with combined coronary and peripheral artery diseases, as they mostly share the same aetiology and risk factors. In these guidelines, the Task Force made a step forward and proposed a new chapter on other cardiac conditions frequently encountered among patients with PADs. Also, as the options for use and combination of antithrombotic drugs have increased, a specific chapter has been dedicated for their use in the management of PADs.

In the following chapters in Section 49, the term 'peripheral arterial diseases' encompasses *all* arterial diseases other than coronary arteries and the aorta. This should be clearly distinguished from the term 'peripheral artery disease' often used to name lower extremity artery disease (LEAD). Indeed, other *peripheral* localizations, including the carotid and vertebral, upper extremities, mesenteric and renal arteries are also frequently affected, mainly by atherosclerosis, and complete the family of PADs. Regarding carotid and vertebral arteries, the following chapters in Section 49 cover only their extracranial segments, as specialists other than cardiologists and vascular surgeons often manage intracranial arterial diseases.

The Task Force has decided to address only PADs secondary to atherosclerosis, with a few exceptions in specific areas where non-atherosclerotic diseases are a frequent differential diagnosis (e.g. fibromuscular dysplasia in renal arteries). For other cases, the readers should always bear in mind the possibility of non-atherosclerotic conditions, and refer to specific documents. The readers are also invited to refer to the web addenda in the ESC Guidelines[1] for further information.

Table 49.1.1 General recommendations on the management of patients with peripheral arterial diseases

Recommendations	Class[a]	Level[b]
In healthcare centres, it is recommended to set up a multidisciplinary vascular team to make decisions for the management of patients with PADs	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases	I	C

PADs, peripheral arterial diseases.
[a] Class of recommendation.
[b] Level of evidence.

The ESC and the ESVS also join their determinations to provide increased medical and public awareness about PADs. Indeed, while stroke is acknowledged as a serious condition with significant burden throughout Europe, other PADs can also be as lethal and disabling. Major efforts are still necessary to sensitize healthcare providers, decision makers, and the general population about the need for earlier and more efficient prevention and management strategies for the 40 million individuals in our continent affected by PADs.[1, 2]

See Table 49.1.1 for general recommendations on the management of patients with PADs.

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Chapter 49.2 Epidemiology and risk factors

Key messages

- Overall, the risk of different localizations of peripheral arterial diseases (PADs) increases sharply with age and with exposure to major cardiovascular risk factors: smoking, hypertension, dyslipidaemia, and diabetes. Other risk factors are still under investigation.
- The strength of association between each risk factor and each vascular territory is variable, but all the major risk factors should be screened and considered.
- When a vascular territory is affected by atherosclerosis, not only is the corresponding organ endangered (e.g. the brain for carotid artery disease) but also the total risk of any cardiovascular event is increased (e.g. coronary events). Each vascular territory affected by atherosclerosis can be considered as a marker of cardiovascular risk.

Epidemiology

Carotid artery disease

In a meta-analysis,[1] the pooled prevalence of moderate to severe (≥ 50%) carotid artery stenoses was 4.2%. In men younger than 70 years, this prevalence was 4.8% versus 2.2% in females. In patients older than 70 years, the prevalence was as high as 12.5% in males and 6.9% in females. In another study including over 3.6 million participants in the United States (36% male, mean age 64 years), moderate to severe carotid stenosis was detected in 3.9%.[2] Lower extremity artery disease (LEAD) was associated with greater odds of carotid stenosis, which was present in 19% and 3% of subjects with and without LEAD, respectively.

Upper extremity arterial disease

Atherosclerosis affects infrequently the upper limb arteries, except for the subclavian arteries. The epidemiology of subclavian stenosis is mostly based on inter-arm systolic blood pressure difference exceeding 10 or 15 mmHg, but this definition is poorly sensitive (50%) although highly specific (90%) when compared to angiography.[3] Based on these definitions, the prevalence of subclavian stenosis is estimated to be around 2% in the general population but increases to 9% in the case of concomitant LEAD.[4]

Mesenteric artery disease

Chronic symptomatic mesenteric artery disease is rare in clinical practice, although often undiagnosed. It accounts for only 5% of all intestinal ischaemic events. The prevalence of asymptomatic mesenteric artery disease is poorly studied. Among 553 participants older than 65 years in the Cardiovascular Health Study, 15% had severe stenosis of the coeliac trunk detected by duplex ultrasound, while only 0.9% had severe stenosis of the superior mesenteric artery and 1.3% had stenosis at both sites.[5] Not all these lesions are related to atherosclerosis. In patients with atherosclerotic disease at other sites, mesenteric artery disease may be relatively common. In patients undergoing routine cardiac catheterization, the prevalence of mesenteric artery disease was 14%, including 11% for coeliac trunk and 3% for superior mesenteric artery,[6] while in patients with LEAD, 27% had 50% or higher stenosis in one of the mesenteric arteries.[7]

Renal artery disease

In the Cardiovascular Health Study, duplex ultrasound detected renal artery stenosis of at least 60% in 9.1% of men and 5.5% of women.[8] Among 450 patients receiving cardiac catheterization for suspected coronary artery disease, the prevalence of renal artery disease was 7.7%, higher in those with versus those without coronary artery disease (9.9% vs 4.1%), and more frequent with increasing numbers of affected coronary arteries.[6]

Lower extremity artery disease

Approximately 202 million people are affected with LEAD worldwide, of whom almost 40 million are living in Europe.[9] LEAD usually appears after the age of 50 years, with an exponential increase after the age of 65. This rate reaches around 20% by the age of 80. In high-income countries, LEAD, especially when symptomatic, is overall more frequent in men, although the difference is mitigated in the elderly. In low- and middle-income countries, the prevalence is overall higher in women than in men.[9] In an unselected cohort of 6880 individuals aged over 65 years followed in primary care in Germany, the prevalence of LEAD, defined by an ankle–brachial index of less than 0.90, was 18%, with only one out of ten with typical intermittent claudication.[10] However, in most studies, the proportion of symptomatic LEAD is 1:3 to 1:5 of all LEAD patients. Among Danish males aged 65–74 years, the prevalence of LEAD was 10%, of whom one-third had symptoms of intermittent claudication.[11] Similarly, in a Swedish population aged 60–90 years, the prevalence of LEAD was 18%, and that of intermittent claudication was 7%.[12] The prevalence of chronic limb-threatening ischaemia is low, at 0.4%, with an estimated annual incidence ranging from 500 to 1000 new cases per million, higher in diabetic patients. The annual incidence of major amputation ranges between 120 and 500 per million, equally distributed above and below the knee.[13] The total number of individuals with LEAD is booming, with a 23% increase in the last decade as a result of total population increase, global ageing, increased incidence of diabetes worldwide, or smoking in low- and middle-income countries.[9] Data on the incidence of LEAD in Europe are scarce: at the age of 60, annual incidence rates of intermittent claudication in men have varied from 0.2% in Iceland to 1% in Israel.[14] In the Netherlands, after a 7.2-year follow-up, the overall incidence for asymptomatic LEAD was 9.9 per 1000 person-years at risk with 7.8 for men and 12.4 for women. For symptomatic LEAD, the incidence was 1.0 overall, 0.4 for men, and 1.8 for women.[15] The global burden of LEAD is considerable. In 2010, the years of life lost due to LEAD were estimated at 31.7, 15.1, and 3.7 years per 100,000 inhabitants in Western, Central, and Eastern Europe, respectively.[16] The mortality related to LEAD increased between 1990 and 2010 in Europe, reaching 3.5 per 100,000 individuals in 2010 in Western Europe. These figures are related to mortality directly related to LEAD, while these patients mostly die from complications related to coronary artery disease and stroke.

Risk factors

Though different localizations of PADs share common major risk factors for atherosclerosis, the impact of those and/or available evidence differ per arterial site.

Smoking

Smoking is associated with PADs, and the risk increases with smoking intensity. Data on the association between smoking and carotid artery disease are limited, with a weak but still significant association. Smoking was independently associated with carotid artery disease in a population-derived cohort of men older than 65 years (odds ratio (OR) 1.70).[17] In that study, 5% of current smokers had significant (>50%) carotid stenosis. In a pooled analysis of four population studies, current smoking was an independent predictor of greater than 50% (OR 2.3) and greater than 70% (OR 3) carotid stenosis.[18] Exposure to parental smoking in childhood has been associated with an increased risk of carotid artery disease in adulthood.[19] Smoking is also associated with carotid plaque progression,[20] and carotid endarterectomy is proposed to be required on average 7 years earlier in smokers.[21] Both past and current smoking have been associated with prevalent subclavian stenosis.[4] Smoking is also associated with an increased risk of renal artery disease, both in cases of atherosclerotic disease and fibromuscular dysplasia.[22, 23] Smoking is a particularly strong risk factor for LEAD[14] with a population attributable fraction estimated at 44%.[24] The association between LEAD and smoking persists after smoking cessation, although it is considerably diminished beyond 10 years of cessation.[24]

Hypertension

Hypertension is associated with an increased risk for carotid artery disease in men and women.[25–27] For upper extremity artery disease (UEAD), significant associations were found with both increasing age and systolic blood pressure.[4] Renal artery disease is associated with pre-existing high blood pressure.[28] Hypertension is associated with an increased prevalence of LEAD with ORs in large epidemiological studies ranging from 1.32 to 2.20.[14, 29] Although the relative risks associated with hypertension are modest in some studies, its high prevalence, particularly among older patients, makes it a significant contributor to the total burden of LEAD in the population. In the presence of hypertension in men aged 40–79 years, the hazard ratio for incident LEAD was 2.42.[24] In an analysis of 4.2 million people and 44,329 incident LEAD events, a 20 mmHg increase of systolic blood pressure was associated with 63% higher risk for LEAD.[30] In a prospective population-based study of 92,728 individuals, hypertension was the strongest predictor of incidence and outcome of all acute PADs including acute mesenteric ischaemia, acute limb ischaemia and chronic limb-threatening ischaemia.[31]

Dyslipidaemia

Several population-based studies have found that high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk for symptomatic and asymptomatic carotid artery disease, irrespective of age.[23–27] A high prevalence of hypercholesterolaemia is a significant contributor to LEAD. In most studies, total cholesterol is associated with prevalent LEAD in multivariable analyses.[14, 32–34] In a prospective study including 51,529 men aged 40–79 over two decades, hypercholesterolaemia demonstrated strong, graded,

and independent associations with incident clinical LEAD.[24] HDL-C has been shown to be protective in all large epidemiological studies. In a comparison of incident cases of LEAD with healthy controls, the ratio of total cholesterol/HDL-C was most strongly associated with the disease.[35] Although triglycerides seem to be associated with LEAD in univariate analyses, they frequently drop out as an independent risk factor in multivariate analyses.[14, 36] Lipoprotein (a) is associated with the presence and progression of LEAD.[37, 38]

Diabetes

Diabetes is associated with an increased risk of carotid artery disease.[18] In contrast, neither the progression of carotid plaque burden nor plaque instability has been found to be specifically associated with diabetes.[20, 39] Diabetes is strongly associated with LEAD, with ORs ranging from 1.9 to 4 in population studies.[14] This risk is increased with diabetes duration. The prognosis of LEAD in diabetic patients is poorer than in non-diabetic patients, with a fivefold increased risk of amputation, in relation to a specific pattern affecting more frequently distal arteries, frequent coexistence of neuropathy, and higher risk for infection.[40]

Other risk factors

Inflammation is involved in atherosclerosis pathophysiology. Several markers of inflammation (e.g. high-sensitivity C-reactive protein, fibrinogen, and interleukin 6) are associated with an increased risk of the presence, progression, and complication of LEAD.[37, 41, 42] Some autoimmune/inflammatory conditions are at increased risk for LEAD (e.g. systemic lupus erythematosus and rheumatoid arthritis).[43] Homocysteine provides weak additive prognostic information in addition to standard lipid measures.[35] Several genotypes serve as potential risk factors for atherosclerosis. However, evidence on their clinical relevance is weak.

Prognosis

Atherosclerosis is often generalized. Patients affected at one site are overall at risk for fatal and non-fatal cardiovascular (CV) events.

Beyond the risk of cerebrovascular events, patients with carotid artery disease are also at risk for myocardial infarction and cardiac death.[44] In a systematic review of 17 studies including 11,391 patients with greater than 50% asymptomatic carotid stenosis, 63% of late deaths were related to cardiac events, with a mean cardiac-related mortality rate of 2.9%/year.[45]

Many studies have shown an increased risk of mortality, CV mortality, and morbidity (myocardial infarction, stroke) in patients with symptomatic or asymptomatic LEAD, even after adjustment for conventional risk factors.[14] An ankle–brachial index of 0.90 or less is associated with more than doubling of the 10-year rates of coronary events, CV mortality, and total mortality.[46] After 5 years, 20% of patients with intermittent claudication present with a myocardial infarction or stroke and mortality is 10–15%.[47]

All these data emphasize the importance of general CV prevention, beyond the management of the disease related to a specific site of atherosclerosis.

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Chapter 49.3 General aspects

Key messages

- Thorough clinical history and physical examination are key steps in peripheral arterial diseases (PADs) management.
- Beyond the diagnosis of lower extremity artery disease (LEAD), ankle–brachial index (ABI) is also a strong marker for cardiovascular (CV) events.
- The management of PADs includes all interventions to address specific arterial symptoms as well as general CV risk prevention.
- Best medical therapy (BMT) includes CV risk factor management, including optimal pharmacological therapy as well as non-pharmacological measures such as smoking cessation, healthy diet, weight loss, and regular physical exercise.

Diagnostic approach

Clinical history

Personal and family clinical history should always be assessed. Family history includes coronary artery disease (CAD), cerebrovascular disease, aortic aneurysm, as well as LEAD.[1–3] Clinical history includes the evaluation of CV risk factors and co-morbidities, as well as a review of the symptoms related to different vascular territories (Table 49.3.1). Lifestyle habits, dietary patterns, walking performances, and physical activity need to be systematically interrogated. Physical activity should be assessed.[4] Questionnaires and functional status provide reasonably accurate outcome measures. They may be useful for determining the impairment level and selection of appropriate care.[5, 6]

Clinical examination

Although physical examination alone is of relatively poor sensitivity, and reproducibility, a systematic approach is mandatory (Table 49.3.2). Beyond their diagnostic importance, clinical signs have a prognostic value. Individuals with carotid bruits have twice the risk of myocardial infarction and CV death as compared with those without.[7] Inter-arm blood pressure (BP) asymmetry (≥15 mmHg) is a marker of vascular disease risk and death.[8] A femoral bruit is an independent marker for ischaemic cardiac events.[9]

Laboratory testing

Investigations should progress from the 'minimal' biological assessment[10] to complementary laboratory tests if necessary (Table 49.3.3).

Diagnostic methods for PADs

Ankle–brachial index

The ABI is a non-invasive tool that is useful for the diagnosis and surveillance of LEAD. It is also a strong marker of generalized

Table 49.3.1 Medical history for assessment of peripheral arterial disease

Family history of CVD (coronary artery disease, cerebrovascular disease, aortic aneurysm, LEAD), and premature CVD (fatal or non-fatal CVD event or/and established diagnosis of CVD in first-degree male relatives before 55 years or female relatives before 65 years)
Personal history of: ◆ Hypertension ◆ Diabetes ◆ Dyslipidaemia ◆ Smoking (present and/or past), passive smoking exposure ◆ Prior CVD ◆ Chronic kidney disease ◆ Sedentary life ◆ Dietary habits ◆ History of cancer radiation therapy ◆ Psycho-social factors
Transient or permanent neurological symptoms
Arm exertion pain, particularly if associated with dizziness or vertigo
Symptoms suggesting angina, dyspnoea
Abdominal pain, particularly if related to eating and associated with weight loss
Walking impairment/claudication: ◆ Type: fatigue, aching, cramping, discomfort, burning ◆ Location: buttock, thigh, calf, or foot ◆ Timing: triggered by exercise, uphill rather than downhill, quickly relieved with rest; chronic ◆ Distance
Lower limb pain (including foot) at rest, and evolution at upright or recumbent position
Poorly healing wounds of the extremities
Physical activity assessment: ◆ Functional capacity and causes of impairment
Erectile dysfunction

CVD, cardiovascular disease; LEAD, lower extremity artery disease.

Table 49.3.2 Physical examination for assessment of peripheral arterial diseases

Auscultation and palpation of cervical and supraclavicular areas
Careful inspection of upper extremities, including hands (i.e. colour, skin integrity)
Palpation of upper extremity pulses
Blood pressure measurement of both arms and notation of inter-arm difference
Auscultation at different levels including the flanks, peri-umbilical region, and groin
Abdominal palpation, palpation of femoral, popliteal, dorsalis pedis, and posterior tibial artery pulses, temperature gradient assessment
Careful inspection of lower limbs, including feet (i.e. colour, presence of any cutaneous lesion). Findings suggestive of lower extremity arterial disease, including calf hair loss and muscle atrophy, should be noted
Peripheral neuropathy assessment in case of diabetes or LEAD: sensory loss (monofilament testing), ability to detect pain and light touch (sharp examination pin, cotton wool), vibration impairment (128 Hz tuning fork); deep tendon reflexes examination; sweating

LEAD, lower extremity artery disease.

Table 49.3.3 Laboratory testing in patients with peripheral arterial diseases

Routine tests
Fasting plasma glucose
Fasting serum lipid profile: ◆ Total cholesterol ◆ Triglycerides ◆ High-density lipoprotein cholesterol ◆ Low-density lipoprotein cholesterol
Serum creatinine and creatinine clearance
Urine analysis: urinary protein by dipstick test, microalbuminuria
Blood count
Uric acid
Additional tests, based on findings from clinical history, physical examination, and routine tests
Either glycated haemoglobin if fasting plasma glucose >5.6 mmol/L (101 mg/dL) or impaired glucose tolerance test when there is doubt
Lipoprotein (a) if there is a family history of premature cardiovascular disease
Quantitative proteinuria if positive dipstick test

atherosclerosis and CV risk (Table 49.3.4). An ABI of 0.90 or less is on average associated with a two- to threefold increased risk of total and CV death. An ABI greater than 1.40 represents arterial stiffening (medial arterial calcification), and is also associated with a higher risk of CV events and mortality.[11, 12] It is more prevalent in elderly patients, mostly in those with diabetes or chronic kidney disease (CKD). When added to a risk score, ABI enables the risk estimation to be upgraded in one-third and one-fifth of 'low-risk' women and men, respectively.[9] It is a valid method of CV risk assessment in diverse ethnic groups, independent of risk factors.[12] In contrast to coronary calcium score and carotid intima–media thickness, ABI is inexpensive and minimally time-consuming. Good training is mandatory.

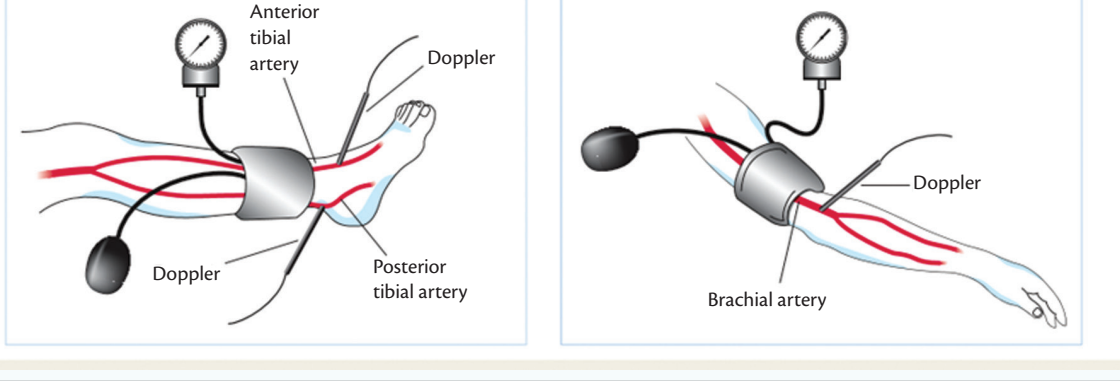
In addition to the general CV risk, ABI measurement can identify a patient's risk for lower extremity events, requiring close attention and education for foot wound prevention.

Duplex ultrasound

Duplex ultrasound (DUS) is often a first step in the vascular work-up both for screening and diagnosis. DUS includes B-mode echography, pulsed-wave, continuous, colour, and power Doppler

Table 49.3.4 The ankle–brachial index

1. Who should have an ABI measurement in clinical practice?
Patients with clinical suspicion for LEAD: ◆ Lower extremities pulse abolition and/or arterial bruit ◆ Typical intermittent claudication or symptoms suggestive for LEAD ◆ Non-healing lower extremity wound Patients at risk for LEAD because of the following clinical conditions: ◆ Atherosclerotic diseases: CAD, any PADs ◆ Other conditions: AAA, CKD, heart failure Asymptomatic individuals clinically-free but at-risk for LEAD: ◆ Men and women aged >65 years ◆ Men and women aged <65 years classified at high CV risk according the ESC guidelines* ◆ Men and women aged >50 years with family history for LEAD
* Subjects with: markedly elevated single risk factors; diabetes mellitus (except for young people with type 1 diabetes without other major risk factors); a calculated SCORE ≥5% and <10%.
2. How to measure the ABI?
In supine position, with cuff placed just above the ankle, avoiding wounded zones. After a 5–10 min rest, the SBP is measured by a Doppler probe (5–10 MHz) on the posterior and the anterior tibial (or dorsal pedis) arteries of each foot and on the brachial artery of each arm. Automated BP cuffs are mostly not valid for ankle pressure and may display overestimated results in case of low ankle pressure. The ABI of each leg is calculated by dividing the highest ankle SBP by the highest arm SBP



(continued)

Table 49.3.4 (Continued)

3. How to interpret the ABI?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg)
- For the CV risk stratification: take the lowest ABI between the two legs
- Interpretation:

AAA, abdominal aorta aneurysm, ABI, ankle–brachial index, BP, blood pressure, CAD, coronary artery disease, CKD, chronic kidney disease, CV, cardiovascular, ESC, European Society of Cardiology; LEAD, lower extremity artery disease, PADs, peripheral arterial diseases, SBP, systolic blood pressure.

modalities to detect and localize vascular lesions, and quantify their extent and severity through velocity criteria. More recent techniques, such as flow imaging or live three-dimensional echography, as well as the use of ultrasound contrast agents, further improve DUS performances although their use is still limited. DUS can detect subclinical artery disease (e.g. carotid plaque), which is important for CV risk assessment.[10]

Digital subtraction angiography

Digital subtraction angiography was considered the standard reference in vascular imaging. Given its invasive character and risk of complications, it has been mostly replaced by other less invasive methods except for below-knee arterial disease. It may be used in the case of discrepancy between non-invasive imaging tools.

Computed tomography angiography

Multidetector computed tomography angiography (CTA) has a short examination time with reduced motion and respiration artefacts while imaging vessels and organs. Advantages of CTA include rapid non-invasive acquisition, wide availability, high resolution, and three-dimensional reformatting. Similar to digital subtraction angiography and magnetic resonance angiography (MRA), CTA displays a 'roadmap' of the vascularization, essential for determining interventional strategies (lesion localization and severity, upstream/downstream status). The drawbacks of CTA include lack of functional and haemodynamic data, exposure to radiation, and use of iodinated contrast agents, which should be limited in the case of CKD, with precautions in case of allergies. Nephrotoxicity can be limited by minimizing contrast agent volume and ensuring adequate hydration before and after imaging. The benefit of acetylcysteine to limit nephrotoxicity is uncertain.[13, 14] Recent studies suggested that statins or sodium bicarbonate could prevent contrast agent nephrotoxicity.[15, 16] Further research is required.

Magnetic resonance angiography

MRA is used for peripheral artery imaging using contrast (i.e. gadolinium) and non-contrast techniques (i.e. phase contrast, and time-of-flight sequences). These latter techniques have inferior resolution and are susceptible to artefacts limiting their interpretation. Their use in patients with mild to moderate CKD is a valuable alternative. Compared to CTA, MRA does not need iodine contrast and has higher soft tissue resolution; however, motion artefacts are more frequent, and contraindications include pacemakers and implantable cardioverter defibrillators (ICDs) (except magnetic resonance imaging-conditional and -compatible pacemakers, ICDs, and leads), claustrophobia, and severe CKD. In the latter case, the risk of nephrogenic systemic fibrosis following gadolinium administration should not be underestimated.[17] Vascular calcifications, potentially affecting revascularization procedures, can be underestimated. Endovascular stents are not evaluable by magnetic resonance imaging.

Treatment approach

The therapeutic approach to patients with PADs includes two aspects. The first is to address specific symptoms of any localization and the risk related to a specific lesion. This is addressed in the following subsections.

The second aspect of management in these patients is related to their increased risk of any CV event (see 'Risk factors' in Chapter 49.2). General CV prevention is of the utmost importance and management should be multidisciplinary. BMT includes CV risk factor management, including best pharmacological therapy as well as non-pharmacological measures such as smoking cessation, healthy diet, weight loss, and regular physical exercise.[18, 19] The pharmacological component of BMT includes antihypertensive, lipid-lowering, and antithrombotic drugs. In diabetic patients, optimal glucose level control should be obtained as recommended.[20]

Smoking cessation

A body of evidence supports the benefits of smoking cessation in reducing CV events, and mortality, especially in patients with cerebrovascular disease and LEAD.[21, 22]

The management and support for smoking cessation has been extensively addressed in the 2016 European Society of Cardiology (ESC) Guidelines on CV disease prevention.[19] Passive smoking should be assessed and prevented.[23]

Lipid-lowering drugs

All patients with PADs should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to less than 1.8 mmol/L (<70 mg/dL), or decreased by 50% or more if the initial LDL-C level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). In

observational studies and limited randomized clinical trials in patients with LEAD (from asymptomatic to severe cases), statin therapy was shown to cause reductions in all-cause mortality and CV events.[24–26] In the Reduction of Atherothrombosis for Continued Health (REACH) registry, among patients with LEAD, statin use was associated with a 17% decrease of adverse CV events rates in patients with LEAD.[27] Even in the most advanced stages of disease, statin therapy is associated with lower 1-year rates of mortality and major CV adverse events.[28] Combination treatment with ezetimibe in selected patients is also beneficial.[29] In a randomized trial, bezafibrate showed no benefit over placebo to reduce coronary and cerebrovascular events in patients with LEAD. [30] In those with carotid artery disease, statins reduce the stroke risk.[31, 32] Recently, the Fourier trial demonstrated the additional benefits of evolocumab, a monoclonal antibody inhibiting the proprotein convertase subtilisin–kexin type 9, to reduce CV events in patients with atherosclerotic disease over statins alone.[33] The results were consistent in the subgroup of 1505 patients with LEAD alone. Further results are awaited.

Antithrombotic drugs

Antiplatelet agents are used for secondary prevention to prevent CV events in patients with symptomatic PADs. The evidence is mostly available in patients with LEAD and cerebrovascular disease (see Chapter 49.4).

Antihypertensive drugs

Lowering systolic blood pressure (SBP) reduces CV events.[34] According to the current ESC/European Society of Hypertension guidelines,[35] a target BP of less than 140/90 mmHg is recommended, except in patients with diabetes for whom a diastolic blood pressure of 85 mmHg or less is considered safe. In patients with LEAD, this is mainly based on data from the INternational VErapamil-SR/Trandolapril (INVEST) study.[36] Caution should be made to avoid an SBP decrease below 110–120 mmHg, since a J-shaped relationship between SBP and CV events has been reported in that trial in LEAD patients.[36] In old and frail patients, these levels should be achieved only if well tolerated, without orthostatic hypotension.[37, 38] In patients with PADs, appropriate lifestyle and salt intake (5–6 g daily) are recommended.[39] Diuretics, beta blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are all suitable for antihypertensive treatment, as monotherapy or in different combinations. In INVEST, no difference in the CV outcomes was found between the verapamil ± trandolapril strategy versus atenolol ± hydrochlorothiazide strategy.[36] Some classes can be preferred according to co-morbidities.[35]

The Heart Outcomes Prevention Trial (HOPE) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) have shown that ACEIs and ARBs significantly reduce CV events in patients with PADs.[40, 41] According to these trials, ACEIs or ARBs are recommended for secondary prevention, even in patients with chronic limb-threatening ischaemia. In this subgroup of patients, use of ACEIs or ARBs is associated with decreased major adverse cardiovascular events and mortality without any effect on limb outcomes.[42]

Importantly, beta blockers are not contraindicated in patients with LEAD as they do not alter walking capacity in patients with mild to moderate LEAD.[43] In an observational study, patients with LEAD and prior myocardial infarction who were taking beta blockers had a significant 53% coronary events risk decrease at 32 months.[44] Nevertheless, they should be carefully prescribed to patients with chronic limb-threatening ischaemia.

See Table 49.3.5 for recommendations in patients with peripheral arterial diseases: best medical therapy.

Table 49.3.5 Recommendations in patients with peripheral arterial diseases: best medical therapy

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with PADs[21, 22]	I	B
Healthy diet and physical activity are recommended for all patients with PADs	I	C
Statins are recommended in all patients with PADs[25, 26]	I	A
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)[19]	I	C
In diabetic patients with PADs, strict glycaemic control is recommended	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs[45]	I	C[d]
In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg [35, 36, 46]	I	A
ACEIs or ARBs should be considered as first-line therapy in patients with PADs and hypertension[41, 47, c]	IIa	B

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; BP, blood pressure; HbA_1c, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; LEAD, lower extremity artery disease; PADs, peripheral arterial diseases.

[a] Class of recommendation.

[b] Level of evidence.

[c] Calcium channel blockers should be proposed in black individuals.

[d] Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding chapters in Section 49.

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Chapter 49.4 Antithrombotic drugs in peripheral arterial diseases

Key messages

- Antiplatelet therapy is indicated in all patients with carotid artery stenosis irrespective of clinical symptoms and revascularization. Dual antiplatelet therapy (DAPT) should be given for at least 1 month after carotid artery stenting.
- Single antiplatelet therapy (SAPT) is indicated only if lower extremity artery disease (LEAD) patients are symptomatic or have undergone revascularization. Clopidogrel is the preferred antiplatelet drug in LEAD patients.
- Chronic anticoagulation therapy is given only if there is a concomitant indication and may be combined with SAPT when there is a recent revascularization procedure.

Antiplatelet therapy is part of best medical therapy for symptomatic peripheral arterial diseases (PADs) (see Chapter 49.3). The specific issues about carotid artery disease and LEAD are addressed here. The question of DAPT after endovascular therapy in other territories, as well as the sensitive issue of PADs patients requiring anticoagulation (e.g. with concomitant atrial fibrillation (AF)), are also addressed.

Antithrombotic treatment in carotid artery disease

Single antiplatelet therapy

While the benefit of SAPT for preventing stroke in asymptomatic patients with carotid artery stenosis greater than 50% is not evidenced through a randomized clinical trial, lifelong low-dose aspirin should be part of best medical therapy to reduce the risk of stroke and other cardiovascular (CV) events,[1] since these patients are also at twofold risk excess of myocardial infarction (MI).[2] In symptomatic extracranial carotid stenosis, antiplatelet monotherapy is recommended.[1, 3] Clopidogrel (75 mg daily) is an alternative in patients with aspirin intolerance.[4]

Dual antiplatelet therapy

In the randomized Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, asymptomatic carotid artery disease was an inclusion criteria in 7% of patients enrolled. No benefit was observed between DAPT versus SAPT.[5] The Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study, conducted in 108 patients, demonstrated that DAPT versus aspirin reduced silent cerebral microemboli by 37% after 7 days.[6] No life-threatening intracranial or major bleeding was observed, but the sample size was small. For these reasons, DAPT may be considered within 24 h of a minor ischaemic stroke or transient ischaemic attack and may be continued for 1 month in patients treated conservatively.[7]

DAPT is recommended in patients undergoing carotid artery stenting (CAS). Two small randomized clinical trials comparing aspirin alone with DAPT for CAS were terminated prematurely due to high rates of stent thrombosis and neurological events in the aspirin-alone group.[8, 9] These data were obtained at 30 days. Most events were procedure related. The optimal duration of DAPT following CAS is unknown. Recent studies showing late brain lesions on diffusion-weighted magnetic resonance imaging after CAS question whether DAPT beyond the first month may be required.[10] However, potential risks include haemorrhagic transformation in patients with recent stroke and intracranial bleeding in patients at risk of reperfusion injury following revascularization. DAPT may be prolonged beyond 1 month after CAS in the presence of recent (<12 months) MI and low bleeding risk (Figure 49.4.1).[11]

Antithrombotic therapy in lower extremity artery disease

Antiplatelet agents are used in patients with LEAD to prevent limb-related and general CV events. A number of antiplatelet

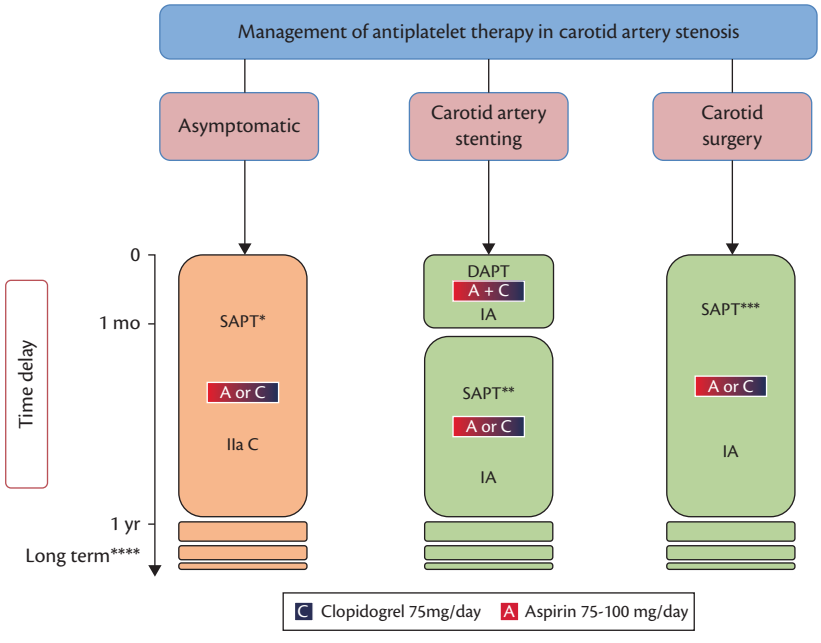

Figure 49.4.1 Management of antithrombotic treatment in patients with carotid artery stenosis. CAS, carotid artery stenting; DAPT, dual antiplatelet therapy, a daily combination of aspirin (75–100 mg) and clopidogrel (75 mg); SAPT, single antiplatelet therapy; TIA, transient ischaemic attack.
* With the exception of patient at very high bleeding risk. ** DAPT may be used if another indication supersedes that of carotid artery stenting such as acute coronary syndrome or percutaneous coronary intervention of less than 1 year. *** In case of recent minor stroke or TIA. A loading dose of aspirin (300 mg) and/or clopidogrel (300/600 mg) is recommended at the acute phase of stroke/TIA or during CAS. **** Stands for as long as it is well tolerated.

strategies are available, but their specific indications remain unclear.[12] One study compared clopidogrel with aspirin[4] and two studies compared clopidogrel plus aspirin to aspirin alone.[13, 14] No specific trial addressed the role of antiplatelet agents in the full spectrum of LEAD (asymptomatic, intermittent claudication, and chronic limb-threatening ischaemia).

Single antiplatelet therapy

Two trials, one in a general population (with ankle–brachial index (ABI) <0.95)[15] and another in diabetic patients (with ABI <1.0)[16] found no benefit from aspirin in subclinical LEAD.

In symptomatic LEAD, the strongest evidence in favour of aspirin to protect against major adverse cardiovascular events (MACE) (combining non-fatal MI and stroke with CV death) comes from the Antithrombotic Trialists Collaboration.[1] In patients with intermittent claudication (n >6200), aspirin significantly reduced MACE over control (6.4% vs 7.9%). Another meta-analysis of randomized clinical trials comparing aspirin to placebo in patients with LEAD (symptomatic or asymptomatic) showed a non-significant reduction in MACE (relative risk (RR) 0.75; 95% confidence interval (CI) 0.48–1.18).[17] No significant benefit was found within the individual components except for a reduction in non-fatal stroke (RR 0.64; 95% CI 0.42 to 0.99).[17] In a post hoc analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, at 3 years, clopidogrel was superior to aspirin in the subgroup of patients with clinical LEAD (n = 6452), with significant reductions in CV mortality (hazard ratio (HR) 0.76; 95% CI 0.64–0.91), and MACE (HR 0.78; 95% CI 0.65–0.93), with similar benefit in the subgroup of LEAD patients with diabetes.[4] In the randomized trial Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease trial (EUCLID), ticagrelor was compared to clopidogrel in 13,885 patients aged 50 years or older with symptomatic LEAD.[18] The trial failed to show any difference regarding MACE (HR 1.02; 95% CI 0.92–1.13) or major bleeding (HR 1.10; 95% CI 0.84–1.43).

Dual and triple antiplatelet therapy

So far, data proving the superiority of DAPT (with clopidogrel) over aspirin alone to reduce CV events in patients with LEAD are lacking.[12] In the subgroup of patients with LEAD enrolled in the CHARISMA trial (n = 3906), DAPT led to a reduction of MI (HR 0.63; 95% CI 0.42–0.95) with a neutral effect on all the other vascular events, at the cost of increased severe, fatal, or moderate bleeding (HR 1.99; 95% CI 1.69–2.34).[14] Because of the post hoc nature of this analysis and the negative results of the overall trial, these findings need confirmation.

Vorapaxar, a protease-activated receptor-1 inhibitor, was tested versus placebo on top of standard antiplatelet therapy in secondary prevention in patients with clinical LEAD (n = 3787).[19] Vorapaxar did not reduce the risk of MACE (HR 0.94; 95% CI 0.78–1.14) but significantly reduced the risk of acute limb ischaemia (HR 0.58; 95% CI 0.39–0.86) and peripheral revascularization (HR 0.84; 95% CI 0.73–0.97).[19] This benefit was observed irrespective of the underlying mechanism of acute limb ischaemia, including surgical graft thrombosis and native vessel thrombosis.[20] These beneficial effects were counterbalanced by an increased risk of bleeding (HR 1.62; 95% CI 1.21–2.18).

Antithrombotic therapy after lower extremity bypass grafting

Antiplatelet agents are mostly used after peripheral percutaneous revascularization, while warfarin has little role (Figure 49.4.2). No conclusive data are yet available for direct oral thrombin and factor Xa inhibitors.[21]

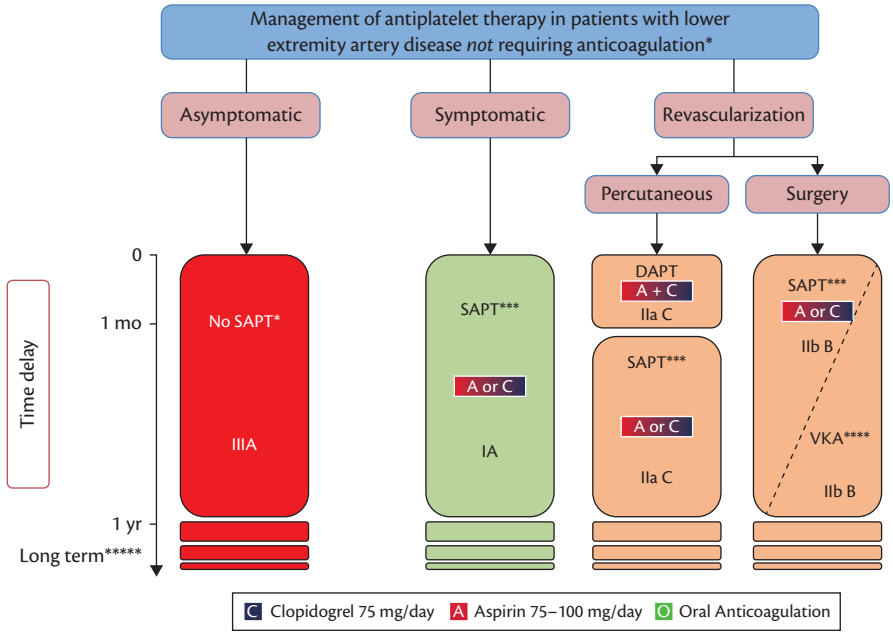

Figure 49.4.2 Antiplatelet therapy in patients with lower extremity artery disease. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; VKA, vitamin K antagonist.
* For example, concomitant atrial fibrillation or mechanical valve prosthesis. ** SAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease). *** DAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization. **** Evidence is weak and bleeding doubles as compared to SAPT. ***** Stands for as long as it is well tolerated.

Aspirin versus placebo

In a meta-analysis (952 patients), graft patency was significantly improved with aspirin (with or without dipyridamole) versus placebo (HR 0.42; $p = 0.01$).[21] Notably, at any of the time points, this effect was not observed for venous grafts alone but for prosthetic grafts (at 12 months: odds ratio (OR) 0.19; $p < 0.00001$). Amputation, survival, and bleeding rates were similar.

Aspirin versus oral anticoagulation

In the Dutch Bypass Oral Anticoagulants or Aspirin Study no difference in graft patency was found between aspirin (or aspirin/dipyridamole) versus vitamin K antagonist (VKA) over 2 years of follow-up (HR 0.64; 95% CI 0.25–1.63).[22] There was no difference in mortality (OR 1.02; 95% CI 0.83–1.26) or amputation (OR 0.99; 95% CI 0.75–1.30). Major bleeding risk doubled under VKA (with high target international normalized ratios (INRs) >3).[22] There were significantly fewer venous bypass occlusions under VKA versus aspirin (HR 0.69; 95% CI 0.51–0.94). In another study, the addition of warfarin to aspirin failed to show any improvement in graft patency versus aspirin alone, with a twofold increased risk of major bleeding.[23] DAPT has been compared to VKA plus clopidogrel ($n = 341$) in femoropopliteal bypass with marginal benefit on graft failure, more bleeding, and no effect on MACE.[24]

Aspirin versus dual antiplatelet therapy

Among the 851 patients with below-knee bypass grafting enrolled in the Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial disease (CASPAR) randomized controlled trial, no difference between aspirin plus placebo versus aspirin plus clopidogrel was found, regarding the occurrence of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death (HR 0.98; 95% CI 0.78–1.23).[13] In the pre-specified subgroup of patients with a prosthetic graft, the primary efficacy endpoint was reduced in DAPT patients versus aspirin alone (HR 0.65; 95% CI 0.45–0.95) with a significant interaction according to the type of graft (venous vs prosthetic). There was no statistically significant difference in the incidence of primary events when a venous graft was used (HR 1.25; 95% CI 0.94–1.67). Although total bleeding was more frequent on DAPT (HR 2.65; 95% CI 1.69–4.15), there was no significant difference regarding severe or fatal bleeding (2.1% vs 1.2%).

Antithrombotic drugs after endovascular therapy for lower extremity artery disease

DAPT is currently recommended, at least 1 month after intervention, irrespective of the stent type (bare-metal vs drug-eluting). In the Zilver PTX randomized trial comparing provisional drug-eluting stents to bare-metal stents, DAPT was mandated for 2 months.[25] In the IN.PACT SFA trial, half of the patients were on DAPT at 1 year.[26] Stenting below-the-knee arteries is often followed by a longer period of DAPT, but no specific evidence is available. Anticoagulation has been prospectively tested after percutaneous infra-inguinal revascularization. Vascular patency was not improved while bleedings were significantly increased.[27]

Patients with lower extremity artery disease and concomitant coronary artery disease

In patients with coronary artery disease, the coexistence of LEAD is associated with a worse prognosis irrespective of the clinical presentation. It has a direct impact on the duration and the type of antiplatelet therapy regimen, in particular when there is a prior history of coronary stenting or acute coronary syndrome. The coexistence of LEAD in patients with coronary artery disease may be an argument for prolonged DAPT. The PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hYperplasia (PRODIGY) trial tested DAPT duration after acute coronary syndrome. Prolonged (24 months) versus short DAPT (6 months) conveyed a lower risk of the primary efficacy endpoint, a composite of death, MI, or cerebrovascular accidents,

in patients with LEAD (HR 0.54; 95% CI 0.31–0.95) but not in those without (HR 1.28; 95% CI 0.92–1.77). A significant interaction (p = 0.01) suggests specific benefits only in patients with concomitant LEAD.[28] In the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, the addition of ticagrelor 90 mg twice daily or 60 mg twice daily on top of low-dose aspirin in stable patients with prior MI (1–3 years) was investigated.[29] Among patients with known LEAD (5% of the entire population), ticagrelor (pooled doses) reduced significantly the risk of major adverse limb outcomes (acute limb ischaemia and peripheral revascularization) (HR 0.65; 95% CI 0.44–0.95). In addition, in patients with LEAD, ticagrelor showed the greatest benefit, with an absolute risk reduction of 4.1% (number needed to treat = 25) for MACE, and an absolute excess major bleeding of 0.12% (number needed to harm = 834).[30] Therefore, long-term ticagrelor on top of low-dose aspirin may be considered in LEAD patients with prior MI (<3 years).

DAPT duration in these settings should follow the current guidelines.[31] In LEAD patients who underwent infra-inguinal percutaneous revascularization, DAPT may be prolonged beyond 1 month when there is a prior history of ACS or percutaneous coronary intervention, or both (<1 year) (Figure 49.4.2). Yearly reassessment of DAPT should be considered according to the patient's clinical status.

Antithrombotic therapy in lower extremity artery disease patients requiring long-term oral anticoagulant

AF is frequent in patients with LEAD with a worse outcome as compared to those without AF (see 'PADs and atrial fibrillation' in Chapter 49.11).[32] Although evidence is scarce to support a specific antithrombotic regimen in patients with LEAD and an indication for oral anticoagulation (OAC), the first step is to reassess the indication for OAC. OAC should be continued only if a compelling indication exists (e.g. paroxysmal, persistent, or permanent AF with a CHA_2DS_2-VASc score ≥2; mechanical heart valve; recent or a history of recurrent deep venous thrombosis or pulmonary embolism). Importantly, LEAD accounts for 1 point in the CHA_2DS_2-VASC score and can shift the indication for OAC. A post hoc analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial reported a significant interaction for major or non-major clinically relevant bleeding in patients with LEAD (n = 839) treated with rivaroxaban versus warfarin (HR 1.40; 95% CI 1.06–1.86) compared to patients without LEAD (HR 1.03; 95% CI 0.95–1.11; interaction p = 0.037).[34] Additional studies are needed.

The duration of combined therapy should be as limited as possible (1 month), depending on the clinical indication and bleeding risk.[31, 32] The addition of an antiplatelet treatment may depend on concomitant coronary artery disease and the need for LEAD endovascular revascularization. With the exception of below-the-knee stenting or complex lesions at very high risk of thrombosis, triple therapy (i.e. aspirin, clopidogrel, and an anticoagulant) is discouraged in this setting. The proposed treatment algorithm taking into account the management strategy and bleeding risk is shown in Figure 49.4.3. Gastric protection with a proton pump inhibitor is recommended and the dose intensity of OAC should be carefully monitored with a target INR of 2.0–2.5 in patients treated with VKA, with the exception of individuals with mechanical prosthetic valves in the mitral position. In patients treated with non-vitamin K antagonist oral anticoagulants, the lowest

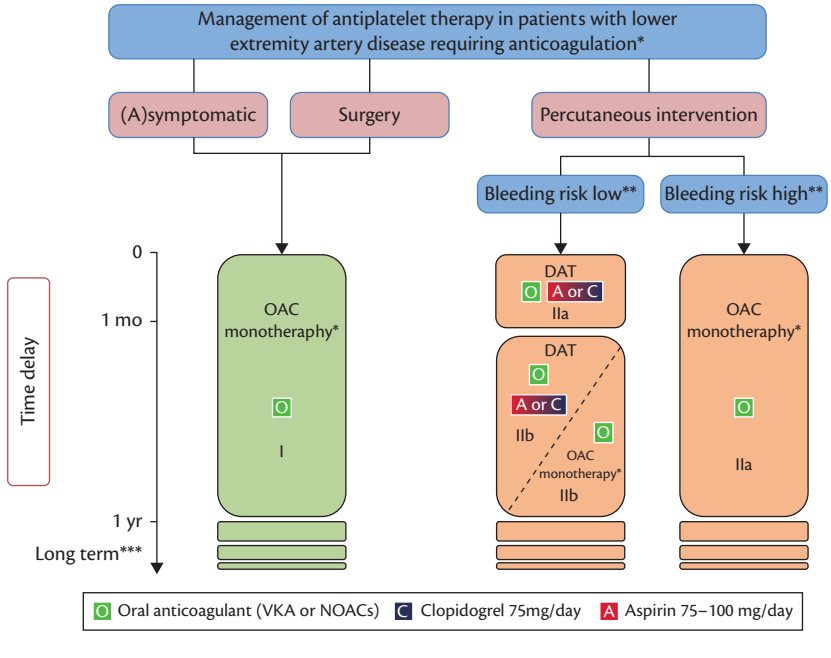

Figure 49.4.3 Antithrombotic therapy in patients with lead requiring oral anticoagulation. ACS, acute coronary syndrome; CAD, coronary artery disease; CLI, chronic limb ischaemia; DAT, dual antithrombotic therapy; LEAD, lower extremity artery disease; NOACs, non-vitamin K oral anticoagulants; OAC, oral anticoagulation; VKA, vitamin K antagonist.
* DAT may be considered in high ischaemic risk patients defined as prior stent thrombosis, acute limb ischaemia or OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization). ** Compared to the risk for stroke/CLI due to stent/graft occlusion. *** Stands for as long as it is well tolerated.

Table 49.4.1 Recommendations on antithrombotic therapy in patients with peripheral arterial diseases

Recommendations	Class[a]	Level[b]
Carotid artery disease		
In patients with symptomatic carotid stenosis, long-term single antiplatelet therapy is recommended[36]	I	A
Dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least 1 month after CAS[9]	I	B
In patients with asymptomatic ≥50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low[c]	IIa	C
Lower extremities artery disease		
Long-term single antiplatelet therapy is recommended in symptomatic patients[1, 4, 17]	I	A
Long-term single antiplatelet therapy is recommended in all patients who have undergone revascularization[37]	I	C
Single antiplatelet treatment is recommended after infra-inguinal bypass surgery[37]	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin[1, 18]	IIb	B
Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass[22]	IIb	B
Dual antiplatelet therapy with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation	IIa	C
Dual antiplatelet therapy combining aspirin and clopidogrel may be considered in below-knee bypass with prosthetic graft[13]	IIb	B
In the lack of proved benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD[15, 16]	III	A
Antithrombotic therapy for PADs patients requiring oral anticoagulant		
In patients with PADs and AF, oral anticoagulation[32]:		
◆ is recommended when CHA_2DS_2-VASc score ≥2	I	A
◆ should be considered in all other patients	IIa	B
In patients with PADs who have an indication for oral anticoagulation (e.g. AF or mechanical prosthetic valve), oral anticoagulants alone should be considered	IIa	B
After endovascular revascularization, aspirin or clopidogrel should be considered in addition to oral anticoagulation for at least 1 month if the bleeding risk is low compared to the risk of stent/graft occlusion	IIa	C
After endovascular revascularization, oral anticoagulation alone should be considered if the bleeding risk is high compared to the risk of stent/graft occlusion	IIa	C
Oral anticoagulation and single antiplatelet therapy may be considered beyond 1 month in high ischaemic risk patients or when there is another firm indication for long-term single antiplatelet therapy	IIb	C

AF, atrial fibrillation; CAS, carotid artery stenting; LEAD, lower extremity artery disease; PADs, peripheral arterial diseases.
CHA_2DS_2-VASc score is calculated as follows: Congestive heart failure history (1 point), Hypertension (1 point), Age >75 years (2 points), Diabetes mellitus (1 point), Stroke or TIA or arterial thromboembolic history (1 point), Vascular disease history (1 point), Age between 65 and 74 years (1 point), Sex category (1 point if female).
[a] Class of recommendation.
[b] Level of evidence.
[c] With the exception of patients with an indication for long-term oral anticoagulation.
[d] Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multisite artery diseases).

dose in approval studies for stroke prevention should be applied when combined with antiplatelet therapy.[32, 35]

See Table 49.4.1 for recommendations on antithrombotic therapy in patients with peripheral arterial diseases.

Antithrombotic therapy after endovascular therapy in other territories

There is currently no trial assessing the benefit of DAPT over SAPT after subclavian, mesenteric, and renal stenting.[38] A combination of clopidogrel (75 mg) and low-dose aspirin is empirically prescribed in most centres, typically from 1 to 3 months, prolonged in some cases up to 1 year. One observational study reported a trend to lower secondary procedures for revascularization failure if the initial stenting was done under DAPT.[39]

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Chapter 49.5 Extracranial carotid and vertebral artery disease

Key messages

- 10–15% of all strokes follow thromboembolism from a 50–99% internal carotid artery (ICA) stenosis.
- The majority of recently symptomatic patients will gain maximum benefit when carotid interventions are performed within 14 days of symptom onset.
- Given the improved prognosis with best medical therapy (BMT), the management of asymptomatic carotid disease remains controversial. However, some subgroups of patients may benefit from revascularization.
- Predicting the magnitude of the perioperative risk of stroke can determine whether carotid endarterectomy (CEA) or carotid artery stenting (CAS) is safer in individual patients, especially in the early time period after onset of symptoms and in patients older than 70 years. After the perioperative period, late stroke rates after CEA and CAS are similar.
- Vertebral artery (VA) stenoses are usually treated medically, unless recurrent symptoms persist despite BMT.

Carotid artery disease

Definition

The different presentation modes of cerebrovascular events are detailed in Table 49.5.1.[1] This chapter primarily deals with stroke secondary to carotid and VA disease, but not cardioembolism. 'Carotid artery stenosis' refers to a 50% or greater stenosis of the extracranial ICA, with stenosis severity estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (Figure 49.5.1).[2]

According to the definitions in major trials, carotid stenosis is defined as 'symptomatic' if associated with symptoms in the preceding 6 months and 'asymptomatic' if no prior symptoms can be identified, or when symptoms occurred beyond 6 months before.

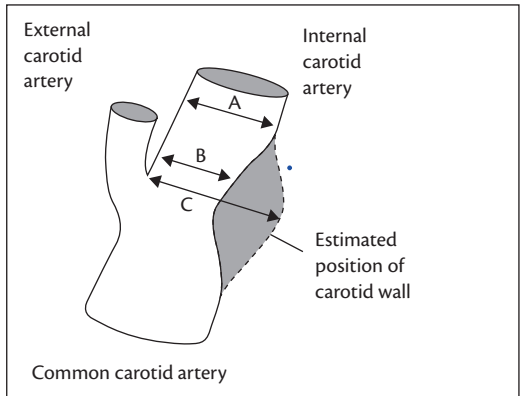
Diagnosis

Clinical evaluation

Hemispheric symptoms include weakness, numbness, or paraesthesia of the face, arm, and leg, contralateral to the carotid stenosis. Neuropsychological symptoms include aphasia (dominant hemisphere), or neglect (non-dominant hemisphere). Retinal

Table 49.5.1 Terminologies and definitions used to define cerebrovascular events

Terminology	Definition
Transient ischaemic attack (TIA)	A brief episode of neurological dysfunction resulting from focal temporary cerebral ischaemia, which is not associated with evidence of acute cerebral infarction
Ischaemic stroke	An episode of neurological dysfunction caused by focal cerebral or retinal infarction, where infarction is defined as brain or retinal cell death attributable to ischaemia, based on neuropathology, neuroimaging, and/or clinical evidence of permanent injury
Silent infarction	Imaging or neuropathological evidence of cerebral/retinal infarction without a history of acute neurological dysfunction attributable to the lesion



NASCET $\frac{A-B}{A}$ ECST $\frac{C-B}{C}$

NASCET	ECST
30 40	65 70
50	75
60	80
70	85
80 90	91 97

Approximate equivalent degrees of internal carotid artery stenosis used in NASCET and ESCT according to recent comparisons

Figure 49.5.1 Angiographic carotid stenosis according to different methods. ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

emboli may cause temporary or permanent blindness. Only a small proportion of transient ischaemic attacks (TIAs)/strokes are haemodynamic. Symptoms such as isolated headache (unless associated with carotid dissection), isolated dizziness, isolated diplopia, frequent falls, and syncope are not suggestive of carotid territory ischaemia.

Imaging

In patients with TIA/stroke, urgent imaging of the brain and supra-aortic vessels is mandatory. Duplex ultrasound (DUS) is usually the first-line carotid imaging modality to assess extracranial ICA stenoses. It includes Doppler velocity measurements and ratios for accurate evaluation of stenosis severity. Multiple criteria should be used for reliable estimation of stenosis. Further details are presented in a recent consensus document.[3]

Plaque morphological evaluation using magnetic resonance imaging (MRI) or DUS (echolucency, intraplaque haemorrhage, surface irregularity) may identify patients with asymptomatic stenoses at higher risk of ipsilateral ischaemic stroke. Other markers are silent infarction on computed tomography (CT)/MRI and the detection of spontaneous embolization using transcranial Doppler monitoring.[4-6] Combining DUS with transcranial Doppler and/or transcranial colour-coded DUS enables a more thorough assessment of intracranial stenoses and an evaluation of impaired cerebrovascular reserve.[7]

Table 49.5.2 Recommendations for imaging of extracranial carotid arteries

Recommendations	Class[a]	Level[b]
DUS (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses[8]	I	B
When CAS is being considered, it is recommended that any DUS study be followed either by MRA or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation[8]	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated either by MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory)[8]	I	B

CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; DUS, duplex ultrasound; MRA, magnetic resonance angiography.
[a] Class of recommendation.
[b] Level of evidence.

The main advantage of computed tomography angiography (CTA)/magnetic resonance angiography (MRA) over DUS is their ability to image simultaneously from the aortic arch up to the intracranial circulation as well as brain parenchyma. While CT is more widely available and differentiates between ischaemic and haemorrhagic stroke, MRI is more sensitive in detecting brain ischaemia, especially in the early post-stroke period. CTA offers excellent sensitivity and specificity for detecting carotid stenosis.[8] Severe calcification may overestimate stenosis severity. MRA does not visualize vascular calcification, an important issue should CAS be considered. In a meta-analysis, DUS, MRA, and CTA were equivalent for detecting significant carotid stenosis.[8] Intra-arterial digital subtraction angiography, necessary for guiding CAS, but not CEA, is rarely required for diagnostic purposes and only in highly selected situations with discordant non-invasive imaging results, or additional intracranial vascular disease. In a patient with recent TIA or stroke with 50–99% ICA stenosis, echocardiography and 24–72 h rhythm monitoring remains suitable to detect the potential source of cardioembolism, but this should not delay any carotid intervention.

See Table 49.5.2 for recommendations for imaging of extracranial carotid arteries.

Treatment

Medical therapy

The medical management of patients with carotid disease is detailed in Chapter 49.3 and Chapter 49.4.

Open surgery

Technical aspects

A meta-analysis of non-randomized studies reported that CEA under loco-regional anaesthesia (compared to general anaesthesia) was associated with reduced perioperative myocardial infarction (MI), stroke, and respiratory complications.[9] However, a Cochrane review of 14 randomized clinical trials (RCTs) (4596

patients) found no evidence that the type of anaesthesia influenced perioperative outcomes, reporting 30-day risk of stroke/death in the local anaesthesia group at 3.6%, compared with 4.2% for patients randomized to general anaesthesia (odds ratio (OR) 0.85; 95% confidence interval (CI) 0.63–1.16).[10]

There are two techniques for performing CEA: traditional endarterectomy with primary closure or patch closure; and eversion endarterectomy. Meta-analyses have shown that (1) procedural stroke/death and late restenosis/ipsilateral stroke after eversion and patched CEA are no different; (2) routine primary closure is inferior to both eversion and patched CEA in terms of procedural stroke/death and late restenosis/ipsilateral stroke; and (3) patch type (prosthetic, vein) has no influence on early outcomes (stroke, thrombosis) or late outcomes (restenosis, recurrent stroke).[11, 12]

Carotid clamping reduces cerebral perfusion, which may cause haemodynamic brain injury. This can be prevented by a temporary shunt. A Cochrane review concluded that no meaningful recommendations could be made regarding shunt usage.[13]

A high bifurcation or stenosis extending distal to the digastric muscle can pose a technical challenge during CEA and may increase the risk of cranial nerve injury.[14] Patients who have previously undergone radical neck surgery or cervical radiation therapy are also at increased risk of cranial nerve injury.

Postoperative outcomes

Several studies have identified prognostic factors and markers for an increased risk of stroke after CEA.

In a subgroup analysis of the European Carotid Surgery Trial (ECST),[15] the following features were associated with a significant increase in perioperative stroke after CEA: (1) no heparin use; (2) operation time less than 1 h or greater than 1.5 h; (3) female gender; (4) a history of lower extremity artery disease; (5) preoperative systolic blood pressure greater than or equal to 180 mmHg; and (6) hemispheric versus retinal symptoms. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) the following features were associated with a significant increase in procedural stroke: (1) left- versus right-sided procedures; (2) contralateral occlusion; (3) ipsilateral CT/MR infarction; (4) irregular plaque; and (5) patients with hemispheric versus retinal symptoms.[16] A meta-analysis of 170 studies (>70,000 patients) observed that contralateral occlusion was associated with significantly higher stroke rates after CEA, but not after CAS.[17]

A meta-analysis of 25 non-randomized studies (936,436 CEAs) observed a significant association between hospital CEA volume and perioperative stroke/death. The pooled effect estimate was an OR of 0.78 (95% CI 0.64–0.92) favouring CEA in higher-volume units, with a critical hospital threshold of 79 CEAs per annum.[18] In another study, higher-volume surgeons (>30 CEAs per year) achieved significantly lower perioperative death/stroke rates than less experienced surgeons.[19]

In the International Carotid Stenting Study (ICSS), the incidence of cranial nerve injury was 5.5% in 821 patients randomized to CEA[14] but only 11 patients (1.3%) had residual symptoms at 30 days. Only one patient (0.12%) had disabling cranial nerve injury at 6 months.

Endovascular techniques

CAS is a potentially less invasive alternative to CEA, with a low risk of cranial nerve injury, wound complications, and/or neck haematoma, but it is vulnerable to access complications. CAS offers advantages over CEA in the presence of a 'hostile neck' (previous radiation, recurrent stenosis), contralateral recurrent laryngeal nerve palsy, or in the case of challenging surgical access (very high ICA lesions, proximal common carotid artery lesions), though not necessarily with a lower risk of perioperative stroke. Patients at higher risk for suffering perioperative cardiac complications may benefit from CAS in order to reduce perioperative MI (more common after CEA).[20] In a subgroup analysis from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the 4-year mortality was significantly higher (hazard ratio (HR) 3.40; 95% CI 1.67–6.92) in patients suffering a perioperative MI.[20]

Carotid stenting: technical aspects

Criteria associated with increased difficulty for CAS Several criteria are associated with increased difficulty in performing CAS. These include a type III aortic arch, a bovine arch, arch atheroma, a diseased external carotid artery, a markedly angulated distal ICA, a long stenosis, and a pinhole stenosis.[21] Analyses from various RCTs have identified clinical and/or angiographic predictors for an increased risk of stroke after CAS, including age greater than 70 years, low-volume units, ICA to common carotid artery angulation greater than 60°, symptomatic patients, lesion length greater than 13 mm, and sequential lesions extending remotely from the ICA stenosis.[22–26]

Embolic protection devices The rationale for cerebral protection devices is supported by the presence of embolic material in distal filters,[27] but their use remains controversial. Using diffusion weighted-MRI, studies have reported lower rates of cerebral embolization with a proximal embolus protection device (EPD), but none was powered to address clinical outcomes.[28–32] A meta-analysis of 24 studies observed that EPD use was associated with lower risk of perioperative stroke (relative risk (RR) 0.59; p <0.001).[33] A pooled analysis of RCTs has also reported significantly lower rates of perioperative stroke/death (RR 0.57) favouring EPD.[34] The benefit of EPDs was also evident in a prospective registry of 1455 patients: in those treated with EPD, in-hospital death/stroke rates were at 2.1% versus 4.9% in patients treated without EPD (p = 0.004).[35] The best results within RCTs were seen in the CREST and the Asymptomatic Carotid Trial (ACT-1), where cerebral protection was mandatory and CAS practitioners were trained for its use.[36] In contrast, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial observed lower ipsilateral stroke rates in CAS patients without EPD (6.2% vs 8.3% with EPD).[37] Given the lack of high-quality data, the revised recommendation in these guidelines is based on a broad consensus that protection devices should be considered when performing CAS.

Table 49.5.3 Recommendation on the use of embolic protection devices during carotid stenting

Recommendation	Class[a]	Level[b]
The use of embolic protection devices should be considered in patients undergoing carotid artery stenting	IIa	C

[a] Class of recommendation.
[b] Level of evidence.

See Table 49.5.3 for a recommendation on the use of embolic protection devices during carotid stenting.

CAS: operator experience and outcome

Evidence suggests that experience does play a role in CAS outcomes.[38, 39] Experience is an advantage, not only regarding catheter skills, but also regarding patient selection and periprocedural patient management. Several CAS versus CEA RCTs have been criticized for the low level of endovascular experience required for CAS operators.[40] However, the paradox remains that in two of these, the most experienced interventionists/centres in the Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) and ICSS reported the highest rates of procedural stroke, compared to less experienced colleagues.[22, 23, 41] An analysis of the independently adjudicated Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Rare Events (CAPTURE 2 Registry) reported a threshold of 72 cases per operator in order to consistently achieve a periprocedural death/stroke rate of less than 3%.[38] While high-volume CAS centres are consistently reporting better outcomes, a great many CAS procedures continue to be performed in low-volume units with poorer outcomes. In a multivariate regression analysis of predictors for procedural stroke in over 1.7 million CEA and CAS interventions, procedural stroke rates were three times higher where CAS practitioners performed two or fewer CAS procedures per year, compared to more experienced interventionists (HR 3.46; p <0.05).[42]

Management of carotid artery disease

Asymptomatic carotid artery disease

Open surgery versus medical therapy

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST-1) compared CEA with medical therapy in asymptomatic patients with 60–99% carotid stenosis.[43–45] In ACAS, 5-year rates of *ipsilateral* stroke/death under CEA versus medical therapy were, respectively, at 5.1% versus 11.0% (p = 0.0001; number needed to treat (NNT) = 18). The 10-year risk of 'any' stroke rates were, respectively, 13.4% versus 17.9% (p = 0.009; NNT = 22). ACST-1 reported 5-year rates of *any* stroke, respectively, at 6.4% versus 11.8% (p <0.0001; NNT = 19). Fatal/disabling stroke rates were at 3.5% versus 6.1% (P = 0.004; NNT = 38). In a combined analysis of both trials, CEA conferred less benefit in women at 5 years.[46] At 10 years, however, ACST-1[44] reported that females gained a small but significant benefit following CEA (absolute risk reduction (ARR) 5.8%; p = 0.05). However, both trials are now rather historical. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person-years in studies completing recruitment before 2000, compared with 1.0/100 person-years during the 2000–2010 period (p <0.001).[47] A 60–70% decline in annual stroke rates was also observed in medically treated patients in both trials over the recruitment period from 1995 to 2010.[43–45, 48]

Table 49.5.4 Features associated with increased risk of stroke in patients with asymptomatic carotid stenosis treated medically[50–57]

Clinical[a]	Contralateral TIA/stroke[51]
Cerebral imaging	Ipsilateral silent infarction[52]
Ultrasound imaging	Stenosis progression (>20%)[53] Spontaneous embolization on transcranial Doppler (HITS)[54] Impaired cerebral vascular reserve[55] Large plaques[b] [56] Echolucent plaques[5] Increased juxta-luminal black (hypoechogenic) area[57]
MRA	Intraplaque haemorrhage[58] Lipid-rich necrotic core

HITS, high-intensity transient signal; MRA, magnetic resonance angiography; TIA, transient ischaemic attack.
[a] Age is not a predictor of poorer outcome.
[b] More than 40 mm² on digital analysis.

Despite the small but significant benefit favouring CEA over medical therapy, the ARR in stroke was only 4.6% at 10 years, indicating that 95% of asymptomatic patients ultimately underwent unnecessary interventions.[6, 44] There is a need to target revascularization in a subgroup of patients with clinical or imaging features, or both, that may make them 'higher risk for stroke' on BMT[6] (Table 49.5.4). Pending the development of better algorithms for patient selection, the presence of one or more of these clinical or imaging features might be useful for selecting patients for revascularization.

Importantly, ACST found no evidence that age greater than 75 years at baseline was associated with any ipsilateral stroke reduction at 5 or 10 years. Additionally, the stenosis severity cannot be a criterion for stratifying late stroke risk. In a meta-analysis of 41 studies, ipsilateral stroke in patients with 50–69% and 70–99% stenosis were at 1.9 and 2.1/100 person-years, respectively p value.[47] Neither ACAS nor ACST found any evidence that stenosis severity or contralateral occlusion increased late stroke risk.[43, 44, 49]

Carotid revascularization: surgery versus stenting

Five RCTs compared CEA with CAS in 'average risk for CEA' asymptomatic patients (Table 49.5.5),[58–61] while SPACE-2 also included a third limb for BMT. The two biggest RCTs (CREST and ACT-1) requested exclusively experienced interventionists. In ACT-1, the 2.9% rate of death/stroke after CAS fell within the 3% accepted risk.

Because of the learning curve associated with CAS, as well as it being performed in low numbers by multiple specialties,[62] there are concerns as to whether the death/stroke rates reported for CAS in these trials can be replicated in 'real-world' practice. While some national CAS registries have published death/stroke rates within 3%,[63, 64] others have reported wide variations in

Table 49.5.5 Thirty-day morbidity and mortality in randomized trials comparing carotid endarterectomy and carotid artery stenosis in 'average risk' asymptomatic patients

30-day outcomes	Brooks[59]		CREST[60]		ACT-1[36]		SPACE-2[61]			Mannheim[62]	
	CEA *n* = 42	CAS *n* = 43	CEA *n* = 587	CAS *n* = 364	CEA *n* = 364	CAS *n* = 1089	CEA *n* = 203	CAS *n* = 197	BMT *n* = 113	CEA *n* = 68	CAS *n* = 68
Death/stroke	0%	0%	1.4%	2.5%	1.7%	2.9%	2.0%	2.5%	0.0%	1.5%	2.9%
Death/major stroke	0%	0%	0.3%	0.5%	0.6%	0.6%					
Death/stroke/MI	0%	0%	3.6%	3.5%	2.6%	3.3%				1.5%	2.9%

ACT-1, Asymptomatic Carotid Trial; BMT, best medical therapy; CAS, carotid artery stenting; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; MI, myocardial infarction; SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

practice. In a review of 19,381 CAS procedures in a registry, there was a fourfold variation regarding in-hospital death/stroke, despite adjusting for case mix.[62] A systematic review in large administrative dataset registries (>1.5 million procedures) suggested that 40% of registries reported death/stroke rates after CAS in excess of 3% in asymptomatic patients, while 14% reported death/stroke rates greater than 5%.[65] In some large registries, the median annual number of CAS procedures in asymptomatic patients may only be 1–2,[66] which is known to be associated with higher rates of perioperative stroke/death.[42]

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized symptomatic and asymptomatic patients deemed 'high risk for surgery' to either CEA or CAS (using EPDs routinely).[67] 'High surgical risk' was defined as clinically significant cardiac disease, severe pulmonary disease, contralateral ICA occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy, recurrent stenosis after CEA, and age over 80 years. The primary endpoint (30-day death/stroke/MI and/or death or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% of CAS patients and 20.1% of CEA patients ($p = 0.053$). At 3 years, major ipsilateral stroke (CAS 1.3% vs CEA 3.3%), minor ipsilateral stroke (6.1% vs 3.0%), and repeat revascularization (3.0% vs 7.1%) were not statistically different.[68] However, 71% of SAPPHIRE patients were asymptomatic, in whom the 30-day rate of death/stroke after CAS was 5.8% versus 6.1% after CEA,[67] both beyond the recommended 3%. If these procedural risk levels reflect contemporary practice, most 'high-risk for surgery' asymptomatic patients would be better treated medically.

See Table 49.5.6 for recommendations for management of asymptomatic carotid artery disease.

Symptomatic carotid artery disease

Open surgery

In a meta-analysis of all symptomatic patients randomized within NASCET and the ECST, those with a NASCET 0–49% stenosis gained no benefit from surgery. CEA conferred a 7.8% ARR in stroke at 5 years in patients with 50–69% stenoses (NNT = 13). The maximum benefit was seen in patients with 70–99% ICA stenoses, where the ARR in stroke was 15.6% (NNT = 6).[69]

A number of clinical/imaging features are associated with an increased rate of late stroke in symptomatic patients with 50–99% stenoses if treated medically: increasing age (especially >75 years); symptoms within 14 days, male sex, hemispheric (vs retinal) symptoms; cortical (vs lacunar) stroke; increasing number of medical comorbidities; irregular stenoses; increasing stenosis severity; contralateral occlusion; tandem intracranial stenoses; and a failure to recruit intracranial collaterals.[70]

A meta-analysis from ECST and NASCET showed that when CEA was performed within 14 days in patients with 50–69% stenoses, the ARR in stroke at 5 years was 14.8% (NNT = 7). The ARR declined to 3.3% where the delay was 2–4 weeks (NNT = 30) and 2.5% when the delay was 4–12 weeks (NNT = 40). Beyond 12 weeks, no strokes were prevented by CEA. In patients with 70–99%

Table 49.5.6 Recommendations for management of asymptomatic carotid artery disease

Recommendations	Class[a]	Level[b]
In 'average surgical risk' patients with an asymptomatic 60–99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years[46]	IIa	B
In asymptomatic patients who have been deemed 'high risk for CEA'[d] and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years[68, 69]	IIa	B
In 'average surgical risk' patients with an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[d] that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years[26, 36, 63, 66]	IIb	B

BP, blood pressure; CAS, carotid artery stenting; CEA, carotid endarterectomy.
[a] Class of recommendation.
[b] Level of evidence.
[c] See Table 49.5.4.
[d] Age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

stenoses who underwent CEA within 14 days, the ARR in stroke at 5 years was 23.0% (NNT = 4), falling to 15.9% where delays were 2–4 weeks (NNT = 6), and 7.9% for delays of 4–12 weeks (NNT = 13). When performed beyond 12 weeks, the ARR was 7.4% at 5 years (NNT = 14).[46, 70] Women appeared to gain almost no benefit from CEA when performed beyond 4 weeks.[46, 69, 70]

The risk of stroke is high within the first days after TIA. The early risk of stroke in patients with 50–99% ICA stenoses ranged from 5–8% within 48 h after TIA, up to 17% by 72 h, 8–22% by 7 days, and 11–25% at 14 days.[70]

There is controversy over whether CEA can be performed safely within the first 48 h after symptom onset. The Swedish Registry (n = 2596 CEAs) reported that when CEA was performed within the first 48 h, 11.5% died or suffered a stroke as compared to a procedural risk less than 5% when done any time afterwards.[71] By contrast, the UK national audit (n = 23,235 CEAs) reported that when CEA was performed within 48 h, death/stroke was much lower than observed in Sweden (3.7%). Thereafter, procedural risks were less than 2%.[72] A similarly low risk (3.0% death/stroke) was observed in Germany when CEA was performed within 48 h.[73] These registries suggest that CEA can be performed safely in the first 7 days after TIA/minor stroke onset. However, not all patients will benefit from urgent revascularization. There may be an increased risk of haemorrhagic transformation within a recent area of infarction. Higher-risk patients include those with acute carotid occlusion or a persisting major neurological deficit, an area of middle cerebral artery infarction exceeding one-third, evidence of pre-existing parenchymal haemorrhage, and evidence of impaired consciousness.

A meta-analysis of five randomized trials has shown that emergency endovascular treatment of acute ischaemic stroke (mechanical thrombectomy and/or intra-arterial thrombolysis) was associated with 2.22 times greater odds of a better functional outcome compared to those randomized to medical management. Endovascular therapy was not associated with modified risk of symptomatic intracerebral hemorrhage.[74] In the MultiCenter Randomized Clinical Trial of Ischemic Stroke in the Netherlands (MR CLEAN), 13% of patients underwent simultaneous CAS, but no data were specifically provided on its procedural risk.[75]

Endovascular therapy versus open surgery

The 30-day outcomes in four large contemporary RCTs comparing CEA with CAS are detailed in Table 49.5.7.[22, 25, 76, 77] Overall, the risk of 'any stroke' and 'death/stroke' was approximately 50% higher following CAS, primarily because CAS was associated with a significantly higher rate of minor stroke. Although CREST reported that the majority of minor perioperative strokes resolved by 6 months,[59, 76]

It was also reported that any type of perioperative stroke was associated with a threefold poorer long-term survival,[59] similar to the poorer 4-year survival observed in patients suffering a perioperative MI.[20]

In a meta-analysis of 13 RCTs (80% involving symptomatic patients), CAS was associated with an increased risk of any stroke, but a decreased risk of perioperative MI and cranial nerve injury.[78] In a Cochrane review (16 RCTs, 7572 patients) CAS was associated with higher periprocedural death/stroke, especially in patients aged over 70 years, but with significantly lower risks for MI, cranial nerve injury, and haematoma.[79]

In an individual-based meta-analysis, patients undergoing CEA within 7 days of symptoms had a 2.8% risk of stroke/death, compared with 9.4% after CAS. Patients undergoing CEA between

Table 49.5.7 Thirty-day outcomes following carotid endarterectomy and carotid artery stenting in trials randomizing more than 500 recently symptomatic patients

30-day risks	EVA-3S[78]		SPACE[25]		ICSS[22]		CREST[77]	
	CEA n = 262	CAS n = 261	CEA n = 589	CAS n = 607	CEA n = 857	CAS n = 853	CEA n = 653	CAS n = 668
Death	1.2%	0.8%	0.9%	1.0%	0.8%	2.3%		
Any stroke	3.5%	9.2%	6.2%	7.2%	4.1%	7.7%	3.2%	5.5%
Ipsilateral stroke			5.1%	6.4%	3.5%	6.8%		
Disabling stroke	0.4%	2.7%	2.9%	4.1%	2.3%	2.0%	0.9%	1.2%
Death/any stroke	3.9%	9.6%	6.5%	7.4%	4.7%	8.5%	3.2%	6.0%
Disabling stroke/death	1.5%	3.4%	3.8%	5.1%	3.2%	4%		
Clinical MI	0.8%	0.4%			0.5%	0.4%		
Clinical/subclinical (troponin) MI							2.3%	1%
Death/stroke/MI					5.2%	8.5%	5.4%	6.7%
Cranial nerve injury	7.7%	1.1%			5.3%	0.1%	5.1%	0.5%
Wound haematoma	0.8%	0.4%			3.3%	1.1%	1.2%	0.9%
Access problems		3.1%						4.4%

CAS, carotid artery stenting; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; EVA-3S, Endarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis; ICCS, International Carotid Stenting Study; MI, myocardial infarction; SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

Table 49.5.8 Relationship between age and 30-day rates of death/stroke after carotid endarterectomy and carotid artery stenting in symptomatic patients randomized within ICSS, CREST, EVA-3S, and SPACE

	CEAHR (95% CI)	CASHR (95% CI)
<60 years	1.0 (ref)	1.0 (ref)
60–64 years	1.01 (0.34–1.9)	1.79 (0.89–3.60)
65–69 years	0.81 (0.43–1.52)	2.16 (1.13–4.13)
70–74 years	1.20 (0.68–2.13)	4.01 (2.19–7.32)
75–79 years	1.29 (0.74–2.25)	3.94 (2.14–7.28)

CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; EVA-3S, Endarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis; HR, hazard ratio; ICCS, International Carotid Stenting Study; SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

8–14 days after symptom onset had a 3.4% risk of stroke/death, compared with 8.6% after CAS.[80] In CREST, CAS performed within 14 days of symptom onset incurred a 5.6% rate of death/stroke, compared with 2.6% after CEA. In symptomatic patients undergoing an intervention between 15–60 days, CAS was associated with a 6.1% risk of death/stroke, compared with 2.3% after CEA.[81]

A meta-analysis[82] of 30-day death/stroke rates after CEA and CAS involving symptomatic patients randomized within CREST, Endarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), SPACE, and International Carotid Stenting Study (ICSS) (Table 49.5.8) reported significantly higher rates of perioperative stroke in patients aged over 70 years undergoing CAS. By contrast, age had little effect on CEA outcomes. The increase in perioperative stroke in elderly CAS patients may be due to a greater burden of aortic arch disease. Beyond the 30-day perioperative period, long-term data suggest that outcomes after CAS are almost identical to those after CEA.[83, 84] Henceforth the predicted magnitude of the 30-day risk will largely determine whether CEA or CAS is preferable in individual patients. Importantly, in a recent systematic review, 72% of registries reported 30-day death/stroke rates after CAS exceeding the 6% recommended risk threshold in patients with symptomatic ICA stenosis.[65]

An algorithm for managing TIA/minor stroke patients with carotid disease is presented in Figure 49.5.2.

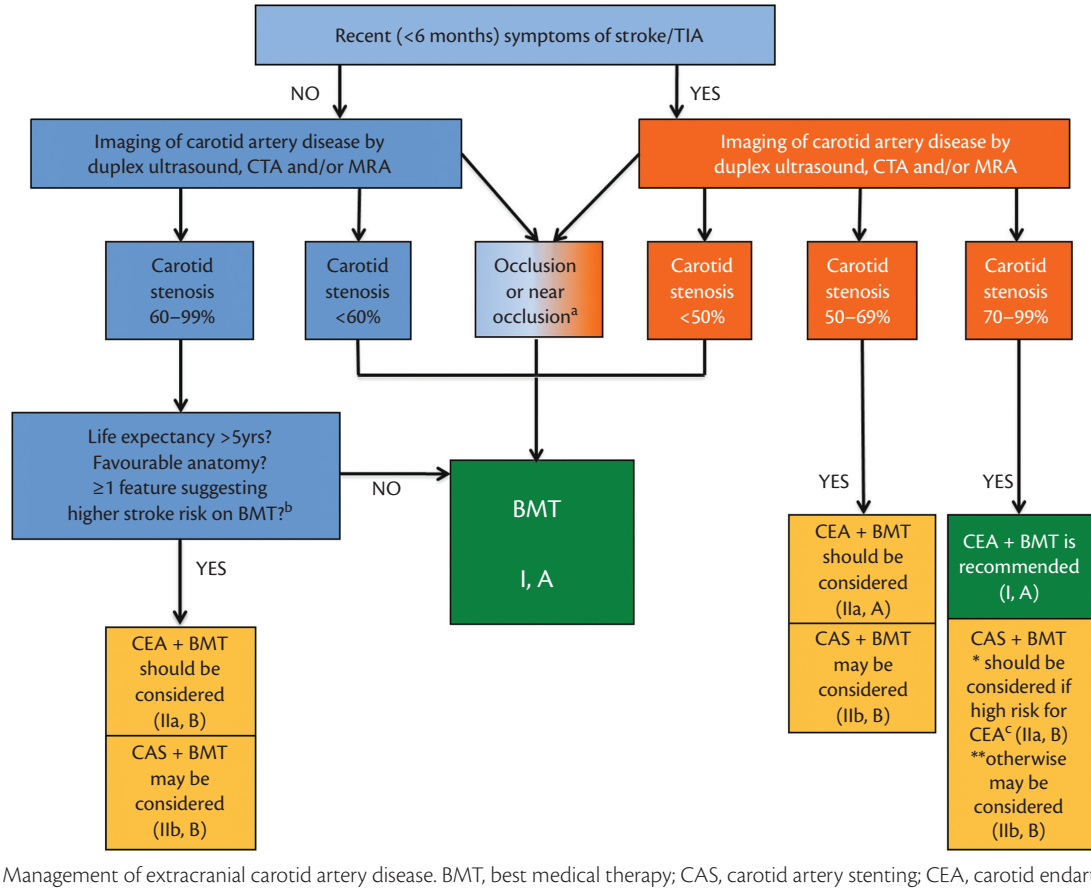


Figure 49.5.2 Management of extracranial carotid artery disease. BMT, best medical therapy; CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TIA, transient ischaemic attack.

[a] With post-stenotic internal carotid artery narrowed to the point of near occlusion.

[b] See Table 49.3.3.

[c] Age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

Table 49.5.9 Recommendations on revascularization in patients with symptomatic* carotid disease

Recommendations	Class[a]	Level[b]
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is <6%[70, 79]	I	A
CEA should be considered in symptomatic patients with 50–69% carotid stenoses, provided the documented procedural death/stroke rate is <6%[70, 79]	IIa	A
In recently symptomatic patients with a 50–99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them 'high risk for CEA', CAS should be considered, provided the documented procedural death/stroke rate is <6%[68, 77, 84]	IIa	B
When revascularization is indicated in 'average surgical risk' patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is <6% [84, 85]	IIb	B
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset[70]	I	A
Revascularization is not recommended in patients with a <50% carotid stenosis[70]	III	A

* Stroke or TIA within 6 months.
a Class of recommendation.
b Level of evidence.

See Table 49.5.9 for recommendations on revascularization in patients with symptomatic carotid disease.

Vertebral artery disease

Definition and natural history

Up to 20% of ischaemic cerebrovascular events involving the posterior circulation are related to VA disease.[85] While fibromuscular dysplasia, trauma, dissection, osteophyte compression, Takayasu arteritis, and aneurysms can affect the VA, atherosclerosis remains the primary aetiology for VA stenotic/occlusive lesions. The majority of vertebrobasilar embolic events originate from the heart, aorta or a proximal vessel (e.g. subclavian artery).[86]

Observational studies suggest that a recently symptomatic 50–99% VA stenosis may be associated with a 30% risk of stroke over a 5-year period.[87] The risk of recurrent stroke is highest in the early period after onset of symptoms. The 90-day stroke risk from first clinical event is 25% in patients with a VA stenosis versus 7% in those without. The risk of recurrent stroke is higher (33%) with intracranial versus extracranial VA stenoses (16%), with the highest risk within the first few weeks after symptoms onset.[87] The natural history of asymptomatic VA stenoses is unknown.

Imaging

CTA and MRA have a higher sensitivity (94%) and specificity (95%) than DUS (sensitivity 70%).[88] Vertebral ostial stenoses are overestimated by MRA,[89] while CTA underestimates the degree and prevalence of ostial vertebral arteries stenoses. Despite these limitations, digital subtraction angiography is rarely required for diagnostic purposes. However, digital subtraction angiography may be necessary in patients with symptomatic vertebral artery disease who are potentially candidates for revascularization. In patients with known VA stenoses, it is reasonable to use DUS to assess stenosis progression and to follow patients after revascularization therapies.

Management of vertebral artery disease

Although no prospective RCTs have evaluated different drug therapies in patients with VA disease, aspirin (or clopidogrel if aspirin is not tolerated) and statins are recommended irrespective of symptoms (see Chapter 49.3 and Chapter 49.4). Most patients with asymptomatic VA disease do not require any revascularization.

In patients with ischaemic events despite antiplatelet therapy, revascularization may be considered. Surgery of extracranial vertebral stenoses (with transposition to common carotid artery, transsubclavian vertebral endarterectomy, distal venous bypass) can be performed with low stroke/death rates in experienced surgical teams.[90, 91] However, in centres with limited expertise of complex VA reconstructions, open surgery has been mostly replaced by endovascular interventions. A systematic review identified 993 patients who were mostly symptomatic, of whom 72% had ostial vertebral stenoses. Overall, 980 were treated with stent implantation with a technical success rate of 99.3% and a 30-day stroke rate of 1.1%. At 24 months, 1.1% had suffered a recurrent vertebrobasilar stroke. Restenosis rates at 24 months were 11% in patients treated with drug-eluting stents and 30% if bare-metal stents were used.[92]

The Vertebral Artery Stenting Trial (VAST)[93] randomized patients with vertebrobasilar symptoms within the preceding 30 days and an extra- or intracranial VA stenosis greater than 50% to stenting plus BMT (n = 57) or BMT alone (n = 58). VAST was suspended after recruiting 115 patients because of regulatory issues. Thirty-day vertebrobasilar stroke or death occurred in 5% of patients randomized to stenting and 2% in the medical arm. At 3 years, 12% of stented patients had recurrent vertebrobasilar stroke, compared with 7% in the medical arm. These results do not support routine endovascular interventions for symptomatic VA stenoses, unless symptoms recur despite optimal medical therapy.

See Table 49.5.10 for recommendations for management of VA stenosis.

Table 49.5.10 Recommendations for management of vertebral artery stenoses

Recommendations	Class[a]	Level[b]
In patients with symptomatic extracranial vertebral artery stenoses, revascularization may be considered for lesions ≥50% in patients with recurrent ischaemic events, despite optimal medical management[91, 92, 94]	IIb	B
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C

[a] Class of recommendation.
[b] Level of evidence.

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Chapter 49.6 Upper extremity artery disease

Key messages

- Upper extremity artery disease due to atherosclerosis is mostly situated at the level of the brachiocephalic trunk, and the subclavian and axillary arteries.
- When clinically suspected, it can be assessed by duplex ultrasound, computed tomography angiography, or magnetic resonance angiography.
- In most asymptomatic patients, medical treatment is the option of choice.
- Revascularization can be proposed in cases of severe/disabling symptoms, bilateral stenosis, stenosis with ipsilateral arteriovenous fistula for dialysis, patients planned for coronary artery bypass grafting or those already operated on with ipsilateral internal mammary artery grafted to coronary arteries with evidence of myocardial ischaemia.
- When revascularization is considered, both endovascular and open surgical options can be proposed, according to lesion characteristics and the patient's risk.

Definition and clinical presentation

The subclavian artery and brachiocephalic trunk are the most common upper extremity locations for atherosclerosis. Distal lesions are mostly related to non-atherosclerotic lesions (Table 49.6.1). Isolated subclavian stenosis is often asymptomatic and may be suspected because of unequal arm blood pressures (BPs) (≥ 10–15 mmHg difference in systolic BP).[1] However, once obstructive disease progresses or affects vertebral vessels and flows, the likelihood of ischaemia or steal symptoms—due to flow reversal in the vertebral artery worsened by arm exercise—increases significantly. Subclavian steal syndrome may be suspected in cases of visual disturbances, syncope, ataxia, vertigo, dysphasia, dysarthria, and facial sensory deficits occurring during efforts made by the arms. Symptoms correlate with the degree of inter-arm BP difference.[2] Brachiocephalic occlusive disease can cause a stroke or transient ischaemic attack in carotid and vertebral territories. Ischaemic symptoms may include exercise-induced fatigue, pain, and arm claudication. In severe cases, especially in distal disease, rest pain and digital ischaemia with necrosis can develop.

Table 49.6.1 Differential diagnosis in upper extremity artery disease by site of lesion

Causes	Subclavian	Axillary	Brachial	Forearm	Hand
Atherosclerosis	•				
Thoracic outlet syndrome	•				
Giant cell arteritis	•				
Takayasu arteritis	•	•			
Radiation artery fibrosis	•	•			
Embolic		•	•	•	•
Fibromuscular dysplasia		•			•
Buerger's disease				•	•
Ergotism				•	•
Connective tissue disease				•	•
Cytotoxic drugs					•
Arterial drug injection					•
Diabetes mellitus					•
Myeloproliferative disorders					•
Hypercoagulative status					•
Cryoglobulins					•
Repetitive trauma					•
Vinyl chloride exposure					•
Iatrogenic lesions	•	•	•	•	•

Natural history

The natural history of subclavian stenosis is poorly studied, but the prognosis is often benign. One particular presentation is when subclavian stenosis occurs in a patient whose corresponding internal mammary artery is grafted to the coronary arteries. Here the subclavian steal may cause angina and other life-threatening cardiac symptoms. Therefore, any symptomatic upper arm arterial occlusive disease should be investigated and treated if necessary. A combination of proximal and distal arm occlusive disease may present a clinical challenge, with poor arm prognosis.

Clinical examination

Although imaging provides a definitive diagnosis, a thorough physical examination is mandatory. Patients may present with unequal arm BP, absent or significantly diminished pulses (axillary, brachial, and radial/ulnar), and cervical or supraclavicular bruits. Ischaemic findings such as finger ulcers or necrosis are rare. Examination should assess cerebral circulation including palpation of carotid pulses and auscultation for vertebral and carotid bruits. The presence of arm pain, pallor, paraesthesia, or coldness should be evaluated. The Allen test confirming adequate hand perfusion should be performed in patients in whom the radial artery will be instrumented or harvested for coronary revascularization.[3]

Diagnostic methods

Duplex ultrasound

Doppler assessment of subclavian arteries enables the detection of high-velocity flows indicating greater than 50% stenosis. Due to the proximal location of subclavian lesions, it is sometimes challenging to differentiate high-grade ostial stenosis from complete occlusion. Monophasic post-stenotic flow and altered flow in the ipsilateral vertebral artery are common in the case of greater than 70% proximal subclavian stenosis. When subclavian steal syndrome is suspected, flow reversal should be assessed in the ipsilateral extracranial vertebral artery by hyperaemia testing. Severe stenosis or occlusion of the right brachiocephalic trunk is associated with reduced flow velocities in the ipsilateral subclavian artery and the common carotid artery. Abnormal or doubtful duplex ultrasound should lead to anatomical imaging (computed tomography angiography or magnetic resonance angiography).

Computed tomography angiography

Computed tomography angiography is an excellent imaging tool for supra-aortic lesions. It can also provide extravascular information, especially when thoracic outlet syndrome is a differential diagnosis.

Magnetic resonance angiography

Magnetic resonance angiography provides both functional and morphological information, which is useful to distinguish anterograde from retrograde perfusion and to estimate stenosis severity.

Digital subtraction angiography

Although considered as the gold standard imaging method, digital subtraction angiography is being increasingly replaced by other imaging modalities. Its main use is in combination with endovascular therapy.

Positron emission tomography

Positron emission tomography is useful for the diagnosis of arteritis (Takayasu disease, giant cell arteritis), but not for assessment of atherosclerotic lesions in clinical practice.

Treatment

Risk factor control and best medial therapy are recommended in all patients with symptomatic upper extremity artery disease to reduce cardiovascular risk.[4] Revascularization is indicated in symptomatic patients with a transient ischaemic attack/stroke, coronary subclavian steal syndrome, ipsilateral haemodialysis access dysfunction, or impaired quality of life. Revascularization should be considered in asymptomatic patients with planned coronary artery bypass grafting using the internal mammary artery, those with ipsilateral haemodialysis access, as well as asymptomatic patients with significant bilateral subclavian stenosis/occlusion for adequate BP surveillance. For revascularization, both endovascular and surgical procedures are available. There are no randomized controlled trials comparing endovascular versus open repair. The risk of severe complications, including vertebrobasilar stroke, is low with both approaches. Post-procedural stroke rate is reported at 2.6% for endovascular therapy[5] and 0.9–2.4% after open surgery.[5–7]

Endovascular treatment

Percutaneous angioplasty for subclavian arterial stenosis is often used with stenting. There is no conclusive evidence to determine whether stenting is more effective than balloon angioplasty.[8] In a systematic review of 544 patients comparing both options, stenting was superior to angioplasty alone with a higher patency rate at 1 year indicated by absence of events.[9] Technical success of endovascular therapy is 100% when treating stenosis, and 80–95% when treating occlusions. Similar results were reported for endovascular therapy of the innominate artery.[10] In heavily calcified ostial lesions, in addition to an easier placement, balloon-expandable stents give more radial force than nitinol stents. Mid-term patency (≥ 24 months) following subclavian endovascular therapy is 70–85%.[11]

Open surgery

An endovascular approach is often the default strategy. However, in selected patients with low operative risk, with subclavian artery occlusion, or after endovascular therapy failure, surgical subclavian–carotid transposition is safe with good long-term patency results (5-year patency: 96%).[7] Carotid–subclavian bypass surgery with a prosthetic graft showed long-term benefit with low operative mortality and morbidity rates, especially in patients with extensive disease or re-occlusion after stenting

Table 49.6.2 Recommendations on the management of subclavian artery stenosis

Recommendations	Class[a]	Level[b]
In symptomatic patients with subclavian artery stenosis/occlusion revascularization should be considered	IIa	C
In symptomatic patients with a stenotic/occluded subclavian artery, both revascularization options (stenting or surgery) should be considered and discussed case by case according to the lesion characteristics and patient's risk	IIa	C
In asymptomatic subclavian artery stenosis, revascularization:		
◆ should be considered in the case of proximal stenosis in patients undergoing CABG using the ipsilateral internal mammary artery	IIa	C
◆ should be considered in the case of proximal stenosis in patients who already have the ipsilateral internal mammary artery grafted to coronary arteries with evidence of myocardial ischaemia	IIa	C
◆ should be considered in the case of subclavian artery stenosis and ipsilateral arteriovenous fistula for dialysis	IIa	C
◆ may be considered in the case of bilateral stenosis, in order to be able to monitor blood pressure accurately	IIb	C

CABG, coronary artery bypass graft surgery.
[a] Class of recommendation.
[b] Level of evidence.

(5-year patency: 97%).[12] Other options are extrathoracic extra-anatomic bypass procedures (axillo–axillary, carotid–axillary, or carotid–carotid bypass).[13, 14] The transthoracic approach is an option in patients with multivessel disease involving the aortic arch and several supra-aortic vessels.[6]

Medical therapy

In symptomatic patients with contraindications for endovascular therapy or open surgery, prostanoid infusion or thoracic sympathectomy may be considered.[15]

See Table 49.6.2 for recommendations on the management of subclavian artery stenosis.

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Chapter 49.7 Mesenteric artery disease

Key messages

- Mesenteric artery disease, acute or chronic, is underdiagnosed and highly lethal.
- The prerequisite of diagnosis is clinical suspicion, followed by imaging.
- In many cases, endovascular surgery should be considered since a less invasive option is preferred in these often frail patients.
- In chronic mesenteric disease, open surgery still has an advantage of better durability in patients with long expected survival.
- In acute embolic occlusion, open and endovascular surgery seem to have similar success rates.

This chapter covers acute and chronic occlusion of the mesenteric arteries. Chronic mesenteric artery disease is related to atherosclerosis as well as non-atherosclerotic conditions. For further information, refer to the recently published European Society for Vascular Surgery Guidelines.[1]

Acute mesenteric ischaemia

Diagnosis

Acute thromboembolic occlusion affects mostly the superior mesenteric artery. Due to the extensive collaterals in the mesenteric circulation, the coeliac trunk or the inferior mesenteric artery occlusion leads infrequently to intestinal infarction. In most population studies, acute mesenteric ischaemia is more often related to embolism than to thrombotic occlusion. Outcome is very time-sensitive, and dependent on clinical suspicion. In almost 80% of cases, acute embolic occlusion of the superior mesenteric artery is associated with the following clinical triad: (1) severe abdominal pain with minimal findings at examination; (2) bowel emptying (often both vomiting and diarrhoea); and (3) the presence of a source of embolus (e.g. atrial fibrillation). Embolism also often affects other localizations, which is helpful for orienting the diagnosis.

Acute thrombotic occlusion of the superior mesenteric artery is most often a result of an ostial proximal stenosis or occlusion, with or without general circulatory factors such as dehydration, low cardiac output, or hypercoagulability. The patients often have previous symptoms of chronic mesenteric ischaemia (CMI), other atherosclerotic manifestations and a smoking history.

Although D-dimer is highly sensitive, it lacks specificity. There are no other reliable plasma markers for acute mesenteric ischaemia.[2–4] In a meta-analysis, the pooled sensitivity for D-dimer was 96%, with a specificity of 40%.[5] Lactate is metabolized effectively by the liver, explaining why it does not serve as an early warning. Lactate is elevated only after bowel gangrene has developed.[5]

Plain abdominal X-ray is not specific. If normal, it does not exclude the diagnosis. High-resolution computed tomography angiography (CTA) is a major breakthrough for the timely diagnosis of acute mesenteric ischaemia. It should be performed in arterial and venous phases, with 1 mm slices. Diagnostic accuracy for CTA in diagnosing acute superior mesenteric artery occlusion is excellent. In a meta-analysis, the pooled estimated sensitivity was 94% and the specificity was 95%. Asking the radiologist specifically about occlusion of the mesenteric arteries improves diagnostic accuracy.[6] Elevated creatinine levels are common but should not contraindicate CTA in the case of clinical suspicion. CT examination of the bowel (venous phase) may show wall thickening, dilatation, intestinal pneumatosis, portal venous air, mesenteric oedema and ascites. There is no role for ultrasound or invasive angiography in diagnosing acute mesenteric ischaemia. Magnetic resonance angiography (MRA) is seldom available outside office hours, explaining why its diagnostic accuracy has not been investigated in this setting.

Treatment

Most patients with an acute occlusion of the superior mesenteric artery require immediate revascularization to survive. Approximately 20–30% can survive with bowel resection only, especially with distal embolism.[7] In other cases, revascularization must be attempted. Whether revascularization or bowel inspection (with possible resection) should be performed first is controversial. Data suggest that revascularization should be attempted first, unless there is serious peritonitis and septic shock.[1]

Another controversy is to determine whether open surgery or endovascular therapy of the occluded superior mesenteric artery should be attempted as first choice.[8–11] Hybrid intervention is an alternative, with retrograde operative mesenteric stenting, where the superior mesenteric artery is punctured in the open abdomen, followed by stenting.[12] In the absence of randomized controlled trials, evidence is based on prospective registries.[8, 10, 13, 14] In the case of embolic occlusion, open and endovascular revascularizations seem to do equally well, whereas with thrombotic occlusion, endovascular therapy is associated with lower mortality and bowel resection rates. The principles of damage control surgery[15] are important to follow when treating these frail patients. This concept focuses on saving life by restoring normal physiology as quickly as possible, so avoiding unnecessary time-consuming procedures.[15] Although laparotomy is not mandatory after endovascular therapy in these patients with acute bowel ischaemia, it is often necessary to inspect the bowel. In this setting, second-look laparotomy is also indicated after open revascularization.[10, 16] Intra-arterial catheter thrombolysis of the superior mesenteric artery has been reported with good results. Severe bleeding complications were uncommon, except when intestinal mucosal gangrene was present.[17]

Table 49.7.1 Recommendations on the management of acute mesenteric ischaemia

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended[5]	I	C
In patients with suspicion of acute mesenteric ischaemia, the measurement of D-dimer should be considered to rule out the diagnosis[3–5]	IIa	B
Treatment		
In patients with acute thrombotic occlusion of the superior mesenteric artery, endovascular therapy should be considered as first-line therapy for revascularization[8, 10, 13, 14]	IIa	B
In patients with acute embolic occlusion of the superior mesenteric artery, both endovascular and open surgery therapy should be considered[8, 10, 13, 14]	IIa	B

CTA, computed tomography angiography.
[a] Class of recommendation.
[b] Level of evidence.

See Table 49.7.1 for recommendations on the management of acute mesenteric ischaemia.

Chronic mesenteric artery disease

Chronic mesenteric artery disease stands either for 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. In patients with abdominal aortic aneurysms and LEAD, significant stenosis (mostly asymptomatic) of at least one of the three arteries was detected in 40% and 27%, respectively.[18]

Diagnosis

Clinical examination

The classical symptoms of CMI are postprandial abdominal pain, weight loss, diarrhoea, or constipation. To avoid pain, the patient suffers from food aversion although appetite is not affected (in contrast to patients with malignancies). As with acute mesenteric ischaemia, clinical suspicion is the key for an early diagnosis, and may be life-saving. Abdominal examination may reveal a bruit. Non-specific laboratory findings include anaemia, leucopenia, electrolyte abnormalities, and hypoalbuminaemia, secondary to malnutrition.

Imaging

Duplex ultrasound is often the imaging tool of first choice. This investigation requires great skills and should be performed in specialized centres. Diagnostic criteria have been suggested, although without consensus.[19, 20] When a decision to treat CMI is taken, an anatomical mapping of the lesions is needed, mostly using CTA. There is no study comparing CTA with MRA or digital subtraction angiography, the latter offering the advantages of mapping the flow and enabling poststenotic pressure measurements.

Functional assessments

There is a need for functional testing, to verify if the patient's symptoms are indeed explained by ischaemia, in particular if the patient has a single-vessel lesion. Several methods were developed: endoscopic assessment of the bowel, measurement of gastrointestinal blood flow, measurement of decreased tissue PO_2 or increased tissue CO_2 (tonometry, often combined with exercise), measurement of ischaemia-specific biomarkers, and laparotomy with histopathology. Although functional testing is crucial in diagnosing chronic mesenteric ischaemia, in particular in one-vessel disease, the methodology is not yet standardized to permit any recommendations at this time.[1]

For more complete information regarding the often difficult diagnosis of chronic mesenteric ischaemia, the reader can refer to the European Society of Vascular Surgery Guidelines.[1]

Treatment

There is no indication for prophylactic revascularization in patients with asymptomatic disease. In symptomatic CMI, it is not recommended to delay revascularization in order to improve the nutritional status. Delayed revascularization has been associated with clinical deterioration, bowel infarction, and sepsis from catheter-related complications.[21] The number of mesenteric revascularizations has increased tenfold over the last decade, as the result of increased recognition and imaging, and the use of endovascular therapy as a less invasive treatment.[14] In most centres, angioplasty and stenting have become the first option, reserving open surgery for patients with failed endovascular therapy. Data from the United States showed lower postoperative mortality after endovascular therapy (odds ratio 0.20, 95% confidence interval 0.17–0.24).[14, 22] Open mesenteric bypass, however, offers improved patency, lower re-intervention rates, and better freedom from recurrent symptoms.[14, 23] In the absence of randomized controlled trials it is not possible to issue a recommendation favouring open surgery or endovascular therapy as first-line therapy. Both alternatives should be discussed on a case-by-case basis by a multidisciplinary team.

Another controversy is whether one or two vessels (superior mesenteric or coeliac artery, or both) should be treated. Two retrospective studies showed a non-significant trend towards lower recurrence rates with two-vessel stenting.[24, 25] Another study reported similar recurrence rates at 2 years.[26] Balloon angioplasty has been replaced by primary stenting in most centres. Regarding the choice between bare-metal or covered stents to treat superior mesenteric artery stenosis, in one non-randomized study of 225 patients,[27] covered stents were associated with lower restenosis and symptom recurrence rates, and fewer re-interventions (10% vs 50%).

Although endovascular therapy has been increasingly used, open surgery is still indicated at least in the following situations: after failed endovascular therapy without possibility for repeat endovascular therapy; extensive occlusion, calcifications, or other technical difficulties; and young patients with non-atherosclerotic lesions due to vasculitis or mid-aortic syndrome. Several different surgical techniques are described with no proof for the superiority of any of them.

Secondary prevention

Following acute mesenteric arterial occlusion, life-long medical treatment should be considered, including lifestyle changes and best medical therapy for atherosclerosis (see Chapter 49.3). After embolic occlusion, treatment of the source of embolus or lifelong anticoagulation therapy, or both, should be considered.[28] After treatment of CMI, antiplatelet therapy is indicated.[29] The potential benefit of dual antiplatelet therapy is unknown.

See Table 49.7.2 for recommendations for management of chronic mesenteric artery disease.

Table 49.7.2 Recommendations for management of chronic mesenteric artery disease

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected CMI, DUS is recommended as the first-line examination[19, 20]	I	C
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[18]	IIa	C
Treatment		
In patients with symptomatic multivessel CMI, revascularization is recommended[18, 21]	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status[18, 21]	III	C

CMI, chronic mesenteric ischaemia; DUS, duplex ultrasound.
[a] Class of recommendation.
[b] Level of evidence.

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Chapter 49.8 Renal artery disease

Key messages

- Atherosclerotic renal artery disease (RAD) is the most common cause of 'renovascular hypertension'.
- In clinical situations with high suspicion, the use of duplex ultrasound, usually as first-line imaging, followed by magnetic resonance angiography (MRA) or computed tomography angiography (CTA), or both, are recommended for the establishment of RAD diagnosis.
- Renal revascularization does not generally improve blood pressure, renal, or cardiovascular outcomes in patients with atherosclerotic RAD.
- With few exceptions, medical therapy with antihypertensive agents, antiplatelet drugs, and statins remain the cornerstone for management of patients with RAD.

Introduction

RAD is generally considered when renal artery stenosis (RAS) is 60% or greater, although additional functional assessment by haemodynamic criteria is advisable. The prevalence of RAD increases with advancing age and is mostly related to atherosclerosis. It is associated with male gender, hypertension, smoking, diabetes mellitus, chronic kidney disease (CKD), aorto-iliac occlusive disease, and coronary artery disease.[1] It may be present in 5–10% of the general population, with a higher prevalence in high-risk populations.[2] Approximately 20% have bilateral disease or a single functioning kidney is affected. Less frequent causes of RAD are fibromuscular dysplasia (FMD)[3] and arteritis. The former is the most frequent cause of RAD in young hypertensive patients (especially in women).

Clinical presentation

Clinical signs include resistant hypertension, unexplained renal failure, and, uncommonly, flash pulmonary oedema (Box 49.8.1). RAD promotes hypertension and subsequent cardiovascular disease, while atherosclerotic disease may in turn cause RAD. The filtration capacity loss in the ischaemic kidney may be due to hypoperfusion or recurrent microembolism, or both. Renal hypoperfusion causes an increase in blood pressure (BP) secondary to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), which may be important in the risk of cardiovascular complications.[4] With unilateral RAS, the contralateral kidney will increase sodium excretion and there is no sodium retention or volume overload. In patients with severe bilateral RAS or unilateral RAS in a single functioning kidney, renal failure and flash pulmonary oedema can occur.[5]

Natural history

Atherosclerotic RAD is progressive and the risk of progression is highest with high-grade stenosis, severe hypertension, and diabetes.[6] Less than 10% of patients with RAS progress to high-grade stenosis or occlusion within 5 years,[7] and renal function deterioration is rare with unilateral RAS, but more evident with bilateral RAS or with a single functioning kidney (3%, 18%, and 55%, respectively, at 2 years).[8]

Diagnostic strategy

Patients with a clinical suspicion of RAS (Box 49.8.1) should undergo a diagnostic evaluation including physical examination, exclusion of other potential causes of secondary hypertension, and ambulatory (or home) BP measurement.

Duplex ultrasound is the first-line imaging modality to screen for significant (≥60%) stenosis,[2, 4, 7, 9] although it may overestimate the degree of stenosis. It can be repeated to assess stenosis progression and its haemodynamic consequences (e.g. flow velocity and vascular resistance). Peak systolic velocity in the main renal artery shows the best sensitivity (85%) and specificity (92%) to identify angiographically significant stenoses.[10] Thus, criteria other than peak systolic velocity should be used to support the diagnosis.[9, 10] The renal resistive index (RRI) may

Box 49.8.1

- 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 CKD 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 a mineralocorticoid-receptor antagonist in appropriate doses).
- Hypertensive crisis (i.e. acute kidney injury, acute heart failure, hypertensive encephalopathy, or grade 3–4 retinopathy).
- New azotaemia or worsening of renal function after treatment with RAAS blockers.
- Unexplained atrophic kidney or discrepancy in kidney size, or unexplained renal failure.
- Flash pulmonary oedema.

help to identify more severe RAS and provide additional information on patient response to intervention.[4, 9] It is measured by Doppler sonography in an intrarenal artery and is defined as the ratio of [peak systolic velocity − end diastolic velocity] to peak systolic velocity. The RRI can provide information on vascular and parenchymal renal abnormalities, but it can also be regarded as a marker of systemic vascular properties. Normal values range between 0.60 and 0.70 and RRI can be abnormal both when high and low. It can be influenced both by renal and extrarenal determinants. Therefore, a low (< 60) RRI can reflect RAS greater than 70% (intrarenal determinant) or valvular aortic stenosis, thoracic or suprarenal abdominal aortic stenosis, tachycardia, hypervolaemia, and parasympathetic activation (extrarenal determinants). A high RRI (>70) can reflect vasoconstriction, arteriolosclerosis, increased interstitial and increased venous pressure (intrarenal determinants) or adrenergic hyperactivity, bradycardia, and increased systemic pulse pressure (extrarenal determinants).[11] The latter is the result of increased aortic stiffening.[12]

In the case of isolated renal diseases (i.e. acute kidney injury, hydronephrosis, renal vein thrombosis), RRI is a reliable index of renal damage. However, in the case of arterial involvement, both renal and systemic (i.e. CKD), RRI predicts renal and general outcomes as a marker of systemic atherosclerotic/arteriosclerotic burden rather than being a marker of renal damage.[13] The latter notion is still a matter of investigation.

In the case of a significant RAS (>75–80%), the Doppler poststenotic flow wave is characterized by a 'tardus' (slow) and 'parvus' (weak) pattern, and thus RRI is low (<0.60). This low RRI suggests that the ischaemic kidney is protected by a marked vasodilatation, modulated by the self-regulating intrarenal mechanisms. However, progression of chronic renal disease leads to an increase in RRI due to an increase in parenchymal vascular resistance, and this may mask the diagnosis and haemodynamic effects of significant artery stenosis. A low RRI (<0.60) may predict a successful outcome of revascularization in terms of renal function recovery and regulation of BP. A high RRI (>0.75–0.80), denoting parenchymal disease, is associated with an unsuccessful outcome post revascularization. Recently, an increased RRI (>0.73) measured in the kidney contralateral to RAS was found to be the best single predictor of worse renal function outcome after renal revascularization,[14] possibly because it represented the state of the small parenchymal renal vessels not subject directly to large renal vessel disease.

Renal duplex ultrasound requires experience. It may be difficult in overweight subjects. Other limitations include failure to visualize the entire renal artery, and missing the highest peak systolic velocity tracing. Accessory renal arteries may be missed.

Multidetector CTA and MRA (with or without gadolinium) show equally high sensitivities (64–100% and 94–97%) and specificities (92–98% and 85–93%) for detection of significant RAS.[15, 16] CTA provides higher spatial resolution but usual limitations should always be considered. Gadolinium-enhanced MRA provides excellent characterization of renal arteries, the surrounding vessels, renal mass, and even renal excretion function. It tends to overestimate the stenosis severity. It is less useful in patients with renal artery stents because of artefacts. Digital subtraction angiography remains the gold standard for the diagnosis of RAS.[7, 15] Since the correlation between the angiographic stenosis and the haemodynamic impact is poor, a major advantage of digital subtraction angiography is the possibility to measure the pressure gradient across the lesion, which is especially useful for moderate stenosis. A systolic pressure gradient greater than 20 mmHg or a resting pressure ratio distal to the stenosis less than 0.90 is considered to confirm significant stenosis in symptomatic patients.[17] Renal artery fractional flow reserve measured during maximum hyperaemia, induced by papaverine, dopamine, or acetylcholine, is an alternative method to assess the stenosis severity, which might predict the clinical response to intervention.[4] Due to the potential risks with invasive procedures, angiography is generally limited to visualization and quantification of the stenosis before vascular intervention. It is also indicated when clinical suspicion is high and the results of non-invasive examinations are inconclusive.[2, 15] Renal scintigraphy, plasma renin measurements before and after angiotensin-converting enzyme inhibitor (ACEI) provocation, and venous renin measurements are not considered anymore for the diagnosis of atherosclerotic RAD.[1, 2]

See Table 49.8.1 for recommendations for diagnostic strategies for RAD.

Table 49.8.1 Recommendations for diagnostic strategies for renal artery disease

Recommendations	Class[a]	Level[b]
DUS (as first-line), CTA,[c] and MRA[d] are recommended imaging modalities to establish a diagnosis of renal artery disease[1, 15]	I	B
DSA may be considered to confirm a diagnosis of renal artery disease when clinical suspicion is high and the results of non-invasive examinations are inconclusive[15]	IIb	C
Renal scintigraphy, plasma renin measurements before and after ACEI provocation, and vein renin measurements are not recommended for screening of atherosclerotic renal artery disease[1]	III	C

ACEI, angiotensin-converting enzyme inhibitor; CTA, computed tomography angiography; DSA, digital subtraction angiography; DUS, duplex ultrasound; eGFR, estimated glomerular filtration rate; MRA, magnetic resonance angiography.
[a] Class of recommendation.
[b] Level of evidence.
[c] When eGFR is ≥60 mL/min.
[d] When eGFR is ≥30 mL/min.

Prognosis

Life expectancy is reduced in patients with RAD without end-stage CKD, as they mostly die from an acute cardiovascular event.[2, 18] Patients who progress to end-stage CKD have even higher mortality rates.[19]

Treatment

Medical therapy

Risk assessment, lifestyle management, and medical treatment should follow current European Society of Cardiology Guidelines.[20–22] Most antihypertensive drugs (ACEIs, angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, and diuretics) are effective for treating hypertension and may lead to slowing of the progression of renal disease.[23, 24] Most patients with significant RAS tolerate ACEIs or ARBs without difficulty. In large observational studies, ACEIs and ARBs have shown benefits in reducing mortality and morbidity in patients with RAD.[24–26] However, these drugs can reduce glomerular capillary hydrostatic pressure enough to cause a transient decrease in glomerular filtration rate and raise serum creatinine, warranting caution and close follow-up. These drugs may be introduced in the case of bilateral RAS and when the lesion affects a single functioning kidney, provided that the patients are very carefully monitored.[23, 25] Optimal BP in the setting of RAD is unknown. It has been hypothesized that severe RAS might require higher BPs to maintain adequate blood flow across the stenosis; however, very low rates of progressive renal failure in medically managed patients argue against such a strategy.

Statins are associated with improved survival, slower lesion progression, and reduced restenosis risk after renal stenting.[27, 28] Antiplatelet therapy should be part of best medical therapy (BMT).

Revascularization

Impact on blood pressure control, renal function, and survival

Uncontrolled trials reported improved BP control in resistant hypertensive patients following renal stenting,[29, 30] but previous[31] and three recent major randomized controlled trials (Table 49.8.2) showed no difference between endovascular therapy and BMT other than a minor reduction of antihypertensive medications

Table 49.8.2 Major clinical trials on renal artery stenting

Trial	Main selection criteria	Treatment group(*n*)	Control group(*n*)	Primary outcome	Main results	Renal outcome	Hypertension outcome	Intervention-related complication (%)
STAR10 centres; follow-up 2 years (2009)	Impaired renal function, ostial renal artery of ≥50%, stable BP	64	76	≥20% eGFR decrease	No difference in GFR decline	No difference in GFR decline	No difference	2 procedure-related deaths (3%), 1 late death secondary to an infected haematoma, and 1 patient who required dialysis secondary to cholesterol embolism
ASTRAL57 centres; follow-up 5 years (2009)	Uncontrolled/ refractory hypertension or unexplained CKD with unilateral or bilateral RAS and clinician unsure of best treatment	403	403	20% reduction in the mean slope of the reciprocal of the serum creatinine level	No difference in BP, renal function, mortality, CV events	No difference in renal function	No difference in BP	Serious complications associated with revascularization occurred in 23 patients, including 2 deaths and 3 amputations of toes or limbs
CORAL109 centres; follow-up 5 years (2014)	Hypertension on ≥2 anti-hypertensive drugs or CKD stage ≥2 with unilateral or bilateral renal stenosis (≥60%)	467	480	Major CV or renal event	No difference in the primary endpoint (HR 0.94; p =0.58)	No difference in renal function or events	Modest difference in systolic BP favouring the stent group (−2.3 mmHg; p =0.03)	Total 26 procedure-related complications (5.5%)

ASTRAL, Angioplasty and Stenting for Renal Artery Lesions; BP, blood pressure; CKD, chronic kidney disease; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HR, hazard ratio; RAS, renal artery stenosis; STAR, Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function.

Comments on the power of each trial:

STAR: the sample size calculation was based on an expected reduction in the incidence of progressive renal failure, defined as serum creatinine levels that increased by at least 20% in the previous 12 months, from 50% in the medication group to 20% in the stent group, with a power of 90%. To detect this difference at a significance level of 5140 patients were needed. The study had a lower rate of primary events than anticipated, which reduced the power of the trial to detect a difference between the two groups

ASTRAL: the trial was designed to detect a reduction of 20% in the mean slope of the reciprocal of the serum creatinine level. Assuming that there would be a mean slope of -1.6×10^{-3} l per mm per year (with a standard deviation of 1.5) in the medical-therapy group, we determined that achieving a mean slope of -1.28×10^{-3} l per mm per year in the revascularization group would require the enrolment of 700 patients, with a power of 80% and a two-tailed p-value of 0.05. Target recruitment was initially set at 1000 patients.

CORAL: 1080 participants would need to be enrolled for the study to have 90% power to test the hypothesis that stenting would reduce the incidence of the primary endpoint by 25% (HR 0.75) at 2 years, at a two-sided type I error rate of 0.05. Because the recruitment was slower than anticipated, the data and safety monitoring board recommended termination of recruitment on 30 January 2010 (at which point 947 participants had undergone randomization), and follow-up was extended through 28 September 2012 to preserve the statistical power.

after revascularization (2.96 vs 3.18 drugs).[32–35] Data do not support a benefit of stenting based on degree of stenosis, haemodynamic significance of the lesion, or higher pre-treatment BP.[34]

Regarding renal function, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial reported no benefit from endovascular therapy over BMT.[36] Progressive renal failure occurred in 16.8% in the endovascular therapy group versus 18.9% in the BMT group (p =0.34), and permanent renal replacement therapy occurred in 3.5% versus 1.7%, respectively (p =0.11). Renal artery dissection was reported in 2.4% of the endovascular therapy group. The two other randomized controlled trials showed similar findings even in the highest risk groups, including severe kidney ischaemia and impaired, or rapidly decreasing, kidney function. There was no advantage for revascularization with regard to cardiovascular morbidity and mortality.[33, 35, 37]

Revascularization in specific indications

With the low evidence of a potential benefit for revascularization over medical therapy, renal revascularization could only be considered in patients with anatomically and functionally significant RAS with the following particular aetiology or clinical scenarios.

RAD due to fibromuscular dysplasia

The prevalence of renal FMD is considered to be less than 1% in the general population,[38] and more common in women than men by a ratio of 9:1. Renovascular hypertension is the most common clinical presentation of FMD. Revascularization of FMD-related lesions should be recommended only in cases of symptomatic FMD with signs of organ ischaemia.[3] Renal balloon angioplasty is the first-line revascularization technique and stenting should be considered in the management of dissection or balloon angioplasty failure.[39–41] In a meta-analysis (47 studies for endovascular therapy, 1616 patients; 23 studies for open surgery, 1014 patients), major complication rates and mortality rates were lower in the case of endovascular therapy (6.3% and 0.9% vs 15.4% and 1.2%, respectively).[41] Therefore, open surgery should be reserved for the management of stenosis associated with complex aneurysms, complex lesions (arterial bifurcation or branches), or endovascular therapy failure.[3]

RAD in flash pulmonary oedema or congestive heart failure

Patients with sudden-onset or 'flash' pulmonary oedema or congestive heart failure predominantly with preserved left ventricular function may be candidates for endovascular therapy,[5, 43, 44] although a sub-analysis of the CORAL trial was not conclusive.[33]

RAD and acute oligo-/anuric renal failure

Patients with acute oligo-/anuric renal failure with kidney ischaemia may be candidates for revascularization in some rare cases of bilateral RAS without significant renal atrophy.

Technical considerations for revascularization

Endovascular therapy

In atherosclerotic RAD, stent placement has consistently proven superior to balloon angioplasty.[45] Restenosis rates range from 4% to 20%[46]; drug-eluting stents have not demonstrated a better outcome.[47, 48] In one study, repeated stenting was associated with similar peri- and postoperative results with low complication rates compared to the primary procedure.[49] The role of distal embolus protection devices was addressed in a small randomized trial, which showed no improved renal function outcome for distal filter protection during stent revascularization except with adjunctive glycoprotein IIb/IIIa receptor antagonist use.[50]

Surgery

Renal artery surgery appears to be superior to endovascular therapy in patients with complex disease of the renal arteries (e.g. aneurysms), failed endovascular procedures (i.e. dissection), and for patients undergoing surgical repair of the aorta with concomitant RAS.[51, 52] While truncal renal artery aneurysms can alternatively be treated with covered stents, aneurysms of the renal artery bifurcation and branches should be operated on, and *ex situ* renal artery revascularization may be recommended in expert centres.[53, 54] Thirty-day mortality rates range from 0% to 9%. After a follow-up of up to 5 years, 5–15% needed a reoperation, and survival was 65–81%.[52, 55–57]

See Table 49.8.3 for recommendations for treatment strategies for RAD.

Table 49.8.3 Recommendations for treatment strategies for renal artery disease

Recommendations	Class[a]	Level[b]
Medical therapy		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral renal artery stenosis[23–26]	I	B
Calcium channel blockers, beta blockers, and diuretics are recommended for treatment of hypertension associated with renal artery disease	I	C
ACEIs/ARBs may be considered in bilateral severe renal artery stenosis and in the case of stenosis in a single functioning kidney, if well tolerated and under close monitoring[23, 25]	IIb	B
Revascularization		
Routine revascularization is not recommended in renal artery stenosis secondary to atherosclerosis[33, 35, 37]	III	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[39–41]	IIa	B
Balloon angioplasty, with or without stenting, may be considered in selected patients with renal artery stenosis and unexplained recurrent congestive heart failure or sudden pulmonary oedema[33, 42, 43]	IIb	C
In the case of an indication for revascularization, surgical revascularization should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure, or during open aortic surgery[51, 52]	IIa	B

ACEIs, angiotensin-converting enzyme inhibitor; ARBs, angiotensin-receptor blockers.
[a] Class of recommendation.
[b] Level of evidence.

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Chapter 49.9 Lower extremity artery disease

Key messages

- Most patients with lower extremity artery disease (LEAD) are asymptomatic. Walking capacity must be assessed to detect clinically masked LEAD.
- The clinical signs vary broadly. Atypical symptoms are frequent.
- Even asymptomatic patients with LEAD are at high risk of cardiovascular (CV) events and must benefit from most CV preventive strategies, especially strict control of risk factors.
- Antithrombotic therapies are indicated in patients with symptomatic LEAD. There is no proven benefit for their use in asymptomatic patients.
- Ankle–brachial index (ABI) is indicated as first-line test for screening and diagnosis of LEAD. Duplex ultrasound (DUS) is the first imaging method.
- Data from anatomical imaging tests should always be analysed in conjunction with symptoms and haemodynamic tests prior to treatment decision.
- In patients with intermittent claudication (IC), CV prevention and exercise training are the cornerstones of management. If daily life activity is severely compromised, first-line revascularization can be proposed, along with exercise therapy (ExT).
- Chronic limb-threatening ischaemia (CLTI) specifies clinical patterns with a vulnerable limb viability related to several factors. The risk is stratified according to the severity of ischaemia, wounds, and infection.
- Early recognition of tissue loss and/or infection and referral to the vascular specialist is mandatory for limb salvage by a multidisciplinary approach. Revascularization is indicated whenever feasible.
- Acute limb ischaemia with neurological deficit mandates urgent revascularization.

Clinical presentation and natural history

LEAD has several different presentations, categorized according to the Fontaine or Rutherford classifications (Table 49.9.1). Even with a similar extent and level of disease progression, symptoms and their intensity may vary from one patient to another.

Most patients are asymptomatic, detected either by a low ABI (<0.90) or pulse abolition. Among these, a subset may have severe disease without symptoms, which can be related to their incapacity to walk enough to reveal symptoms (e.g. heart failure) or reduced pain sensitivity (e.g. diabetic neuropathy), or both of these. This subgroup should be qualified as 'masked LEAD'. In a study of 460 patients with LEAD, one-third of asymptomatic patients were unable to walk more than six blocks, corresponding to this concept.[1] These patients were older, more often women, with higher rates of neuropathy and multiple co-morbidities. While all asymptomatic patients are at increased risk of CV events, the subgroup with masked LEAD is also at high risk of limb events. This situation explains how a subset of patients presents a specific path with 'asymptomatic' disease shifting rapidly to severe LEAD. A typical presentation is an elderly patient with several co-morbidities who presents with toe necrosis after a trivial wound (e.g. after aggressive nail clipping). Identifying these patients is important to educate about foot protection. Hence, prior to the estimation of pain when walking, a clinical assessment of walking abilities is necessary, and clinical examination should also look for neuropathy. LEAD can also be clinically masked in one leg when the other one has more disabling disease.

Table 49.9.1 Clinical stages of lower extremity artery disease

Fontaine classification				Rutherford classification		
Stage		Symptoms		Grade	Category	Symptoms
I		Asymptomatic	⇔	0	0	Asymptomatic
II	IIa	Non-disabling intermittent claudication	⇔	I	1	Mild claudication
				I	2	Moderate claudication
	IIb	Disabling intermittent claudication		I	3	Severe claudication
III		Ischaemic rest pain	⇔	II	4	Ischaemic rest pain
IV		Ulceration or gangrene	⇔	III	5	Minor tissue loss
				III	6	Major tissue loss

In symptomatic patients, the most typical presentation is IC. The Edinburgh Claudication Questionnaire is a standardized method to screen and diagnose typical IC.[2]

CLTI is the recent denomination of the clinical state defined by the presence of ischaemic rest pain, with or without tissue loss (ulcers, gangrene) or infection. When present, arterial ulcers are usually painful, and often complicated by local infection and inflammation. When pain is absent, peripheral neuropathy should be considered. While CLTI is a clinical diagnosis, it is often associated with an ankle pressure less than 50 mmHg or toe pressure less than 30 mmHg.[3] Investigation of the microcirculation (i.e. transcutaneous oxygen pressure or $TcPO_2$) is helpful in some cases of medial calcinosis.

Regular clinical examination is important in elderly patients, especially diabetic patients.[4] Early recognition of tissue loss and referral to the vascular specialist is mandatory to improve limb salvage. Primary major amputation rates in patients unsuitable for revascularization are high (20–25%).[5] CLTI is also a marker for generalized, severe atherosclerosis, with a threefold increased risk of myocardial infarction (MI), stroke, and vascular death as compared to patients with IC.[3, 5]

Clinical examination is fundamental but the diagnosis must be confirmed by objective tests. Pulse palpation should be systematic. Abdominal or groin auscultation (or both) is poorly sensitive. In severe cases, inspection may show foot pallor in a resting leg, with extended recoloration time (>2 s) after finger pressure.

Regarding the natural history, in a recent meta-analysis,[6] most patients with IC present increased 5-year cumulative CV-related morbidity at 13% versus 5% in the reference population. Regarding the limb risk, at 5 years, 21% of patients progress to CLTI, of whom 4–27% have amputations.[3]

Diagnostic tests

Ankle–brachial index

ABI is the first diagnostic step after clinical examination (see Chapter 49.3). An ABI of 0.90 or less has 75% sensitivity and 86% specificity to diagnose LEAD.[7] Its sensitivity is poorer in patients with diabetes or end-stage chronic kidney disease because of medial calcification.[8] Patients with borderline (0.90–1.00) ABI need further diagnostic tests (see Table 49.3.4 in Chapter 49.3). When clinically suspected, a normal ABI (>0.90) does not definitely rule out the diagnosis of LEAD; further post-exercise ABI and/or DUS are necessary. In case of high ABI (>1.40) related to medial calcification, alternative tests such as toe pressure, toe–brachial index (TBI), or Doppler waveform analysis of ankle arteries are useful. Along with DUS, ABI can be used during patient follow-up. It is also a good tool for stratifying the CV risk (see Chapter 49.3).[9]

See Table 49.9.2 for recommendations for ABI measurement.

Treadmill test

The treadmill test (usually using the Strandness protocol, at 3 km/h speed and 10% slope) is an excellent tool for objective functional assessment, unmasking moderate stenosis, as well as for exercise rehabilitation follow-up. It is also helpful when the ischaemic origin of limb pain is uncertain. The test is stopped when the patient is unable to walk further because of pain, defining maximal walking distance (WD). A post-exercise ankle-systolic blood pressure drop greater than 30 mmHg or a post-exercise ABI drop greater than 20% is diagnostic for LEAD.[8]

Table 49.9.2 Recommendations for ankle–brachial index measurement

Recommendations	Class[a]	Level[b]
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD[10, 11]	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated[12]	I	C

ABI, ankle-brachial index; LEAD, lower extremity artery disease.
[a] Class of recommendation.
[b] Level of evidence.

Imaging methods

Ultrasound

DUS provides extensive information on arterial anatomy and haemodynamics. It must be combined with ABI measurement. DUS has a sensitivity of 85–90% and specificity of greater than 95% to detect a stenosis greater than 50%.[13] A normal DUS at rest should be completed by a post-exercise test when iliac stenosis is suspected, because of lower sensitivity. DUS is operator dependent and good training is mandatory. DUS does not present as a roadmap the entire vasculature. Another imaging technique is usually required when revascularization is considered. DUS is also important to address vein quality for bypass substitutes. It is the method of choice for routine follow-up after revascularization.

Computed tomography angiography

In a meta-analysis, the reported sensitivity and specificity of computed tomography angiography (CTA) to detect aorto-iliac stenoses greater than 50% were 96% and 98%, respectively, with similar sensitivity (97%) and specificity (94%) for the femoropopliteal region.[14] Main advantages are visualization of calcifications, clips, stents, bypasses, and concomitant aneurysms. Beyond general limitations (radiation, nephrotoxicity, and allergies), pitfalls are severe calcifications (impeding the appreciation of stenosis, mostly in distal arteries).

Magnetic resonance angiography

The sensitivity and specificity of magnetic resonance angiography (MRA) are approximately 95% for diagnosing segmental stenosis and occlusion. However, MRA tends to overestimate the degree of stenosis.[15] It cannot visualize arterial calcifications, useful for the estimation of stenosis severity in highly calcified lesions, but is a limitation for the selection of the anastomotic site of surgical bypass. The visualization of steel stents is poor. In expert centres, MRA has a higher diagnostic accuracy for tibial arteries than DUS and CTA.

Digital subtraction angiography

Digital subtraction angiography (DSA) is often required for guiding percutaneous peripheral interventional procedures or for the identification of patent arteries for distal bypass. It is also often needed for below-the-knee arteries, especially in patients with CLTI, because of the limitation of all other imaging tools to detect ankle/pedal segments suitable for distal bypass.

Cardiovascular screening in patients with LEAD

Patients with LEAD have often other concomitant arterial lesions, including other peripheral arterial diseases and abdominal aorta aneurysm (AAA).

Abdominal aortic aneurysm

LEAD is often associated with AAAs.[16] In observational studies, the prevalence of AAAs (aortic diameter ≥3 cm) was higher in patients with symptomatic LEAD than in the general population and in a population of patients with atherosclerotic risk factors. The prevalence of AAA among patients with LEAD increased with age, beginning in patients 55 years of age and older, and was highest in patients 75 years of age or older. Often AAA is incidentally detected in patients with LEAD during imaging assessment.

Other arterial beds

The prevalence of atherosclerosis in the coronary, carotid, and renal arteries is higher in patients with LEAD than in those without. For details refer to Chapter 49.10.

Other tests

Toe systolic blood pressure, TBI, and $TcPO_2$ are useful in patients with medial calcinosis and incompressible arteries.

In healthy young adults, normal values of TBI for men and women are, respectively, at 0.98±0.12 and 0.95±0.12.[17] There are discrepancies in the literature regarding the cut-off value,[10] ranging from 0.60 to 0.75, but TBI is mostly considered as abnormal when less than 0.70. The diagnostic accuracy varied in small studies, with sensitivity and specificity ranges of 45–100% and 16–100%, respectively. Overall, the TBI had good performance in patients with diabetes, claudicants, and those at risk of LEAD. Toe pressure and $TcPO_2$ are useful for CLTI assessment.

To define CLTI, pressure cut-offs of less than 50 mmHg, less than 30 mmHg, and less than 30 mmHg are proposed for ankle pressure, toe pressure, and $TcPO_2$, respectively. $TcPO_2$ is often used to determine the healing capacity after amputation. If $TcPO_2$ is 10 mmHg or less, wound healing is improbable. If $TcPO_2$ is greater than 40 mmHg, wound healing capacity is good after minor amputation. For values in between (10–40 mmHg), provocation tests allow better stratification. For a provocation test, $TcPO_2$ is measured in addition to supine position, when the patient breaths 60% O_2 or when the patient's leg is elevated. The following results in provocation tests may predict sufficient wound healing capacity and minor amputation should be attempted if there is no revascularization possibilities: increase in $TcPO_2$ greater than 10 mmHg or 50% or higher from the baseline value when the patient is breathing oxygen, or decrease less than 10 mmHg when leg is elevated.

Table 49.9.3 Recommendations on imaging in patients with lower extremity artery disease

Recommendations	Class[a]	Level[b]
DUS is indicated as first-line imaging method to confirm LEAD lesions[18]	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy[19, 20]	I	C
The data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to treatment decision[3]	I	C
DUS screening for AAA should be considered[21]	IIa	C

AAA, abdominal aorta aneurysm; CTA, computed tomography angiography; DUS, duplex ultrasound; LEAD, lower extremity artery disease; MRA, magnetic resonance angiography.
[a] Class of recommendation.
[b] Level of evidence.

See Table 49.9.3 for recommendations on imaging in patients with LEAD.

Medical treatment

The therapeutic options addressed here are those to improve limb symptoms/salvage. Treatments proposed to reduce other CV events and mortality are addressed in Chapter 49.3.

General prevention strategies can improve limb events. Smoking cessation provides the most noticeable improvement in WD when combined with regular exercise, especially when lesions are located below the femoral arteries. In patients with IC, the natural history is deteriorated by ongoing tobacco use, with increased risk of amputation.[11, 22]

Several studies have shown that statins improve significantly the CV prognosis of patients with IC or CLTI.[23,24] Additionally, several meta-analyses showed a relevant improvement in pain-free and maximal WD with use of statins.[23, 18] It is suggested that statins could limit adverse limb events in patients with LEAD.[25]

In subjects with hypertension, calcium antagonists or ACEIs/ARBs should be preferred because of their potential in peripheral arterial dilatation. A meta-analysis[19] showed improved maximal- and pain-free WD when using ACEI over placebo; however, two out of six randomized clinical trial (RCT) reports have been recently withdrawn because of unreliable data, and the meta-analysis of the remaining studies is inconclusive.[20] The benefit of verapamil in improving WD in LEAD has been shown in a randomized study.[21] Because of co-morbidities such as heart failure, beta blockers are indicated in some patients with LEAD. Studies showed that beta blockers, in particular nebivolol, are safe in patients with IC without negative effects on WD.[26] Metoprolol and nebivolol have been compared in a double-blind RCT including 128 beta blocker-naive patients with IC and hypertension.[27] After a 48-week treatment period, both drugs had been well tolerated and decreased blood pressure equally. In both groups maximal WD improved significantly. Nebivolol showed an advantage with significant improvement in pain-free WD (+34% (p <0.003)

versus + 17% for metoprolol (p <0.12)). In a single-centre study of 1873 consecutive CLTI patients who received endovascular therapy, those treated with other beta blockers did not have a poorer clinical outcome.[12] In a multicentre registry of 1273 patients hospitalized for severe LEAD (of whom 65% had CLTI and 28% were under beta-blocker therapy), death and amputation rates did not differ among those with versus without beta blocker.[28]

Revascularization options: general aspects

The rapid progress in the field of endovascular therapy has led to the extension of its use for complex lesions. The mainstay technique is balloon angioplasty; however, restenosis occurs very frequently in lower limb arteries, with lowest rates in the common iliac artery and increasing distally as well as with lesion lengthening, calcification, poor quality run-off, diabetes, and chronic kidney disease. Therefore, stenting is often performed to improve an insufficient primary result (residual stenosis, extensive recoil, flow-limiting dissection) and long-term patency. Several types of stents with different mechanical properties are available. In-stent restenosis is more frequent in lower limb arteries, and is generally more difficult to treat than restenosis after balloon angioplasty. Stents should generally be avoided in bending areas (hip and knee joints), as well as in arterial segments suited as a landing zone for a potential bypass. The recent innovations to improve the results of endovascular therapy are drug-eluting stents and balloons, which decrease the development of neointimal hyperplasia. The results have been better compared to conventional balloon dilatation or bare-metal stents up to 24-months follow-up, but results beyond 2 years are lacking. Additional endovascular tools with a niche role include atherectomy catheters and devices for crossing chronic total occlusions.

Surgical revascularization can be performed, either by open surgery techniques and/or by a hybrid procedure combining open and endovascular strategies.

Beyond clinical presentation and lesion distribution, one key element to discuss indications for open surgery is the availability of venous material for bypass grafting.

Surgical options range from a local procedure for limited femoral lesions to long full-leg bypasses. The optimal bypass material varies depending on the location of the lesion, outflow conditions, availability of material, and absence or presence of infection. For aortic or iliac bypass surgery, mostly prosthetic material (polyester or polytetrafluoroethylene) is used. In the infra-inguinal segment, autologous vein (e.g. great saphenous vein) is preferred. In selected patients arterial homografts or biological grafts from ovine or bovine pericardium are implanted. Few centres use human venous allografts under study conditions.

Management of intermittent claudication

Exercise therapy

In patients with IC, ExT is effective and improves symptoms and quality of life and increases maximal WD. In 30 RCTs including 1816 patients with stable leg pain, compared with usual care, ExT improved maximal WD on treadmill by almost 5 min.[29] Pain-free and maximal WD were respectively increased on average by 82 and 109 m. Improvement was observed up to 2 years. Moreover, ExT improved quality of life. Exercise did not improve ABI. Whether ExT reduces CV events and improves life expectancy is still unclear. Supervised ExT is more effective than non-supervised ExT.[30, 31] In 14 trials with participants assigned to either supervised ExT or non-supervised ExT (1002 participants), lasting from 6 weeks to 12 months, maximal and pain-free WD increased by almost 180 m in favour of supervised ExT. These benefits remained at one year. Most studies use programmes of at least 3 months, with a minimum of 3 h/week, with walking to the maximal or submaximal distance. Long-term benefits of ExT are less clear and largely depend on patient compliance. Supervised ExT is safe and routine cardiac screening beforehand is not required.[32] It is also more cost-effective than non-supervised ExT,[33] but is not reimbursed or available everywhere. Though home-based walking ExT is not as effective as supervised ExT, it is a useful alternative with positive effects on quality of life and functional walking capacity versus walking advice alone.[34, 35] Alternative exercise modes (e.g. cycling, strength training, and upper-arm ergometry) may be useful when walking exercise is not an option for the patients as these have also been shown to be effective.[36] ExT is impossible in patients with CLTI but can be considered after successful revascularization.[37, 38]

Pharmacotherapy to decrease walking impairment

Some antihypertensive drugs (e.g. verapamil),[21] statins,[39, 40] antiplatelet agents, and prostanoids (prostaglandins I2 and E1)[41] have some favourable effects on WD and leg functioning. Other pharmacological agents claim to increase more specifically WD in patients with IC without other effects on CV health. The drugs mostly studied are cilostazol, naftidrofuryl, pentoxifylline, buflomedil, carnitine, and propionyl-L-carnitine.[18, 42] However, objective documentation of such an effect is limited. The beneficial effects on WD, if any, are generally mild to moderate, with large variability.[118] Also, the incremental benefit of these treatments in addition to ExT and statins are unknown.

Cilostazol is an inhibitor of phosphodiesterase type III. Several clinical trials showed an improvement of maximal walking distance (MWD) by cilostazol compared with placebo as well as pentoxyfilline.[42–44] But there is a wide range of effects on MWD. In a current Cochrane analysis, 100 mg twice a day increased MWD to a mean of 76% compared to 20% in the placebo groups.[43] Another review described only an average improvement of 25% under cilostazol.[42] Side effects like headache, flush symptoms, or diarrhoea are frequent. Cilostazol also has antiplatelet effects and should therefore be combined cautiously with other anticoagulant and antiplatelet substances.[44] Of interest, cilostazol reduced restenosis after endovascular therapy in randomized trials but also increased bleeding complications.[45]

Naftidrofuryl oxalate has been tested in six older studies included in a Cochrane analysis.[46] Studies showed an increase

in MWD of 74% on average and an improvement in quality of life.[46, 47] In a systematic review the average improvement of absolute walking distance was 60% compared with placebo.[42] Currently a dosage of 200 mg naftidrofuryl oxalate three times a day is recommended. Relevant side effects associated with naftidrofuryl are mainly gastrointestinal such as nausea, vomiting, or diarrhoea.

Other pharmacological medications such as prostanoids, pentoxifylline, L-arginine, buflomedil, or Ginko biloba do not have enough consistent data from RCTs to be recommended in patients with IC.[41, 48, 49]

Revascularization for intermittent claudication

The anatomical location and extension of arterial lesions has an impact on revascularization options.

Aorto-iliac lesions

Isolated aorto-iliac lesions are a common cause of claudication. In the case of short stenosis/occlusion (<5 cm) of iliac arteries, endovascular therapy gives good long-term patency (≥90% in 5 years) with low risk of complications.[50] In cases of iliofemoral lesions, a hybrid procedure is indicated, usually endarterectomy or bypass at the femoral level combined with the endovascular therapy of iliac arteries, even in most cases with long occlusions. If the occlusion extends to the infrarenal aorta, covered endovascular reconstruction of an aortic bifurcation can be considered. In a small series 1- and 2-year primary patency was at 87% and 82%, respectively.[51] If the occlusion comprises the aorta up to the renal arteries and iliac arteries, aortobifemoral bypass surgery is indicated in fit patients with severe life-limiting claudication.[52] In these extensive lesions, endovascular therapy may be an option but it is not free of perioperative risk and long-term occlusion. In the absence of any other alternative, extra-anatomic bypass (e.g. axillary to femoral bypass) may be considered.

Femoropopliteal lesions

Femoropopliteal lesions are common in claudicants. If the circulation to the profunda femoral artery is normal, there is a good possibility that the claudication will be relieved with ExT and intervention is mostly unnecessary. If revascularization is needed, endovascular therapy is the first choice in stenosis/occlusions smaller than 25 cm. If the occlusion/stenosis exceeds 25 cm, endovascular recanalization is still possible, but better long-term patency is achieved with surgical bypass, especially when using the great saphenous vein. No head-to-head trials comparing endovascular therapy and surgery are yet available. In the Zilver PTX trial, the 5-year primary patency with conventional and drug-eluting stents was 43% and 66%, respectively.[53] The 5-year patency after above-knee femoropopliteal bypass exceeds 80% with great saphenous vein and 67% with prosthetic conduits.[54] The challenge of endovascular therapy is the long-term patency and durability of stents in the femoropopliteal region, where the artery is very mobile. Several new endovascular solutions, such as atherectomy devices, drug-eluting balloons, and new stent designs, have been shown to improve long-term patency.

Management strategy for intermittent claudication

Several studies have demonstrated the efficacy of endovascular therapy and open surgery on symptom relief, WD, and quality of life in claudicants. However, these interventions have limited durability and may be associated with mortality and morbidity. Thus, they should be restricted to patients who do not respond favourably to ExT (e.g. after a 3-month period of ExT), or when disabling symptoms alter substantially daily life activities. A systematic review of 12 trials (1548 patients) comparing medical therapy, ExT, endovascular therapy, and open surgery in claudicants showed that, compared to the former, each of the three other alternatives were associated with improved WD, claudication symptoms, and quality of life.[55] Compared with endovascular therapy, open surgery may be associated with longer hospital stay and higher complication rate but results in more durable patency. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial randomized 111 patients with IC and aorto-iliac lesions to BMT alone, or in combination with supervised-ExT or stenting.[56] At 6 months, changes in maximal WD were the greatest with supervised-ExT, while stenting provided greater improvement in peak walking time than BMT alone. At 18 months, the difference in terms of peak walking time was not statistically different between supervised-EXT and stenting.[56] The management of patients with IC is summarized in Figure 49.9.1.

See Table 49.9.4 for recommendations for the management of patients with IC.

See Table 49.9.5 for recommendations on revascularization of aorto-iliac occlusive lesions.

See Table 49.9.6 for recommendations on revascularization of femoropopliteal occlusive lesions.

Chronic limb-threatening ischaemia

This entity includes clinical patterns with a threatened limb viability related to several factors. In contrast to the formerly used 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.[76] 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 does not only depend on the severity of ischaemia but also the presence of wound and infection. This explains why the ankle or toe pressures, measured to address LEAD severity, are not a definition component of CLTI.

Chronic limb-threatening ischaemia severity and risk stratification: the WIfI classification

A new classification system (WIfI) has been proposed as the initial assessment of all patients with ischaemic rest pain or wounds.[77] The target population for this system includes any patient with:

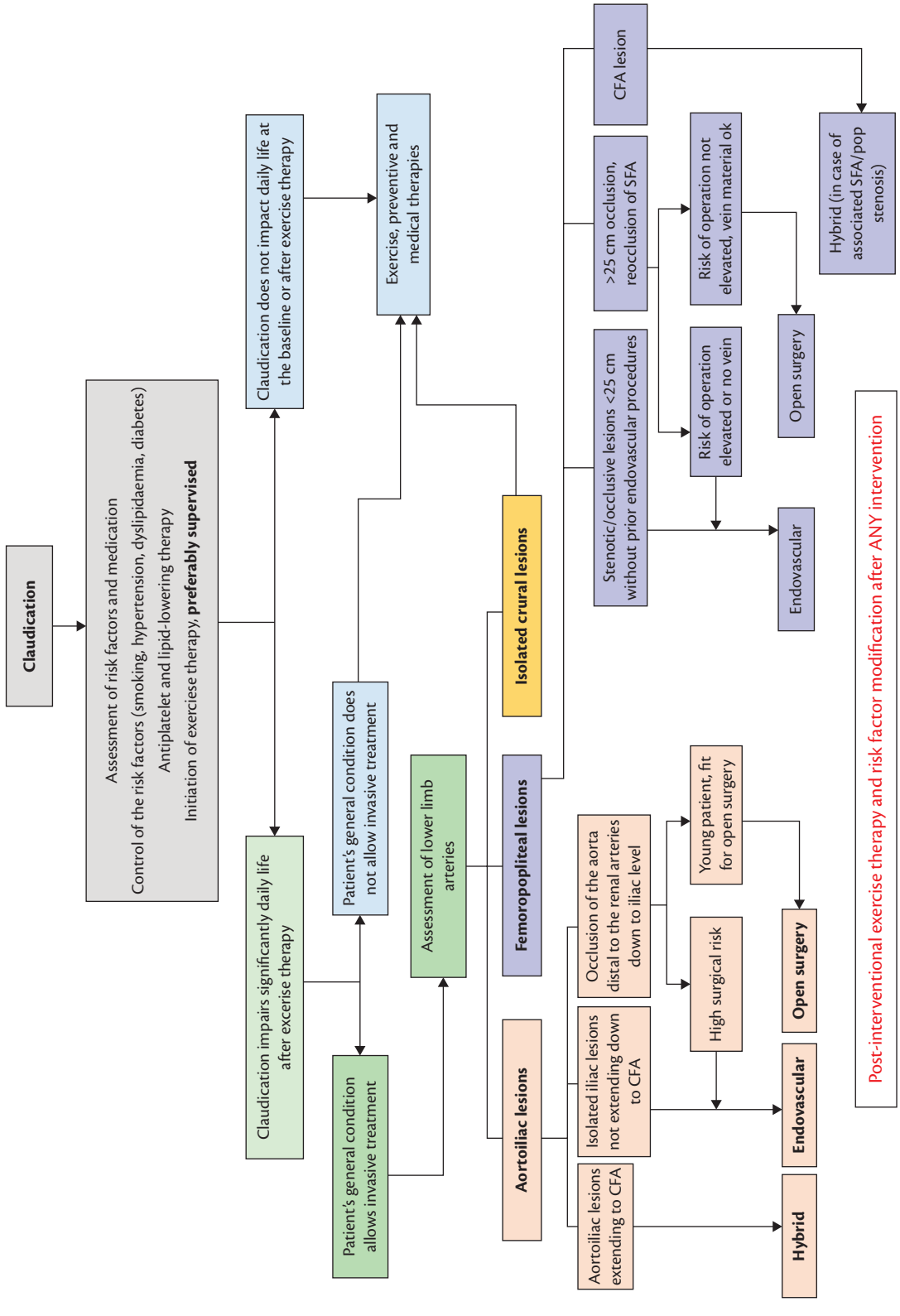

Figure 49.9.1 Management of patients with intermittent claudication (related to atherosclerotic lower extremity artery disease). CFA, common femoral artery; SFA, superficial femoral artery.

Table 49.9.4 Recommendations for the management of patients with intermittent claudication

Recommendations	Class[a]	Level[b]
On top of general prevention, statins are indicated to improve walking distance[23, 47]	I	A
In patients with intermittent claudication:		
◆ supervised exercise training is recommended[35]	I	A
◆ non-supervised exercise training is recommended when supervised exercise training is not feasible or available	I	C
When daily life activities are compromised despite exercise therapy, revascularization should be considered	IIa	C
When daily life activity is severely compromised, first-line revascularization should be considered, in association with exercise therapy	IIa	B

[a] Class of recommendation.
[b] Level of evidence.

Table 49.9.5 Recommendations on revascularization of aorto-iliac occlusive lesions[c]

Recommendations	Class[a]	Level[b]
An endovascular-first strategy is recommended for short (e.g. <5 cm) occlusive lesions[57]	I	C
In patients fit for surgery, aorto-(bi)femoral bypass should be considered in aorto-iliac occlusion(s)[50, 58]	IIa	B
An endovascular-first strategy should be considered in long and/or bilateral lesions in patients with severe co-morbidities[59, 60]	IIa	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[36, 50–53, 56]	IIb	B
Primary stent implantation, rather than provisional stenting, should be considered[59, 60]	IIa	B
Open surgery should be considered in fit patients with an aortic occlusion extending up to the renal arteries	IIa	C
In the case of ilio-femoral occlusive lesions, a hybrid procedure combining iliac stenting and femoral endarterectomy or bypass should be considered[61, 62]	IIa	C
Extra-anatomical bypass may be indicated only for patients with no other alternatives for revascularization	IIb	C

[a] Class of recommendation.
[b] Level of evidence.
[c] These recommendations apply both for patients with intermittent claudication and severe chronic limb ischaemia.

- Ischaemic rest pain, typically in the forefoot with objectively confirmed haemodynamic studies (ABI <0.40, ankle pressure <50 mmHg, toe pressure <30 mmHg, $TcPO_2$ <30 mmHg)
- Diabetic foot ulcer

Table 49.9.6 Recommendations on revascularization of femoropopliteal occlusive lesions[c]

Recommendations	Class[a]	Level[b]
An endovascular-first strategy is recommended in short (e.g. <25 cm) lesions[63, 64]	I	C
Primary stent implantation should be considered in short (e.g. <25 cm) lesions[65, 66]	IIa	A
Drug-eluting balloons may be considered in short (e.g. <25 cm) lesions[67, 68–70]	IIb	A
Drug-eluting stents may be considered for short (e.g. <25 cm) lesions[63, 64, 71]	IIb	B
Drug-eluting balloons may be considered for the treatment of in-stent restenosis[72, 73]	IIb	B
In patients who are not at high risk for surgery, bypass surgery is indicated for long (e.g. ≥25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy exceeds 2 years[74]	I	B
The autologous saphenous vein is the conduit of choice for femoropopliteal bypass[54, 75]	I	A
When above-knee bypass is indicated, in the absence of any autologous saphenous vein, the use of a prosthetic conduit should be considered[54]	IIa	A
In patients unfit for surgery, endovascular therapy may be considered in long (e.g. ≥25 cm) femoropopliteal lesions[72]	IIb	C

[a] Class of recommendation.
[b] Level of evidence.
[c] These recommendations apply both for patients with intermittent claudication and severe chronic limb ischaemia.

- Non-healing lower limb or foot ulceration of 2 or more weeks' duration
- Gangrene involving any portion of the foot or lower limb.

The three primary factors that constitute and contribute to the risk of limb threat are: Wound (W), Ischaemia (I), and foot Infection (fI).

Each factor is graded into four categories (0 = none; 1 = mild; 2 = moderate; 3 = severe). Table 49.9.7 displays the coding and clinical staging according to the WIfI classification. Table 49.9.8 provides an estimation of the amputation risk at 1 year according to the WIfI classification. The management of patients with CLTI should consider the three components of this classification system. Revascularization should always be discussed as its suitability is increased with more severe stages (except stage 5).

Management of patients with chronic limb-threatening ischaemia

The management of patients with CLTI is summarized in Figure 49.9.2. All patients with CLTI must have the BMT with correction of risk factors (see 'Medical treatment'). In those with diabetes, glycaemic control is particularly important, with improved limb-related outcomes, including lower rates of major amputation and increased patency after infra-popliteal revascularization.[78, 79] Proper wound care must be started

Table 49.9.7 Assessment of the risk of amputation: the WIfI classification (for further details see Mills et al.[77])

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or $TcPO_2$
	0	≥0.80	>100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fI (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

Example: a 65-year-old male diabetic patient with gangrene of the big toe and a <2 cm rim of cellulitis at the base of the toe, without any clinical/biological sign of general infection/inflammation, whose toe pressure is at 30 mmHg would be classified as Wound 2, Ischaemia 2, foot Infection 1 (WIfI 2-2-1). The clinical stage would be 4 (high risk of amputation). The benefit of revascularization (if feasible) is high, also depending on infection control.

ABI, ankle–brachial index; $TcPO_2$, transcutaneous oxygen pressure.

Table 49.9.8 Estimation of the amputation risk at 1 year according to the WIfI classification (see also Table 49.9.7)

	Ischaemia – 0				Ischaemia – 1				Ischaemia – 2				Ischaemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fL-0	fL-1	fL-2	fL-3	fL-0	fL-1	fL-2	fL-3	fL-0	fL-1	fL-2	fL-3	fL-0	fL-1	fL-2	fL-3

fI, foot infection; H, high risk; L, low risk; M, moderate risk; VL, very low risk; W, wound.

immediately, as well as adapted shoe wear, treatment of concomitant infection, and pain control.

Revascularization

Revascularization should be attempted as much as possible.[3,80–82] So far, only one randomized trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, has directly compared endovascular therapy to open surgery in CLTI patients.[74] At 2 years, there was no significant difference between endovascular therapy and surgery regarding amputation-free survival. In survivors after 2 years, bypass surgery was associated with improved survival (on average 7 months, $p = 0.02$) and amputation-free survival (6 months, $p = 0.06$).[83] These data are challenged by more recent endovascular therapy techniques. So far, drug-eluding balloons in below-the-knee disease have shown no superiority over plain balloon angioplasty.[84] The results of two ongoing RCTs, BASIL-2 and Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI), are awaited.[85, 86] Meanwhile, in each anatomical region, both revascularization options should be individually discussed.

Aorto-iliac disease

CLTI is almost never related to isolated aorto-iliac disease, and downstream lesions are often concomitant. In addition to CTA and/or MRA, complete DSA down to the plantar arches is required for proper arterial network assessment and procedure planning.[87] Hybrid procedures (e.g. aorto-iliac stenting and distal bypass) should be encouraged in a one-step modality when necessary.

Femoropopliteal disease

CLTI is unlikely to be related to isolated superficial femoral artery lesions; usually femoropopliteal involvement combined with aorto-iliac or below-the-knee disease are found. In up to 40% of cases, inflow treatment is needed.[84] The revascularization strategy should be judged upon lesion complexity. If endovascular therapy is chosen first, landing zones for potential bypass grafts should be preserved. When bypass surgery is decided, the bypass should be as short as possible, using the saphenous vein.

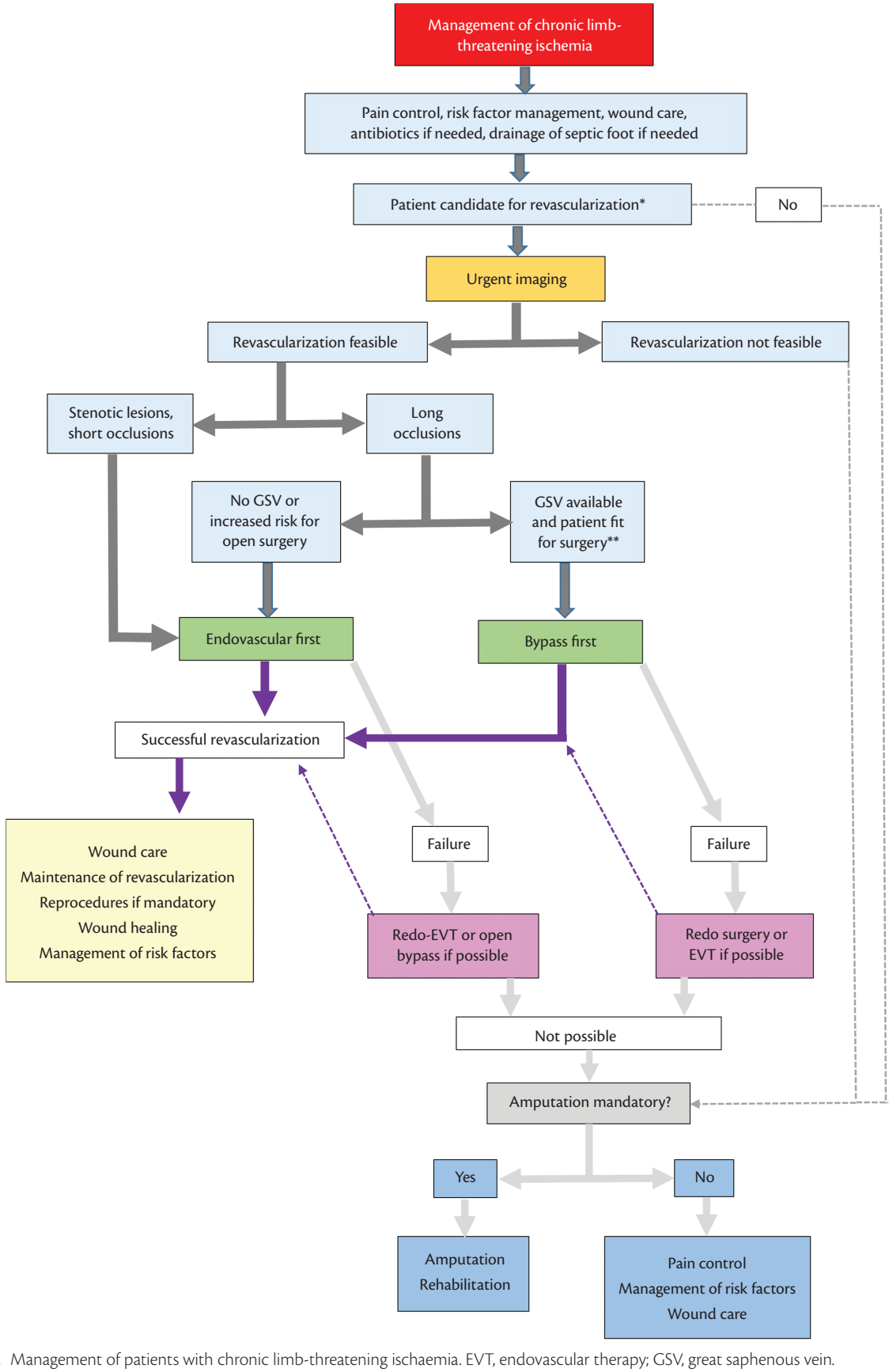

Figure 49.9.2 Management of patients with chronic limb-threatening ischaemia. EVT, endovascular therapy; GSV, great saphenous vein.
* In bedridden, demented and/or frail patients, primary amputation should be considered. ** In the absence of contraindication for surgery and in the presence of adequate target for anastomosis/runoff.

Infrapopliteal disease

Extended infrapopliteal artery disease is mainly seen in diabetic patients, often associated with superficial femoral artery lesions (inflow disease). Full-leg DSA down to the plantar arches is mandatory to explore all revascularization options.[87] In stenotic lesions and short occlusions, endovascular therapy can be the first choice. In long occlusions of crural arteries, bypass with an autologous vein gives superior long-term patency and leg survival. If the patient has increased risk for surgery or does not have an autologous vein, endovascular therapy can be attempted. The decision of revascularization should also consider the angiosome concept, to target at best the ischaemic tissues.

Despite an aggressive approach for revascularization, amputation rates of up to 20% can occur despite a patent bypass in patients with CLTI and tissue loss.[88] This has led to the proposal of an angiosome-based revascularization strategy (where the specific artery perfusing the corresponding diseased territory is revascularized).[89]

There is no question that clinicians would opt to revascularize the blood vessel which directly feeds an involved angiosome if the vessel is accessible and open to the foot. Several meta-analyses compare outcomes after direct and indirect revascularization strategies and suggest that there may be a benefit for patients undergoing direct versus indirect revascularization for wound healing.[90, 91] However, the quality of evidence on which these conclusions are based is low. Most of the studies have used historical data and retrospectively applied criteria. Furthermore, details on the status and quality of the pedal arch were not consistently evaluated. Some authors reported that time to healing for foot tissue loss was significantly influenced by the patency of the pedal arch rather than the revascularized angiosome.[92]

In summary, the angiosome model should not be used as an absolute strategy for interventions on patients with CLTI. Further well-structured prospective studies are needed to assess the value of the angiosome concept.

See Table 49.9.9 for recommendations on revascularization of infrapopliteal occlusive lesions.

Table 49.9.9 Recommendations on revascularization of infrapopliteal occlusive lesions

Recommendations	Class[a]	Level[b]
In the case of CLTI, infrapopliteal revascularization is indicated for limb salvage [74, 80–82, 84–86]	I	C
For revascularization of infra-popliteal arteries:		
◆ bypass using the great saphenous vein is indicated	I	A
◆ endovascular therapy should be considered[74, 80–82, 84–86]	IIa	B

CLTI, chronic limb-threatening ischaemia.
[a] Class of recommendation.
[b] Level of evidence.

Spinal cord stimulation

Spinal cord stimulation can improve limb salvage and pain relief in selected patients with CLTI who are unfit for revascularization or experience persistent ischaemic-related pain following revascularization. Due to the costs of the device and the risk of relatively mild complications, candidates must be selected using a microcirculatory evaluation (baseline and changes in $TcPO_2$ measurements) and after a trial period with an external device.[93]

Stem cell and gene therapy

Angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favour of these treatments.[94, 95]

The development of therapeutic angiogenesis is based on the use of angiogenic factors or stem cells to promote revascularization and remodelling of collaterals, with the aim of reducing ischaemia, ameliorating symptoms, and preventing amputation. Several trials reported relief of ischaemic symptoms, functional improvement, and prevention of amputation, but others failed to confirm this early promise of efficacy.[96–98]

In a meta-analysis of 12 RCTs, autologous cell therapy was effective in improving surrogate indexes of ischaemia, subjective symptoms, and hard endpoints (ulcer healing and amputation). Patients with thromboangiitis obliterans showed greater benefits than patients with atherosclerotic LEAD.[99] The largest randomized placebo-controlled trial of gene therapy is the Efficacy and Safety of XRP0038/NV1FGF in Critical Limb Ischemia Patients With Skin Lesions (TAMARIS) study, including 520 patients from 30 countries with CLTI and skin lesions, unsuitable for standard revascularization. This study found no statistical difference between the two groups regarding the primary efficacy endpoint of death or first major amputation on the treated leg, whichever came first (37.0% vs 33.2%; $p = 0.48$).[94]

Amputation

Minor amputation

In case of CLTI, minor amputation (up to the forefoot level) is often necessary to remove necrotic tissues with minor consequences on a patient's mobility. Revascularization is needed before amputation to improve wound healing. Foot $TcPO_2$ and toe pressure can be useful to delineate the amputation zone (see 'Other tests').

Major amputation

Patients with extensive necrosis or infectious gangrene and those who are non-ambulatory with severe co-morbidities may be best served with primary major amputation. This remains the last option to avoid or halt general complications of irreversible limb ischaemia, allowing in some cases patient recovery with rehabilitation and prosthesis. For a moribund patient, adequate analgesia and other supportive measures may also be the best option.

Secondary amputation should be performed when revascularization has failed and reintervention is no longer possible, or when the limb continues to deteriorate because of infection or

Table 49.9.10 Recommendations on the management of chronic limb-threatening ischaemia

Recommendations	Class[a]	Level[b]
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage[77]	I	C
In patients with CLTI, assessment of the risk of amputation is indicated[77]	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended[78, 79]	I	C
For limb salvage, revascularization is indicated whenever feasible[83]	I	B
In CLTI patients with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularization	IIa	C
In patients with CLTI, stem cell/gene therapy is not indicated[94]	III	B

CLTI, chronic limb-threatening ischaemia.
[a] Class of recommendation.
[b] Level of evidence.

necrosis despite patent graft and optimal management. In any case infragenicular amputation should be preferred because the knee joint allows better mobility with a prosthesis. For bedridden patients, femoral amputation may be the best option.

See Table 49.9.10 for recommendations on the management of CLTI.

Acute limb ischaemia

Acute limb ischaemia 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.

Once the clinical diagnosis is established, treatment with unfractionated heparin should be given, along with appropriate analgesia.[3, 100] The emergency level and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficits. The clinical categories are presented in Table 49.9.11.[101]

In the case of neurological deficit, urgent revascularization is mandatory; imaging should not delay intervention. The imaging method depends on its immediate availability. DUS and DSA are mostly used in these situations.

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, co-morbidities, 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 co-morbidities. 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. The modern concept of the combination of intra-arterial thrombolysis and catheter-based clot removal is associated with 6-month amputation rates less than 10%.[3] Systemic thrombolysis has no role in the treatment of patients with acute limb ischaemia.

Based on RCTs, there is no clear superiority of local thrombolysis versus open surgery on 30-day mortality or limb salvage.[102] After thrombus removal, the pre-existing arterial lesion should be treated by endovascular therapy or open surgery. Lower extremity four-compartment fasciotomies should be performed in patients with long-lasting ischaemia to prevent a post-reperfusion compartment syndrome. The management of acute limb ischaemia is summarized in Figure 49.9.3.

See Table 49.9.12 for recommendations for the management of patients presenting with acute limb ischaemia.

Blue toe syndrome

Another clinical presentation is the blue toe syndrome characterized by a sudden cyanotic discoloration of one or more toes; it is usually due to embolic atherosclerotic debris from the proximal arteries.

Blue toe syndrome is the result of atheroembolism, a process in which emboli from proximal arterial lesions produce ischaemia in distal arterial beds. These emboli are due to atherosclerotic plaque fragmentation, with resulting showers of cholesterol debris and platelet aggregates. When it occurs in the lower extremities,

Table 49.9.11 Clinical categories of acute limb ischaemia

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

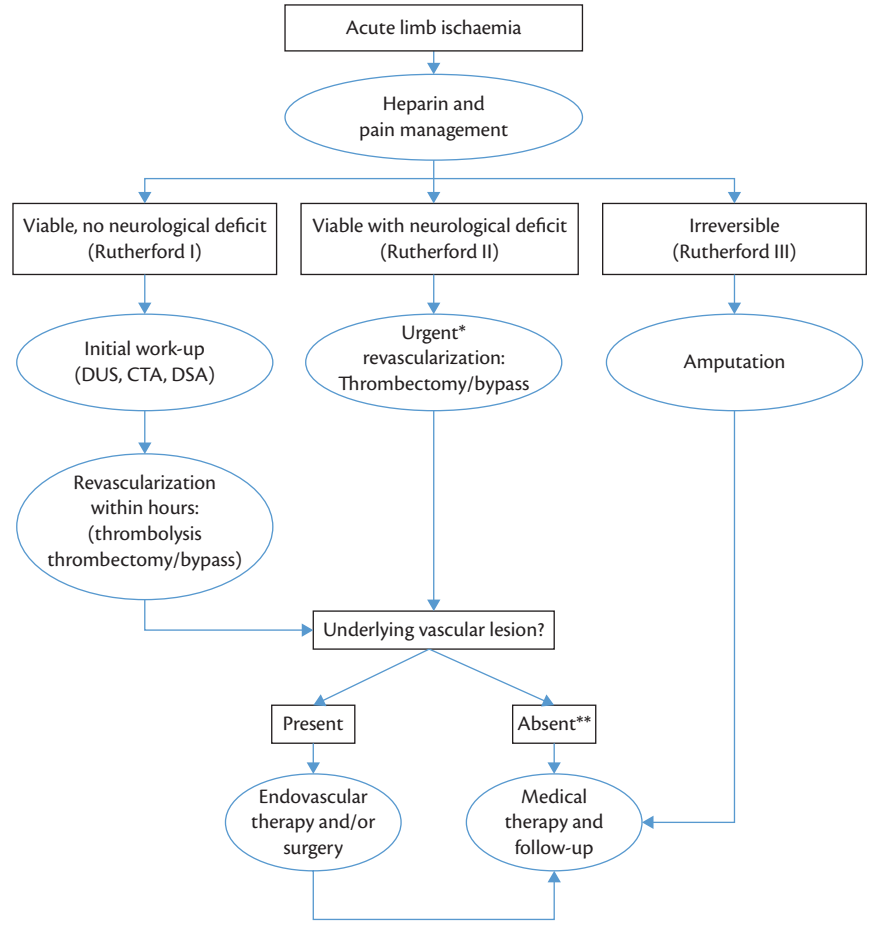

Figure 49.9.3 Management of acute limb ischaemia. CTA, computed tomography angiography; DSA, digital subtraction ultrasound; DUS, duplex ultrasound.
* Imaging should not delay revascularization. ** Specific aetiological work up is necessary (cardiac, aorta).

arterioles are occluded and blue toe syndrome is demonstrated. The microembolic process can occur anywhere in the body; it was first reported by Flory[103] in 1945, and Hoye and colleagues[104] first described the clinical presentation in the lower extremities. The term 'blue toe syndrome' was first used by Karmody and colleagues[105] in 1975 in a series of 31 patients.

Controversy exists over the most appropriate treatment for these patients.[106–115] Surgical treatment of these lesions has been aimed at removing the source lesion by means of endarterectomy or bypass. There are a few reports of endovascular treatment of these lesions, including thrombolytic administration,[116] percutaneous atherectomy,[117, 118] and balloon and stent angioplasty.[119, 120] Often, antiplatelet therapy alone or in combination with surgical or endovascular treatment has been advocated. More controversial is the use of anticoagulation because there have been reports that indicate anticoagulation may promote atheroembolism.[121–128]

Many of the lesions that are the source of blue toe syndrome also produce significant obstruction that could be appropriately treated.[129–131] Stents, although currently non-covered, could treat the obstruction and also stabilize these lesions from producing emboli.[132]

Atherosclerotic lesions that produce blue toe syndrome appear to be equally distributed from the aorta, and iliac and femoropopliteal regions.[110] Classically, this entity presents as painful, blue or purple toes in patients without proximal obstruction but with multiple levels of disease, including ulcerated plaques, making determination of the source difficult.

The natural history of patients with blue toe syndrome is repeated microemboli, with a reported rate of tissue loss/amputation up to 45%.[112, 115] Most reports advocate the isolation or removal of the embolic source.[111, 115] Stents theoretically provide a scaffold that would prevent plaque embolization and promote

Table 49.9.12 Recommendations for the management of patients presenting with acute limb ischaemia

Recommendations	Class[a]	Level[b]
In the case of neurological deficit, urgent revascularization is indicated[3, 100 c]	I	C
In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case to case decision[3, 100]	I	C
Heparin and analgesics are indicated as soon as possible[14, 100]	I	C

[a] Class of recommendation.
[b] Level of evidence.
[c] In this case imaging should not delay intervention.

remodelling of the lesion, but there is concern about producing additional emboli during stent placement.

Brewer and colleagues[116] hypothesized the lesion producing blue toe syndrome could be adequately treated first by stabilizing the plaque with antiplatelet therapy, and then by percutaneous transluminal angioplasty 6 weeks later, if no new symptoms occurred. In another study, Kumpe and colleagues[120] reported successful results in treating ten patients with percutaneous transluminal angioplasty and antiplatelet therapy; only one patient experienced recurrent emboli, but the mortality rate in this group was high (60%). Karmody and colleagues[105] describe at least three recurrent embolic events in his group of 31 surgically treated patients (10%), with a 0% mortality rate and a 32% amputation rate. Wingo and colleagues[115] reported the largest series of 48 patients (31 treated surgically, 11 treated medically, and 22 receiving no treatment) with no differences in outcomes between the groups with an overall rate of tissue loss of 38% in addition to the 22% amputation rate.

To compare reports of endovascular, surgical, and combinations of treatment for blue toe syndrome is difficult since most studies are retrospective, limited by small numbers of patients, with variations in treatments, undefined and short follow-up times, and variable endpoints.

Nevertheless, when applicable, stent placement appears to be as effective as surgical, medical, or other endovascular therapies. Considering the possible deleterious effects of vitamin K antagonists in patients with blue toe syndrome, the use of antiplatelet therapy has become standard.

In conclusion, whether treated surgically or by endovascular techniques with the association of antiplatelet therapy, there is a high risk of limb loss and a high mortality rate in patients with blue toe syndrome. Physicians should be aggressive in the diagnosis. Covered-stent placement is an alternative to bypass but further studies are needed to ensure efficacy and safety.

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Chapter 49.10 Multisite artery disease

Key messages

- Multisite artery disease (MSAD) is common in patients with atherosclerotic involvement in one vascular bed, ranging from 10–15% in patients with coronary artery disease (CAD) to 60–70% in patients with severe carotid stenosis or lower extremity artery disease (LEAD).
- MSAD is invariably associated with worse clinical outcomes; however, screening for asymptomatic disease in additional vascular sites has not been proved to improve prognosis.
- In patients with any presentation of peripheral arterial diseases (PADs), clinical assessment of symptoms and physical signs of other localizations and/or CAD is necessary, and in case of clinical suspicion, further tests may be planned.
- Systematic screening for asymptomatic MSAD is not indicated for any presentation of PADs as it would not consistently lead to a modification of management strategy. It may be interesting in some cases for risk stratification (e.g. antiplatelet therapy strategy beyond 1 year in patients who benefited from coronary stenting for acute coronary syndrome).
- In some situations, the identification of asymptomatic lesions may affect patient management. This is the case for patients undergoing coronary artery bypass graft surgery (CABG), where an ankle–brachial index (ABI) measurement may be considered especially when saphenous vein harvesting is planned, and carotid screening should be considered in a subset of patients at high risk of carotid artery disease.
- In patients scheduled for CABG with severe carotid stenoses, prophylactic carotid revascularization should be considered in recently symptomatic cases and may be considered in asymptomatic cases, after multidisciplinary discussion.

- In patients planned for carotid artery revascularization for asymptomatic stenosis, a preoperative coronary angiography for detection (and revascularization) of CAD may be considered.

MSAD is defined by the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories. Subclinical plaques are beyond the scope of this chapter. While patients with MSAD are regularly encountered in clinical practice, robust data on the management of these patients are scarce. For the management of these patients, clinical status and comorbidities should be considered, in addition to the lesion sites. Generally, the treatment strategy should be decided on a case-by-case basis within a multidisciplinary team and should focus first on the symptomatic vascular site.

Multisite artery disease: epidemiology and impact prognosis

Among 3.6 million American volunteers for a systematic ultrasound screening for LEAD, carotid artery disease, and abdominal aorta aneurysm, the proportion of subjects with two or more localizations increased with age, from 0.04% at 40–50 years to 3.6% at 81–90 years.[1] Figure 49.10.1 summarizes the prevalence of MSAD when atherosclerotic disease is diagnosed in one territory. [2, 3-11]

Although several studies demonstrated that patients with MSAD have a significantly worse clinical outcome as compared to patients with single vascular site disease, the only randomized clinical trial (RCT) designed to assess the impact on prognosis of systematic screening for MSAD in patients with high-risk CAD (three-vessel CAD or with an acute coronary syndrome, or both of these, at age >75 years) failed to prove any significant benefit.[12] The Aggressive detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis (AMERICA) trial randomized 521 patients to a proactive strategy (total-body duplex ultrasound (DUS) and ABI measurement, associated with intensive medical therapy) or to conventional strategy (no screening for asymptomatic MSAD and standard medical therapy); at 2-year follow-up, the primary composite endpoint, including death, any ischaemic event leading to rehospitalization or any evidence of organ failure, occurred in 47.4% and 46.9% of patients, respectively (p >0.2).[12] Hence, the clinical benefit of systematic screening for asymptomatic MSAD in patients with known atherosclerotic disease appears questionable.

Screening for and management of multisite artery disease

PADs in patients presenting with coronary artery disease

Carotid artery disease in patients scheduled for CABG

Table 49.10.1 details the epidemiology of carotid artery disease, and the incidence of stroke among patients undergoing isolated CABG (without synchronous/staged coronary endarterectomy (CEA)).[14] In another study, unilateral 50–99% carotid stenosis was found in 11% of patients, bilateral 50–99% stenosis in 5.6%, and unilateral occlusion in 1.3%.[13]

Ischaemic stroke after CABG is multifactorial: aortic embolism during manipulation, cannulation/decannulation, and graft anastomosis to the ascending aorta; platelet aggregation during cardiopulmonary bypass (CPB) and hypercoagulable states; carotid embolization; postoperative atrial fibrillation; and haemodynamic instability, especially in patients with impaired cerebral vascular reserve.[15]

The impact of asymptomatic carotid stenosis on stroke risk after CABG is modest, except for bilateral stenoses or unilateral occlusion. In a systematic review, 86% of postoperative strokes were not attributed to carotid disease. Carotid stenosis appears as a marker of severe aortic atherosclerosis and stroke risk, rather than the direct cause. Conversely, a history of prior stroke/transient ischaemic attack is a significant risk factor for post-CABG stroke.[9, 16–18] Evidence on the benefits of prophylactic revascularization of asymptomatic carotid stenoses in all CABG candidates to reduce perioperative stroke is lacking. The decision to perform CEA/carotid artery stenting (CAS) in these patients should be made by a multidisciplinary team. It may be reasonable to restrict prophylactic carotid revascularization to patients at highest risk of postoperative stroke, that is, patients with severe bilateral lesions, or history of prior stroke/transient ischaemic attack.[9, 17–19]

The timing and the modality of carotid revascularization (CEA or CAS) are controversial and should be individualized based on clinical presentation, level of emergency, and severity of carotid and coronary artery diseases. Table 49.10.2 details the results of

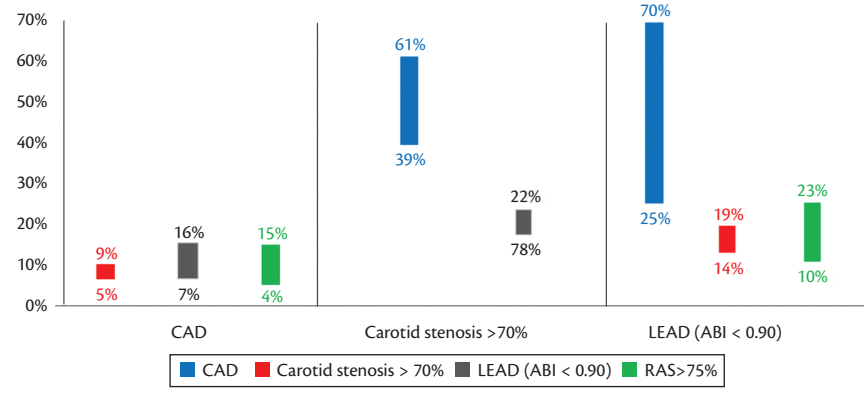

Figure 49.10.1 Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease. The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g. in patients with CAD, 5–9% of cases have concomitant carotid stenosis >70%). ABI, ankle–brachial index; CAD, coronary artery disease; LEAD, lower extremity artery disease; RAS, renal artery stenosis.

Table 49.10.1 Prevalence of internal carotid stenosis and risk of stroke after isolated coronary artery bypass graft surgery in duplex ultrasound screened patients

	Prevalence in 7512 duplex-screened CABG patients	Stroke rate in 4674 duplex-screened patients undergoing isolated CABG
Carotid stenoses <50%	90.8%	1.8%
Unilateral stenosis 50–99%	5.5%	3.2%
Bilateral stenosis 50–99%	2.2%	5.2%
Unilateral occlusion	1.5%	9.0%

CABG, coronary artery bypass graft surgery.

Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg 2002;23:283–94.

meta-analyses evaluating outcomes following different scenarios. No specific strategy is clearly safer.[20]

A RCT did not report lower stroke rate for off-pump versus on-pump surgery.[21]

The two-staged CEA strategies provide higher risk of periprocedural myocardial infarction (MI) if the carotid artery is revascularized first, and a trend to increased cerebral risk if CABG is performed first. In a RCT in patients with unilateral asymptomatic carotid stenosis, CABG followed by CEA was the worst strategy, with a higher 90-day stroke and death rate compared with CABG with previous or synchronous CEA (8.8% vs 1.0%; $p = 0.02$).[22]

The higher risk of cerebral embolization from aortic arch plaques may explain why CAS is not associated with lower procedural risks. If CAS is performed before elective CABG, the need for dual antiplatelet therapy (DAPT) usually delays cardiac surgery for at least 4 weeks, exposing the patient to the risk of MI between the staged CAS and CABG (0–1.9%).[23, 24] Some authors performed CAS immediately prior to CABG and reported low death/stroke rates.[25] Among 132 patients with same-day CAS + cardiac surgery, in-hospital stroke rate was 0.75%, while 5- and 10-year freedom from neurological events was 95% and 85%, respectively.[26] In a single-centre propensity-matched analysis of 350 patients undergoing carotid revascularization within 90 days before cardiac surgery, staged CAS-cardiac surgery and combined CEA-cardiac surgery had similar early outcomes (death/stroke/MI), whereas staged CEA-cardiac surgery incurred the highest risk driven by inter-stage MI. Beyond 1 year, patients with either staged or combined CEA-cardiac surgery had a threefold higher rate of major adverse cardiovascular events (MACE) compared with patients undergoing staged CAS-cardiac surgery.[27] However, staged CAS-cardiac surgery entails an increased bleeding risk during CABG (if performed within the DAPT period).

Two studies suggest that limiting DUS to patients with at least one risk factor (age >70 years, history of cerebrovascular disease, presence of a carotid bruit, multivessel CAD, or LEAD) identifies all patients with carotid stenosis greater than 70%, reducing the total number of scans by 40%.[6, 28] However, a study comparing patients undergoing a preoperative carotid scan before cardiac surgery with those without screening reported no difference in perioperative mortality and stroke.[13] But only 12% of those with severe carotid stenosis underwent synchronous CABG + CEA. Hence, routine carotid DUS identifies only the minority of patients who will develop perioperative stoke, without clearly evidenced benefit of prophylactic carotid revascularization. Carotid DUS is indicated in patients with recent (<6 months) stroke/transient ischaemic attack. No carotid imaging is indicated when CABG is urgent, unless neurological symptoms occurred in the previous 6 months.

Table 49.10.2 Meta-analyses of death/stroke/myocardial infarction following staged or synchronous carotid endarterectomy + coronary artery bypass graft surgery or carotid artery stenting + coronary artery bypass graft surgery

Parameter	*n*	Death % (95% CI)	Stroke % (95% CI)	MI % (95% CI)	Death/stroke % (95% CI)	Death/stroke/MI % (95% CI)
Synchronous CEA + CABG with CEA done pre-bypass	5386	4.5% (3.9–5.2)	4.5% (3.7–5.3)	3.6% (2.8–4.4)	8.2% (7.1–9.23)	11.5% (10.1–13.1)
Synchronous CEA + CABG with CEA done on bypass	844	4.7% (3.1–6.4)	3.8% (2.0–5.5)	2.9% (1.3–4.6)	8.1% (5.8–10.3)	9.5% (5.9–13.1)
Synchronous CEA + OPCAB	324	1.5% (0.3–2.8)	n/a	n/a	2.2% (0.7–3.7)	3.6% (1.6–5.5)
Staged CEA then CABG	917	3.9% (1.1–6.7)	2.7% (1.6–3.9)	6.5% (3.2–9.7)	6.1% 2.9–9.3)	10.2% (7.4–13.1)
Reverse staged CABG then CEA	302	2.0% (0.0–6.1)	6.3% (1.0–11.7)	0.9% (0.5–1.4)	7.3% (1.7–12.9)	5.0% (0.0–10.6)
Staged CAS then CABG	2378	4.5% (3.3–6.2)	5.3% (4.3–6.4)	2.4% (1.5–3.9)	8.6% (6.9–10.6)	9.9% (7.9–12.2)
Synchronous CAS + CABG	550	4.5% (2.9–6.9)	3.1% (1.8–5.3)	1.8% (0.9–3.6)	5.6% (3.8–8.1)	6.3% (4.3–8.9)

CABG, coronary artery bypass graft surgery; CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; OPCAB, off-pump coronary artery bypass.

Adapted from Paraskevas KI, Nduwayo S, Saratzis A, Bown MJ, Naylor AR. Synchronous/staged carotid stenting and coronary bypass surgery: an updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2017;53:309–19.

Table 49.10.3 Recommendations on screening for carotid disease in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, DUS is recommended in patients with recent (<6 months) history of TIA/stroke[29, 30]	I	B
In patients with no recent (<6 months) history of TIA/stroke, DUS may be considered in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit[29, 30]	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA	III	C

CABG, coronary artery bypass grafting; DUS, duplex ultrasound; LEAD, lower extremity artery disease; TIA, transient ischaemic attack.
[a] Class of recommendation.
[b] Level of evidence.

See Table 49.10.3 for recommendations on screening for carotid disease in patients undergoing CABG.

See Table 49.10.4 for recommendations on the management of carotid stenosis in patients undergoing CABG.

Table 49.10.4 Recommendations on the management of carotid stenosis in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
It is recommended that the indication (and if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with recent (< 6 months) history of TIA/stroke:		
◆ Carotid revascularization should be considered in patients with 50–99% carotid stenosis[20, 31]	IIa	B
◆ Carotid revascularization with CEA should be considered as first choice in patients with 50–99% carotid stenosis[20, 31]	IIa	B
◆ Carotid revascularization is not recommended in patients with carotid stenosis <50%	III	C
In neurologically asymptomatic patients scheduled for CABG:		
◆ Routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended[19]	III	B
◆ Carotid revascularization may be considered in patients with bilateral 70–99% carotid stenoses or 70–99% carotid stenosis + contralateral occlusion[19]	IIb	B
◆ Carotid revascularization may be considered in patients with a 70–99% carotid stenosis, in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke,[c] in order to reduce stroke risk beyond the perioperative period	IIb	C

CABG, coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy
[a] Class of recommendation.
[b] Level of evidence.
[c] See Table 49.3.3 in Chapter 49.3.

Carotid artery stenosis in other coronary artery disease patients (without CABG)

The available data regarding the prevalence of carotid stenosis in these patients, and the lack of evidence of any effect on outcome, leads to the conclusion that carotid screening in patients with CAD is not recommended other than in candidates for CABG.

Overall, the prevalence of significant carotid stenosis in CAD patients is relatively low, but increases concurrently with the severity of CAD.[28] In a general review of 20,395 consecutive CAD patients, the prevalence of carotid stenosis greater than 70% was 5%.[28] Among patients undergoing coronary angiography, the prevalence was as high as 7% in the case of three-vessel disease and 10% in the case of left main coronary disease.[10]

In the 4-year follow-up of the Reduction of Atherothrombosis for Continued Health (REACH) registry, the presence of carotid atherosclerosis (carotid plaque or history of carotid revascularization) in patients with CAD resulted in adjusted hazard ratios (HRs) of 1.25 for coronary events.[32]

The identification of severe asymptomatic carotid disease in CAD patients does not change medical treatment, as antiplatelet therapy and lipid-lowering therapy are already recommended for all patients with known CAD.

Considering the low prevalence of severe carotid stenosis in all-comers CAD patients, and considering that revascularization of asymptomatic carotid disease should be considered only in selected patient populations, systematic screening for carotid stenosis in CAD patients is not recommended. Moreover, the identification of carotid disease does not have an impact on the medical treatment of patients with known CAD.

Renal artery disease in patients presenting with coronary artery disease

The prevalence of renal artery stenosis (RAS) of 75% or higher has been reported at 5–15% in recent studies on patients with CAD undergoing coronary angiography,[33, 34] and is twice more common in females than in males.[33] Hypertension, diabetes, multivessel CAD, severe chronic kidney disease, and concomitant LEAD are more prevalent in patients with significant RAS.[33, 35]

The presence of RAS at abdominal aortography in 3987 patients undergoing coronary angiography has been found to be associated with a twofold increase in midterm mortality, independent of the treatment of CAD, either medical, percutaneous coronary intervention (PCI), or CABG.[36] However, in a series of 401 patients scheduled for CABG, increased renal resistive index (>0.80), but not RAS (>60%), was associated with a fourfold increase in 30-day death/stroke/MI rate, as well as with a higher midterm CV morbidity and mortality.[34]

The identification of RAD in CAD patients does not change medical treatment, as antiplatelet therapy and lipid-lowering therapy are already recommended for all patients with known CAD. Renin–angiotensin–aldosterone system (RAAS) blockers should be given with caution in the case of bilateral or unilateral RAS with non-functional/absent contralateral kidney.

Systematic screening for RAD in patients with CAD cannot be recommended, since the prevalence of significant RAS is low

and the therapeutic value of renal artery stenting is questionable (see Chapter 49.8). Similar to other patients, the indications for imaging renal arteries are presented in Table 49.8.1. In those cases, DUS is recommended to diagnose RAS. If DUS is positive or inconclusive, renal angiography can be performed at the time of coronary angiography. Systematic renal angiography is not recommended (increased volume of contrast media).

LEAD in patients with coronary artery disease

LEAD often coexists with CAD (Figure 49.10.1). It is often asymptomatic or masked by limiting angina or dyspnoea, or both. LEAD (ABI <0.90) is present in 13–16% of patients who have CAD at coronary angiography.[37, 38] Left main coronary artery stenosis and multivessel CAD were independent predictors. Patients with LEAD exhibit more extensive, calcified, and progressive coronary atherosclerosis.[39]

The coexistence of LEAD in CAD patients has been consistently associated with worse outcome, although it is unclear whether LEAD is a marker or a cause of cardiac adverse events.[40, 41] In the 3-year follow-up of the PEGASUS trial, patients with concomitant LEAD had adjusted twofold increased rates of all-cause death, CV death, stroke, and MACE.[42] In acute coronary syndrome registries, in-hospital mortality, acute heart failure, and recurrent ischaemia rate were significantly higher (up to fivefold) in subjects with LEAD.[8, 11] In a pooled analysis of 19,867 patients enrolled in RCTs on PCI, 8% had clinical LEAD, identified as an independent predictor of mortality at 30 days (HR 1.67), 6 months (HR 1.76), and 1 year (HR 1.46).[43] Concomitant LEAD (clinical or subclinical) is also associated with worse outcome in patients undergoing CABG.[44, 45]

In patients with CAD who have concomitant LEAD, strict risk factor control is mandatory, although no specific recommendations exist, as compared to CAD patients without MSAD. In a post hoc analysis of the CHARISMA trial, DAPT with aspirin and clopidogrel was associated with a significant decrease in non-fatal MI compared with aspirin alone[46] at a cost of increased minor bleeding. The potential benefits of DAPT in these patients need further confirmation.

In LEAD patients requiring coronary revascularization, the treatment of CAD is usually prioritized, except in the case of chronic limb-threatening ischaemia (CLTI). Whether PCI or CABG should be favoured to treat CAD in patients with LEAD is controversial.[47, 48] In the case of PCI, radial artery access should be favoured. If the femoral approach is necessary, pre-interventional assessment of the iliac and common femoral arteries should be performed to minimize the risk of ischaemia/embolization and to identify the best location for arterial puncture, since access site complications are more frequent in these patients, particularly when closure devices are used.[49] In patients undergoing CABG with advanced LEAD, the great saphenous vein should be spared whenever possible; later success of peripheral arterial revascularization is strongly dependent on the availability of sufficient autologous venous segments.[50] Also, saphenous vein harvesting may be associated with wound healing delays in severe LEAD. This justifies the screening for LEAD prior to the use of the saphenous vein as bypass material, at least by clinical examination or ABI, or both of these. CPB during CABG causes mean arterial pressure drop and loss of pulsatile flow, entailing the risk of worsening CLTI. When off-pump CABG is not feasible, maintaining an adequate mean arterial pressure and monitoring peripheral oxygen saturation in CLTI patients are strongly advisable during CPB. Postoperatively, an active clinical surveillance is needed to diagnose in a timely fashion the compartment syndrome potentially caused by ischaemia–reperfusion injury during CPB.

The coexistence of LEAD, even asymptomatic, may upset cardiac rehabilitation.[51]

Screening for LEAD by means of ABI could represent a non-invasive and inexpensive method for prognostic stratification of patients. However, the AMERICA trial failed to demonstrate the benefit of a proactive strategy of MSAD screening in patients.[12] However, the trial was small with some limitations. It does not exclude a role for screening for asymptomatic LEAD in CAD patients for prognostic stratification.

Importantly, in patients with severe CAD, the presence of symptomatic or asymptomatic LEAD is associated with a high probability (almost 20%) of carotid stenosis.[52]

See Table 49.10.5 for recommendations for screening and management of concomitant lower extremity artery disease and CAD.

Coronary artery disease in patients presenting with PADs

CAD in patients with carotid artery stenosis

In a study including 276 patients with non-cardioembolic ischaemic stroke/transient ischaemic attack, coronary computed tomography angiography detected coronary stenosis (>50%) in 18% of cases. The prevalence was fourfold higher in the case of carotid stenosis greater than 50%.[58] In a prospective investigation of 390 patients undergoing elective CAS, systematic

Table 49.10.5 Recommendations for screening and management of concomitant lower extremity artery disease and coronary artery disease

	Class[a]	Level[b]
In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention[41]	I	C
In patients with LEAD undergoing CABG, sparing the autologous great saphenous vein for potential future use for surgical peripheral revascularization should be considered	IIa	C
In patients undergoing CABG and requiring saphenous vein harvesting, screening for LEAD should be considered	IIa	C
In patients with CAD, screening for LEAD by ABI measurement may be considered for risk stratification[8, 11, 12, 43–45, 53–57]	IIb	B

ABI, ankle–brachial index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LEAD, lower extremity artery disease; TIA, transient ischaemic attack.
[a] Class of recommendation.
[b] Level of evidence.

Table 49.10.6 Recommendation on screening for coronary artery disease in patients with carotid disease

	Class[a]	Level[b]
In patients undergoing elective CEA, preoperative CAD screening, including coronary angiography, may be considered[60, 61]	IIb	B

CAD, coronary artery disease; CEA, carotid endarterectomy.
[a] Class of recommendation.
[b] Level of evidence.

coronary angiography found coronary artery stenosis of 70% or greater in 61% of cases.[59]

In the case of severe carotid artery stenosis, the presence of associated CAD requires prioritization of revascularization according to the patient's clinical status and to the severity of carotid and coronary disease. Carotid revascularization should be performed first only in the case of unstable neurological symptoms; asymptomatic carotid stenosis should be treated, whenever appropriate, following CAD revascularization.

In an RCT, 426 patients without CAD history and normal electrocardiogram (ECG) and cardiac ultrasound were randomized to either systematic coronary angiography (with subsequent revascularization) or no coronary angiography.[60] Significant CAD was found (and treated) before CEA in 39% of those randomized to angiography, with no postoperative MI, versus 2.9% in the no-angiography group ($p = 0.01$). Importantly, PCI delayed CEA by a median of 4 days (range 1–8 days), without neurological event meanwhile, and without bleeding complications in patients operated on DAPT. At 6 years, patients allocated to systematic coronary angiography had a lower rate of MI (1.4% vs 15.7%, $p < 0.01$) and improved survival (95% vs 90%, $p < 0.01$).[61] Hence, routine preoperative coronary angiography may be considered in patients undergoing elective CEA.

See Table 49.10.6 for recommendation on screening for CAD in patients with carotid disease.

CAD in patients undergoing vascular surgery of lower limbs

In patients undergoing surgery for LEAD, the probability of significant concomitant CAD at coronary angiography is around 50–60%.[62–64] For the management of these patients, aortic and major vascular surgery are classified as 'high-risk' for cardiac complications, with an expected 30-day MACE rate (cardiac death and MI) greater than 5%.[65] The management of CAD in patients requiring vascular surgery should be based on the 2014 European Society of Cardiology/European Society of Anaesthesiology Guidelines on non-cardiac surgery.[65]

CAD in patients with LEAD not undergoing vascular surgery

At least one-third of patients with LEAD have a history or ECG signs (or both) of CAD, while two-thirds have an abnormal stress test, and up to 70% present at least single-vessel disease at coronary angiography.[66, 67] The prevalence of CAD is two- to fourfold higher in patients with LEAD versus those without; in the Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter (CONFIRM) registry, among 7590 patients with LEAD without history and symptoms of heart disease, the prevalence of obstructive CAD at coronary computed tomography angiography was 25%.[68] In the REACH registry, 57% of the participants with LEAD also suffered from CAD.[69] The severity of LEAD is related to the prevalence of associated CAD; up to 90% of patients presenting with CLTI also have CAD.

There is no evidence that the presence of CAD directly influences limb outcomes in LEAD patients; however, in the CONFIRM registry, obstructive CAD was associated with an annual mortality rate of 1.6%, versus 0.7% in the absence of severe CAD.[68]

The presence of CAD in patients with LEAD may require coronary revascularization, pending on the severity and urgency of LEAD symptoms. Risk factor modification and medical treatment recommended for CAD also apply to LEAD.[70] Screening for CAD in LEAD patients may be useful for risk stratification, as morbidity and mortality are mainly cardiac. Non-invasive screening can be performed by stress testing or coronary computed tomography angiography, but there is no evidence of improved outcomes in LEAD patients with systematic screening for CAD.

Other peripheral localizations in patients with PADs

Carotid artery stenosis in patients with LEAD

Carotid stenosis is frequent in patients with LEAD (Figure 49.10.1) but there is no evidence that the presence of carotid artery stenosis would influence lower limb outcomes.

The presence of carotid artery disease is a marker of worse CV prognosis.[32]

Table 49.10.7 Indication for screening of associated atherosclerotic disease in additional vascular territories

Leading disease \ Screened disease	CAD	LEAD	Carotid	Renal
CAD				
Scheduled for CABG		IIa[a]	IIb[c] / I[b]	U
Not scheduled for CABG		IIb	NR	U
LEAD				
Scheduled for surgery	I[d]		NR	U
Not scheduled for surgery	NR		NR	U
Carotid stenosis				
Scheduled for CEA/CAS	IIb	NR		U
Not scheduled for CEA/CAS	NR	NR		U

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAS: carotid artery stenting; CEA, coronary endarterectomy; CKD, chronic kidney disease; ECG, electrocardiogram; LEAD, lower extremity artery disease; NR, no recommendation (not enough evidence to support systematic screening); TIA, transient ischaemic attack; U, uncertain.
[a] Especially when venous harvesting is planned for bypass.
[b] In patients with symptomatic cerebrovascular disease.
[c] In patients with asymptomatic carotid disease and: age ≥70 years, multivessel CAD, associated LEAD or carotid bruit.
[d] Screening with ECG is recommended in all patients and with imaging stress testing in patients with poor functional capacity and more than two of the following: history of CAD, heart failure, stroke or TIA, CKD, diabetes mellitus requiring insulin therapy.

In a population-based study including 3.67 million self-referred subjects with a mean age of 64 years, those with an ABI less than 0.9 had a higher prevalence of carotid stenosis (>50%) than those without (18.8% vs 3.3%; p <0.0001).[71] In multivariate analysis, both symptomatic LEAD (odds ratio (OR) 3.7) and asymptomatic LEAD (OR 2.9) were associated with carotid disease, with increasing LEAD severity, up to a 7.6 OR for patients with an ABI of 0.40 or less. In a meta-analysis of 19 studies including a total of 4573 patients, the prevalence of carotid stenosis greater than 70% in patients with LEAD was reported at 14%.[72] Risk factors for the association of carotid disease and LEAD include age, smoking, and concomitant CAD; carotid disease appears to be twice as common among LEAD patients than among CAD patients.[4]

The presence of associated carotid artery stenosis requires prioritization of revascularization, if needed, according to the patient's clinical status and to the severity of carotid disease and LEAD. In general, risk factor modification and medical treatment recommended for LEAD also apply to the management of asymptomatic carotid disease.

There is a paucity of data regarding the usefulness of screening for carotid artery stenosis in patients with LEAD.

Renal artery disease in patients with LEAD

While RAS is frequently discovered incidentally during imaging for LEAD, it requires specific intervention exceptionally. Opinions on whether atherosclerotic RAD could be a marker of worse CV prognosis in LEAD patients are conflicting.[3, 73] The only report looking also at limb outcome found no prognostic alteration in the case of concomitant RAS.[3]

The prevalence of RAS greater than 60% ranges between 10% and 23% in studies assessing renal arteries during angiography for LEAD, and can reach 40% in patients with aorto-iliac disease requiring revascularization (Figure 49.10.1).[4] Risk factors for the association of RAS and LEAD include age, female sex, aorto-iliac LEAD, SCLI, smoking, hypertension, and renal failure.[4]

The identification of RAD in LEAD patients does not change medical treatment, as antiplatelet therapy and lipid-lowering therapy are already recommended for all patients with LEAD. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers should be given with caution in cases of bilateral RAS or unilateral stenosis with a non-functional/absent contralateral kidney.

Systematic screening for RAD in patients with LEAD cannot be recommended, since the therapeutic value of renal artery stenting is questionable (see Chapter 49.8). See Table 49.10.7.

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Chapter 49.11 Cardiac conditions in peripheral arterial diseases

Key messages

- Cardiac conditions other than coronary artery disease (CAD) are frequent in patients with peripheral arterial diseases (PADs). This is especially the case for heart failure and atrial fibrillation in patients with lower extremity artery disease (LEAD).
- In patients with symptomatic PADs, screening for heart failure should be considered.
- In patients with heart failure, screening for LEAD may be considered. Full vascular assessment is indicated in patients planned for heart transplantation or a cardiac assist device.
- In patients with stable PADs who have atrial fibrillation (AF), anticoagulation is the priority and suffices in most cases. In the case of recent endovascular revascularization, a period of combination therapy (anticoagulant plus antiplatelet therapies) should be considered according to the bleeding and thrombotic risks. The period of combination therapy should be as brief as possible.
- In patients undergoing transcatheter aortic valve implantation (TAVI) or other structural interventions, screening for LEAD and upper extremity artery disease (UEAD) is indicated.

Introduction

Cardiac diseases are frequent in patients with PADs. The simultaneous presence of PADs and CAD is addressed in Chapter 49.10. Here, we address the most important issues related to PADs patients with coexisting heart failure, AF, and valvular heart disease. Such coexistence may carry important prognostic and therapeutic implications and often needs a multidisciplinary approach.

Heart failure and PADs

There are multiple pathways linking LEAD and heart failure (Figure 49.11.1). Together with diabetes, smoking, and other risk factors, inflammation may be one of the common factors leading to the development of heart failure in PADs patients.[1] Data on the coexistence of the two conditions are generally limited to subjects with heart failure and LEAD.

LEAD is associated with increased risk for incident heart failure. It is often associated with overt atherosclerosis involving CAD, which may cause subsequent heart failure.[2] In addition, elevated aortic stiffness increases left ventricular (LV) afterload and high pulse pressure impairs coronary blood flow, resulting in hypertension, LV hypertrophy and diastolic dysfunction, and ultimately heart failure.[3, 4] Importantly, skeletal muscle involvement and deconditioning in LEAD may affect heart failure severity.[5, 6] On the other hand, functional limitation due to heart failure is likely to mask symptoms of LEAD, causing underestimation of the number of patients with both conditions.

Epidemiology

Overall, LV dysfunction and heart failure are more frequent in patients with PADs. The evidence is mostly presented in patients with LEAD.

One-third of patients with symptomatic PADs have reduced LV ejection fraction.[7, 8] LV dysfunction is at least twice as prevalent in patients with LEAD as in the general population, matched for age and sex.[8–10] This association with LV dysfunction may be even stronger for carotid artery disease than for LEAD.[9] In a community-based study with participants over 65 years of age, an ankle–brachial index (ABI) less than 0.90, as compared to 0.90 or greater, increased the relative risk for incident heart failure by 1.61 (95% confidence interval (CI) 1.14–2.29) over a 6-year follow-up period. However, this increase was not observed among patients with prevalent CAD.[11] In a population of older adults followed for a median of 7.5 years, the multivariable-adjusted hazard ratio (HR) for heart failure with symptomatic LEAD was 3.92 (95% CI 2.13–7.21).[12] Also in a younger population with cardiovascular (CV) disease or high CV risk, the incidence of heart failure was higher in patients with an ABI less than 0.90, as compared to 0.90 or greater (4.6% vs 2.6%).[2] In a large, middle-aged population with an 18-year follow up, incident cases of heart failure occurred in 23% of patients with an ABI less than or equal to 0.90, compared to 18%, 13%, and 14% of patients with an ABI of 0.91–1.00, 1.01–1.40, and greater than 1.40, respectively.[13] These associations persisted after adjustment for carotid plaques, CAD,

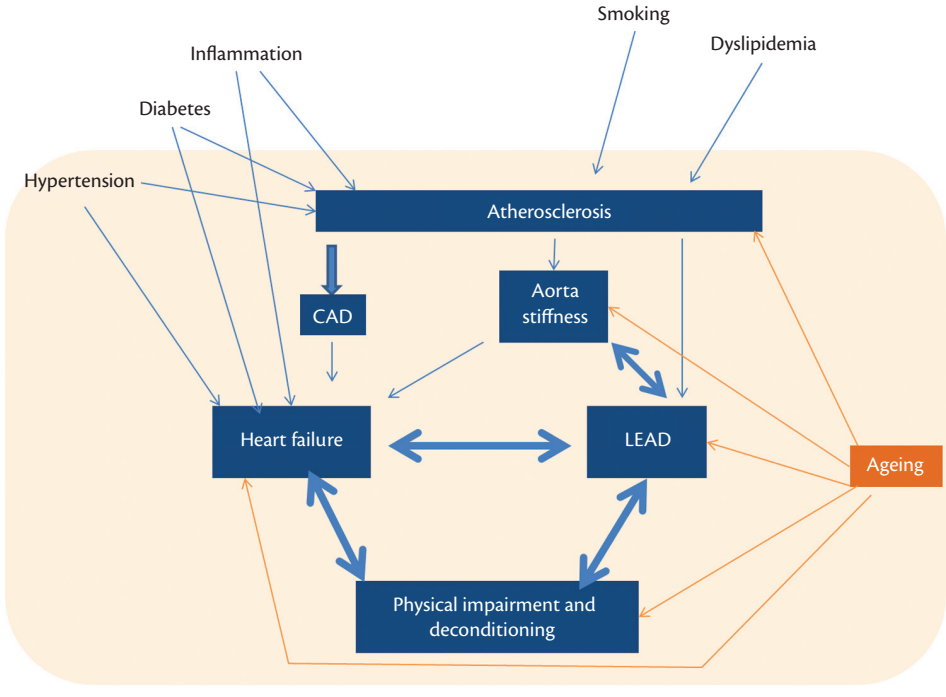

Figure 49.11.1 Interrelations between heart failure and lower extremity artery disease. CAD, coronary artery disease; LEAD, lower extremity artery disease.

and other risk factors for heart failure. The multivariable-adjusted population attributable risk for incident heart failure by an ABI of 1.00 or less was 6%, compared to 8% for CAD, 15% for hypertension, and 14% for diabetes.[13]

Heart failure in patients with PADs

Despite the high prevalence and incidence of heart failure in patients with PADs, outcome data for this group are very limited. It is most likely, however, that this combination is associated with increased CV morbidity and mortality. Evaluation of LV function in PADs may be of value for a better risk stratification for future CV events and a comprehensive management of patients' CV diseases.[9] This is particularly important when an intermediate- or high-risk vascular intervention is planned.[14] The primary assessment should include medical history, physical examination, and resting electrocardiogram. In case of any abnormalities suggestive of heart failure, transthoracic echocardiography (TTE) or measurement of natriuretic peptides should be undertaken.[15] Natriuretic peptides are particularly useful in patients with a poor echocardiographic window and in those with diastolic dysfunction.[16] In patients with LEAD, heart failure may be associated with reduced patency after endovascular therapy.[17] TTE and natriuretic peptides can also be proposed in patients with claudication, even if no revascularization is planned.

PADs in patients with heart failure

Observational studies and meta-analyses consistently show that the presence of LEAD in heart failure patients is an independent predictor of hospitalizations and mortality.[18–21] In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, LEAD was reported in around 7% of patients with heart failure and LV ejection fraction less than 35%, and was associated with an increased risk of all-cause hospitalization and mortality (HR 1.31; $p = 0.011$).[20] Other studies reported an increased risk for progressive heart failure (HR 1.35; $p = 0.03$), all-cause mortality (HR 1.36; $p < 0.001$),[22] and CV mortality (HR 1.31; $p = 0.02$).[23] Among hospitalized patients with heart failure, the prevalence of subclinical (ABI ≤0.90) and symptomatic LEAD was 19% and 7%, respectively, and was associated with increased cardiac and all-cause mortality.[21] Therefore, in heart failure patients, screening for PADs may be considered.

Finally, flash pulmonary oedema may be due to severe renal artery stenosis (see 'Clinical presentation' in Chapter 49.8). Therefore, in patients with this condition, testing for renal artery stenosis may be considered.

PADs and atrial fibrillation

General considerations

Ageing is a strong risk factor for AF[24] and PADs. Thus, a frequent coexistence of the two conditions is expected. In an analysis from the Cardiovascular Health Study, LEAD was associated with a higher risk of AF (HR 1.52; $p < 0.01$).[25]

Despite a considerable variability in blood pressure due to the beat-to-beat variability in stroke volume, ABI appears to be a reliable method to detect unknown LEAD in patients with AF.[26] In patients with AF receiving anticoagulant treatment, abnormal ABI was an independent predictor of all-cause death and major bleeding complications.[27]

Among 41,882 patients hospitalized for LEAD, the prevalence of AF was 13%.[24] Those with AF tend to be older, more often hypertensive, female, with diabetes, chronic kidney disease, CAD, and/or heart failure, than patients in sinus rhythm. LEAD

was overall more severe in patients with AF, as assessed by the Rutherford classification. In-hospital complications, including renal failure, myocardial infarction, stroke, infections, and death, occurred more frequently in the presence of AF. In other studies, AF associated with LEAD was an independent predictor of stroke, amputation, and death.[28, 29] In the REACH registry, AF was present in 10% of patients with LEAD.[30] Compared with patients without AF, the 2-year CV and all-cause mortality was higher, 7.7% and 5.6% versus 2.5% and 1.6%, respectively (p <0.001 for both). Those with AF also had higher incidences of heart failure, unstable angina, and severe bleeding.

Antithrombotic treatment in patients with atrial fibrillation

Except for recent stenting, patients with PADs and AF should mostly be under oral anticoagulants alone. See 'Antithrombotic therapy in lower extremity artery disease patients requiring long-term oral anticoagulant' in Chapter 49.4.

PADs and valvular heart disease

PADs are common among patients with valvular heart disease, especially among the elderly with symptomatic aortic stenosis. The presence of LEAD is captured within the scores used to predict outcome after cardiac surgery.[31] Among patients with symptomatic aortic stenosis not eligible for surgical aortic valve replacement, the prevalence of LEAD is as high as 40%.[32–34] It often coexists with other manifestations of systemic atherosclerosis, including CAD and cerebrovascular disease. This has an impact on patient care with respect to the timing of coronary revascularization if needed,[35] and the vascular access site for TAVI.[36] Systematic computed tomography scan imaging of the aorta, including all major peripheral arteries, has become the standard of care in patients eligible for TAVI.

PADs and vascular access site for cardiac interventions

Patient evaluation for the presence of LEAD and UEAD is pivotal for access site choice in patients eligible for TAVI, and their diagnosis has a great impact on clinical outcome after TAVI because of the increased rate of peri- and post-procedural complications.[34, 38] The presence of LEAD or UEAD is an independent predictor of mortality following TAVI with both percutaneous and surgical access, independent of the occurrence of vascular complications.[37–39] The use of low-profile devices for TAVI and alternative access sites, such as direct aortic, carotid, or subclavian, may also reduce vascular complications.

Acute limb ischaemia is a complication of intra-aortic balloon pump insertion in the setting of cardiogenic shock or in the prophylaxis of the low-output syndrome. LEAD is a major risk factor for this complication, and preliminary iliac artery stenting with the use of an unsheathed device may avoid such complications.[40] These complications are also common in LV assist device recipients, where sheaths are usually larger, resulting in higher 30-day mortality in patients with LEAD.[41] The added risk of underlying LEAD is not clearly established in that particular setting and deserves additional investigations. These patients often need lower limb revascularization and surgical vascular closure when weaned off LV assist devices.

See Table 49.11.1 for recommendations on the management of cardiac conditions associated with peripheral arterial diseases.

Table 49.11.1 Recommendations on the management of cardiac conditions associated with peripheral arterial diseases

Recommendations	Class[a]	Level[b]
PADs and heart failure		
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation	I	C
In patients with symptomatic PADs, screening for heart failure with TTE and/or natriuretic peptides assessment should be considered	IIa	C
Screening for LEAD may be considered in patients with heart failure	IIb	C
Testing for renal artery disease may be considered in patients with flash pulmonary oedema	IIb	C
PADs and atrial fibrillation[c]		
In patients with LEAD and atrial fibrillation, oral anticoagulation[42]:		
◆ is recommended when CHA_2DS_2-VASc score ≥2	I	A
◆ should be considered in all other patients.	IIa	B
PADs and valvular heart disease		
Screening for LEAD and UEAD is indicated in patients undergoing TAVI or other structural interventions requiring an arterial approach.	I	C

LEAD, lower extremity artery disease; PADs, peripheral arterial diseases; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiography; UEAD, upper extremity artery disease.
CHA_2DS_2VASc: Congestive heart failure; *H*ypertension; *A*ge ≥ 75 years; *D*iabetes mellitus; prior Stroke or TIA; *V*ascular disease; *A*ge 65–74 years; *S*ex Category female.
[a] Class of recommendation.
[b] Level of evidence.
[c] For more detail please refer to Chapter 49.3.

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Chapter 49.12 Gaps in evidence

Rapid changes in therapeutic techniques create the situation in which clinical practice tends to follow technical developments without evidence from randomized clinical trials. In addition, randomized clinical trials often yield conflicting results because of technical evolution. Moreover, peripheral arterial diseases may involve multiple sites, creating a large number of clinical scenarios to investigate. All these contribute to the broad spectrum of gaps in evidence, of which the most relevant are listed in the Table 49.12.1.

Table 49.12.1 Main gaps in evidence in the management of patients with peripheral arterial diseases

Epidemiology
Data on epidemiology of PADs in Europe are scarce.
Important challenges are associated with PADs in women. This group has classically been underrepresented in research studies. Therefore, several sex-related challenges regarding diagnosis and management issues should be acknowledged.
Carotid artery disease
The benefits of new antiplatelet drugs for the management of asymptomatic carotid artery disease should be assessed by RCTs.
A multifactorial and standardized score is necessary to stratify the risk of stroke in patients with asymptomatic carotid artery stenosis, to determine the subgroup who may benefit from revascularization, in addition to best medical therapy.
The efficacy of embolic protection devices during CAS has not been studied in adequately powered RCTs, and the available evidence is conflicting.
The optimal duration of dual antiplatelet therapy after CAS is not well established.
The timing of carotid revascularization in the acute phase of stroke after intracerebral thrombolysis/thrombectomy is not yet defined and should be investigated.
Vertebral artery disease
Almost no data are available on the comparison between surgical and endovascular revascularization in symptomatic patients.
Upper extremity artery disease
Little is known about the natural course in upper extremity artery disease.
Almost no data are available on the long-term clinical benefit of revascularization (and the optimal mode) of symptomatic subclavian artery stenosis/occlusion.
Optimal duration for DAPT after subclavian artery stenting is unknown.
Mesenteric artery disease
The potential benefits of prophylactic revascularization for asymptomatic mesenteric artery disease involving multiple vessels need investigations.
In case of symptomatic mesenteric artery disease, no data are available on the potential benefit of covered versus bare stents.
Optimal duration for DAPT after mesenteric stenting is unknown.
Renal artery disease
The role of renal artery stenting for patients with pulmonary flash oedema remains to be demonstrated by RCT.

Table 49.12.1 (Continued)

Appropriate treatment of in-stent renal artery restenosis is not yet defined.
Risk stratification would be necessary to clarify whether a subgroup of patients with RAS may benefit from renal revascularization. In case of renal stenting, optimal duration for DAPT is unknown.
Lower extremity artery disease
The role of drug-eluting stents and drug-eluting balloons in superficial femoral artery and below-the-popliteal artery interventions has to be established.
Optimal treatment for popliteal artery stenosis needs to be addressed.
Clinical studies on self-expanding stents, drug-coated balloons, and drug-eluting stents for below-the-knee interventions in patients with CLTI should include amputation-free survival, wound healing, and quality of life in addition to standard-patency outcomes.
Optimal duration of DAPT after stenting, as well as the potential benefit of its long-term use in patients with CLTI, should be further investigated.
The rationale of the angiosome concept to decide on modality of revascularization in patients with CLTI remains to be demonstrated.
There is a need to develop European registries for patients with LEAD in order to provide 'real-world' assessment of clinical outcomes and practices.
There is a need to validate improved classification systems for CLTI that incorporate wound, ischaemia, and foot infection such as the WIfI classification.
Multisite artery disease
Whether the screening for other sites of atherosclerosis (e.g. CAD) in patients with PADs may improve their outcome needs further investigation.
Cardiac conditions in patients with PADs
The impact of heart failure screening and treatment and its impact on outcome of patients with PADs require further investigations.
The optimal strategy of antithrombotic treatment in patients with atrial fibrillation and PADs requires specific RCTs.

CAD, coronary artery disease; CAS, carotid artery stenting; CLTI, chronic limb-threatening ischaemia; DAPT, dual antiplatelet therapy; LEAD, lower extremity artery disease; PADs, peripheral arterial diseases; RAS, renal artery stenosis; RCT, randomized clinical trial; WIfI, wound, ischaemia, and foot infection.