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ESC Guidelines on the diagnosis and treatment of peripheral artery diseases

Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries

The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC)

Endorsed by: the European Stroke Organisation (ESO)

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Abbreviations and acronyms

2D	two-dimensional
3D	three-dimensional
ABI	ankle–brachial index
ACAS	Asymptomatic Carotid Atherosclerosis Study
ACCF	American College of Cardiology Foundation
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACST	Asymptomatic Carotid Surgery Trial
ALI	acute limb ischaemia
ASTRAL	Angioplasty and Stenting for Renal Artery Lesions trial
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
BOA	Dutch Bypass Oral Anticoagulants or Aspirin
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events
CAPTURE	Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events

CARP	Coronary Artery Revascularization Prophylaxis
CAS	carotid artery stenting
CASPAR	Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease
CASS	Coronary Artery Surgery Study
CAVATAS	CArotid and Vertebral Artery Transluminal Angioplasty Study
CEA	carotid endarterectomy
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance
CI	confidence interval
CLEVER	Claudication: Exercise Versus Endoluminal Revascularization
CLI	critical limb ischaemia
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
COURAGE	Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation
CPG	Committee for Practice Guidelines
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
CT	computed tomography
CTA	computed tomography angiography
CVD	cardiovascular disease
DECREASE-V	Dutch Echocardiographic Cardiac Risk Evaluation
DRASTIC	Dutch Renal Artery Stenosis Intervention Cooperative Study
DSA	digital subtraction angiography
DUS	duplex ultrasound/duplex ultrasonography
EACTS	European Association for Cardio-Thoracic Surgery
EAS	European Atherosclerosis Society
ECST	European Carotid Surgery Trial
EPD	embolic protection device
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESRD	end-stage renal disease
EUROSCORE	European System for Cardiac Operative Risk Evaluation
EVA-3S	Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis
EXACT	Emboshield and Xact Post Approval Carotid Stent Trial
GALA	General Anaesthesia versus Local Anaesthesia for Carotid Surgery
GFR	glomerular filtration rate
GRACE	Global Registry of Acute Coronary Events
Hb_{A1c}	glycated haemoglobin
HDL	high-density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HR	hazard ratio
IC	intermittent claudication
ICSS	International Carotid Stenting Study
IMT	intima–media thickness
ITT	intention to treat
LDL	low-density lipoprotein
LEAD	lower extremity artery disease
MACCEs	major adverse cardiac and cerebrovascular events
MDCT	multidetector computed tomography
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OR	odds ratio
PAD	peripheral artery diseases
PARTNERS	Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival
PCI	percutaneous coronary intervention
PET	positron emission tomography
PRO-CAS	Predictors of Death and Stroke in CAS
PTA	percutaneous transluminal angioplasty
RAAS	renin–angiotensin–aldosterone system
RADAR	Randomized, Multicentre, Prospective Study Comparing Best Medical Treatment Versus Best Medical Treatment Plus Renal Artery Stenting in Patients With Haemodynamically Relevant Atherosclerotic Renal Artery Stenosis
RAS	renal artery stenosis
RCT	randomized controlled trial
REACH	Reduction of Atherothrombosis for Continued Health
RR	risk ratio
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SCAI	Society for Cardiovascular Angiography and Interventions
SIR	Society of Interventional Radiology
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study
STAR	Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function
SSYLVIA	Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries
SVMB	Society for Vascular Medicine and Biology
TASC	TransAtlantic Inter-Society Consensus
TIA	transient ischaemic attack
UEAD	upper extremity artery disease
VA	vertebral artery

1. Preamble

Guidelines summarize and evaluate all available evidence, at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies

for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help the physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management, and/or prevention of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and 2.

The experts of the writing and reviewing panels filled in declarations of interest forms of all relationships which might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*.

The task of developing Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, and electronic version for digital applications (smartphones, etc.), are produced. These versions are abridged and, thus, if needed, one should always refer to the full text version which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of Guidelines, and implementing them into clinical practice.

The Guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***	**Should be considered**
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***	**May be considered**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**	**Is not recommended**

Table 2 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

patient, and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death and disability in Europe, posing a great social and economic burden. Coronary artery disease (CAD) is the cause of death in a large percentage of individuals, but stroke, renal failure, and complications from severe ischaemia of the lower extremities also contribute to an adverse prognosis.

Since atherosclerosis is a systemic disease, physicians must appreciate the importance of detecting atherosclerosis in other vascular beds in order to establish the correct treatment to prevent organ damage. As shown recently by the Reduction of Atherothrombosis for Continued Health (REACH) Registry, a substantial percentage of patients with chronic CAD have associated cerebrovascular disease, lower extremity artery disease (LEAD), or both.[1]

This is the first document produced by the ESC addressing different aspects of peripheral artery diseases (PAD). This task has been undertaken because an increasing proportion of patients with heart disease need to be assessed for vascular problems in other territories, both symptomatic and asymptomatic, that may affect their prognosis and treatment strategy. It is also recognized that patients with PAD will probably die from CAD.[2]

In this document the term PAD is used to include all vascular sites, including carotid, vertebral, upper extremity, mesenteric, renal, and lower extremity vessels. Diseases of the aorta are not covered.

Although different disease processes may cause PAD, the Task Force decided to focus on atherosclerosis. Other aetiologies, specific for different vascular territories, are mentioned but not discussed.

Atherosclerosis in the peripheral arteries is a chronic, slowly developing condition causing narrowing of the arteries. Depending on the degree of narrowing at each vascular site, a range of severity of symptoms may occur, while many patients will remain asymptomatic throughout their life. Occasionally acute events occur, often associated with thrombosis and/or embolism and/or occlusion of a major artery.

In the first section of this document the general issues are addressed, whereas the detailed clinical presentations are covered in specific sections for each vascular site. Special emphasis is put on multisite artery disease (e.g. patients with CAD plus disease in another vascular bed), addressing most common aspects from a diversity of complex clinical scenarios encountered in clinical practice. Finally, major gaps in evidence are identified, which may hopefully stimulate new research.

These guidelines are the result of a close collaboration between physicians from many different areas of expertise: cardiology, vascular surgery, vascular medicine/angiology, neurology, radiology, etc., who have worked together with the aim of providing the medical community with the data to facilitate clinical decision making in patients with PAD.

3. General aspects

This section covers the epidemiology of PAD and associated risk factors, as well as aspects of diagnosis and treatment common to all specific vascular sites.

3.1 Epidemiology

The epidemiology of LEAD has been investigated in many countries, including several in Europe. In a recent study in a population aged 60–90 years in Sweden, the prevalence of LEAD was 18% and that of intermittent claudication was 7%.[3] Typically, one-third of all LEAD patients in the community are symptomatic. The prevalence of critical limb ischaemia (CLI) is very much less—0.4% in those over 60 years of age in the Swedish study.[3] The estimated annual incidence of CLI ranges from 500 to 1000 new cases per 1 million population, with a higher incidence among patients with diabetes.

The frequency of LEAD is strongly age related: uncommon before 50 years, rising steeply at older ages. In a recent study in Germany the prevalence of symptomatic and asymptomatic LEAD in men aged 45–49 years was 3.0%, rising to 18.2% in those aged 70–75 years. Corresponding rates for women were 2.7% and 10.8%.[4] Prevalence rates between men and women are inconsistent. There is, however, some suggestion of an equilibration between the sexes with increasing age. Incidence rates are less often reported, but also show a strong relationship with age. In the Framingham Study, the incidence of intermittent claudication in men rose from 0.4 per 1000 aged 35–45 years to 6 per 1000 aged 65 years and older.[5] The incidence in women was around half that in men, but was more similar at older ages.

The annual incidence of major amputations is between 120 and 500 per million in the general population, of which approximately equal numbers are above and below the knee. The prognosis for such patients is poor. Two years following a below-knee amputation, 30% are dead, 15% have an above-knee amputation, 15% have a contralateral amputation, and only 40% have full mobility.[6]

Future trends in the epidemiology of LEAD are difficult to predict due to changes in risk factors in the population, especially tobacco smoking and diabetes, and due to the increased survival from CAD and stroke, allowing LEAD to become manifest. Limited evidence on trends during the past few decades has suggested a decline in the incidence of intermittent claudication.

In 50-year-old Icelandic men the incidence decreased from 1.7 per 1000 in 1970 to 0.6 per 1000 in 1984,[7] whereas in the Framingham Study, the incidence decreased from 282 per 100 000 person-years in 1950–1959 to 225 per 100 000 person-years in 1990–1999.[8]

In the Rotterdam Study of elderly people over 55 years of age, a reduction in lumen diameter of the right internal carotid artery from 16% to 49% was found in 3%, whereas severe stenosis (≥50% reduction) was found in 1.4%.[9] Likewise in the Tromso Study of the general population over 50 years of age, the prevalence of carotid stenosis was 4.2% in men, which was significantly higher than in women (2.7%) ($P = 0.001$).[10] Minor degrees of stenosis are much more common. In the Cardiovascular Health Study in subjects >65 years of age, 75% of men and 62% of women had carotid plaques,[11] and in the Framingham Study in men aged 75 years, >40% had stenosis >10%.[8]

Renal artery disease has been found frequently in post-mortem studies, but evidence on prevalence in the general population is limited. In the Cardiovascular Health Study of an elderly population with mean age 77 years, the prevalence of renal artery disease, defined as stenosis reducing arterial diameter by ≥60% or occlusion, was 9.1% in men and 5.5% in women.[12] However, much information on the prevalence of renal artery disease has been derived from studies of patients undergoing coronary angiography or abdominal aortography in which the renal arteries have been imaged. A systematic review of such studies found that between 10% and 50% of patients had renal artery stenosis (RAS) depending on the risk group being examined.[13] Owing to the selection of patients for such studies, the prevalences were likely to be much higher than those found in the general population.

Chronic symptomatic mesenteric artery disease is found rarely in clinical practice although at times is under/misdiagnosed. It accounts for only 5% of all intestinal ischaemic events and is often severe, even fatal. The prevalence of asymptomatic mesenteric artery disease in the general population is not well established. In patients with atherosclerotic disease at other sites, atherosclerosis in the mesenteric arteries may be relatively common: in patients with LEAD and renal artery disease, 27% of patients had ≥50% stenosis in a mesenteric artery.[14]

Atherosclerosis occurs much less frequently in the arteries of the upper extremity compared with the lower extremity. The subclavian artery is often affected. In a study using data from four cohorts in the USA, the prevalence of subclavian artery stenosis in the general population was 1.9%, with no significant difference between the sexes.[15] Prevalence increased with age from 1.4% in those <50 years of age to 2.7% in those >70 years. Subclavian stenosis was defined in this study as an inter-arm pressure difference of ≥15 mmHg, but, using angiography as the gold standard, the sensitivity of this definition has been shown to be only ~50% and specificity 90%. Thus the true prevalence of subclavian artery stenosis may be much higher than that observed in the cohorts. The majority of these cases are asymptomatic.

Given the common aetiology of peripheral atherosclerosis occurring at different vascular sites, the presence of disease at one site increases the frequency of symptomatic and asymptomatic disease at another. The degree of concordance observed between sites is, however, dependent on the methods of diagnosis and on the selected population. From a clinical perspective, such findings indicate the need for a heightened awareness of the possibility of atherosclerotic disease occurring at sites other than the presenting one. This is especially so in the elderly in whom the degree of overlap of CAD, cerebrovascular disease, and LEAD is particularly high.

3.2 Risk factors

Risk factors for PAD are similar to those important in the aetiology of CAD and are the typical risk factors for atherosclerotic disease. These include the traditional risk factors: smoking, dyslipidaemia, diabetes mellitus, and hypertension. However, for some peripheral artery sites the evidence linking these factors to the development of disease is limited. Also, specific risk factors could be more important for the development of disease at certain sites, but there are few comparative studies.

In LEAD, cigarette smoking has been shown consistently in several epidemiological studies to be an important risk factor and to be dose dependent.[16,17] Smoking would appear to be a stronger risk factor for LEAD than for CAD and, in most studies, patients with claudication have had a history of smoking at some point in their lives. Smoking cessation is associated with a rapid decline in the incidence of claudication, which equates to that in non-smokers after 1 year of stopping.[7] Diabetes mellitus is the other risk factor especially important in the development of LEAD. This is certainly true for severe disease, notably gangrene and ulceration, but for intermittent claudication the strength of the association with diabetes may be comparable with that for coronary heart disease. The association of diabetes with LEAD is inconsistent on multivariable analysis, which includes other risk factors, but it appears that the duration and severity of diabetes affect the level of risk.[16,17]

Most epidemiological studies show an association between hypertension and the presence of LEAD, although interpretation of such findings is difficult because blood pressure is a component in the definition of disease [the ankle–brachial index (ABI)] and may also affect the degree of ischaemia and the occurrence of symptoms. However, no association has been found between increased blood pressure and claudication. In contrast, in the Limburg PAOD study, hypertension was associated with an increased relative risk of 2.8 for LEAD[18] and in the Rotterdam Study a low ABI (<0.90) was associated with both increased systolic and diastolic blood pressure.[19]

Most epidemiological studies have found that high total cholesterol and low high-density lipoprotein (HDL) cholesterol are independently related to an increased risk of LEAD. In the US Physicians Health Study, the ratio of total/HDL cholesterol was the lipid measure most strongly related to disease.[20]

For other factors associated with CVD, such as obesity, alcohol consumption, and plasma homocysteine levels, the associations with LEAD have been inconsistent. In recent years, particular interest in haemostatic, rheological, and inflammatory markers, such as plasma fibrinogen and C-reactive protein,[20] has led to studies that have shown independent associations with both the prevalence and incidence of LEAD, although whether such associations are primarily the cause or the effect is not clearly known. Currently genetic factors and many other novel biomarkers are being studied.

In general, the risk factors for carotid stenosis are similar to those for LEAD, although smoking, while commonly associated with carotid disease, is not so dominant as with LEAD. Several population-based studies have found in both symptomatic and asymptomatic disease that the classic risk factors of smoking, high low-density lipoprotein (LDL) cholesterol, low HDL cholesterol, hypertension, and diabetes mellitus are associated with higher risk in both men and women irrespective of age.[9–11] The risk factors for carotid artery disease, however need to be distinguished from those for ischaemic stroke, which is not necessarily related to stenosis in the carotid arteries.

Likewise, for atheromatous renal artery disease the pathogenesis is similar to that seen in other vascular sites and, although the evidence is limited, would appear to be associated with typical cardiovascular risk factors.[21] These include pre-existing high blood pressure in which the hypertension is not necessarily a complication but may be a cause of the RAS and may partly explain why in many patients revascularization may not lead to a reduction in blood pressure.

In chronic mesenteric artery disease, the atheromatous lesions normally occur in the proximal segments of the splanchnic arteries. The frequency of diffuse atherosclerosis has not been well described but would appear to occur mostly in patients with end-stage renal disease (ESRD) or diabetes. The classic cardiovascular risk factors appear to be important, although hypocholesterolaemia (rather than hypercholesterolaemia) may be a presenting finding due to a patient's chronic malnourished state.

Significant associations were found between both increasing age and higher systolic blood pressure with the presence of upper extremity artery disease (UEAD).[15] Compared with never smokers, the risks were increased in current and past smokers, and the odds ratio (OR) of 2.6 for current smokers was the highest of any risk factor, perhaps mirroring that found for LEAD. While a higher HDL cholesterol level appeared to be protective, surprisingly no association was found between total cholesterol and subclavian stenosis. Diabetes mellitus was also not related, although in another study the prevalence of UEAD was found to be slightly higher in diabetic compared with non-diabetic patients.[22] Interestingly, in the four cohort study, LEAD, compared with CAD and cerebrovascular disease, was much more strongly related to UEAD.[15]

3.3 General diagnostic approach

3.3.1 History

History of risk factors and known co-morbidities is mandatory. Hypertension, dyslipidaemia, diabetes mellitus, smoking status, as well as history of CVD must be recorded. Medical history should include a review of the different vascular beds and their specific symptoms:

- Family history of CVD.
- Symptoms suggesting angina.
- Any walking impairment, e.g. fatigue, aching, cramping, or pain with localization to the buttock, thigh, calf, or foot, particularly when symptoms are quickly relieved at rest.
- Any pain at rest localized to the lower leg or foot and its association with the upright or recumbent positions.
- Any poorly healing wounds of the extremities.
- Upper extremity exertional pain, particularly if associated with dizziness or vertigo.
- Any transient or permanent neurological symptom.
- History of hypertension or renal failure.
- Post-prandial abdominal pain and diarhoea, particularly if related to eating and associated with weight loss.
- Erectile dysfunction.

This cannot be an exhaustive list, and a review of symptoms should include all domains. It is important to emphasize that history is a cornerstone of the vascular evaluation.

One should remember that many patients, even with advanced disease, will remain asymptomatic or report atypical symptoms.

3.3.2 Physical examination

Although physical examination alone is of relatively poor sensitivity, specificity, and reproducibility, a systematic approach is mandatory. It must include at least:

- Measurement of blood pressure in both arms and notation of inter-arm difference.
- Auscultation and palpation of the cervical and supraclavicular fossae areas.
- Palpation of the pulses at the upper extremities. The hands must be carefully inspected.
- Abdominal palpation and auscultation at different levels including the flanks, periumbilical region, and the iliac regions.
- Auscultation of the femoral arteries at the groin level.
- Palpation of the femoral, popliteal, dorsalis pedis, and posterior tibial sites.
- The feet must be inspected, and the colour, temperature, and integrity of the skin, and the presence of ulcerations recorded.
- Additional findings suggestive of LEAD, including calf hair loss and skin changes, should be noted.

Beyond their diagnostic importance, clinical signs could have a prognostic value. A meta-analysis published in 2008 emphasized the prognostic value of carotid bruit.[23] People with carotid bruits have twice the risk of myocardial infarction and cardiovascular death compared with those without. This predictive value can be extended to other clinical signs, such as femoral bruit, pulse abnormality in the lower extremity, or inter-arm blood pressure asymmetry. All of these abnormalities can be an expression of subclinical vascular disease.

3.3.3 Laboratory assessment

The aim of the laboratory assessment is to detect major risk factors of CVD. The assessment should be performed according to the ESC Guidelines on Cardiovascular Disease Prevention[24] and the ESC/EAS Guidelines for the Management of Dyslipidaemias.[25]

3.3.4 Ultrasound methods

3.3.4.1 Ankle–brachial index

The ABI is a strong marker of CVD and is predictive of cardiovascular events and mortality. Low ABI values (<0.90) are predictive of atherosclerosis, such as CAD and carotid artery disease. A reduced ABI has been associated in several studies with an

increased risk of cardiovascular morbidity and mortality.[26] Also a very high ABI (>1.40) in relation to stiffened arteries is associated with increased mortality.[27] Recently, the ABI has been shown to be a valid method of cardiovascular risk assessment in diverse ethnic groups, independent of traditional and novel risk factors, as well as other markers of atherosclerosis such as the coronary artery calcium score.[27] ABI is recommended as an office measurement in selected populations considered at high risk of CVDs. When performed with a handheld Doppler device, the measurement remains inexpensive and minimally time consuming.

The use of ABI to diagnose LEAD is discussed in Section 4.5.2.1.

3.3.4.2 Duplex ultrasound

Duplex ultrasound (DUS) is now widely available for the screening and diagnosis of vascular lesions. Initially, with continuous wave Doppler, severe stenoses were identified and quantified mainly by the peak systolic velocities. Nowadays, DUS includes B-mode echography, pulsed-wave Doppler, colour Doppler, and power Doppler in order to detect and localize vascular lesions and quantify their extent and severity.

By detecting subclinical artery disease, DUS provides relevant information regarding cardiovascular risk assessment. B-mode ultrasound is also a robust technique for the measurement of the intima–media thickness (IMT), which has been studied (mostly in the carotid arteries) and validated in several epidemiological and interventional studies as a marker of atherosclerotic burden in individuals and a predictor of cardiovascular morbidity and mortality. Further, DUS allows a complete vascular evaluation of the different beds and is often the first step in the clinical management. New techniques, such as B-flow imaging or live three-dimensional (3D) echography, as well as the use of ultrasound contrast agents, will further improve the performance of DUS.

3.3.5 Angiography

In the past, digital subtraction angiography (DSA) was the gold standard of vascular imaging. Given its invasive characteristics, this method has now been replaced by other effective non-invasive diagnostic methods and is used almost exclusively during endovascular procedures.

3.3.6 Computed tomography angiography

The introduction of multidetector computed tomography (MDCT) has shortened the examination time and reduced motion and respiration artefacts while imaging the vessels and organs. The use of computed tomography angiography (CTA) is not recommended for screening purposes due to the high doses of radiation used, potential contrast nephrotoxicity, and the lack of data demonstrating the effect of screening with CT.

When CTA is used for diagnostic purposes, nephrotoxicity can be limited by minimizing the volume of contrast agents and ensuring adequate hydration before and after imaging. The potential benefit of acetylcysteine to limit nephrotoxicity is uncertain.

3.3.7 Magnetic resonance angiography

High-performance scanning is used during magnetic resonance angiography (MRA) with a high signal–noise ratio and rapid data acquisition. Morphological and functional studies require at least a 1.0 Tesla system. In order to increase the resolution, special phased-array surface coils are placed directly on the body, which provide a homogeneous magnetic field over a large area.

Absolute contraindications include cardiac pacemakers, implantable cardioverter defibrillators, neurostimulators, cochlear implants, first-trimester pregnancy, and severe renal failure [glomerular filtration rate (GFR) <30 mL/min per 1.73 m^2]. Pacing systems suitable for magnetic resonance imaging (MRI) have been developed. Claustrophobia, metallic foreign objects, and second- or third-trimester pregnancy are regarded as relative contraindications.

Time-of-flight angiography and phase-contrast angiography, without intravenous contrast, can be used to image the vascular bed. Development of the 'Angiosurf' and 'Bodysurf' techniques[28,29] has been a breakthrough in imaging. Based on the 'Angiosurf' MRA approach, a fairly comprehensive combined protocol can be used, which accomplishes the depiction of the head, thoracic, and all peripheral arteries from the carotids to the ankles.[30,31]

Detailed descriptions of CTA and MRA are provided in Appendix 1 (available online at www.escardio.org/guidelines).

3.4 Treatment—general rules

Patient management should include lifestyle modification, focusing on smoking cessation, daily exercise (30 min/day), normal body mass index (≤25 kg/m^2), and a Mediterranean diet.[24] Pharmacological treatment can be added for blood pressure control and a lipid-lowering treatment to achieve LDL cholesterol <2.5 mmol/L (100 mg/dL) with an option of <1.8 mmol/L (<70 mg/dL) if feasible. In diabetic patients, glucose control should be obtained, with the target glycated haemoglobin (Hb_{A1c}) <7%. Site-dependent therapy and revascularization strategy are discussed in the respective sections. It must be emphasized that the management of patients with PAD should always be decided after multidisciplinary discussion, also including (depending on lesion site) specialists beyond the area of cardiovascular medicine, e.g. neurologists or nephrologists.

3.4.1 Smoking cessation

Smoking is an important risk factor for PAD.[32] In the general population smoking increased the risk of LEAD between two- and six-fold.[16] Current smokers with LEAD also have an increased risk of amputation, and are at increased risk of postoperative complications and mortality.[33] Smokers should be advised to quit smoking and be offered smoking cessation programmes. Nicotine replacement therapy and/or bupropion or varenicline can facilitate cessation in patients with a high level of nicotine dependence, which can be estimated by the Fagerström's questionnaire or biomarkers such as exhaled carbon monoxide concentrations.[34] All three medications are safe to use in patients with CVD.[35]

3.4.2 Lipid-lowering drugs

Statins reduce the risk of mortality, cardiovascular events, and stroke in patients with PAD with and without CAD. In the

Heart Protection Study, 6748 participants had PAD; at 5-year follow-up, simvastatin caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independently of age, gender, or serum lipid levels.[36] All patients with PAD should have their serum LDL cholesterol reduced to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (<70 mg/dL), or ≥50% LDL cholesterol reduction when the target level cannot be reached.[24,25]

3.4.3 Antiplatelet and antithrombotic drugs

The Antithrombotic Trialists' Collaboration meta-analysis combined data from 42 randomized studies of 9706 patients with intermittent claudication and/or peripheral arterial bypass or angioplasty. The incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke at follow-up was significantly decreased, by 23%, by antiplatelet drugs.[37] Low-dose aspirin (75–150 mg daily) was at least as effective as higher daily doses. The efficacy of clopidogrel compared with aspirin was studied in the randomized Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, including a subgroup of 6452 patients with LEAD.[38] At 1.9-year follow-up, the annual combined incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke in the LEAD group was 3.7% and 4.9%, respectively, in the clopidogrel and aspirin groups, with a significant 23.8% decrease with clopidogrel. These benefits appeared higher than in patients enrolled for CAD or stroke. The small benefits of dual antiplatelet therapy do not justify its recommendation in patients with LEAD due to an increased bleeding risk.[39,40]

3.4.4 Antihypertensive drugs

Arterial hypertension in patients should be controlled adequately according to the current ESC/European Society of Hypertension guidelines.[41] In general, target blood pressures of ≤140/90 mmHg are recommended, and ≤130/80 mmHg in patients with diabetes or chronic kidney disease. However, the latter target has recently been contested.[42]

Treatment with angiotensin-converting enzyme (ACE) inhibitors has shown a beneficial effect beyond a blood pressure decrease in high-risk groups. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitor treatment with ramipril significantly reduced cardiovascular events by 25% in patients with symptomatic PAD without known low ejection fraction or heart failure.[43] The ONTARGET trial showed equivalence of telmisartan to ramipril in these patients.[44]

Importantly, β-blockers are not contraindicated in patients with LEAD. A meta-analysis of 11 randomized controlled studies found that β-blockers did not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild to moderate LEAD.[45] At 32-month follow-up of 490 patients with LEAD and prior myocardial infarction, β-blockers caused a 53% significant independent relative decrease in new coronary events.[46] Considering the cardioprotective effects of a low-dose, titrated β-blocker regimen in the perioperative setting, β-blockers are recommended in patients scheduled for vascular surgery according to the ESC guidelines.[47]

Recommendations in patients with PAD: general treatment

Recommendations	Class[a]	Level[b]	Ref[c]
All patients with PAD who smoke should be advised to stop smoking.	I	B	48
All patients with PAD should have their LDL cholesterol lowered to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (70 mg/dL), or ≥ 50% when the target level cannot be reached.	I	C[d]	-
All patients with PAD should have their blood pressure controlled to ≤140/90 mmHg.	I	A	41
ß-Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant coronary artery disease and/or heart failure.	IIa	B	46, 47
Antiplatelet therapy is recommended in patients with symptomatic PAD.	I	C[d]	37
In patients with PAD and diabetes, the HbA1c level should be kept at ≤6.5%.	I	C[d]	-
In patients with PAD, a multidisciplinary approach is recommended to establish a management strategy.	I	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in the respective sections.
$Hb_{A1}c$ = glycated haemoglobin; LDL = low-density lipoprotein; LEAD = lower extremity artery disease; PAD = peripheral artery disease.

4. Specific vascular areas

4.1 Extracranial carotid and vertebral artery disease

4.1.1 Carotid artery disease

4.1.1.1 Definition and clinical presentations

In the Western world, ischaemic stroke has a major public health impact as the first cause of long-term disability and the third leading cause of death. Stroke mortality ranges from 10% to 30%, and survivors remain at risk of recurrent neurological and cardiac ischaemic events. The risk of stroke and transient ischaemic attacks (TIAs), defined in most studies as transient neurological deficits usually lasting 1–2 h and no longer than 24 h, increases with age. Major risk factors for stroke include hypertension, hypercholesterolaemia, smoking, diabetes, cerebrovascular

disease, atrial fibrillation, and other cardiac conditions that increase the risk for embolic complications. Large artery atherosclerosis, and specifically internal carotid artery stenosis, accounts for ~20% of all ischaemic strokes.[49] Carotid artery stenosis is considered symptomatic in the presence of TIA or stroke affecting the corresponding territory within the previous 6 months.[50,51] In the vast majority of cases, carotid artery stenosis is caused by atherosclerosis. Rare aetiologies include radiation therapy, vasculitis, dissection, or fibromuscular dysplasia.

For the purpose of these guidelines, the term carotid artery stenosis refers to a stenosis of the extracranial portion of the internal carotid artery, and the degree of stenosis is according to the NASCET criteria (see online Appendix 2).

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the risk of recurrent ipsilateral stroke in patients with symptomatic carotid artery stenosis treated conservatively was 4.4% per year for 50–69% stenosis and 13% per year for >70% stenosis.[52] In patients with asymptomatic carotid artery stenosis >60%, the risk of stroke is ~1–2% per year.[53,54] However, the risk may increase to 3–4% per year in elderly patients or in the presence of contralateral carotid artery stenosis or occlusion, evidence of silent embolization on brain imaging, carotid plaque heterogeneity, poor collateral blood supply, generalized inflammatory state, and associated coronary or peripheral artery disease.[1,52] Currently there are indications that the risk of stroke in patients with asymptomatic carotid artery disease is lower due to better medical treatment.[55,56]

4.1.1.2 Diagnosis

4.1.1.2.1 Clinical evaluation

The decision to revascularize patients with carotid artery stenosis is based on the presence of signs or symptoms related to the affected carotid artery, the degree of internal carotid artery stenosis, and on patient age, gender, co-morbidities, and life expectancy. Additional factors such as the presence of silent brain infarction in the corresponding territory, microembolization on intracranial Doppler, or the degree of stenosis progression may also be taken into account.

Neurological evaluation is essential to differentiate asymptomatic and symptomatic patients. All patients with neurological complaints should be seen as soon as possible by a neurologist since it may be challenging to determine whether symptoms are related to a carotid artery stenosis. Manifestations of carotid artery disease may be divided into hemispheric and/or ocular. Hemispheric (cortical) ischaemia usually consists of a combination of weakness, paralysis, numbness, or tingling (all affecting the same side of the body) and contralateral to the culprit carotid artery. Neuropsychological symptoms may also be present and may include aphasia if the dominant hemisphere (usually left) is affected, or neglect if the non-dominant hemisphere (usually the right, even in most left-handed individuals) is affected. Emboli to the retinal artery may cause temporary or permanent partial or total blindness in the ipsilateral eye. A temporary ocular deficit is called amaurosis fugax. While neurological symptoms of carotid disease are usually caused by distal embolization, they may seldom be due to cerebral hypoperfusion, either transient ('low-flow TIA') or permanent (haemodynamic stroke).

4.1.1.2.2 Imaging

Urgent imaging of the brain and supra-aortic vessels is mandatory in all patients presenting with TIA or stroke. While CT scan is widely available and allows for a differentiation between ischaemic and haemorrhagic stroke, MRI is more sensitive in the detection of brain ischaemia.

The risk of recurrent TIA or stroke in the first month is 10–30%.[57] In patients with carotid artery stenosis, imaging conveys important information such as the degree of carotid artery stenosis, carotid plaque morphology, the presence of intracranial disease, intracranial collateral circulation, asymptomatic embolic events, or other intracranial pathologies.

DUS is commonly used as the first step to detect extracranial carotid artery stenosis and to assess its severity. The peak systolic velocity measured in the internal carotid artery is the primary variable used for this purpose; secondary variables include the end-diastolic velocity in the internal carotid artery as well as the ratio of peak systolic velocity in the internal carotid artery to that in the common carotid artery.[58] Although DUS evaluation may be hampered by severe plaque calcifications, tortuous vessels, tandem lesions, and slow turbulent flow in subtotal stenoses, this imaging modality allows for a reliable estimation of the degree of the stenosis as well as for the assessment of plaque morphology in the hands of an experienced investigator.

The advantages of CTA and MRA include the simultaneous imaging of the aortic arch, the common and internal carotid arteries in their totality, the intracranial circulation, as well as the brain parenchyma. MRA is more time-consuming than CTA but does not expose patients to radiation, and the used contrast agents are far less nephrotoxic. CTA offers excellent sensitivity and specificity for the detection of carotid artery stenosis; however, the presence of severe plaque calcification may lead to overestimation of the degree of stenosis. In a systematic review and meta-analysis, no major difference was found between DUS, MRA, and CTA for the detection of a significant carotid artery stenosis.[59] In order to improve the accuracy of the diagnosis, the use of two imaging modalities prior to revascularization is suggested. DSA may be required for diagnostic purposes only in selected cases (e.g. discordant non-invasive imaging results, additional intracranial vascular disease). In patients with severe asymptomatic carotid artery stenosis, imaging of the brain to detect asymptomatic embolic events and a transcranial Doppler for emboli detection may be considered.

Recommendation for evaluation of carotid artery stenosis

Recommendations	Class[a]	Level[b]	Ref[c]
DUS, CTA, and/or MRA are indicated to evaluate carotid artery stenosis.	I	A	59

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference.
CTA = computed tomography angiography; DUS = duplex ultrasonography; MRA = magnetic resonance angiography.

4.1.1.3 Treatment modalities

4.1.1.3.1 Medical therapy

The overall benefit of aspirin to prevent cardiovascular events in patients with atherosclerosis have been presented earlier (Section 3.4.3). Although, the use of antiplatelet agents has not been specifically addressed in patients with carotid artery disease (i.e. carotid plaques), low-dose aspirin (or clopidogrel in case of aspirin intolerance) should be administered to all patients with carotid artery disease irrespective of symptoms. The effectiveness of statins in patients with symptomatic cerebrovascular disease is well proven, irrespective of the initial cholesterol concentration. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study evaluated the results of high-dose atorvastatin (80 mg/day) vs. placebo in 4731 patients with TIA or stroke. Patients allocated to atorvastatin had a significant 26% relative risk reduction of the primary endpoint of fatal and non-fatal stroke at 5 years.[60] Among 1007 patients with carotid artery stenosis enrolled in the trial, the benefit of statin therapy was even more pronounced, with a 33% reduction of stroke, a 43% reduction of major coronary events, and a 56% reduction of carotid revascularization procedures at 5 years.[61]

4.1.1.3.2 Surgery

The benefits of carotid endarterectomy (CEA) over medical management in randomized trials were conveyed by low perioperative complication rates [e.g. a stroke and death rate of 5.8% in NASCET[52] and of 2.7% in the Asymptomatic Carotid Atherosclerosis Study (ACAS)[53]] achieved by high-volume surgeons in low-risk patients.

Temporary interruption of cerebral blood flow during CEA can cause haemodynamic neurological deficits. This can potentially be avoided by using a shunt. Currently there is insufficient evidence to support or refute the use of routine or selective shunting as well as perioperative neurological monitoring during CEA. As suggested by a Cochrane review of seven trials, CEA using a patch (either prosthetic or vein based) may reduce the risk of restenosis and neurological events at follow-up compared with primary closure.[62] A more recent randomized trial confirmed the lower restenosis rate associated with the patch, but could not find any difference in perioperative complications.[63] Usually, CEA is performed using a longitudinal arteriotomy. However, CEA with arterial eversion implies a transverse arteriotomy and reimplantation of the internal carotid artery on the common carotid artery. A Cochrane analysis on this subject suggested that CEA with eversion may be associated with a lower risk of (sub)acute occlusion and restenosis than conventional CEA, but no difference in clinical events was detected.[64]

For decades it has been debated whether local anaesthesia is superior to general anaesthesia for CEA. The randomized General Anaesthesia versus Local Anaesthesia for Carotid Surgery (GALA) trial including 3526 patients showed no difference in terms of perioperative death, stroke, or myocardial infarction between general (4.8%) and local (4.5%) anaesthesia.[65]

All patients undergoing CEA should receive perioperative medical management according to proper cardiovascular risk assessment. Low-dose aspirin is efficacious to reduce perioperative stroke.[37,52,54,66] There is no clear benefit of dual therapy or high-dose antiplatelet therapy in patients undergoing CEA.

Technical aspects of CEA are addressed in Appendix 2.

4.1.1.3.3 Endovascular techniques

Carotid artery stenting (CAS) is a revascularization option less invasive than CEA. It is performed under local anesthaesia, avoids neck dissection with the consequent risk of peripheral nerve damage, and is less painful. Although patients at high risk for surgery are not well defined, CAS is frequently advocated for patients at increased cardiopulmonary risk or with unfavourable neck anatomy, restenosis after CEA, prior neck dissection or radiation therapy, as well as in the presence of carotid artery stenosis difficult to access (i.e. high internal carotid or low common carotid artery lesions).

The optimal anticoagulation regimen for CAS remains unknown. Periprocedure unfractionated heparin is commonly used. Dual antiplatelet therapy with aspirin and clopidogrel (or ticlopidine) is recommended. Two small, randomized trials comparing aspirin alone with double antiplatelet therapy for CAS were terminated prematurely due to high rates of stent thrombosis and neurological events in the aspirin-alone group.[67,68]

In patients with proven intolerance to dual antiplatelet therapy, CEA should be preferred to CAS. Newer antiplatelet agents such as prasugrel or ticagrelor have not yet been adequately tested in CAS.

4.1.1.3.4 Operator experience and outcomes of carotid artery stenting

While comparing the results of CAS and CEA, it should be acknowledged that CAS gained maturity more recently than CEA, and that the endovascular technique is evolving rapidly. Overall, available evidence supports the notion that experience does play a major role in CAS outcomes. The benefit is probably conveyed by optimal procedure management and appropriate patient selection. In this respect, several CAS vs. CEA trials have been criticized for the insufficient endovascular experience required and for the possibility of treating patients with CAS under proctoring conditions.[69]

More detailed information on the importance of operator experience in CAS is provided in Appendix 2.

4.1.1.3.5 Embolic protection devices

The use of embolic protection devices (EPDs) during CAS remains controversial. At present, only two very small, randomized studies have evaluated CAS with vs. without EPDs, and failed to prove an improved clinical outcome with the use of the devices.[70,71]

Opposing these results, two systematic reviews showed a reduction in neurological events associated with protected CAS.[72,73] A benefit from EPDs was also suggested from a large-scale prospective registry documenting an in-hospital death or stroke rate of 2.1% among 666 patients undergoing CAS with adjunctive EPD and of 4.9% in the group of patients ($n = 789$) treated without EPDs ($P = 0.004$).[74] In the same study, the use of EPDs was identified in multivariable analysis as an independent protective factor for this endpoint (adjusted OR 0.45, $P = 0.026$). Importantly, the complication rate associated with the use of EPD appears to be low (<1%).[75]

In contrast, secondary analyses from two randomized CAS vs. CEA trials reported a lack of benefit from EPD use during CAS. In the SPACE trial, the rate of 30-day ipsilateral stroke or death after CAS was 8.3% among 145 patients treated with EPDs and 6.5% in 418 patients treated without EPDs ($P = 0.40$).[76] In a substudy of the ICSS trial, new diffusion-weighted MRI lesions after CAS were observed in 38 (68%) of 56 patients who had stenting with EPDs and in 24 (35%) of 68 patients who had unprotected

stenting [OR 3.28, 95% confidence interval (CI) 1.50–7.20; $P = 0.003$].[77] Importantly, the use of EPDs in both trials was left to the discretion of the operator. The best results for CAS so far in randomized trials—for both symptomatic and asymptomatic patients—have been obtained in studies that mandated embolic protection with a single device and in which operators were trained in the use of the specific device [Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)[78] and CREST,[79] as detailed below]. Finally, recent registry data suggest that proximal occlusion systems may be useful in embolic protection.[80]

4.1.1.4 Management of carotid artery disease

The management of carotid artery disease is summarized in *Figure 1*.

Recommendations for embolic protection in patients undergoing CAS

Recommendations	Class[a]	Level[b]	Ref[c]
Dual antiplatelet therapy with aspirin and clopidogrel is recommended for patients undergoing CAS.	I	B	67, 68
The use of EPDs may be considered in patients undergoing CAS.	IIb	B	73

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAS = carotid artery stenting; EPD = embolic protection device.

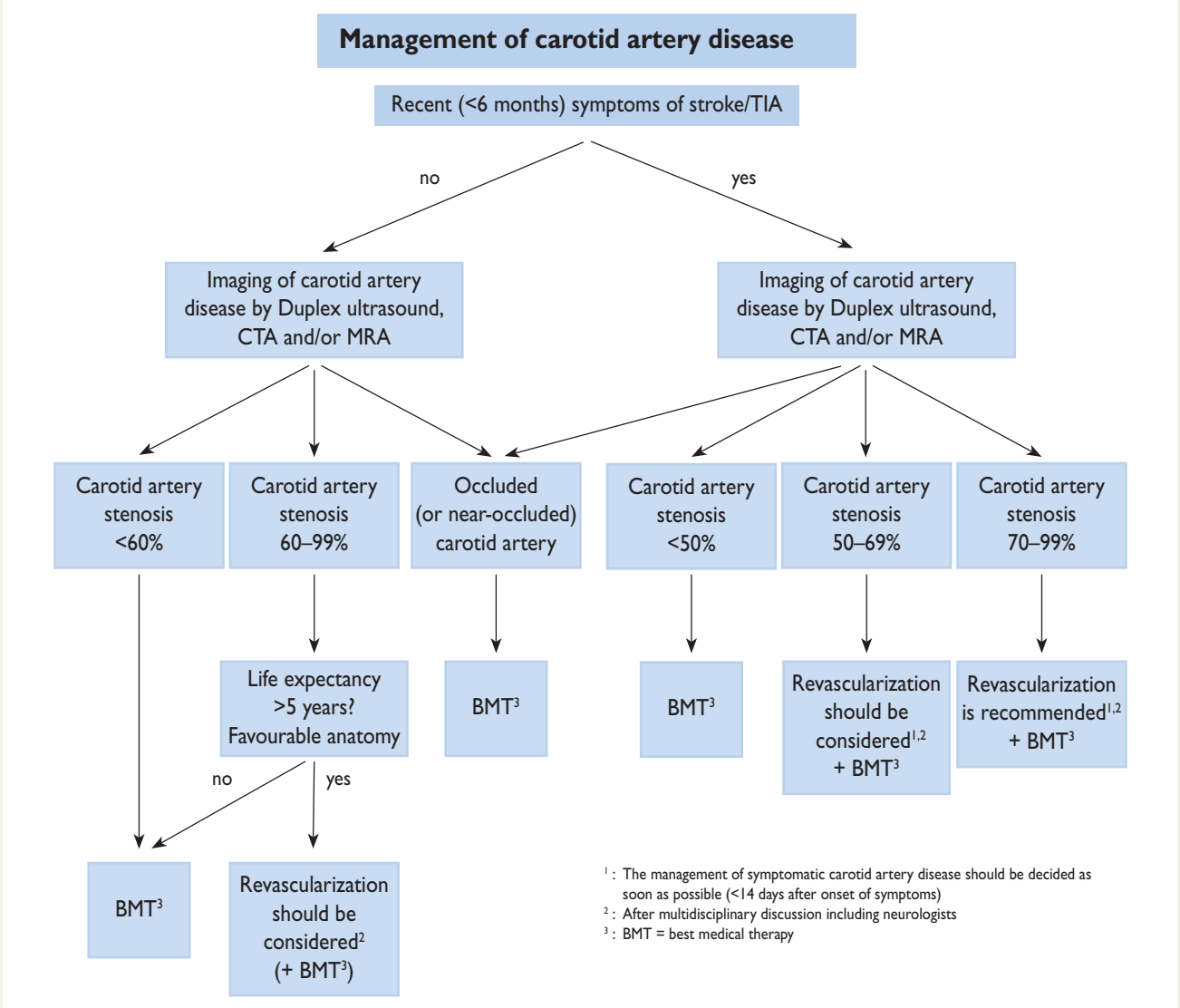

Figure 1 Algorithm for the management of extracranial carotid artery disease. CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.

4.1.1.4.1 Asymptomatic carotid artery disease

4.1.1.4.1.1 Surgery

A total of 5233 patients with asymptomatic carotid artery disease were enrolled in randomized multicentre trials comparing CEA with medical management.[53,54,66,81] After 4657 patient-years of follow-up, the randomized Asymptomatic Carotid Atherosclerosis Study (ACAS) estimated the 30-month risk of ipsilateral stroke in the case of carotid artery stenosis >60% at 5.1% for patients who underwent CEA in addition to best medical therapy (at that time) vs. 11.0% for those with best medical therapy alone.[53] The Asymptomatic Carotid Surgery Trial (ACST) randomized 3120 asymptomatic patients to either immediate CEA or indefinite deferral of CEA.[54] The 5-year risks were 6.4% vs. 11.8% for all strokes (absolute risk reduction 5.4%, $P = 0.0001$), 3.5% vs. 6.1% for fatal or disabling stroke (absolute risk reduction 2.6%, $P = 0.004$), and 2.1% vs. 4.2% for fatal strokes (absolute risk reduction 2.1%, $P = 0.006$), respectively. Combining perioperative events and strokes, net risks were 6.9% vs. 10.9% at 5 years (gain 4.1%, 2.0–6.2) and 13.4% vs. 17.9% at 10 years (gain 4.6%, 1.2–7.9).[66] Medication was similar in both groups; throughout the study, most patients were on antithrombotic and antihypertensive therapy. Net benefits were significant irrespective of the use of lipid-lowering therapy, for men and women under the age of 75 years at entry. In the three trials, the benefit was greater in men than in women, but the number of women enrolled was low.

It can be concluded that CEA is beneficial in asymptomatic patients (especially men) between 40 and 75 years of age with >60% stenosis, if their life expectancy is >5 years and operative mortality <3%.[66,70–77,79,81] However, the absolute benefit of revascularization in terms of stroke prevention is small (1–2% per year), and those trials were performed prior to extensive use of statins. Therefore, the benefit of revascularization on top of optimal medical management should be reassessed.

4.1.1.4.1.2 Endovascular therapy

The results of eight CAS registries enrolling >1000 patients have been published recently (*Table 3*).[82] The registries included >20 000 patients at high surgical risk, mainly asymptomatic. Pre- and post-procedure neurological assessment and blinded event adjudication were required in most studies. Overall, the studies demonstrated that death and stroke rates with CAS are in the range expected in current recommendations for CEA even in patients at high surgical risk, and that CAS results tend to improve over time.

So far, the randomized evidence for CAS in asymptomatic patients is limited. While no study has compared endovascular treatment with medical therapy, two trials (SAPPHIRE and CREST) comparing CAS vs. CEA have also enrolled asymptomatic patients (for details see Section 4.1.1.4.2.2).

4.1.1.4.2 Symptomatic carotid artery disease

It should be emphasized that neurological assessment and appropriate treatment should be proposed as soon as possible after the index event. At a very minimum patients need to be seen and treated within 2 weeks, with important benefit of instituting medical treatment[88] and performing revascularization as soon as possible after the onset of symptoms.[89,90]

4.1.1.4.2.1 Surgery

Pooled data from the NASCET, the European Carotid Surgery Trial (ECST), and the Veterans Affairs Trial included >35 000 patient-years of follow-up in patients (28% women) with symptomatic disease.[50,51,91,92] CEA increased the 5-year risk of ipsilateral ischaemic stroke over medical therapy alone in patients with

Table 3 Thirty-day event rates in carotid artery stenting registries enrolling >1000 patients

Name	Year	N	Industry sponsored	Surgical high-risk	EPD	Sympt patients	Neurologist[a]	CEC	D/S	D/S/MI	D/S sympt	D/S asympt
CAPTURE[83]	2007	3500	Yes	Yes	Mandatory	14%	Yes	Yes	5.7%	6.3%	10.6%	4.9%
CASES-PMS[84]	2007	1493	Yes	Yes	Mandatory	22%	Yes	Yes	4.5%	5.0%	NA	NA
PRO-CAS[85]	2008	5341	No	No	75%	55%	70%	No	3.6%[b]	NA	4.3%[b]	2.7%[b]
SAPPHIRE–W[78]	2009	2001	Yes	Yes	Mandatory	28%	No[c]	Yes	4.0%	4.4%	NA	NA
Society for Vascular Surgery[86]	2009	1450	No	No	95%	45%	No	No	NA	5.7%	NA	NA
EXACT[87]	2009	2145	Yes	Yes	Mandatory	10%	Yes	Yes	4.1%	NA	7.0%	3.7%
CAPTURE-2[87]	2009	4175	Yes	Yes	Mandatory	13%	Yes	Yes	3.4%	NA	6.2%	3.0%
Stabile et al.[80]	2010	1300	No	No	Mandatory	28%	Yes	No	1.4%	NA	3.0%	0.8%

[a]Independent pre- and post-procedural assessment by a neurologist.
[b]In-hospital events.
[c]Neurological assessment performed by stroke-scale-certified staff member.
CAPTURE = Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events; CASES-PMS = Carotid Artery Stenting with Emboli Protection Surveillance Study; CEC = clinical event committee adjudication; D = death; EPD = embolic protection device; EXACT = Emboshield and Xact Post Approval Carotid Stent Trial; MI = myocardial infarction; N = number of patients; NA = not available; PRO-CAS = Predictors of Death and Stroke in Carotid Artery Stenting; S = stroke; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.
Reproduced with permission from Roffi *et al.*[82]

<30% stenosis ($n = 1746$, absolute risk increase 2.2%, $P = 0.05$). CEA had no effect in patients with 30–49% stenosis ($n = 1429$, absolute risk reduction 3.2%, $P = 0.06$) and had a small benefit in patients with 50–69% stenosis ($n = 1549$, absolute risk reduction 4.6%, $P = 0.04$). CEA was highly beneficial in patients with >70% stenosis but with no near occlusion ($n = 1095$, absolute risk reduction 16.0%, $P < 0.001$; the number needed to treat to prevent one ipsilateral stroke in 5 years was 6). In contrast, in patients with a 99% stenosis (near occlusion) and sluggish antegrade flow ('string-flow') in the internal carotid artery, CEA did not show any advantage over medical treatment.

A pooled analysis of the ESCT and NASCET trials (5893 patients with 33 000 patient-years of follow-up) convincingly demonstrated that carotid revascularization should be performed rapidly in symptomatic patients with TIA or mild stroke. The number needed to treat to prevent one ipsilateral stroke in 5 years was 5 for those randomized within 2 weeks after the last ischaemic event vs. 125 for patients randomized after 12 weeks.[93]

In symptomatic patients, the benefit of surgery is clearly established for patients with stenosis >70%, but no near occlusion, and to a lesser degree in patients with stenosis 50–69%. It should be underscored that medical therapy in these old trials did not include the use of statins.

4.1.1.4.2.2 Endovascular therapy versus surgery

A total of six large-scale (i.e. enrolling >300 patients) clinical trials comparing CEA and CAS have been published. The CAVATAS,[94] EVA-3S,[95] ICSS,[96] and SPACE[97] trials enrolled exclusively symptomatic patients. The SAPPHIRE[98,99] and CREST[79] trials included both symptomatic and asymptomatic patients at high and conventional risk for surgery, respectively.

In the CAVATAS study (504 symptomatic patients), performed prior to the introduction of EPDs, most patients allocated to endovascular therapy were treated with angioplasty alone. Only 26% received a stent. There was no statistical difference in terms of any stroke or death at 30 days between CEA and angioplasty (9.9% vs. 10%).[94] Despite higher restenosis rates in the endovascular arm, no difference in the rates of non-periprocedural ipsilateral stroke was reported at 8-year follow-up.[100]

The SAPPHIRE study randomized symptomatic and asymptomatic patients at high risk for surgery.[98] All endovascular patients were systematically treated with the same stent and a protection device. The trial was designed to prove non-inferiority of CAS and was terminated prematurely because of slow enrolment. The primary endpoint of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke occurring between 31 days and 1 year. Among the 334 randomized patients (29% symptomatic), the primary endpoint occurred in 12.2% in the CAS group and in 20.1% in the CEA group ($P = 0.053$). The difference was driven mainly by the rate of myocardial infarction (2.4% in the CAS group vs. 6.1% in the CEA group; $P = 0.10$). No cranial nerve injury was observed in the CAS group, compared with 5.3% in the CEA group. The durability of CAS was documented by a comparable cumulative percentage of major (1.3% for CAS vs. 3.3% for CEA) and minor (6.1% for CAS vs. 3.0% for CEA) ipsilateral strokes at 3 years and a low rate of repeat revascularization during the same period (3.0% for CAS vs. 7.1% for CEA).[99]

The SPACE study randomized 1200 symptomatic patients.[101] Left at the discretion of the treating physician, EPDs were used in 27% of the cases. The trial was prematurely stopped because of slow enrolment and lack of funding. The incidence of ipsilateral stroke or death at 30 days was the primary endpoint of the study and did not differ between the groups. With an insufficient sample size, SPACE failed to prove the non-inferiority of CAS with the pre-specified absolute difference of 2.5% ($P = 0.09$). Follow-up analysis showed no difference in the 2-year rate of adverse events between groups (8.8% for CEA and 9.5% for CAS; $P = 0.62$).[102]

The EVA-3S trial randomized 527 symptomatic patients with a stenosis ≥60% to CAS or CEA.[95] The primary endpoint was the cumulative incidence of any stroke or death within 30 days after treatment. Although not mandated, CAS without EPD protection was rapidly halted because of excessive risk of stroke compared with those with an EPD (OR 3.9, 95% CI 0.9–16.7).[103] The trial was stopped prematurely because of significant increased event rates in the CAS arm (death or stroke 9.6% vs. 3.9% in the CEA arm; $P = 0.01$). Beyond 30 days, no difference in death or stroke rate was observed, but at 4-year follow-up, the results of CEA were still more favourable than those of CAS, driven by the periprocedural events.[104]

The ICSS study randomized 1710 symptomatic patients to CEA or CAS (EPD use was not mandatory and protected CAS was performed in 72% of patients). The primary endpoint was the 3-year rate of fatal or disabling stroke. While follow-up is ongoing, an interim safety analysis of events between randomization and 120 days reported an incidence of death, stroke, or periprocedural myocardial infarction in favour of CEA, with an incidence of 8.5% in the CAS group and 5.2% in the CEA group [hazard ratio (HR) 1.69, 95% CI 1.16–2.45; $P = 0.004$].[96] The difference was driven mainly by a lower rate of non-disabling strokes in the CEA arm.

The CREST study was a multicentre, randomized controlled trial (RCT) with the primary endpoint of periprocedural stroke, myocardial infarction, or death, plus ipsilateral stroke up to 4 years. The study was characterized by strict requirements in terms of endovascular credentialing and a lead-in phase that included the treatment of 1541 patients with CAS that preceded the randomized enrolment. Owing to slow enrolment, this study—initially designed for symptomatic patients—was then extended to include asymptomatic individuals.[79] The primary endpoint occurred in 7.2% of the CAS group and in 6.8% of the CEA group (HR 1.11, 95% CI 0.81–1.51; $P = 0.51$). With respect to periprocedural death, stroke, or myocardial infarction, no difference was observed, with an event rate of 5.2% in the CAS group and 4.5% in the CEA group ($P = 0.38$). Patients randomized to CAS had more periprocedural strokes (HR 1.79, 95% CI 1.14–2.82; $P = 0.01$), but they had fewer myocardial infarctions (1.1% vs. 2.3%; 95% CI 0.26–0.94; $P = 0.03$) compared with those receiving CEA. The incidence of major periprocedural strokes was low and not different between the two groups (0.9% vs. 0.6%; $P = 0.52$). Cranial nerve palsy occurred in 0.3% of patients randomized to CAS and in 4.7% of those treated with CEA (HR 0.07, 95% CI 0.02–0.18; $P < 0.0001$). At 4 years, no difference in rates of ipsilateral stroke after the periprocedural period was observed (HR 0.94, 95% CI 0.50–1.76; $P = 0.85$).

A meta-analysis of 13 randomized trials and including those mentioned above involved 7484 patients, of which 80% had symptomatic disease. Compared with CEA, CAS was associated with

increased risk of any stroke (RR 1.45; 95% CI 1.06–1.99), decreased risk of periprocedural myocardial infarction (RR 0.43; 95% CI 0.26–0.71), and non-significant increase in mortality (RR 1.40; 95% CI 0.85–2.33).[105]

Recommendations for management of asymptomatic carotid artery disease

Recommendations	Class[a]	Level[b]	Ref[c]
All patients with asymptomatic carotid artery stenosis should be treated with long-term antiplatelet therapy.	I	B	52, 54, 66
All patients with asymptomatic carotid artery stenosis should be treated with long-term statin therapy.	I	C	-
In asymptomatic patients with carotid artery stenosis ≥60%, CEA should be considered as long as the perioperative stroke and death rate for procedures performed by the surgical team is <3% and the patient's life expectancy exceeds 5 years.	IIa	A	52, 54, 66
In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centres with documented death or stroke rate <3%.	IIb	B	79, 99

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAS = carotid artery stenting; CEA = carotid endarterectomy.

4.1.2 Vertebral artery disease

4.1.2.1 Definition and natural history

The prevalence of vertebral artery (VA) disease due to atherosclerotic disease in the general population is unknown as this condition often remains undiagnosed, because it is either asymptomatic or due to neglected symptoms of vertebrobasilar ischaemia.[106] Approximately 20% of all ischaemic strokes are estimated to involve the vertebrobasilar territory.[107,108] Vertebrobasilar stroke is primarily the result of an embolic process—most frequently artery-to-artery embolism from the VA origin or cardioembolism. On occasion, dissection, thrombotic, and low-flow haemodynamic mechanisms may be involved.[109] A significant stenosis of the extracranial VA—mostly located at its origin—may account for up to 20% of all vertebrobasilar strokes or TIAs.[110]

4.1.2.2 Imaging

Data on the accuracy of non-invasive imaging for the detection of extracranial VA are limited and none of the studies has compared different imaging modalities against contrast angiography. A recent systematic review suggested that MRA offers better sensitivity and specificity than DUS for extracranial VA stenosis.[111] While CTA is increasingly used for assessment of VA disease, this technique still needs validation.[111] Both MRA and CTA may be inadequate for ostial VA lesions, especially in the presence of severe angulation or tortuosity of the VA take-off. Despite those limitations, contrast angiography is rarely used merely for diagnostic purposes.

Recommendations for management of symptomatic carotid artery disease

Recommendations	Class[a]	Level[b]	Ref[c]
All patients with symptomatic carotid stenosis should receive long-term antiplatelet therapy.	I	A	37
All patients with symptomatic carotid stenosis should receive long-term statin therapy.	I	B	60, 61
In patients with symptomatic 70-99% stenosis of the internal carotid artery, CEA is recommended for the prevention of recurrent stroke.	I	A	50, 51, 91, 92
In patients with symptomatic 50-69% stenosis of the internal carotid artery, CEA should be considered for recurrent stroke prevention, depending on patient-specific factors.	IIa	A	50, 51, 91, 92
In symptomatic patients with indications for revascularization, the procedure should be performed as soon as possible, optimally within 2 weeks of the onset of symptoms.	I	B	93
In symptomatic patients at high surgical risk requiring revascularization, CAS should be considered as an alternative to CEA.	IIa	B	79, 99, 102
In symptomatic patients requiring carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centres with documented death or stroke rate <6%.	IIb	B	79, 99, 102

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAS = carotid artery stenting; CEA = carotid endarterectomy.

4.1.2.3 Management of vertebral artery disease

The overall benefits of antiplatelet and statin therapy have been presented earlier in these guidelines (Section 3.4.3). Although there are no prospective studies evaluating different therapeutic

strategies in patients with VA disease, aspirin (or if not tolerated clopidogrel) and statins should be administered in all patients, irrespective of symptoms. Asymptomatic VA disease does not require intervention. In general, the need to intervene is tempered by the fact that the posterior circulation is supplied by the confluence of the two VAs, and a large proportion of patients remain asymptomatic despite an occlusion of one VA. However, in patients with recurrent ischaemic events under antiplatelet therapy or refractory vertebrobasilar hypoperfusion, revascularization may be considered.

Although surgery of extracranial VA stenosis has been performed with low rates of stroke and mortality by surgeons with extensive experience,[112] in most centres the surgical approach has been replaced by endovascular techniques. However, data for VA revascularization are limited to retrospective and mainly single-centre studies.

More information is provided in the online Appendix 2.

Recommendations for revascularization in patients with VA stenosis

Recommendations	Class[a]	Level[b]
In patients with symptomatic extracranial VA stenosis, endovascular treatment may be considered for lesions ≥50% in the case of recurrent ischaemic events despite optimal medical management.	IIb	C
Revascularization of an asymptomatic VA stenosis is not indicated, irrespective of the degree of severity.	III	C

[a]Class of recommendation.
[b]Level of evidence.
VA = vertebral artery.

4.2 Upper extremity artery disease

4.2.1 Definition and clinical presentation

The subclavian artery and brachiocephalic trunk are the most common locations for atherosclerotic lesions in the upper extremities. However, UEAD can be caused by a number of conditions, involving different levels of the upper extremity arterial system (see online Appendix 3). The most common manifestation for subclavian arterial occlusive disease is unequal arm pressures. A difference of ≥15 mmHg is highly suspicious for subclavian stenosis. It is not uncommon to detect this occlusive disease in asymptomatic patients. Nevertheless, when the subclavian or brachiocephalic trunk becomes symptomatic, the clinical scenario can be diverse. Subclavian steal syndrome due to flow reversal in the VA, which is worsened by exercising the arm, can evoke symptoms of vertebrobasilar insufficiency (dizziness, vertigo, blurred vision, alternating hemiparesis, dysphasia, dysarthria, confusion, and loss of consciousness, drop attacks, ataxia or other postural disturbances including sensory and visual changes). Patients with coronary bypass with an internal mammary artery can develop symptoms of myocardial ischaemia as the manifestation of subclavian steal syndrome. Brachiocephalic occlusive disease can also lead to stroke related to the carotid and vertebral territories. Ischaemic arm symptoms are characterized by crampy pain on exercise—also referred to as arm claudication. In more severe cases—especially in more distal disease—rest pain and digital ischaemia with gangrene can develop.

4.2.2 Natural history

Little is known about the natural history of subclavian stenosis, but the prognosis appears relatively benign. Only subclavian steal with myocardial ischaemia in patients revascularized using the internal mammary artery as well as symptomatic brachiocephalic atherosclerosis with stroke episodes can be considered as life-threatening clinical conditions. However, any symptomatic subclavian occlusive disease should be investigated and treated. Vertebrobasilar insufficiency related to subclavian artery stenosis can be recurrent even after revascularization procedures. It can be explained by numerous other conditions such as cardiac arrhythmias, or intracerebral small vessel disease that can mimic symptoms of vertebrobasilar insufficiency. The combination of proximal and distal arm occlusive disease can present a clinical challenge, with poor prognosis for the extremity.

4.2.3 Clinical examination

Clinical diagnosis of upper limb ischaemia is based on history and physical examination including bilateral blood pressure measurement and assessment of the axillary, brachial, radial, and ulnar artery pulses. Auscultation is an important part of upper extremity examination and should begin in the supraclavicular fossa. Signs and symptoms, such as pulse deficit, arm pain, pallor, paraesthesia, coldness, and unequal arm pressures, warrant further investigation for occlusive artery disease of the upper limb. The Allen test should be performed in patients in whom the radial artery is instrumented or harvested for coronary revascularization. Adequate collateral flow via the ulnar artery is to be confirmed by this test.

4.2.4 Diagnostic methods

4.2.4.1 Duplex ultrasonography

The proximal location of subclavian arterial occlusive disease makes DUS challenging. However, duplex scanning is of particular value in differentiating occlusion from stenosis, in determining the direction of the vertebral blood flow, and in screening for concurrent carotid artery stenosis. Subclavian steal can be present in the absence of retrograde vertebral flow at rest. Dynamic examination with cuff compression of the upper arm and consecutive hyperaemia after decompression can change the vertebral flow direction.

4.2.4.2 Computed tomography angiography

Upper limb atherosclerosis can be imaged in excellent detail using CTA. To avoid misinterpretations, it is important to detect congenital abnormalities, in order to define precisely the four vessels perfusing the head. CTA should be analysed interactively, based on a combination of axial images and post-processed views.

4.2.4.3 Magnetic resonance angiography

The use of MRI and contrast-enhanced MRA should also be considered because it enables acquisition of both functional and

morphological information. This information can be used to distinguish antegrade from retrograde perfusion. MRA can be combined with special sequences to detect vessel wall oedema and contrast enhancement after administration of intravenous contrast. MRA can detect dilatation and stenosis of the supra-aortic vessels that may be associated with both arteritis and atherosclerosis. Assessment of antegrade and retrograde flow is particularly helpful when steal syndrome is suspected. MRA is particularly useful for follow-up studies.

4.2.4.4 Digital subtraction angiography

DSA is the gold standard in imaging. However, it is increasingly being replaced by other imaging modalities, such as CTA and MRA.

4.2.5 Treatment

Control of the risk factors for atherosclerosis should be offered to all patients with UEAD, including asymptomatic subjects, because they are at increased risk of death.[113]

Revascularization is sometimes indicated in asymptomatic patients, such as CAD patients with planned use of the internal mammary artery for the coronary bypass grafting, or patients with bilateral upper limb lesions to enable blood pressure measurement.

In symptomatic patients endovascular and surgical treatment options are available.

Neither acute results nor long-term patency rates have been compared in randomized studies for the two techniques. The risk of severe complications is low with both approaches, and in particular the risk of vertebrobasilar stroke is rarely reported. Atherosclerotic lesions of the upper extremities, mostly subclavian lesions, are nowadays treated primarily by endovascular techniques. The primary technical success rate is very high and similar to that for surgical treatment. The less invasive nature of endovascular treatment outweighs supposedly better long-term results of surgical interventions.[114]

Ostial lesions should preferably be treated with balloon-expandable stents because they can be placed more precisely than self-expanding stents. Furthermore, the ostial lesions are more likely to be highly calcified, and in this situation the higher radial force of balloon-expandable stents might be beneficial.

Sixt *et al.*[114] reported a primary success rate of 100% for treatment of stenoses and 87% for occlusions. They also compared stenting procedures with balloon angioplasty and found a trend for an improved 1-year primary patency rate after stent-supported angioplasty (89% vs. 79%). For occlusions, the primary patency rate was 83%.

De Vries *et al.*[115] reported an initial technical success rate of 100% for stenosis and 65% for occlusions. However devices and the experience of the interventionists have since improved and are associated with better results, including for treatment of occlusions. The long-term clinical results in that study were favourable, with a 5-year primary patency rate of 89%.

For subclavian artery occlusions, surgical reimplantation demonstrated long durability with low operative mortality and morbidity rates. Carotid–subclavian bypass with a prosthetic graft is a good surgical alternative.[116]

Other extra-anatomical bypass modalities, such as axilloaxillary and subclavian–subclavian, are considered the third surgical choice for this pathology. The transthoracic approach is generally reserved for patients with multivessel aortic and supraortic trunk disease, which may preclude an extra-anatomical repair. The latter surgical option is related to higher mortality and morbidity when compared with transpositions or extra-anatomical reconstructions.[117]

Some clinical or anatomical circumstances, such as old age, high surgical risk, previous sternotomy, or calcified ascending aorta, can preclude the transthoracic surgical approach. In these cases, an extra-anatomical or endovascular approach can be applied.[118] Nevertheless, no randomized trials have been performed to compare different therapeutic options. Other therapies, including prostanoid infusion and thoracocervical sympathectomy, may be considered when revascularization is not possible.[119]

Recommendations for the management of upper extremity artery disease

Recommendations	Class[a]	Level[b]
Revascularization is indicated in symptomatic patients.	I	C
When revascularization is indicated, an endovascular-first strategy is recommended in patients with atherosclerotic lesions of the upper extremities.	I	C
Surgery should be considered after failed endovascular treatment in low-surgical-risk patients.	IIa	C
Revascularization may be considered in asymptomatic patients with former or future mammary-coronary bypass or to monitor blood pressure in bilateral upper limb occlusions.	IIb	C

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

4.3 Mesenteric artery disease

4.3.1 Definition

Patients with mesenteric artery disease may be asymptomatic.[120] Symptomatic mesenteric artery disease is an uncommon, potentially underdiagnosed condition caused by fixed stenoses or occlusion of at least two visceral arteries. Stenosis of one and even two visceral vessels is usually well tolerated because of the abundant collateral circulation between the coeliac trunk, the superior mesenteric artery, and the inferior mesenteric artery—the latter

being connected to branches of the internal iliac arteries. Atherosclerosis is the leading cause of mesenteric artery disease (95%). Typically, patients affected by mesenteric artery disease have diffuse atherosclerotic disease including CAD.[120,121] Non-atherosclerotic causes of mesenteric artery disease such as fibromuscular disease, Dunbar syndrome (compression of the coeliac trunk by the arcuate ligament), and vasculitis will not be discussed.

4.3.2 Clinical presentation

Patients with mesenteric artery disease usually present with abdominal angina, a clinical syndrome characterized by painful abdominal cramps and colic occurring typically in the post-prandial phase.[121] Patients may suffer from ischaemic gastropathy, a condition characterized by the fear of food, nausea, vomiting, diarrhoea, malabsorption, and unintended progressive weight loss.[122,123] Acute mesenteric ischaemia may also be caused by mesenteric artery thrombosis, with a grim prognosis.

4.3.3 Prevalence and natural history

The incidence of mesenteric artery disease in the general population is ~1 per 100 000 per year.[124] In patients with known atherosclerotic disease, the prevalence of mesenteric artery disease may range from 8% to 70%, and a >50% stenosis of more than one splanchnic artery may be detected in up to 15% of cases.[125–128] In patients with abdominal aortic aneurysm, aortoiliac occlusive disease, and infrainguinal LEAD, a significant stenosis of at least one of the three visceral arteries may be found in 40, 29, and 25% of cases, respectively.[120] Predisposing conditions for the development of mesenteric artery disease include arterial hypertension, diabetes mellitus, smoking, and hypercholesterolaemia. Untreated symptomatic mesenteric artery disease may lead to starvation, bowel infarction, and death.

4.3.4 Diagnostic strategy

DUS has become the imaging method of choice for mesenteric artery disease.[129–133] The diagnostic performance may be improved by a post-prandial test, revealing increased velocity and turbulences, which may seem trivial in a fasting patient. CTA and gadolinium-enhanced MRA are useful initial tests for supporting the clinical diagnosis of symptomatic mesenteric artery disease if the results of DUS are inconclusive.[134–137] Recently, 24 h gastrointestinal tonometry has been validated as a diagnostic test to detect splanchnic ischaemia and to guide treatment.[138] Basically, gastrointestinal tonometry measures gut intraluminal CO_2. Intraluminal gut CO_2 is elevated when local perfusion is compromised based on the concept that in situations where gastrointestinal perfusion is reduced oxygen delivery falls below a critical level, resulting in anaerobic cellular metabolism that leads to local lactic acidosis and generation of CO_2.

Ischaemic colitis is frequently diagnosed by histology following biopsy during bowel endoscopy. DSA is still considered the diagnostic gold standard, but its use is now limited to peri-interventional imaging.[139,140]

Recommendations for diagnosis of symptomatic chronic mesenteric ischaemia

Recommendations	Class[a]	Level[b]	Ref[c]
DUS is indicated as the first-line diagnostic test in patients suspected of mesenteric artery disease.	I	A	129-133, 138
When DUS is inconclusive, CTA or gadolinium-enhanced MRA are indicated.	I	B	135-137, 139, 141
Catheter-based angiography is indicated exclusively during the endovascular therapy procedure.	I	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CTA = computed tomography angiography; DUS = duplex ultrasonography; MRA = magnetic resonance angiography.

4.3.5 Prognostic stratification

Five-year mortality in asymptomatic patients with mesenteric artery disease is estimated at 40%, and up to 86% if all three main visceral arteries are affected.[120] Diffuse mesenteric artery disease in asymptomatic subjects should be considered as a marker of increased cardiovascular mortality, justifying aggressive management of cardiovascular risk factors.

4.3.6 Treatment

Recent reports have suggested that endovascular therapy, with or without stenting, may have a lower perioperative mortality rate than open surgery for revascularization of mesenteric artery disease. Retrospective data from a US nationwide inpatient sample analysis (1988–2006) including >22 000 patients suggested a lower mortality rate after endovascular therapy compared with surgical bypass (3.7% vs. 13%, $P < 0.01$).[142] In addition, bowel resection was less frequent in the endovascular group than in the surgical group (3% vs. 7%, $P < 0.01$). Bowel resection was, in general, associated with a high in-hospital mortality rate [percutaneous transluminal angioplasty (PTA)/stenting 25% and surgery 54%, respectively]. The lower in-hospital mortality rates reported after angioplasty with or without stenting indicate that this strategy should be proposed when possible. Longitudinal data are needed to determine the durability of this benefit. So far no randomized controlled data are available.

Symptom relief following revascularization is reported in up to 100% of cases, although restenosis after endovascular therapy may be frequent (29–40%). Although no controlled data support the strategy, dual antiplatelet therapy for 4 weeks post-procedure, followed by long-term aspirin treatment, has become the standard of care. DUS follow-up every 6–12 months is recommended. The use of drug-eluting stents, flared stent devices, or drug-eluting balloons in conjunction with bare-metal stents has not yet been evaluated in larger studies.

Recommendations for the management of mesenteric artery disease

Recommendations	Class[a]	Level[b]	Ref[c]
Mesenteric revascularization should be considered in patients with symptomatic mesenteric artery disease.	IIa	B	120, 143–150
In the case of revascularization, endovascular treatment should be considered as the first-line strategy.	IIa	C	-

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

4.4 Renal artery disease

Renal artery disease is increasingly related to atherosclerosis with advancing age and prevalent hypertension, diabetes mellitus, renal disease, aortoiliac occlusive disease, and CAD.[151] In the elderly population, atherosclerosis accounts for ~90% of cases and usually involves the ostium and proximal third of the main renal artery and the perirenal aorta. Less frequent causes are fibromuscular dysplasia and arteritis. Screening angiography in potential kidney donors indicates that RAS can be asymptomatic and may be present in up to 3–6% of normotensive individuals.[152]

4.4.1 Clinical presentation

Major clinical signs of RAS include refractory hypertension, unexplained renal failure, and flash pulmonary oedema (*Table 4*). RAS may cause or deteriorate arterial hypertension and/or renal failure. Hypoperfusion of the kidney activates the renin–angiotensin–aldosterone system (RAAS), causing classic renovascular hypertension, primarily in young patients with fibromuscular dysplasia.[151,153] However, in patients with atherosclerosis, RAS may induce an acute or subacute acceleration of a pre-existing essential hypertension including flash pulmonary oedema usually in bilateral kidney disease.[151] The association between RAS severity and ischaemic nephropathy[154,155] has recently been challenged.[156] The loss of filtration capacity of the kidney in RAS may be due not only to hypoperfusion, but also to recurrent microembolism.

Renal failure may occur with severe bilateral RAS or unilateral stenosis in a single functional kidney.

Kidney disease and renovascular disease promote CVD and hypertension. Increased risk of CVD in atherosclerotic RAS patients may result from activation of the RAAS and sympathetic nervous systems, decreased GFR, or concomitant atherosclerosis in other vascular beds.[157–159] The prevalence of left ventricular hypertrophy with RAS is 79% vs. 46% in patients with essential hypertension, with a substantial impact on morbidity and mortality.[160–162]

4.4.2 Natural history

Data on progression of atherosclerotic RAS are inconsistent. More recent studies show significant disease progression to high-grade stenosis or occlusion in only 1.3–11.1% of patients, whereas older studies documented occlusion rates up to 18% over 5 years.[163–166] After 2 years, 3, 18, and 55% of the kidneys had lost their function in the case of unilateral stenosis, bilateral stenosis, and contralateral occlusion, respectively.[167]

Table 4 Clinical situations where the diagnosis of RAS should be considered

Clinical presentation
• Onset of hypertension before the age of 30 years and after 55 years
• Hypertension with hypokalemia, in particular when receiving thiazide diuretics
• Hypertension and abdominal bruit
• Accelerated hypertension (sudden and persistent worsening of previously controlled hypertension)
• Resistant hypertension (failure of blood-pressure control despite full doses of an appropriate three-drug regimen including a diuretic)
• Malignant hypertension (hypertension with coexistent end-organ damage, i.e. acute renal failure, flash pulmonary oedema, hypertensive left ventricular failure, aortic dissection, new visual or neurological disturbance, and/or advanced retinopathy)
• New azotemia or worsening renal function after the administration of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker
• Unexplained hypotrophic kidney
• Unexplained renal failure

RAS = renal artery stenosis.

4.4.3 Diagnostic strategy

Baseline diagnostic evaluation includes physical examination, exclusion of other potential causes of secondary hypertension, and ambulatory blood pressure measurement. In clinical situations in which RAS is suspected, such as those listed in *Table 4*, renal artery imaging should be considered.

DUS is the first-line screening modality for atherosclerotic RAS. It can be applied serially to assess the degree of stenosis and physiological patterns, such as flow velocities and vascular resistance. Increased peak systolic velocity in the main renal artery associated with post-stenotic turbulence is most frequently used to determine relevant RAS, and corresponds to ≥60% angiographic RAS with a sensitivity and specificity of 71–98% and 62–98%, respectively.[168–170] Several duplex criteria should be used to identify significant (>60%) stenosis. These include imaging of intrarenal interlobar or segmental arteries, including calculation of the side-difference of the intrarenal resistance index, missing early systolic peak, retarded acceleration, and increased acceleration time, which are less specific and should be used to support the diagnosis based on peak systolic velocity.[171–173]

Common pitfalls of DUS include failure to visualize the entire renal artery and missing the highest peak systolic velocity during spectral Doppler tracing. Accessory renal arteries are generally not adequately examined or identified. The accuracy of DUS is operator dependent.

Both 3D MRA and multidetector CTA have demonstrated equally high sensitivities (>90%) for detection of haemodynamically significant stenoses, with excellent interobserver and intermodality agreement.[174]

Currently CTA provides higher spatial resolution than MRA and may be more readily available; however, the requirement to use iodinated contrast makes it an unattractive modality in patients with impaired renal function.

Gadolinium-enhanced MRA provides excellent characterization of the renal arteries, surrounding vessels, renal mass, and occasionally renal function. It is less useful in patients with renal artery stents because of artefacts. In addition, MRA tends to overestimate the degree of luminal narrowing. A recent concern in the use of gadolinium-enhanced MRI is nephrogenic systemic fibrosis, with an incidence ranging from 1% to 6% for dialysis patients, and a GFR <30 mL/min was designated as a contraindication.[175]

In recent years measuring the translesional pressure gradient with a dedicated pressure wire was proposed to identify a significant RAS. A distal-to-the-lesion to aortic pressure ratio at rest of <0.9 was linked to an upregulation of renin production.[151] This ratio correlates to a papaverine-induced hyperaemic systolic pressure gradient of >21 mmHg.[176] A dopamine-induced mean pressure gradient of >20 mmHg predicted a beneficial blood pressure response to renal stenting.[177]

DSA is generally limited to pre-angioplasty visualization and quantification of the stenosis. It may also be considered in patients with high clinical suspicion of RAS already scheduled for another angiographic examination (e.g. coronary angiography) or in the case of inconclusive non-invasive imaging.

Recommendations for diagnostic strategies for RAS

Recommendations	Class[a]	Level[b]	Ref[c]
DUS is recommended as the first-line imaging test to establish the diagnosis of RAS.	I	B	171, 172
CTA (in patients with creatinine clearance >60 mL/min) is recommended to establish the diagnosis of RAS.	I	B	151, 174
MRA (in patients with creatinine clearance >30 mL/min) is recommended to establish the diagnosis of RAS.	I	B	174
When the clinical index of suspicion is high and the results of non-invasive tests are inconclusive, DSA is recommended as a diagnostic test (prepared for intervention) to establish the diagnosis of RAS.	I	C	-
Captopril renal scintigraphy, selective renal vein renin measurements, plasma renin activity, and the captopril test are not recommended as useful screening tests to establish the diagnosis of RAS.	III	B	151, 178

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CTA = computed tomography angiography; DSA = digital subtraction angiography; DUS = duplex ultrasonography; MRA = magnetic resonance angiography; RAS = renal artery stenosis.

4.4.4 Prognostic stratification

Among patients with ESRD, the life expectancy of those with RAS is the poorest.[179] However, life expectancy is also significantly reduced in patients with RAS without ESRD.[179] Two-year mortality in patients with baseline serum creatinine concentrations before revascularization of <1.2 mg/dL, 1.2–2.5 mg/dL, and >2.5 mg/dL were 5, 11, and 70%, respectively.[180] More than 80% of patients die due to cardiovascular events.

4.4.5 Treatment

Beyond secondary prevention of atherosclerosis, the treatment of renal artery disease should be aimed at control of blood pressure and preservation of renal function.

4.4.5.1 Medical treatment

ACE inhibitors and calcium channel blockers are effective in the treatment of hypertension in the presence of RAS and may lead to slowing of the progression of renal disease.[181] Most patients with haemodynamically significant RAS tolerate RAAS blockade without difficulty. However, ACE inhibitors can reduce glomerular capillary hydrostatic pressure enough to cause a transient decrease in GFR and raise serum creatinine, warranting caution and close follow-up. A significant (≥30%) fall in GFR (or a >0.5 mg/dL rise in serum creatinine) may be an indication to consider renal revascularization. ACE inhibitors are contraindicated in the case of bilateral RAS and when this lesion affects a single functional kidney.

There is evidence that thiazides, hydralazine, angiotensin II receptor blockers, and β-blockers are also effective in achieving target blood pressures in individuals with RAS.[182–184]

All patients with atherosclerotic RAS should be treated according to the European Guidelines on Cardiovascular Disease Prevention.[24]

4.4.5.2 Revascularization

The decision regarding the potential revascularization strategy should be based on the patient's individual characteristics, such as life expectancy, co-morbidities, quality of blood pressure control, and renal function.

Evidence supporting the benefit of aggressive diagnosis and timing of renal revascularization remains unclear. Among patients receiving medical therapy alone, there is the risk for deterioration of kidney function with worsening morbidity and mortality. Renal artery revascularization can provide immediate improvement in kidney function and blood pressure; however, as with all invasive interventions, it may result in mortality or substantial morbidity in a small percentage of patients. This is particularly the case for renovascular lesions that pose no immediate hazard or risk of

progression. There is general consensus that renal revascularization should be performed in patients with anatomically and functionally significant RAS who present with particular clinical scenarios such as sudden onset or 'flash' pulmonary oedema or congestive heart failure with preserved left ventricular function and acute oligo-/anuric renal failure with kidney ischaemia.

4.4.5.2.1 Impact of revascularization on blood pressure control

Twenty-one uncontrolled series of stenting/angioplasty published before 2007 in 3368 patients gave no unifying pattern regarding mortality rates. Cure, improvement, or worsening of arterial hypertension was documented to range from 4% to 18%, from 35% to 79%, and from 0% to 13%, respectively. Two studies reported a statistically significant reduction in the New York Heart Association functional class after stent placement in patients with either bilateral disease or stenosis to a solitary functioning kidney (global ischaemia). For these patients with congestive heart failure and repeated admissions for pulmonary oedema not associated with CAD, improved volume management, restored sensitivity to diuretics, and lowered rehospitalization rates suggest that some individualized patient categories benefit substantially from renal revascularization.[185–188]

Three RCTs compared endovascular therapy with medical treatment with ≥6 months of follow-up.[166,183,189] Notably, these trials were small and had no adequate power for clinical outcomes. Stents were rarely used and medical therapies varied both between and within studies. In a randomized study including 49 patients, the investigators concluded that endovascular therapy in unilateral atherosclerotic RAS enables reduction of the number of antihypertensive drugs,[189] but that previous uncontrolled studies overestimated the potential for lowering blood pressure. In the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study involving 106 patients,[166] there were no significant differences between the angioplasty and drug therapy groups in terms of systolic and diastolic blood pressures or renal function, whereas daily drug doses were reduced in the angioplasty group. However, a significant improvement in systolic and diastolic blood pressures was reported after angioplasty in a meta-analysis of these three studies.[190] Two recent randomized trials comparing stent angioplasty combined with medical therapy with medical therapy alone [Angioplasty and Stenting for Renal Artery Lesions trial (ASTRAL) and the Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR)] failed to demonstrate any significant difference in blood pressure.[191,192] However, in the ASTRAL trial, the daily drug dosage was reduced.[191]

4.4.5.2.2 Impact of revascularization on renal function

The ASTRAL trial is so far the largest RCT to determine whether percutaneous revascularization combined with medical therapy compared with medical therapy alone improves renal function.[191] Eight-hundred and six patients with atherosclerotic RAS in whom the need for revascularization was uncertain were enrolled. Fifty-nine per cent of patients were reported to have RAS >70%, and 60% had a serum creatinine of ≥150 μmol/L. At a mean follow-up of 33.6 months (range 1–4 years), differences in renal function and kidney and cardiovascular events were all similarly unimpressive, even in the highest risk groups, which included patients with global ischaemia or impaired or rapidly decreasing kidney function. The primary study endpoint—the decline in renal function over time—calculated as the mean slope of the reciprocal of the serum creatinine concentration over time, was slightly slower in the revascularization group, but the difference was not statistically significant. The STAR multicentre trial enrolled 140 patients to detect a ≥20% decrease in creatinine clearance.[192] At 2 years, the primary endpoint was reached in 16% of patients in the stented group and in 22% of patients in the medical treatment group. The difference was not statistically significant and was inconclusive, given the wide confidence intervals around the estimate of effect. It was noteworthy that >50% of the patients randomized to stenting had a <70% diameter stenosis and 28% of patients did not receive a stent (19%) because of no RAS >50%. This largely underpowered trial showed that deterioration of renal function may progress despite successful revascularization, underscoring the complex cause of ischaemic nephropathy, with an important parenchymal component affected by risk factors for atherosclerosis. It also showed that if technical skills are insufficient, a considerable number of stent-related complications can occur (two procedure-related deaths, one death secondary to an infected haematoma, and one case of deterioration of renal function resulting in dialysis).

4.4.5.2.3 Impact of revascularization on survival

In the ASTRAL and STAR trials no difference was seen in the secondary endpoints—cardiovascular morbidity and death. A recent analysis of two consecutive registries comparing conservative treatment with revascularization showed a 45% reduction in mortality for the revascularization cohort.[193] To date, no major differences in survival are evident between patients undergoing either surgical or endovascular procedures, although only a few studies addressed this issue directly.

Several factors may argue against renal revascularization or predict poorer outcomes, including the presence of proteinuria >1 g/24 h, renal atrophy, severe renal parenchymal disease, and severe diffuse intrarenal arteriolar disease. Moreover, adverse consequences of renal atheroembolization at the time of surgical revascularization have been documented.[194] Similarly, atheroembolization may be provoked by percutaneous revascularization.[192,195,196]

The potential physiological benefits of renal stent placement include reperfusion of the ischaemic kidney(s), resulting in a reduction in the stimulus to renin production, which decreases angiotensin and aldosterone production, thereby decreasing peripheral arterial vasoconstriction and preventing hypervolaemia. Improvement in renal perfusion enhances glomerular filtration and therefore promotes natriuresis. Moreover, reduction of humoral activation may result in reduction of left ventricular mass and improvement of diastolic dysfunction.[197–199]

The ASTRAL study did not provide information on how to treat patients with a clinical need for revascularization. This question is being addressed by two ongoing RCTs. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial tests the hypothesis that stenting atherosclerotic RAS >60% (systolic pressure gradient >20 mmHg) in patients with systolic hypertension reduces the incidence of cardiovascular and renal events. The Randomized, Multicentre, Prospective Study Comparing Best Medical Treatment Versus Best Medical Treatment Plus Renal Artery Stenting in Patients With Haemodynamically Relevant

Atherosclerotic Renal Artery Stenosis (RADAR) investigates the impact of renal stenting on the change in renal function in 300 patients.[200]

4.4.5.2.4 Technical outcomes of endovascular revascularization

Balloon angioplasty with bailout stent placement if necessary is recommended for fibromuscular dysplasia lesions.[201–204] In atherosclerotic RAS, stent placement has consistently proven superior to balloon angioplasty in the treatment of renal artery atherosclerotic lesions.[205] Restenosis rates range from 3.5% to ~20%[206,207]; drug-eluting stents have not yet been shown to achieve a significantly better outcome.[208,209] The appropriate treatment modality of in-stent RAS has not yet been defined. Balloon angioplasty, bare-metal stent, covered stent, and drug-eluting stent placement are still under investigation.[210–213] The role of distal protection devices is still a matter of debate. Following several promising single-centre reports, results from a small, randomized trial[196] showed no significantly improved renal function outcome for distal filter protection during stent revascularization except when an adjunctive glycoprotein IIb/IIIa receptor antagonist was used.

Recommendations: treatment strategies for RAS

Recommendations	Class[a]	Level[b]	Ref[c]
Medical therapy			
ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers are effective medications for treatment of hypertension associated with unilateral RAS.	I	B	166, 182, 183, 189, 192, 219
ACE inhibitors and angiotensin II receptor blockers are contraindicated in bilateral severe RAS and in the case of RAS in a single functional kidney.	III	B	151, 166, 182, 183, 189, 192
Endovascular therapy			
Angioplasty, preferably with stenting, may be considered in the case of >60% symptomatic RAS secondary to atherosclerosis.	IIb	A	151, 201-204
In the case of indication for angioplasty, stenting is recommended in ostial atherosclerotic RAS.	I	B	205, 220
Endovascular treatment of RAS may be considered in patients with impaired renal function.	IIb	B	193, 206, 221-223
Treatment of RAS, by balloon angioplasty with or without stenting, may be considered for patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema and preserved systolic left ventricular function.	IIb	C	-
Surgical therapy			
Surgical revascularization may be considered for patients undergoing surgical repair of the aorta, patients with complex anatomy of the renal arteries, or after a failed endovascular procedure.	IIb	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACE = angiotensin-converting enzyme; RAS = renal artery stenosis.

4.4.5.2.5 Role of surgical revascularization

Renal artery surgery offers major benefits for patients undergoing surgical repair of the aorta, and for patients with complex disease of the renal arteries, e.g. aneurysms or failed endovascular procedures. Thirty-day mortality rates range from 3.7% to 9.4%. After a follow-up of up to 5 years, the need for reoperation has been reported in 5–15% and survival in 65–81% of patients.[214–218] Major arguments against surgical revascularization include higher mortality linked to surgery in patients with co-morbidities and similar benefits of endovascular repair.

The list of pivotal published and ongoing trials in patients with RAS is provided in Appendix 4.

4.5 Lower extremity artery disease

4.5.1 Clinical presentation

LEAD has several different presentations, categorized according to the Fontaine or Rutherford classifications (*Table 5*). Importantly, even with a similar extent and level of disease progression, symptoms and their severity may vary from one patient to another.

4.5.1.1 Symptoms

Many patients are asymptomatic. In this situation, LEAD is diagnosed by clinical examination (absent pulses) or by the ABI. Importantly, asymptomatic patients are also at high risk for cardiovascular events.[2]

The most typical presentation of LEAD is intermittent claudication, characterized by pain in the calves, increasing with walking; the pain typically disappears quickly at rest (Fontaine stage II; Rutherford grade I). In the case of a more proximal level of arterial obstruction (i.e. the aortoiliac segment), patients may complain of pain extension into the thighs and buttocks. Isolated buttock claudication is rare and due to bilateral hypogastric severe disease. The pain should be distinguished from that related to venous disease (usually at rest, increasing in the evening, often disappearing with some muscle activity), hip or knee arthritis (pain on walking but not disappearing at rest), and peripheral neuropathy (characterized more by instability while walking, pain not relieved by resting). Typical intermittent claudication can also be caused by lumbar spinal stenosis. The Edinburgh Claudication Questionnaire[224] is a standardized method to screen and diagnose intermittent claudication, with a 80–90% sensitivity and >95% specificity (available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560464/?page=1). More recently, several studies highlighted that a substantial proportion of patients with symptomatic LEAD present with atypical symptoms.[225]

In more severe cases pain is present at rest, in the supine position (Fontaine stage III; Rutherford grade II). Rest pain is localized more often in the foot and should be distinguished from muscle cramping or arthritis. Patients often complain of permanent coldness in the feet. Ulcers and gangrene (Fontaine stage IV; Rutherford grade III) indicate severe ischaemia and begin mostly at the level of toes and the distal part of the limb. Arterial ulcers are, in most cases, extremely painful; they are frequently secondary to local trauma, even minor, and should be distinguished from venous ulcers. When pain is absent, peripheral neuropathy should be considered. Ulcers are often complicated by local infection and inflammation.

Critical limb ischaemia is the most severe clinical manifestation of LEAD, defined as the presence of ischaemic rest pain, and ischaemic lesions or gangrene objectively attributable to arterial occlusive disease.

Table 5 Clinical staging of LEAD

Fontaine classification			Rutherford classification		
Stage	Symptoms	↔	Grade	Category	Symptoms
I	Asymptomatic	↔	0	0	Asymptomatic
II	Intermittent claudication	↔	I	1	Mild claudication
			I	2	Moderate 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

LEAD = lower extremity artery disease.

4.5.1.2 Clinical examination

Clinical examination can be quite informative both for screening and for diagnosis. Patients should be relaxed and acclimatized to the room temperature. Inspection may show pallor in more severe cases, sometimes at leg elevation. Pulse palpation is very informative for screening purposes and should be done systematically. Pulse abolition is a specific rather than a sensitive clinical sign. Auscultation of bruits over the femoral artery at the groin and more distally is also suggestive, but poorly sensitive. The value of the clinical findings in patients with LEAD can be strongly improved by measuring the ABI. The blue toe syndrome is characterized by a sudden cyanotic discolouration of one or more toes; it is usually due to embolic atherosclerotic debris from the proximal arteries.

4.5.2 Diagnostic tests

4.5.2.1 Ankle–brachial index

The primary non-invasive test for the diagnosis of LEAD is the ABI. In healthy persons, the ABI is >1.0. Usually an ABI <0.90 is used to define LEAD. The actual sensitivity and specificity have been estimated, respectively, at 79% and 96%.[226] For diagnosis in primary care, an ABI <0.8 or the mean of three ABIs <0.90 had a positive predictive value of ≥95%; an ABI >1.10 or the mean of three ABIs >1.00 had a negative predictive value of ≥99%.[227] The level of ABI also correlates with LEAD severity, with high risk of amputation when the ABI is <0.50. An ABI change >0.15 is generally required to consider worsening of limb perfusion over time, or improving after revascularization.[228]

For its measurement (*Figure 2*), a 10–12 cm sphygmomanometer cuff placed just above the ankle and a (handheld) Doppler instrument (5–10 MHz) to measure the pressure of the posterior and anterior tibial arteries of each foot are required. Usually the highest ankle systolic pressure is divided by the highest brachial systolic pressure, resulting in an ABI per leg. Recently some papers reported higher sensitivity to detect LEAD if the ABI numerator is the lowest pressure in the arteries of both ankles.[229]

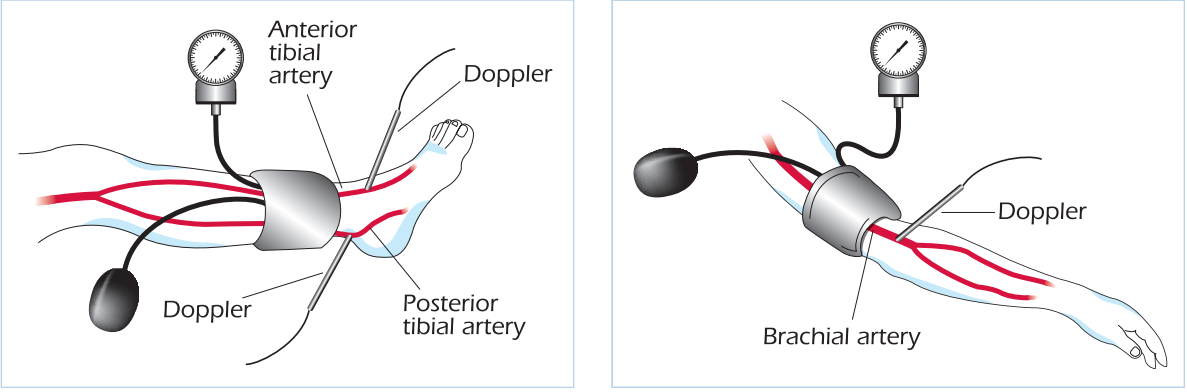

Figure 2 Measurement of the ankle–brachial index (ABI), calculated by dividing the ankle systolic blood pressure by the arm systolic blood pressure.

Measuring ABI after exercise enables the detection of additional subjects with LEAD, who have normal or borderline ABI at rest. The patient is asked to walk (commonly on a treadmill at 3.2 km/h at a 10–20% slope) until claudication pain occurs and impedes walking. An ABI drop after exercise seems especially useful when resting ABI is normal but there is clinical suspicion of LEAD.[230]

Some patients have an ABI >1.40, related to stiff (calcified) arteries, a condition often observed in the case of diabetes, ESRD, and in the very elderly. Importantly, a substantial proportion of patients with an elevated ABI actually do have occlusive artery disease.[231] Alternative tests such as measurement of toe systolic pressures and Doppler waveform analysis are useful to unmask LEAD.[231] A toe–brachial index <0.70 is usually considered diagnostic of LEAD.

Recommendations for ABI measurement

Recommendations	Class[a]	Level[b]	Ref[c]
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	B	226
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 should be used.	I	B	231

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ABI = ankle–brachial index; LEAD = lower extremity artery disease.

4.5.2.2 Treadmill test

The treadmill test is an excellent tool for obtaining objective functional information, mainly on symptom onset distance and maximum walking distance. It is useful in patients with borderline ABI at rest with symptoms suggestive of LEAD. It can also help to differentiate vascular claudication (with leg pressure drop after exercise) from neurogenic claudication (leg pressure remains stable or increases). The standardized treadmill test is also proposed to assess treatment efficacy (exercise rehabilitation, drug therapies, and/or revascularization) during follow-up. Usually the test is performed on a treadmill walking at 3.2 km/h with a 10% slope. However, there are several technical variations,[232] such as introducing a steady increase in elevation of the treadmill every 3 min while keeping the speed constant. The test should be supervised to observe all symptoms occurring during the test. It should be avoided in the case of severe CAD, decompensated heart failure, or major gait disturbances. It is usually associated with ABI measurement before and after exercise. A pressure drop >20% immediately after exercise confirms the arterial origin of symptoms.[233] For patients unable to perform treadmill exercise, alternative tests such as repeated pedal flexions can be used, with excellent correlation with the treadmill test.

Recommendations for treadmill testing in patients with LEAD

Recommendations	Class[a]	Level[b]	Ref[c]
The treadmill test should be considered for the objective assessment of treatment to improve symptoms in claudicants.	IIa	A	234, 235
In the case of typical or atypical symptoms suggestive of LEAD, the treadmill test should be considered for diagnostic confirmation and/or for baseline quantification of functional severity.	IIa	B	234

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LEAD = lower extremity artery disease.

4.5.2.3 Ultrasound methods

DUS provides extensive information on both arterial anatomy and blood flow. Compared with DSA, several concordant meta-analyses estimated DUS sensitivity to detect >50% diameter angiographic stenosis at 85–90%, with a specificity >95%.[236–238] No significant differences were found between the above- and below-knee lesions.[236,238] DUS can also visualize run-off vessels, especially when using the colour mode. DUS depends greatly on the examiner's experience, and adequate qualification and training are mandatory. Combined with the ABI, DUS provides all the information necessary for management decisions in the majority of patients with LEAD, confirms the diagnosis, and provides information on lesion location and severity. The lesions are located by two-dimensional (2D) ultrasonography and colour-Doppler mapping, while the degree of stenosis is estimated mostly by Doppler waveform analysis and peak systolic velocities and ratios. The interobserver reproducibility of the DUS to detect >50% stenosis in lower extremity arteries is good, except for pedal arteries.[239,240]

DUS is also highly useful for the follow-up after angioplasty or to monitor bypass grafts.[241,242] Excellent tolerance and lack of radiation exposure make DUS the method of choice for routine follow-up.

Pitfalls of DUS are related mainly to difficulties in assessing the lumen in highly calcified arteries. Insonation in the area of open ulcers or excessive scarring may not be possible. Also in some cases (e.g. obesity, gas interpositions), the iliac arteries are more difficult to visualize and alternative methods should be considered when the imaging is suboptimal. The major disadvantage of DUS compared with other imaging techniques (DSA, CTA, or MRA) is that it does not provide full arterial imaging as a clear roadmap, as do the other techniques. However, in contrast to other imaging technique (DSA, CTA, and MRA), DUS provides important information on haemodynamics. Complete DUS scanning of the entire arterial network can be time-consuming. Although aggregate images or schemas can be provided, another imaging technique is usually required, especially when bypass is

considered.[243] However, even in this situation, DUS can be an important aid in determining the most appropriate site of anastomosis by identification of the least calcified portion of the vessel.[244]

Intravascular ultrasound has been proposed for plaque characterization and after angioplasty, but its routine role in the clinical setting requires further investigation.

4.5.2.4 *Computed tomography angiography*

CTA using MDCT technology allows imaging with high resolution. Compared with DSA, the sensitivity and specificity for occlusions reported using the single-detector techniques already reached a high degree of accuracy. In a recent meta-analysis, the reported sensitivity and specificity of CTA to detect aortoiliac stenoses >50% were 96% and 98%, respectively.[245] The same study showed similar sensitivity (97%) and specificity (94%) for the femoropopliteal region, comparable with those reported for the below-knee arteries (sensitivity 95%, specificity 91%).[245]

The great advantage of CTA remains the visualization of calcifications, clips, stents, and bypasses. However, some artefacts may be present due to the 'blooming effect'.

4.5.2.5 *Magnetic resonance angiography*

MRA can non-invasively visualize the lower limb arteries even in the most distal parts. The resolution of MRA using gadolinium-enhanced contrast techniques reaches that of DSA. In comparison with DSA, MRA has an excellent sensitivity (93–100%) and specificity (93–100%).[237,246–250] Owing to different techniques (2D and 3D, with or without gadolinium), the results are not as uniform as for CTA, and studies comparing MRA with CTA are not available. In direct comparison, MRA has the greatest ability to replace diagnostic DSA in symptomatic patients to assist decision making, especially in the case of major allergies. There are also limitations for the use of MRA in the presence of pacemakers or metal implants (including stents), or in patients with claustrophobia. Gadolinium contrast agents cannot be used in the case of severe renal failure (GFR <30 mL/min per 1.73 m^2). Of note, MRA cannot visualize arterial calcifications, which may be a limitation for the selection of the anastomotic site for a surgical bypass.

4.5.2.6 *Digital subtraction angiography*

For the aorta and peripheral arteries, retrograde transfemoral catheterization is usually used. Cross-over techniques allow the direct antegrade flow imaging from one side to the other. If the femoral access is not possible, transradial or transbrachial approaches and direct antegrade catheterization are needed. Considered as the gold standard for decades, DSA is now reserved for patients undergoing interventions, especially concomitant to endovascular procedures. Indeed, the non-invasive techniques provide satisfying imaging in almost all cases, with less radiation, and avoiding complications inherent to the arterial puncture, reported in <1% of cases.

4.5.2.7 *Other tests*

Several other non-invasive tests can be used routinely, either to localize the lesions or to evaluate their effect on limb perfusion: segmental pressure measurements and pulse volume recordings,[251] (laser) Doppler flowmetry, transcutaneous oxygen pressure assessment ($TCPO_2$), and venous occlusion plethysmography before and during reactive hyperaemia.[252]

Recommendations for diagnostic tests in patients with LEAD

Recommendations	Class[a]	Level[b]	Ref[c]
Non-invasive assessment methods such as segmental systolic pressure measurement and pulse volume recording, plethysmography, Doppler flowmetry, and DUS are indicated as first-line methods to confirm and localize LEAD lesions.	I	B	251, 252
DUS and/or CTA and/or MRA are indicated to localize LEAD lesions and consider revascularization options.	I	A	237, 238, 241–250
The data from anatomical imaging tests should always be analysed in conjunction with haemodynamic tests prior to therapeutic decision.	I	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CTA = computed tomography angiography; DUS = duplex ultrasonography; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography.

4.5.3 Therapeutic strategies

All patients with LEAD are at increased risk of further CVD events, and general secondary prevention is mandatory to improve prognosis. Patients with asymptomatic LEAD have no indication for prophylactic revascularization. The following paragraphs focus on the treatment of symptomatic LEAD.

4.5.3.1 *Conservative treatment*

The aim of conservative treatment in patients with intermittent claudication is to improve symptoms, i.e. increase walking distance and comfort. To increase walking distance, two strategies are currently used: exercise therapy and pharmacotherapy.

4.5.3.1.1 *Exercise therapy*

In patients with LEAD, training therapy is effective in improving symptoms and increasing exercise capacity. In a meta-analysis[253] including data from 1200 participants with stable leg pain, compared with usual care or placebo, exercise significantly improved maximal walking time, with an overall improvement in walking ability of ~50–200%. Walking distances were also significantly improved. Improvements were seen for up to 2 years. Best evidence comes from studies with a short period of regular and intensive training under supervised conditions.[254] In a meta-analysis of eight trials collecting data from only 319 patients, supervised exercise therapy showed statistically significant and clinically relevant differences in improvement of maximal treadmill walking distance compared with non-supervised exercise therapy regimens (+150 m on average).[255] In general, the training programme lasts for 3 months, with three sessions per week. The training intensity on the treadmill increases over time, with a session duration of

30–60 min.[256] Of note, in a small randomized trial[257] comparing supervised exercise therapy with usual care, while no significant changes in peak cardiovascular measurements were noted after 12 weeks of exercise, patients under supervised exercise therapy were more efficient in meeting the circulation and ventilation demands of exercise.

Individuals with LEAD should undertake exercise as a form of treatment. Any type of regular exercise should be continued after completion of the intensive training programme. Daily walking, or repeated series of heel raising or knee bending, are realistic possibilities.[258] Other training programmes have been suggested, but their effectiveness is less well documented. In a pilot trial, dynamic arm exercise training was followed by similar improvement (pain-free and maximal walking distance) to that seen with treadmill walking exercise training.[259]

There are obvious limitations to training therapy. Muscular, articular, or neurological diseases may be limiting factors. General cardiac and/or pulmonary diseases can decrease capacity to achieve a level of training that is sufficient to obtain positive results. In conjunction with practical aspects, such as difficulties in attending the sessions or neglecting continuous training, the actual results in the clinical setting have often been poorer than in trials. Patients with Fontaine class IV should not be submitted to regular exercise training.

4.5.3.1.2 Pharmacotherapy

Several pharmacological approaches were claimed to increase walking distance in patients with intermittent claudication. However, objective documentation of such an effect is often lacking or limited. In terms of walking distance improvement, the benefits, if any, are generally mild to moderate, with wide confidence of intervals. Also, mechanisms of action are diversified and often unclear. The drugs with best proof of efficacy are discussed briefly below. Among them, the best-documented drugs are cilostazol and naftidrofuryl.

4.5.3.1.2.1 Cilostazol

Cilostazol is a phosphodiesterase-3 inhibitor. In a pooled analysis of nine trials (1258 patients) comparing cilostazol with placebo,[260] this drug was associated with an absolute improvement of +42.1 m vs. placebo ($P < 0.001$) over a mean follow-up of 20 weeks. In another meta-analysis,[261] maximal walking distance increased on average by 36 m with cilostazol 50 mg/day, and almost twice (70 m) with the 100 mg dose. Improvement in quality of life is also reported in claudicants.[262] Owing to its pharmacological properties, it should be avoided in the case of heart failure. The most frequent side effects are headache, diarrhoea, dizziness, and palpitations.

4.5.3.1.2.2 Naftidrofuryl

Naftidrofuryl has been available in Europe for many years. It is a 5-hydroxytryptamine type 2 antagonist that reduces erythrocyte and platelet aggregation. The efficacy of naftidrofuryl was examined in a meta-analysis of five studies including 888 patients: pain-free walking distance was significantly increased by 26% vs. placebo.[263] This positive effect on intermittent claudication was confirmed by a recent Cochrane analysis.[264] Quality of life was also improved with naftidrofuryl treatment.[265] Mild gastrointestinal disorders are the most frequently observed side effect.

4.5.3.1.2.3 Pentoxifylline

This phosphodiesterase inhibitor was among the first drugs to show improvement in red and white cell deformability, and, as a consequence, decrease blood viscosity. In a recent meta-analysis[261] of six studies including 788 patients, a significant increase in maximal walking distance was found with pentoxifylline (+59 m).

4.5.3.1.2.4 Carnitine and propionyl-L-carnitine

These drugs are likely to have an effect on ischaemic muscle metabolism. In two multicentre trials,[266,267] propionyl-L-carnitine improved walking distance and quality of life better than placebo. Additional trials are expected to evaluate their efficacy in large groups of patients.

4.5.3.1.2.4 Buflomedil

Buflomedil may cause inhibition of platelet aggregation and improve red blood cell deformability. It also has α-1 and α-2 adrenolytic effects. In a recent placebo-controlled study in 2078 patients,[268] significant symptomatic improvement was shown. However, in a recent meta-analysis,[269] these results were quoted as 'moderately' positive, with some degree of publication bias. The therapeutic dose range is narrow, with a risk of seizures.[270] Buflomedil has been recently withdrawn from the market in some European countries for potential major side effects and uncertain benefits.

4.5.3.1.2.5 Antihypertensive drugs

In a recent review, antihypertensive drugs did not differ in respect of their effect on intermittent claudication.[271]According to a recent meta-analysis of four studies, the benefits of ACE inhibitors on walking distance are uncertain, and the main expectation of prescribing this drug class is in the general prognostic improvement of these patients (see Section 3.4.4).[272] Notably, β-blockers do not exert a negative effect on claudication.[273,274]

4.5.3.1.2.6 Lipid-lowering agents

Beyond the evidence that statins improve the cardiovascular prognosis of patients with LEAD, several studies reported preliminary positive effects of statins on intermittent claudication.[261] The increase in maximal walking distance reported varied, on average, from 50 to 100 m. In one meta-analysis, the pooled effect estimate was in favour of lipid-lowering agents, with a relevant increase in maximal walking distance of 163 m.[261]

4.5.3.1.2.7 Antiplatelet agents

The use of antiplatelet drugs is indicated in patients with LEAD to improve event-free survival (see Section 3.4.3). In contrast, data on the potential benefits of antiplatelet drugs to improve clinical symptoms are scarce. In a recent meta-analysis,[261] data from studies assessing five drugs (ticlopidine, cloricromene, mesoglycan, indobufen, and defibrotide) were pooled, with a significant increase in maximal walking distance of 59 m. Available data are too disparate to formulate any conclusions.

4.5.3.1.2.8 Other therapies

Other pharmacological agents assessed are inositol, proteoglycans, and prostaglandins. Although positive, the results require further

confirmation. A recent meta-analysis showed no significant improvement in walking distance with gingko biloba.[275]

Intermittent pneumatic compression may be a relevant treatment for symptomatic LEAD. In a review,[276] concordant data are reported in several studies showing increased flow (13–240%) in the popliteal or infragenicular arteries. Rest pain and walking distance were also improved. In a recent small, randomized trial comparing a portable intermittent pneumatic compression device with best medical therapy, maximal walking distance improved by 50% (90 m).[277]

4.5.3.2 Endovascular treatment of lower extremity artery disease

Endovascular revascularization for the treatment of patients with LEAD has developed rapidly during the past decade, and a great number of patients can now be offered the less invasive treatment option. An increasing number of centres favour an endovascular-first approach due to reduced morbidity and mortality—compared with vascular surgery—while preserving the surgical option in case of failure.

The optimal treatment strategy concerning endovascular vs. surgical intervention is often debated due to the paucity of randomized studies; furthermore, most of these studies are underpowered. Moreover, owing to the rapid development, a thorough evaluation of new endovascular treatment options within adequately designed clinical studies is difficult. Another problem is the lack of uniform endpoint definitions, making a direct comparison among studies difficult.[278] It is important to report results including clinical, morphological, and haemodynamic outcomes.

The selection of the most appropriate revascularization strategy has to be determined on a case-by-case basis in a specialized vascular centre in close cooperation with an endovascular specialist and a vascular surgeon. The main issues to be considered are the anatomical suitability (*Table 6*), co-morbidities, local availability and expertise, and the patient's preference.

While revascularization is obligatory in patients with CLI, the evidence of any long-term benefit of endovascular treatment over supervised exercise and best medical treatment is inconclusive, especially in patients with mild to moderate claudication.[279] However, advances in the endovascular treatment of LEAD have prompted many physicians to consider more liberal indications for percutaneous intervention. Endovascular revascularization is also indicated in patients with lifestyle-limiting claudication when clinical features suggest a reasonable likelihood of symptomatic improvement and there has been an inadequate response to conservative therapy. In aortoiliac lesions, endovascular revascularization can be considered without initial extensive conservative treatment.

The major drawback of endovascular interventions—compared with surgery—is the lower long-term patency. The primary patency after angioplasty is greatest for lesions in the common iliac artery and decreases distally, and with increasing length, multiple and diffuse lesions, poor-quality run-off, diabetes, and renal failure. Currently there is no established method—besides stent implantation—to improve at least the mid-term patency of angioplasty. The use of drug-eluting balloons seems promising; however, the current limited data do not justify a general recommendation.

In general, endovascular interventions are not indicated as prophylactic therapy in an asymptomatic patient. Patients undergoing

Table 6 Lesion classification according to the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)

Aorto-iliac lesions	
Lesion type	**Description**
Type A	- Unilateral or bilateral stenosis of CIA - Unilateral or bilateral single short (≤3 cm) stenosis of EIA
Type B	- Short (≤3 cm) stenosis of infrarenal aorta - Unilateral CIA occlusion - Single or multiple stenosis totaling 3-10 cm involving the EIA not extending into the CFA - Unilateral EIA occlusion not involving the origins of internal iliac or CFA
Type C	- Bilateral CIA occlusions - Bilateral EIA stenoses 3-10 cm long not extending into the CFA - Unilateral EIA stenosis extending into the CFA - Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA - Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA
Type D	- Infra-renal aorto-iliac occlusion - Diffuse disease involving the aorta and both iliac arteries requiring treatment - Diffuse multiple stenosis involving the unilateral CIA, EIA and CFA - Unilateral occlusions of both CIA and EIA - Bilateral occlusions of EIA - Iliac stenosis in patients with AAA requiring treatment and not amenable to endograft placement or other laesions requiring open aortic or iliac surgery
Femoral-popliteal lesions	
Lesion type	**Description**
Type A	- Single stenosis ≤10 cm in length - Single occlusion ≤5 cm in length
Type B	- Multiple lesions (stenoses or occlusions), each ≤5 cm - Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal artery - Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass - Heavily calcified occlusion ≤5 cm in length - Single popliteal stenosis
Type C	- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcifications - Recurrent stenoses or occlusions that need treatment after two endovascular interventions
Type D	- Chronic total occlusion of CFA or SFA (>20 cm, involving the popliteal artery) - Chronic total occlusion of popliteal artery and proximal trifurcation vessels

AAA = abdominal aortic aneurysm; CFA = common femoral artery; CIA = common iliac artery; EIA = external iliac artery; SFA = superficial femoral artery.
After Norgren *et al.*[6] with permission.

endovascular revascularization for claudication or CLI should be entered into a clinical surveillance programme.

The primary goals of stent implantation are: (i) to improve an insufficient primary result—residual stenosis, extensive recoil, flow-limiting dissection; and (ii) to improve long-term patency. The placement of stents should generally be avoided in bending areas (hip and knee joints), although special stents have been developed recently. Stent implantation should also be avoided in a segment suitable as a landing zone for a potential bypass.

4.5.3.2.1 Aortoiliac segment

Obstructive atherosclerotic disease of the distal aorta and iliac arteries is preferentially treated with endovascular techniques, and an endovascular-first strategy can be recommended for all TransAtlantic Inter-Society Consensus (TASC) A–C lesions. Low morbidity and mortality as well as a >90% technical success rate justify the endovascular-first approach. In experienced centres, TASC D lesions are also primarily treated percutaneously. The main limitation in recommending the endovascular-first strategy for almost all aortoiliac lesions is the lack of published data from randomized trials.

The only randomized trial comparing primary stent implantation with provisional stenting in the case of a persistent pressure gradient after angioplasty alone did not demonstrate any benefit of primary stent implantation.[280] Based on an older meta-analysis, stenting can be recommended as the primary therapy for common and external iliac stenosis and occlusions.[281] The patency rates with stenting of iliac arteries compare favourably with those of surgical revascularization.[282]

The choice of balloon vs. self-expandable stents is determined mainly by operator preference. The main advantages of balloon-expandable stents are the higher radial stiffness and the more accurate placement, which is especially important in bifurcation lesions.[283] In the external iliac artery, a primary stenting strategy using self-expandable stents compared with provisional stenting is preferred mainly due to a lower risk of dissection and elastic recoil.

In the case of doubt about the haemodynamic significance of morphologically borderline iliac lesions, pressure gradients at rest and with induced hyperaemia should be measured.[284]

Recommendations for revascularization in patients with aortoiliac lesions

Recommendations	Class[a]	Level[b]
When revascularization is indicated, an endovascular-first strategy is recommended in all aortoiliac TASC A–C lesions.	I	C
A primary endovascular approach may be considered in aortoiliac TASC D lesions in patients with severe comorbidities, if done by an experienced team.	IIb	C
Primary stent implantation rather than provisional stenting may be considered for aortoiliac lesions.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
TASC = TransAtlantic Inter-Society Consensus.

4.5.3.2.2 Femoropopliteal segment

One of the main problems with endovascular therapy in this segment is the high prevalence of diffuse disease. Furthermore, different mechanical forces act on the superficial femoral artery. This artery is deformed repetitively in multiple directions by leg movements. A high technical success rate, due to technical developments and increasing operator experience, in combination with low risk, make endovascular therapy the preferred choice also in patients with long and complex femoropopliteal lesions.

The landscape of endovascular treatment of femoropopliteal disease has changed decisively with the development of self-expandable nitinol stents. The previous strategy was to use stents as the treatment option only in the case of initial PTA failure or late recurrence. However, according to an increasing number of randomized studies, primary nitinol stenting can now be recommended as the first-line treatment for intermediate length superficial femoral artery lesions due to improvement of at least mid-term patency.[285,286] The restenosis rate after 1–2 years is 20–30% lower after primary stenting compared with angioplasty.

The decision to stent the superficial femoral artery is based mainly on the clinical indication for revascularization and on the lesion length and complexity. In the case of CLI, stenting can be applied more liberally for limb salvage and ulcer healing.

In the past, there was much concern about stent fractures. Several risk factors have been identified for stent fractures: number and length of implanted stents, overlapping stents, amount of calcification, and deployment technique.[287] The higher fracture resistance of the latest generation of stents in combination with the production of long nitinol stents (up to 20 cm in length) broadens the possibilities of endovascular therapies in the case of more difficult and complex lesions.

In-stent restenosis is the major drawback of stent implantation. To date there is no proof of any impact of stent design on restenosis rates. Isolated balloon angioplasty of restenosis lesions has a very high failure rate. Other treatment modalities have been investigated, but there is no single randomized trial in patients with in-stent restenosis demonstrating the superiority of one technique over the other. Drug-eluting stents have been investigated in a few studies in the superficial femoral artery, and until now no advantage has been shown compared with bare-metal nitinol stents.[288] Early studies with drug-eluting balloons in the femoropopliteal arteries showed improved short-term patency rates compared with plain balloon angioplasty.[289]

Covered stents (stent grafts) appear to be a viable option for the treatment of complex superficial femoral artery lesions, with outcomes comparable with prosthetic above-knee femoropopliteal bypass surgery.[290]

Despite its widespread use, research data regarding subintimal angioplasty are sparse. There are no data comparing patency rates between intraluminal and subintimal angioplasty. However, in many interventions an unintentional subintimal passage is unavoidable. Regarding atherectomy, different devices are used with unclear long-term benefits. Currently there are niche indications in severely calcified lesions and non-stent areas (e.g. the common femoral and popliteal artery). However, there are some concerns regarding the risk of distal embolization with these devices.

Recommendations for revascularization in patients with femoropopliteal lesions

Recommendations	Class[a]	Level[b]	Ref[c]
When revascularization is indicated, an endovascular-first strategy is recommended in all femoropopliteal TASC A–C lesions.	I	C	-
Primary stent implantation should be considered in femoropopliteal TASC B lesions.	IIa	A	285, 286, 291
A primary endovascular approach may also be considered in TASC D lesions in patients with severe comorbidities and the availability of an experienced interventionist.	IIb	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
TASC = TransAtlantic Inter-Society Consensus.

4.5.3.2.3 Infrapopliteal arteries

Most patients with CLI have multisegmental disease involving the infrapopliteal arteries. Therefore, limb salvage is the primary indication for endovascular treatment of infrapopliteal lesions, while angioplasty of these arteries is usually not indicated in patients with intermittent claudication. There is increasing evidence to support a recommendation for angioplasty in patients with CLI where straight-line flow to the foot in at least one lower leg artery can be re-established according to the pre-interventional angiogram and in the case of important co-morbidities.[292]

Primary PTA remains the standard of care, as it provides an acceptable clinical outcome at a low procedural cost.[293] The limb salvage rate is definitely higher than the angiographic patency rate after initially successful intervention below the knee. Therefore, long-term patency is not obligatory in CLI patients with persistent clinical improvement. Stent implantation in infrapopliteal vessels is generally reserved for cases with a suboptimal outcome after PTA. The use of drug-eluting stents is associated with a favourable restenosis rate[294]; the balloon-expandable sirolimus-eluting stent is approved in Europe for this indication.

Recommendations for revascularization in patients with infrapopliteal lesions

Recommendations	Class[a]	Level[b]
When revascularization in the infrapopliteal segment is indicated, the endovascular-first strategy should be considered.	IIa	C
For infrapopliteal lesions, angioplasty is the preferred technique, and stent implantation should be considered only in the case of insufficient PTA.	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
PTA = percutaneous transluminal angioplasty.

4.5.3.3 Surgery

Vascular surgery offers different revascularization techniques for lower limb ischaemia. Bypass surgery presents the most common surgical approach for diffuse occlusive disease and creates new conduits following anatomical or extra-anatomical routes. In some circumstances, local endarterectomy with or without patching can restore blood perfusion. Different graft materials can be applied. Autologous vein or artery grafts are the best options, but are not always available or applicable. In such cases, prosthetic grafts are considered. Homografts represent the third option for vascular substitution, especially in the case of infective complications.

Patients with extensive necrosis or infectious gangrene and those who are non-ambulatory may best be served with primary amputation. Amputation remains the last surgical step to solve irreversible limb ischaemia, allowing patient recovery with rehabilitation and prosthesis. For a moribund patient, adequate analgesia and other supportive measures may also be the best option. Other adjuvant surgical options can be considered. Skin reconstruction is useful to cover large areas of lost tissue. The use of lumbar sympathectomy is controversial and is not supported by evidence.

4.5.3.3.1 Aortoiliac disease

Aorto-biiliac or -bifemoral bypass is usually recommended for diffuse aortoiliac disease. In some situations, when an abdominal approach is perilous, a modified retroperitoneal approach or a unilateral bypass with a femoro-femoral cross-over may be considered. Other extra-anatomical surgical alternatives are axillo(bi)femoral or thoracic(bi)femoral bypasses. The surgical strategy depends on the lesion location and technical possibilities. Compared with the aorto-femoral bypass, extra-anatomical bypasses present poorer patency rates and higher risk of complications. The 10-year primary patency rates of aortobifemoral bypass range from 80% to 90%.[295]

4.5.3.3.2 Infrainguinal disease

When infrainguinal disease is the cause of claudication, the appropriateness of intervention is more debated than for aortoiliac disease, depending on the level of symptoms, quality of femoral profundis artery and its collaterals, and local haemodynamic status. In contrast, in the case of CLI, any patent proximal vessel, including the iliac, common, or superficial femoral arteries, femoral profundis, and popliteal arteries, may serve as the inflow vessel for distal arterial reconstruction. Autologous vein grafts (*in situ* or reversed vein graft, or using the contralateral saphenous vein) provide the best patency results.[296] Prosthetic grafts may be used if the autogenous vein is not available. Conflicting results are reported on the usefulness of vein cuffs to improve graft patency.[297,298] In a recent meta-analysis[299] involving data from seven contemporary trials (1521 patients) comparing Dacron with polytetrafluoroethylene femoropopliteal bypasses, the cumulative primary patency rates were similar at 3 years (60.2% vs. 53.8%, respectively) and at 5 years (49.2% vs. 38.4%). Pooling the three studies that included exclusively above-knee femoropopliteal

bypasses revealed lower risk for primary occlusion with Dacron grafts (HR 0.71 vs. polytetrafluoroethylene, $P = 0.003$), but long-term results are awaited. The pooled weighted data for 1-, 3-, and 5-year primary patency rates for femorodistal (tibial or pedal) bypasses are, respectively, reported at 85, 80, and 70% for venous bypass and 70, 35, and 25% with a prosthetic graft.[6] In one trial with above-knee grafting, the 4-year primary and secondary patency rates were significantly better with the use of the saphenous vein (73% and 90%, respectively) compared with polytetrafluoroethylene (47% and 47%, both $P < 0.05$) and Dacron (54% and 60%, both $P < 0.01$). Two trials comparing *in situ* and reversed saphenous vein grafts to the above- and below-knee popliteal artery revealed no differences in primary and secondary patency as well as survival with an intact limb. Three trials comparing polytetrafluoroethylene with human umbilical vein showed significantly higher secondary patency rates with the latter.[300] Comparison of polytetrafluoroethylene grafts with and without a vein cuff found no difference in above-knee grafts. However, primary patency for below-knee bypass was higher with a polytetrafluoroethylene prosthesis with vein cuff bypass at 2 years.[296,301]

Only one randomized trial has compared angioplasty with infrainguinal bypass. In the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, 452 patients with severe limb ischaemia due to infrainguinal disease were randomized to angioplasty or infrainguinal bypass. The primary endpoint was amputation-free survival. Secondary endpoints included all-cause mortality, morbidity, reintervention, quality of life, and hospital costs.[302] The 30-day mortality was similar in both groups (5% for surgery and 3% for angioplasty). However, surgery was associated with a higher morbidity (57% vs. 41%), mainly due to myocardial infarction and wound infection. Moreover, surgery was more expensive during the first year, due to the longer hospital stay. The 6-month amputation-free survival was similar in both strategies. Angioplasty patients presented higher failure rates (20% vs. 3% at 1 year), resulting in higher reintervention rates (27% vs. 17%). These results suggest that surgical revascularization is superior to angioplasty in patients with good quality veins for bypass. Recently additional data with a longer follow-up period (>3 years) have been published[211,303]: overall, there was no significant difference in amputation-free or overall survival between the two strategies. However, for patients who survived for at least 2 years after randomization, the surgery-first revascularization strategy was associated with a significant increase in subsequent overall survival and a trend towards improved amputation-free survival.

One small, randomized trial comparing stenting with femoral-to-above-knee prosthetic bypass found no difference in primary and secondary patency rates at 12 months.[290] Further trials are required comparing infrainguinal stenting with surgery.

Another infrainguinal surgical reconstruction is the profundoplasty, the correction of a stenosis at the origin of the deep femoral artery. It may be considered as an inflow procedure, instead of a distal bypass, in the presence of an excellent proximal inflow, >50% stenosis of the proximal third of the profunda femoris artery, and the presence of excellent collateral flow to the tibial vessels.

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 necrosis despite a patent graft. The goals of secondary amputation are: ischaemic pain relief, complete removal of diseased, necrotic, or infected tissue, and construction of a stump suitable for ambulation with prosthesis.

Recommendation for surgical revascularization in patients with LEAD

Recommendations	Class[a]	Level[b]	Ref[c]
When surgery is considered to revascularize infrailiac lesions, the autologous saphenous vein is the bypass graft of choice.	I	A	296, 304

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LEAD = lower extremity artery disease.

4.5.3.3.3 Surveillance

Clinical surveillance including clinical assessment and ankle pressure follow-up should be performed following any revascularization procedure. Although there is no consensual protocol of surveillance, regular monitoring of revascularized limbs can permit a prompt prophylactic intervention (e.g. repair of an arterial bypass at high risk of occlusion according to DUS criteria) and improve long-term patency.[305] However, in a multicentre randomized trial including 594 patients with vein grafts, a systematic duplex surveillance programme was not found to be beneficial in terms of graft patency and limb survival rates, and was less cost-effective than clinical surveillance.[306] DUS could be useful to select high-risk prosthetic grafts, which may require long-term anticoagulation to reduce the risk of graft thrombosis,[307] but these data are based on observational series and require confirmation in trials.

4.5.3.3.4 Antiplatelet and anticoagulant therapy after revascularization

Beyond potential benefits of antiplatelet agents to reduce fatal or non-fatal CVD events in patients with LEAD, these drugs are also specifically proposed after revascularization to improve patency rates. In a meta-analysis of 16 studies, the effect of antiplatelet therapy administered post-operatively was evaluated in patients receiving infrainguinal bypasses.[308] Antiplatelet treatment with aspirin or a combination of aspirin and dipyridamole had an overall positive effect on primary patency 12 months after the procedure (OR 0.59, 95% CI 0.45–0.79). Subgroup analysis indicated that patients receiving a prosthetic graft were more likely to benefit from administration of platelet inhibitors than patients treated with venous grafts.[308] The multicentre, prospective Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial[309] randomized 2690 lower extremity bypass patients into two groups: anticoagulation (with the international normalized ratio targeted within the 3.0–4.5 interval) vs. antiplatelet therapy (aspirin 80 mg/day). Overall patency rates did not differ, but the results of a subgroup analysis suggested that oral anticoagulation improved vein graft patency compared with aspirin. Conversely, aspirin

improved prosthetic graft patency vs. anticoagulation. Notably, the risk of major bleeding was two-fold higher in the anticoagulation group. In another trial,[310] 665 patients undergoing femoropopliteal bypass were randomized to aspirin (325 mg/day) plus warfarin (goal international normalized ratio 1.4–2.8) vs. aspirin (325 mg/day) alone. This trial failed to demonstrate any improvement in terms of graft patency with dual therapy. However, the results were in favour of combination therapy for patients with prosthetic bypasses. The haemorrhagic risk doubled when warfarin was added to aspirin. In another randomized study,[311] warfarin (international normalized ratio 2.0–3.0) plus aspirin (325 mg/day) was compared with aspirin (325 mg/day) alone in 56 patients with high-risk vein grafts (defined as poor arterial run-off, suboptimal vein conduit, and repeat interventions). At 3 years, patency and limb salvage rates were significantly higher in those receiving warfarin and aspirin, with in turn higher bleeding rates with this combination. Recently, the Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral ARterial disease (CASPAR) randomized double-blind trial assessed the efficacy of aspirin plus clopidogrel vs. aspirin alone to increase primary patency, limb salvage, and survival in patients receiving a below-knee bypass graft.[312] Among the 851 patients enrolled, almost 70% had a venous graft and 30% a prosthetic graft. After a mean follow-up of 1 year, no overall difference was found regarding the combined primary outcome between the two groups. Subgroup analysis was in favour of a beneficial effect of clopidogrel in association with aspirin in prosthetic grafts. The number needed to treat using the dual antiplatelet therapy to save one limb after below-knee surgery was dramatically low, estimated at 10.2 patients.

The role of anticoagulation after infrainguinal balloon PTA and stenting has been assessed in three prospective randomized trials.[313] None of these trials showed any significant improvement in arterial patency with the use of anticoagulation therapy, while bleeding complications increased.[313] Yet, anticoagulation therapy cannot be recommended routinely after lower extremity PTA or stenting.

4.5.3.4 Stem cell and gene therapy for revascularization

The development of novel therapies to stimulate neovascularization, known as therapeutic angiogenesis, is based on the use of angiogenic factors or stem cells to promote revascularization and remodelling of collaterals with the aim of ameliorating symptoms and preventing amputation.

While several trials reported relief of ischaemic symptoms, functional improvement, and prevention of amputation,[314–317] others failed to confirm this early promise of efficacy.[318–320]

For autologous cell transplantation in humans, bone marrow and peripheral blood are rich sources of stem and progenitor cells. Bone marrow is currently the most frequent source of cells used for clinical repair trials, because it is easy to obtain and no complex purification steps are required. Another advantage is that it contains a variety of stem and progenitor cells with suggested superiority over one selected type of progenitor cell. With the many different cell types that can be used for stem cell therapy, it is not yet clear which ones are the most promising.[321] In a recent meta-analysis of 37 trials, 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 larger benefits than patients with atherosclerotic LEAD. The TAMARIS study is the largest randomized placebo-controlled trial of gene therapy in CLI, including >520 patients from 30 countries with CLI 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%, $P = 0.48$).[322] At present angiogenic gene and stem cell therapy are still being investigated and it is too early to give firm recommendations.

Recommendations for antiplatelet and anticoagulant therapy after revascularization

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy with aspirin is recommended in all patients with angioplasty for LEAD to reduce the risk of systemic vascular events.	I	C	
Dual antiplatelet therapy with aspirin and a thienopyridine for at least one month is recommended after infrainguinal bare-metal-stent implantation.	I	C	
Antiplatelet treatment with aspirin or a combination of aspirin and dipyridamole is recommended after infrainguinal bypass surgery.	I	A	308
Antithrombotic treatment with vitamin K antagonists may be considered after autogenous vein infrainguinal bypass.	IIb	B	309
Dual antiplatelet therapy combining aspirin and clopidogrel may be considered in the case of below-knee bypass with a prosthetic graft.	IIb	B	312

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LEAD = lower extremity artery disease.

4.5.4 Management of intermittent claudication

The management of intermittent claudication consists of optimal risk factor control in order to improve the vital prognosis (see Section 3.4) and the symptoms. Therapeutic options to relieve symptoms are non-invasive (mostly exercise therapy and drug therapy) or invasive (revascularization). An algorithm for the management of intermittent claudication is proposed in *Figure 3*. With the increasing use of endovascular therapy to improve walking distance, there is an apparent need to compare it with 'supervised exercise training'. In a study of 51 patients with intermittent

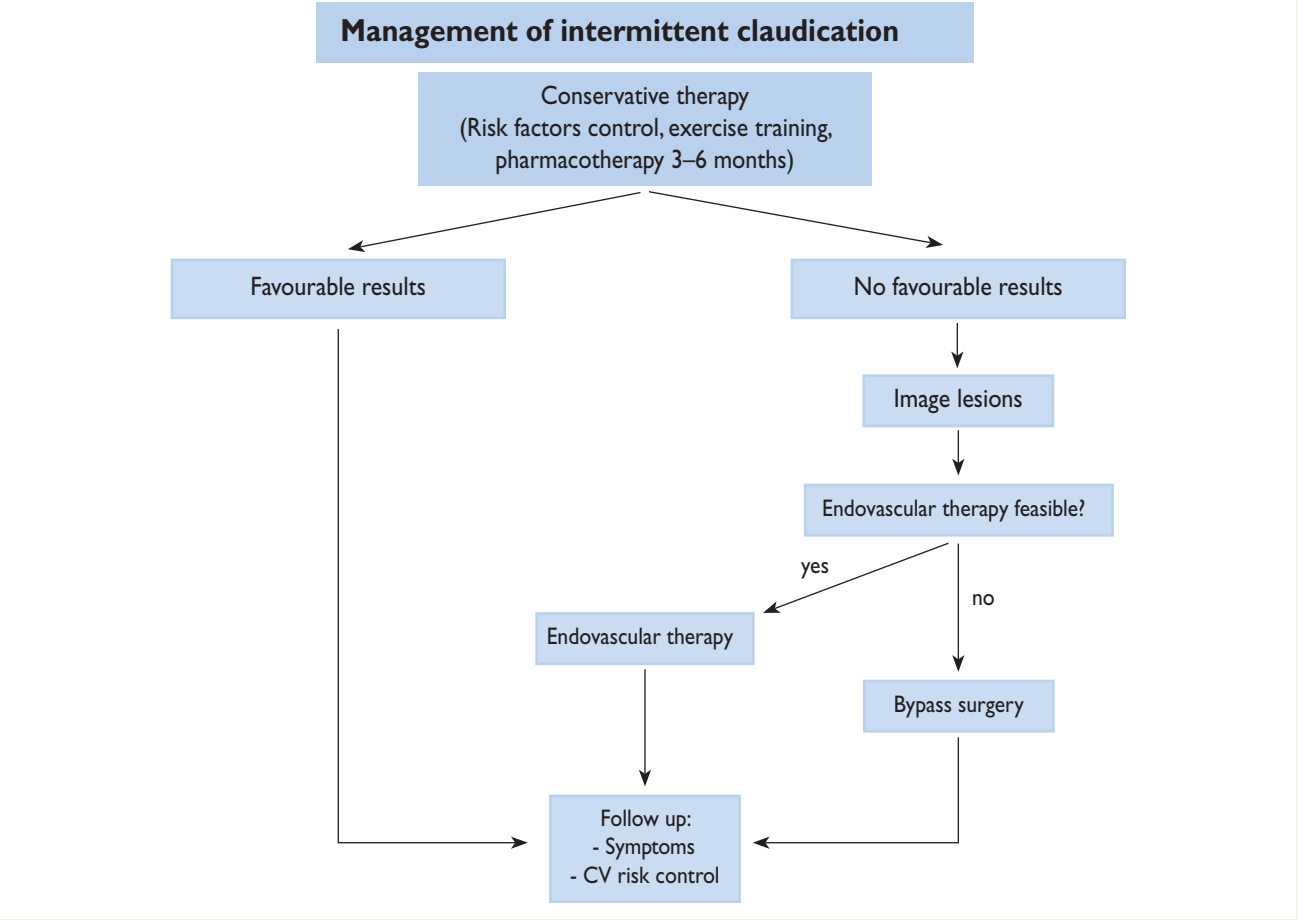

Figure 3 Algorithm for the management of intermittent claudication. CV = cardiovascular.

claudication, there was no significant difference in walking distance or quality of life 2 years after treatment.[323] More recently, a randomized controlled study initiated in 151 patients with intermittent claudication confirmed no difference in quality of life 12 months after intervention. However, this study showed a higher cost for the endovascular intervention group.[279] The adjuvant benefit of endovascular therapy to 'supervised exercise training' associated with best medical therapy has been assessed in patients with mild to moderate intermittent claudication.[324] Although no difference in quality of life was reported in this study, at 24 months the improvement in walking distance in the angioplasty group was 38% greater than that in the control group in the case of femoropopliteal lesions, and 78% in the case of aortoiliac lesions. The ongoing Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial will provide important insights into the indications of these therapeutic options in the management of patients with intermittent claudication.[325]

4.5.4.1 Medical treatment

In patients with intermittent claudication, the primary goal is to reduce the risk of CVD morbidity and mortality. This risk is present in all patients with LEAD, including those with mild, atypical, and even no symptoms.[2,326] Therefore, the management and control of risk factors is necessary in every patient with LEAD, to reach the goals of secondary prevention. Among them, smoking cessation also provides the most noticeable improvement in walking distance when combined with regular exercise training, especially when lesions are located below the femoral arteries.

Symptoms can be improved by exercise training (preferably supervised) and drug therapy. Walking tests on the treadmill should be performed regularly to assess the evolution objectively. Patients should also be advised to keep a logbook to follow their home training and the evolution of their walking distance and symptoms. The logbook can help the patient adhere to medical advice. In the case of typical claudication, drug therapy to improve walking distance can be initiated.

In many patients with mild to moderate symptoms, these first steps will lead to a significant improvement in claudication and in quality of life. In this case, training (and eventually drug therapy) should be continued and the patients should be evaluated at regular intervals. ABI should be controlled periodically, although substantial functional improvement may not necessarily follow significant ABI change. The risk factor profile should be checked regularly and treatment adapted accordingly.

4.5.4.2 Interventional therapy

In severe cases with disabling claudication, medical therapy including 'supervised exercise training' is often insufficient to improve

symptoms, and imaging of the lesions should be performed to define the exact location and characteristics of the lesions. This will help to decide whether interventional treatment is indicated and/or possible.

Evidence for any long-term benefit of revascularization over supervised exercise and best medical therapy is inconclusive, especially in patients with mild to moderate claudication.[324] However, the expansion of endovascular therapy has prompted many physicians to consider more liberal indications for percutaneous intervention. The indications for endovascular revascularization also depend on the level of daily disability related to claudication, when clinical and imaging features suggest a reasonable likelihood of symptomatic improvement and there is insufficient response to exercise or pharmacological therapy. Owing to the limited probability of improvement in symptoms with exercise therapy in the case of aortoiliac lesions, revascularization should be considered without initial conservative treatment. Surgery is limited to extensive lesions without the possibility for endovascular treatment. The management of patients with intermittent claudication is summarized in *Figure 3*.

Recommendations for patients with intermittent claudication

Recommendations	Class[a]	Level[b]	Ref[c]
Supervised exercise therapy is indicated.	I	A	255
Non-supervised exercise therapy is indicated when supervised exercise therapy is not feasible or available.	I	C	-
In patients with intermittent claudication with symptoms affecting daily life activity, drug therapy may be considered.	IIb	A	260-265, 269
In the case of intermittent claudication with poor improvement after conservative therapy, revascularization should be considered.	IIa	C	-
In patients with disabling intermittent claudication that impacts their activities of daily living, with culprit lesions located at the aorta/iliac arteries, revascularization (endovascular or surgical) should be considered as first-choice therapeutic option, along with the risk factor management.	IIa	C	-
Stem cell/gene therapy is not indicated.	III	C	-

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

4.5.5 Critical limb ischaemia (CLI)

4.5.5.1 Definition and clinical presentation

CLI is the most severe clinical manifestation of LEAD, defined as the presence of ischaemic rest pain, and ischaemic lesions or gangrene objectively attributable to arterial occlusive disease. It implies a chronic condition, to be distinguished from acute limb ischaemia (ALI) (see Section 4.5.6). An ankle pressure $<$50 mmHg is usually recommended as a diagnostic criterion because it includes most patients for whom rest pain or ischaemic lesions do not improve spontaneously without intervention. Since healing needs additional perfusion above that required for supporting intact skin, the ankle and toe pressure levels needed for healing are higher than the pressures found in ischaemic rest pain. For patients with ischaemic lesions or gangrene, CLI is suggested by an ankle pressure of $<$70 mmHg. Toe pressure $<$30 mmHg replaces the ankle pressure criteria in case of medial calcinosis.[6] The investigation of the microcirculation (i.e. transcutaneous oxygen pressure) is also helpful in some cases, not only for diagnostic and prognostic purpose, but also sometimes to determine the level of amputation (*Table 7*).

Primary amputation rates range from 5% to 20%, mainly in patients unsuitable for revascularization, who are neurologically impaired or non-ambulatory.[6,327] CLI is also a marker for generalized, severe atherosclerosis, with a three-fold risk excess of future myocardial infarction, stroke, and vascular death compared with patients with intermittent claudication.[6]

4.5.5.2 Therapeutic options

Comprehensive management requires multidisciplinary care to control atherosclerotic risk factors, provide revascularization as far as possible, optimize wound care, adapt shoe wear, treat infection, and initiate rehabilitation therapy (*Figure 4*).

The cornerstone of the management is arterial reconstruction and limb salvage.[328] Revascularization should be attempted without delay in all patients presenting CLI, whenever technically possible. The screening or assessment of coronary or cerebrovascular diseases should not delay the management of patients with CLI if clinically stable. Medical baseline therapy including at least platelet inhibitors and statins should be initiated.[329,330]

All patients with CLI should be referred to a vascular specialist early in the course of their disease, to plan revascularization. The most significant change in the treatment of CLI is the increasing tendency to shift from bypass surgery to less invasive endovascular procedures as an accepted first-choice revascularization strategy including tibial arteries, with bypass surgery reserved as a back-up option if necessary.[6] The main advantages of endovascular revascularization are the low complication rates, ranging from 0.5% to 4.0%, high technical success rates (even in long occlusions) approaching 90%, and an acceptable short-term clinical outcome. The BASIL trial demonstrated that rates of amputation-free survival are similar for surgery and balloon angioplasty for at least 2 years after the procedure.[302,331] The endovascular approach, including liberal use of stents above the knee level, is justified as long as low rates of complications are encountered and the surgical landing zone for the distal anastomosis of a potential secondary bypass remains unaffected by the interventional procedure. In patients with extensive foot gangrene or sepsis, open procedures possibly deliver more immediate pulsatile flow to the limb; however, the higher morbidity of surgery and the risk of graft

Table 7 Presentation of a patient with CLI

Assessment	Feature	Presentation to define CLI	Remarks
History	Duration of symptoms and clinical signs of CLI	>2 weeks	Needs morphine analgesics to be controlled
Symptoms	Rest pain	Toe, forefoot	Especially with elevation of limb (i.e. during night sleep). Calf pain/cramps do not constitute clinical presentation of CLI
	Ischaemic lesions	Periungual, toes, heel, over-bone prominences	
	Infection		Secondary complication: inflammation and infection
	Probe-to-bone test		Positive test identifies osteomyelitis with high specificity and sensitivity
Haemodynamics	Absolute ankle pressure	<50 mmHg or <70 mmHg	Plus rest pain Plus ischaemic lesion(s)
	Absolute great toe pressure	<30 mmHg	To be measured in the presence of medial calcinosis (incompressible or falsely elevated ankle pressure, ABI >1.40)
	Transcutaneous partial oxygen pressure	<30 mmHg	Estimation of wound healing, considerable variability

ABI = ankle–brachial index; CLI = critical limb ischaemia.

infection must be kept in mind.[332] Very distal venous bypass grafts to the pedal arteries are feasible and are characterized by an excellent patency rate of 88% at 4 years.[333,334]

There are large discrepancies between the reported results of arterial reconstruction,[335] mostly because of the inappropriate inclusion of patients with non-critical limbs in studies on CLI. Of note, there is a lower risk group consisting of patients with rest pain, and a higher risk group consisting of patients with true limb ischaemia with major tissue loss. At 1 year, 73% of patients in the low-risk group lost their leg or died if treated conservatively. For those patients fitting the high-risk criteria, 95% of those treated conservatively required amputation within a year. In comparison, for those high-risk patients who received reconstruction, only 25% required major amputation.[336] The primary efficacy endpoint of therapy is vascular reconstruction patency and limb salvage, whereas the patient-related main successful outcome includes maintenance of ambulation and independence. Despite acceptable patency and limb salvage rates, reinterventions within 3 months and readmission to the hospital within 6 months occur in over a half of patients. Independent predictors of failure include impaired ambulatory status at presentation (HR 6.44), presence of infrainguinal disease (HR 3.93), ESRD (HR 2.48), and presence of gangrene (OR 2.40).[337]

In patients with CLI unsuitable for revascularization, the only drugs with some positive results within randomized studies are prostanoids.[338,339] However, due to some divergent results in other studies, there is no conclusive evidence on effectiveness.[340] The safety and efficacy of various forms of therapeutic angiogenesis (gene or stem cell therapy) are promising, but robust evidence from RCTs is needed. The benefits of spinal cord stimulation are still debated, but a Cochrane review published in 2005 suggests some efficacy.[341]

The management of patients with CLI is summarized in *Figure 4*.

Recommendations for the management of critical limb ischaemia

Recommendations	Class[a]	Level[b]	Ref[c]
For limb salvage, revascularization is indicated whenever technically feasible.	I	A	302, 331, 336
When technically feasible, endovascular therapy may be considered as the first-line option.	IIb	B	302, 331
If revascularization is impossible, prostanoids may be considered.	IIb	B	338, 339

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

4.5.6 Acute limb ischaemia (ALI)

ALI is related to a sudden decrease in arterial perfusion in the limb. Thrombotic or embolic causes can be involved. Artery disease progression, cardiac embolization, aortic dissection or embolization, graft thrombosis, thrombosis of a popliteal aneurysm, entrapment or cyst, trauma, phlegmasia cerulea, ergotism, hypercoagulable states, and iatrogenic complications related to cardiac catheterization, endovascular procedures, intra-aortic balloon pump, extra-corporeal cardiac assistance, as well as

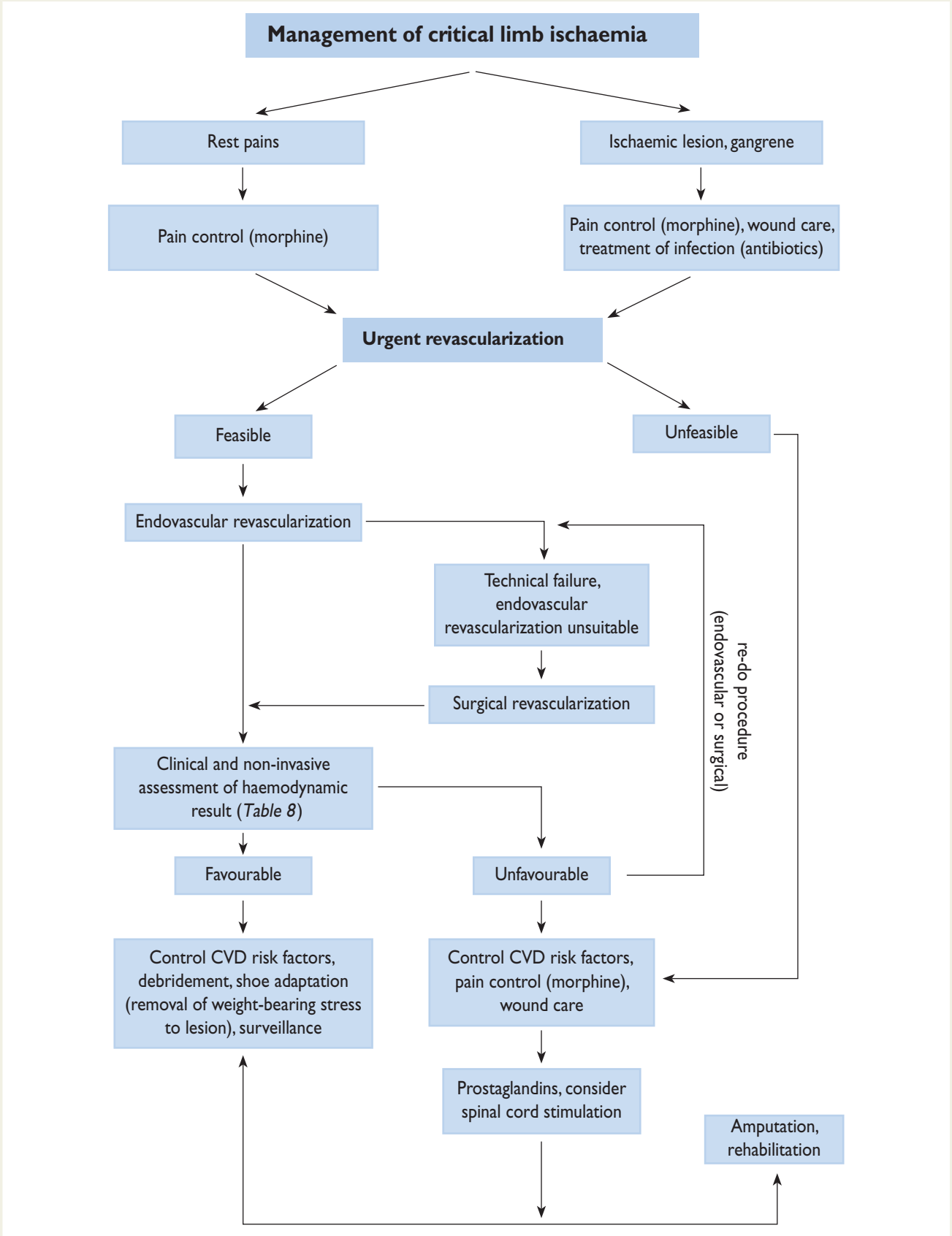

Figure 4 Management of critical limb ischaemia. CVD = cardiovascular disease.

vessel closure devices are the potential causes of ALI. The viability of the limb is mostly threatened in this context. Quick and proper management is needed for limb salvage.

Once the clinical diagnosis is established, treatment with unfractionated heparin should be given.[6,342] Analgesic treatment is often necessary. The level of emergency and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficiencies, and the thrombotic vs. embolic cause. The clinical categories are presented in *Table 8*.

An irreversible or unsalvageable extremity may require amputation before deterioration of the patient's clinical condition, although attempts are usually made to save the limb, or at least to limit the level of amputation. A viable limb mandates urgent imaging as well as the assessment of major co-morbidities. In the case of severely deteriorated renal function, detailed DUS imaging may replace angiography. In some cases, a clear cardiac embolization in potentially normal arteries can be treated by surgical embolectomy without previous angiographic imaging. Otherwise, given the emergency level of care, angiography can be performed with no previous vascular ultrasound to avoid therapeutic delays.

Different revascularization modalities can be applied (*Figure 5*). The options for quick revascularization consist of percutaneous catheter-directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thromboaspiration (with or without thrombolytic therapy), and surgical thrombectomy, bypass, and/or arterial repair. The therapeutic strategy will depend on the type of occlusion (thrombus or embolus) and its location, duration of ischaemia, co-morbidities, type of conduit (artery or graft), and therapy-related risks and outcomes. Owing to reduced morbidity and mortality compared with open surgery, endovascular therapy is the initial treatment of choice, especially in patients with severe co-morbidities, if the degree of severity allows time for revascularization, and pending local availability of an emergency interventional team. Treatment results are best with an ALI duration <14 days.[6] Intra-arterial thrombolysis is the classic endovascular technique for thrombus removal. Various techniques and different thrombolytic agents are currently used.[6] Intrathrombotic delivery of the thrombolytic agent is more effective than non-selective catheter-directed infusion. Different devices aiming at mechanical removal of the clot have been developed and are commonly used alone or in combination with thrombolysis, with the main advantage of decreasing delay to reperfusion. The modern concept of the combination of intra-arterial thrombolysis and catheter-based clot removal is associated with 6-month amputation rates <10%.[6] Systemic thrombolysis has no role in the treatment of patients with ALI.

Based on the results of old randomized trials,[343–345] there is no clear superiority of thrombolysis vs. surgery on 30-day mortality or limb salvage. Thrombolysis offers better results when applied within the first 14 days after the onset of symptoms. Thrombectomy devices have been proposed to treat ALI, but the benefits are not well documented. After thrombus removal, the pre-existing arterial lesion should be treated by endovascular methods or open surgery. Based on clinical presentation and availability of an emergency centre, surgical revascularization should be preferred when limb ischaemia is highly threatening and catheter-based treatment attempts may delay revascularization. Lower extremity four-compartment fasciotomies are sometimes performed to prevent a post-reperfusion compartment syndrome, especially in the setting of class IIb and III ischaemia with surgical revascularization. In cases of viable limb, open or endovascular revascularization may not be possible, especially in the case of absent distal arteries, even after primary *in situ* thrombolysis; the only option then is to stabilize the ischaemic status with medical therapy (anticoagulation, prostanoids).

Table 8 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 Amputation. Permanent nerve damage inevitable

Adapted from Rutherford *et al.*, with permission.[328]

Recommendations for acute limb ischaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Urgent revascularization is indicated for ALI with threatened viability (stage II).	I	A	6, 342
In the case of urgent endovascular therapy, catheter-based thrombolysis in combination with mechanical clot removal is indicated to decrease the time to reperfusion.	I	B	6, 304
Surgery is indicated in ALI patients with motor or severe sensory deficit (stage IIB).	I	B	304
In all patients with ALI, heparin treatment should be instituted as soon as possible.	I	C	-
Endovascular therapy should be considered for ALI patients with symptom onset <14 days without motor deficit (stage IIA).	IIa	A	6, 304

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ALI = acute limb ischaemia.

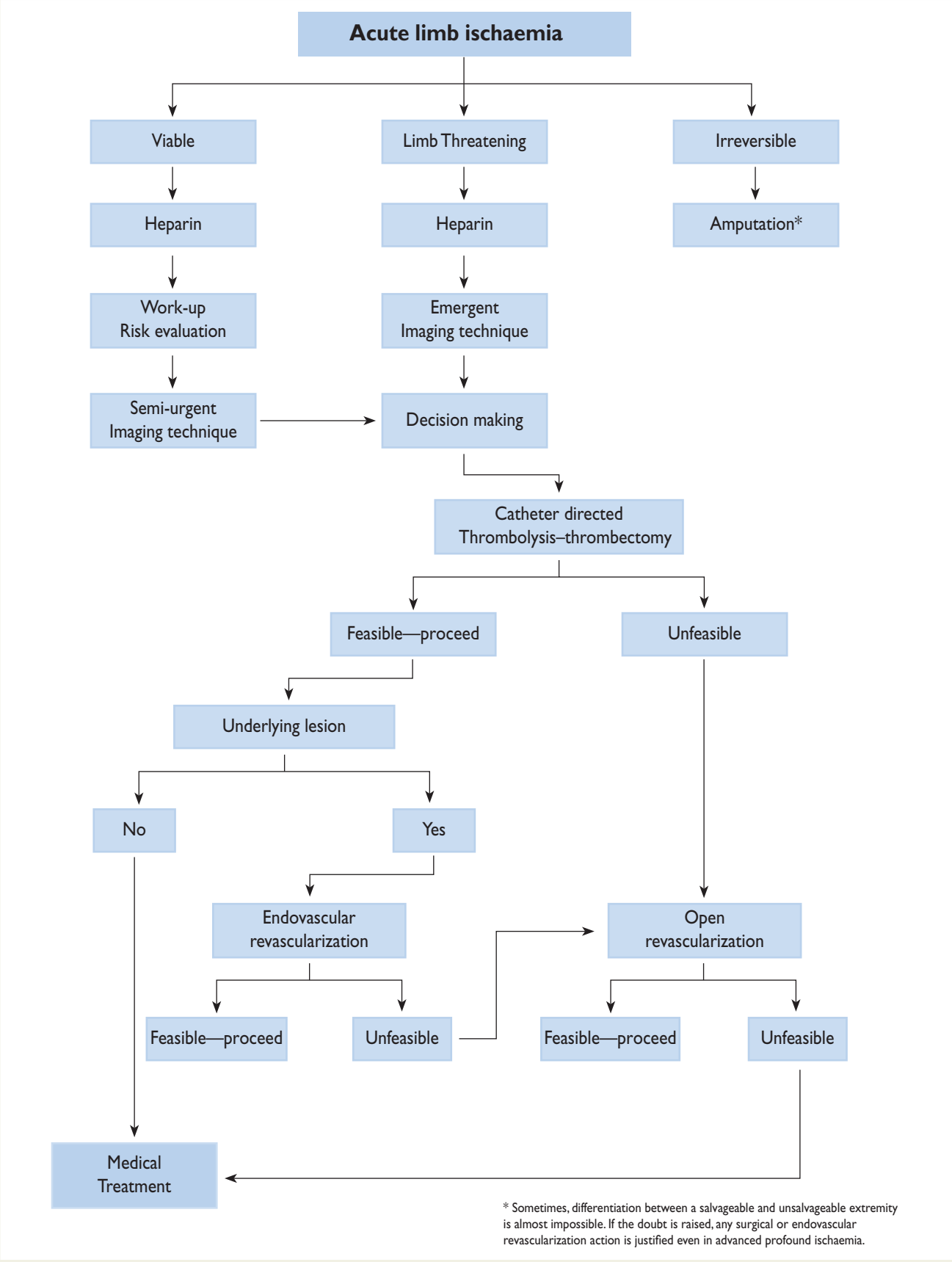

Figure 5 Decision-making algorithm in acute limb ischaemia.

4.6 Multisite artery disease

4.6.1 Definition

Multisite artery disease is defined as the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories. Although patients with multisite artery disease are encountered regularly in clinical practice, no randomized trials have been designed to compare different treatment strategies, and the available data originate only from subgroup analyses or consecutive patient series.

The recent ESC/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization offer for the first time specific recommendations for the management of patients suffering from CAD associated with carotid artery disease, renal artery disease, or LEAD.[346]

When dealing with a patient with multisite artery disease, one must focus attention not only on lesion sites and inherent technical difficulties related to specific treatment options, but also on the overall clinical status of the patient, taking into account the presence of cardiovascular risk factors and co-morbidities. Consequently, the treatment strategy should be chosen individually, based more on clinical rather than technical issues. A multidisciplinary team approach is required.

The present guidelines address the impact of multisite artery disease on prognosis, as well as the screening for and management of multisite artery disease, taking into account the combinations most relevant for clinical practice.

4.6.2 Impact of multisite artery disease on prognosis

In patients with atherosclerotic disease in one vascular site, the presence of co-existing disease in a different vascular bed is associated with a higher risk of recurrent symptoms and complications in the first site. In fact, among 828 patients enrolled in the Framingham Study who had a myocardial infarction, those with a history of stroke or symptomatic LEAD had a two-fold increase in the risk of recurrent myocardial infarction.[347] The REACH Registry enrolled 68 236 patients with either established atherosclerotic arterial disease (CAD, LEAD, cerebrovascular disease; $n = 55\,814$) or three or more risk factors for atherothrombosis ($n = 12\,422$).[348] The incidence of cardiovascular death, myocardial infarction, stroke, or hospitalization for atherothrombotic events at 1 year increased with the number of symptomatic sites, ranging from 5.3% for patients with risk factors only to 12.6, 21.1, and 26.3% for patients with one, two, and three symptomatic sites, respectively ($P < 0.001$ for trend).[1] At 3 years, the rates of myocardial infarction/stroke/vascular death/rehospitalization were 25.5% for patients with symptomatic vascular disease in one vascular site vs. 40.5% for patients symptomatic in multiple vascular sites ($P < 0.001$).[348] In a survey on 7783 outpatients who had experienced an atherothrombotic event, the rate of a first recurrent event at 1 year was almost doubled for patients with multisite disease vs. single disease location.[349]

4.6.3 Screening for and management of multisite artery disease

4.6.3.1 Peripheral artery disease in patients presenting with coronary artery disease

Screening for and management of carotid artery disease, renal artery disease, and LEAD in patients presenting with CAD are addressed below.

4.6.3.1.1 Carotid artery disease in patients presenting with coronary artery disease

4.6.3.1.1.1 Carotid artery stenosis in patients not scheduled for coronary artery bypass grafting

In patients with CAD, the prevalence of severe carotid stenosis increases concurrently with the severity of CAD and is a known predictor of worse cardiovascular prognosis. Furthermore, a complex morphology of carotid plaque, such as echolucent plaque, is associated with heterogeneous coronary plaques and clinically unstable CAD. In a general review of cohorts with consecutive CAD patients enrolled without exclusion criteria,[350] an average prevalence of >50, >60, >70, and >80% carotid stenosis was reported in 14.5, 8.7, 5.0, and 4.5% of patients, respectively. Thus, although the association between carotid artery stenosis and CAD is evident, the prevalence of significant carotid stenosis over the entire cohort is relatively low. Therefore, systematic carotid duplex screening is of limited value.

4.6.3.1.1.2 Carotid artery stenosis in patients scheduled for coronary artery bypass grafting

The question of prophylactic carotid revascularization in patients needing coronary artery bypass grafting (CABG) who also have a severe carotid artery stenosis arises from the higher risk of stroke in this population (*Table 9*).

Table 9 Risk of stroke related to CABG

Patient category	Stroke risk (%)
No carotid stenosis	1.4–3.8
Unilateral >50% carotid stenosis	3.0
Bilateral >50% carotid stenosis	5.0
Carotid occlusion	7.0
Previous stroke or TIA	8.5

CABG = coronary artery bypass grafting; TIA = transient ischaemic attack.
Modified from Blacker *et al.*[351]

4.6.3.1.1.2.1 Screening for carotid stenosis in patients undergoing coronary artery bypass grafting

The prevalence of carotid stenosis in patients undergoing CABG varies in the literature, because of patient specificities, selection bias, DUS diagnostic criteria, and the extent of stenosis considered. Several studies attempted to identify clinical risk factors for the presence of significant carotid artery stenosis among patients undergoing planned CABG.[352] The most frequent risk factors are increasing age, history of cerebrovascular disease, or the co-existence of LEAD. Other risk factors mostly reported are female sex, multivessel CAD, and smoking. These risk factors are taken into consideration in the ESC/EACTS guidelines on myocardial revascularization.[346] The criteria for screening carotid artery disease in patients undergoing CABG differ slightly from their expert-based recommendation, based on data from a study which assessed the efficacy of a clinical score to propose carotid DUS scanning in patients undergoing CABG.[352] The authors

identified four independent risk factors for carotid stenosis in candidates for CABG: age >70 years, neck bruit, history of cerebrovascular disease, and presence of clinical or subclinical LEAD. In a prospective assessment, they found that performing DUS scanning only in patients with at least one of these risk factors detected 100% of those with a carotid stenosis >70%, and decreased the number of useless scans by 40%. This approach does, however, need validation in a multicentre study.

Recommendations for screening for carotid artery stenosis in patients undergoing CABG

Recommendations	Class[a]	Level[b]	Ref[c]
In patients undergoing CABG, DUS scanning is recommended in patients with a history of cerebrovascular disease, carotid bruit, age ≥70 years, multivessel CAD, or LEAD.	I	B	352
Screening for carotid stenosis is not indicated in patients with unstable CAD requiring emergent CABG with no recent stroke/TIA.	III	B	352

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; DUS = duplex ultrasonography; LEAD = lower extremity artery disease; TIA = transient ischaemic attack.

4.6.3.1.1.2.2 Management of carotid artery disease in patients undergoing coronary artery bypass grafting

It is unclear whether the benefits expected from CEA in the case of asymptomatic carotid artery stenosis are similar in those with concomitant CAD, and no specific randomized trial has been conducted in CAD patients with asymptomatic carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study (ACAS) trial[53] found no interaction between perioperative outcomes after CEA and a history of myocardial infarction. A subgroup analysis of the ACST[54] observed long-term benefits with carotid surgery similar to those for the overall sample in the subset of 830 patients with CAD. However, the occurrence of stroke after CABG is multifactorial. In patients with carotid stenosis who undergo CABG without intervention on the carotid arteries, only 40% of post-operative strokes are ipsilateral to the carotid lesion. Besides, only a quarter of the strokes in patients with combined carotid and coronary surgery are exclusively ipsilateral to the stenotic carotid artery.[353] In fact, the most common single cause of stroke after CABG is embolization with atherothrombotic debris from the aortic arch, while atrial fibrillation, low cardiac output, and hypercoagulation states resulting from tissue injury also contribute to the risk of stroke. Thus, the presence of carotid stenosis appears more as a marker of high risk of stroke after CABG rather than the causal factor. Only those patients who have symptomatic carotid artery disease and those with asymptomatic bilateral carotid artery stenosis or unilateral carotid occlusion are definitely at higher risk of stroke during cardiac surgery, compared with patients without carotid artery stenosis.[351,354]

Owing to the multitude of causes of stroke during CABG, prophylactic carotid revascularization before coronary surgery offers a partial solution for stroke risk reduction, at the expense of the risk related to the carotid revascularization itself, including the risk of myocardial infarction if carotid surgery is considered before coronary surgery in patients who often have severe CAD. Irrespective of whether the patient will undergo prophylactic carotid revascularization, the risk of stroke in these patients is overall higher than in the absence of CAD. The 30-day rate of stroke/death after combined (either synchronous or staged) CABG + CEA[353,355–363] or CABG + CAS[363–368] is >9% in most reports (ranging from 4.0% to 19.2%). On the other hand, a recent study reported a 5-year rate of death/stroke or myocardial infarction as low as 8% after isolated CABG in low-risk patients with asymptomatic carotid stenosis >70%.[369] Thus, in the absence of clear proof that CEA or CAS is beneficial in patients undergoing CABG, all patients should be assessed on an individual basis, by a multidisciplinary team including a neurologist. Based on trials in patients with symptomatic carotid disease, it is reasonable to propose carotid revascularization (see Section 4.1.1.3.2) in patients scheduled for non-emergency CABG with recent (<6 months) TIA/stroke and symptomatic carotid stenosis, although those trials do not address the specific issue of patients undergoing coronary bypass.

Management of asymptomatic carotid stenosis should be delayed in cases of acute coronary events, because of increased rates of unstable carotid plaques concomitant to unstable CAD, with high perioperative risk of stroke in the case of carotid intervention.[350] Selected patients with high-grade, asymptomatic carotid stenosis, particularly in the case of bilateral stenosis, may benefit from prophylactic carotid revascularization. The preoperative evaluation of such patients should include a detailed neurological examination, history aimed at unreported TIA symptoms, and a brain CT or MRI study to assess the presence of 'silent' ipsilateral infarcts.

Choice of carotid revascularization method in patients scheduled for coronary artery bypass grafting

Timaran *et al.* compared the in-hospital outcome of patients who underwent CAS before CABG with those who were treated by combined CEA and CABG between 2000 and 2004.[363] During this 5-year period, 27 084 concurrent carotid revascularizations and CABGs were done. Of these, 96.7% underwent CEA–CABG, whereas only 3.3% (887 patients) had CAS–CABG. Patients undergoing CAS–CABG had significantly lower rates of post-operative stroke (2.4% vs. 3.9%; $P < 0.001$) and tended to have lower rates of combined stroke and death (6.9% vs. 8.6%; $P = 0.1$) compared with patients undergoing CEA–CABG, although in-hospital death rates were similar (5.2% vs. 5.4%, respectively). After risk stratification, CEA–CABG patients had a 65% increased risk of post-operative stroke compared with patients undergoing CAS–CABG (OR 1.65, 95% CI 1.1–2.6; $P = 0.02$). However, no differences in the risk of combined

stroke and death were observed (OR 1.26, 95% CI 0.9–1.6; P = not significant).

The most recent meta-analysis on the management of concomitant coronary and carotid artery disease was published by Naylor *et al.*, in 2009.[370] The results of different strategies (timing, revascularization modalities) are presented in *Table 10*. Of note, these results are stratified neither according to the coronary and neurological symptoms nor according to the severity of coronary and carotid artery disease.

An overview of these results indicates no strong benefit of one strategy over another, although some need further studies to narrow their confidence intervals. Interestingly, the presence of carotid artery stenosis may lead to reconsideration of the technique of surgical coronary revascularization. Indeed, the co-existence of severe carotid disease in patients with CAD indicates widespread atherosclerosis with high risk for the presence of atherothrombotic lesions of the aortic arch, a risk factor for stroke. The avoidance of cross-clamping of the aorta during off-pump surgery may explain the lower rates of perioperative stroke when combined with CEA, although the number of patients subject to this strategy (n = 324) is too low to draw firm conclusions. Similarly, the higher risk of lesions of the aortic arch, a risk factor for stroke during catheterization of the carotid arteries, may explain why—although apparently less invasive—CAS does not present superior results to CEA in this situation. As expected, the staged approaches provide different myocardial and neurological protection, depending on the timing of the two interventions. This is probably the key issue when the staged approach is considered, and the neurological or myocardial risk may be prioritized according to the patient's clinical presentation as well as the level of severity of carotid and CADs.

Of note, in both the SAPPHIRE and CREST trials of CEA vs. CAS, the 30-day rate of myocardial infarction after carotid revascularization was significantly lower with CAS vs. CEA.[79,98] Moreover, in a recent meta-analysis evaluating 2973 patients enrolled in randomized CAS vs. CEA trials, Wiesmann *et al.* reported a myocardial infarction rate of 2.3% with CEA vs. 0.9% with CAS (P = 0.03; OR 0.37).[373] However, although CAS appears to be associated with a lower risk of periprocedural myocardial infarction compared with CEA, the overall data including death and stroke reported in *Table 10* do not clearly favour one revascularization strategy over another. If CAS is performed before elective CABG, the need for double antiplatelet therapy usually delays cardiac surgery for ~5 weeks. Such deferral of CABG may expose the patient to the risk of myocardial infarction between CAS and CABG procedures (0–1.9%), and presents a major drawback of this treatment strategy.[364,366,368] Recently, a few studies described the results of synchronous CAS + CABG, with CAS performed immediately before cardiac surgery.[367,374] Such a strategy yielded a more favourable 4.0% 30-day rate of death or stroke.[374] However, the bleeding risk during CABG, a factor predictive of long-term mortality, has not been considered extensively when comparing CAS with CEA concomitant (or before) to CABG.

More details on the management of carotid stenosis in patients with CAD are given in Appendix 5.

Table 10 Meta-analysis of cumulative results of revascularization strategies, with an indication for CABG and concomitant carotid revascularization

Strategy	Operative mortality (%)	Death ± any stroke/ TIA (%)	Death ± any stroke/ TIA ± MI (%)
Synchronous CEA+CABG			
CEA prebypass (n = 5386)	4.5 (3.9–5.2)	8.2 (7.1–9.3)	11.5 (10.1–13.1)
CEA performed on bypass (n = 844)	4.7 (3.1–6.4)	8.1 (5.8–10.3)	9.5 (5.9–13.1)
CEA+off-pump CABG (n = 324)	1.5 (0.3–2.8)	2.2 (0.7–3.7)	3.6 (1.6–5.5)
Staged CEA–CABG			
CEA then CABG (n = 917)	3.9 (1.1–6.7)	6.1 (2.9–9.3)	10.2 (7.4–13.1)
CABG then CEA (n = 302)	2.0 (0.0–6.1)	7.3 (1.7–12.9)	5.0 (0.0–10.6)
Staged CAS–CABG			
Staged CAS+CABG (n = 760)	5.5 (3.4–7.6)	9.1 (6.2–12.0)	9.4 (7.0–11.8)

CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; MI = myocardial infarction; TIA = transient ischaemic attack.
Two other recent meta-analyses on CAS + CABG[371,372] provided similar results.
Adapted from Naylor *et al.*[370]

Recommendations for the management of carotid stenosis in patients undergoing CABG

Recommendations	Class[a]	Level[b]
The indication for carotid revascularization should be individualized after discussion by a multidisciplinary team including a neurologist.	I	C
If carotid revascularization is indicated, the timing of the carotid and coronary interventions should be decided according to the clinical presentation, level of emergency, and severity of carotid disease and CAD.	I	C

[a]Class of recommendation.
[b]Level of evidence.
CABG = coronary artery bypass grafting; CAD = coronary artery disease.

Recommendations for carotid artery revascularization in patients undergoing CABG

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, with a <6-month history of TIA/stroke and corresponding carotid artery disease		
Carotid revascularization is recommended in 70–99% carotid stenosis.	I	C
Carotid revascularization may be considered in 50–69% carotid stenosis, depending on patient-specific factors and clinical presentation.	IIb	C
Carotid revascularization is not recommended if the carotid stenosis is <50%.	III	C
In patients undergoing CABG with no history of TIA/ stroke within 6 months		
Carotid revascularization may be considered in men with bilateral 70–99% carotid stenosis or 70–99% carotid stenosis and a contralateral occlusion.	IIb	C
Carotid revascularization may be considered in men with 70–99% carotid stenosis and ipsilateral previous silent cerebral infarction.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
CABG = coronary artery bypass grafting; TIA = transient ischaemic attack.

4.6.3.1.2 Renal artery disease in patients presenting with coronary artery disease

In patients with CAD, RAS >50% is found in 10–20% of cases, mostly using renal angiography concomitant to cardiac catheterization, with almost a quarter being bilateral.[13,375–380] These studies are concordant in reporting even higher rates in patients with triple-vessel CAD, as well as in those with hypertension or renal failure, although the use of contrast agents should be limited in patients with renal failure. Other situations where renal artery disease should be considered are recurrent episodes of heart failure and/or refractory angina, pulmonary oedema, and renal function deterioration after the introduction of ACE inhibitors or angiotensin receptor antagonists.

In CAD patients with a suspicion of renal artery disease, as for any other patient, DUS should be used as the first-line non-invasive imaging test (see Section 4.4.3),[171,172] even in the case of planned cardiac catheterization, in order to limit the use of ionized contrast agents and irradiation, and for cost issues. While CTA or MRA are usual second-line imaging tests, in the case of planned coronary angiography with a suspicion of renal artery disease after DUS (or poor quality imaging) in the absence of renal failure, renal angiography during the same procedure can be considered.

Although the co-existence of significant renal artery disease in patients with CAD is not negligible, a systematic screening for RAS does not appear reasonable because the management of these patients is barely affected. The use of systematic renal angioplasty has been challenged recently by the results of the ASTRAL trial[191] (see Section 4.4.5.2), and there are no specific data for patients who also suffer from CAD. Similarly, the presence of renal artery disease does not affect the management of patients with CAD, with the exception of renal failure after the use of ACE inhibitors or angiotensin II receptor antagonists. Yet, the indications for screening renal artery disease in patients with CAD are similar to those for any patient.

Screening for RAS in patients planned for coronary angiography

Recommendations	Class[a]	Level[b]
DUS should be considered first in the case of clinical suspicion of renal artery disease in patients planned for coronary angiography.	IIa	C
Renal angiography concomitant to cardiac catheterization may only be considered in the case of persisting suspicion after DUS.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
DUS = duplex ultrasound; RAS, renal artery stenosis.

4.6.3.1.3 Lower extremity artery disease in patients presenting with coronary artery disease

The co-existence of LEAD in CAD patients is associated with worse prognosis. In the REACH registry,[1] the 1-year rate of cardiovascular death/myocardial infarction/stroke/hospitalization for other atherothrombotic event(s) was 13.0% for patients with CAD alone, and 23.1% for patients with both conditions. LEAD is often under-recognized in CAD, as patients are largely asymptomatic; in patients with limiting angina, failure to recognize the condition may be because these patients exercise to a degree insufficient to evoke intermittent claudication. Therefore, a systematic approach, with ABI measurement, could lead to better identification of LEAD in patients with CAD.

In a cross-sectional study performed in primary care, ABI detected LEAD in 26.6% of 1340 patients with CAD and no other known location of atherothrombotic disease.[381] The prevalence of LEAD was increased significantly in patients with diabetes mellitus. Similar findings were reported in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study.[382]

In different studies, the prevalence of ABI <0.90 can be estimated at 25–40% in patients hospitalized for CAD,[383–385] while only <10% would be detected by clinical examination.[386–388] Among patients with CAD, older age, intermittent claudication or atypical leg pain, smoking, diabetes, uncontrolled arterial hypertension, and elevated LDL cholesterol can be identified as factors suggestive of LEAD.

At any stage of CAD, the presence of LEAD is associated with a more severe and poorer prognosis. In 234 consecutive patients who underwent coronary angiography, Brevetti *et al.* found higher rates of multivessel CAD in patients with LEAD (60% vs. 20%, P <0.01), which were associated with higher concentrations of C-reactive protein.[389] In the Global Registry of Acute Coronary Events (GRACE), the in-hospital mortality of patients with acute

coronary syndromes (ACS) as well as the presence of cardiogenic shock was significantly higher in subjects with LEAD. At 6 months the rate of major cardiovascular events was 14.6% in patients with LEAD vs. 7.2% in those without.[390] In the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, the mortality rates in ACS were 18.8% and 13.1% in patients with vs. without LEAD, respectively.[391]

The presence of LEAD is associated with a worse prognosis not only in patients with ACS but also in those with chronic stable angina as in the Coronary Artery Surgery Study (CASS), where the mortality rate was 25% higher in patients with PAD as compared with non-PAD patients, during a follow up of >10 years.[386]

After percutaneous coronary intervention (PCI), patients with LEAD have a worse outcome. In a meta-analysis of eight studies, the HRs for 30-day, 6-month, and 1-year mortality were, respectively, 1.67, 1.76, and 1.46 (1.08–1.96) in patients with concomitant LEAD.[392] Similarly, the prognosis of CAD patients after CABG was poorer in those with clinical or subclinical LEAD.[393,394]

In summary, patients with LEAD associated with CAD are at twice the level of risk as those presenting with CAD alone. However, whether the management of CAD patients should differ in the case of concurrent LEAD is not obvious, because there are no specific trials related to this situation. To date, the co-existence of LEAD and CAD should only lead to closer attention, with a strict control of risk factors and the use of preventive treatments. Lowering the target for LDL cholesterol from 2.6 to 1.8 mmol/L should be considered. Regarding the use of antiplatelet therapy in stable CAD, given the greater benefits of clopidogrel vs. aspirin found in those with LEAD, clopidogrel rather than aspirin may be considered for the long-term treatment.[38] In a post-hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance (CHARISMA) study, there was a benefit of the combination of aspirin and clopidogrel in patients with LEAD.[40] Because of the post-hoc nature of this analysis, the benefit of such an approach needs confirmation.

In the case of severe LEAD in CAD patients undergoing CABG, the use of venous bypass should be limited as far as possible, because this may lead to healing issues in the lower limbs, and because the venous material should be spared for potential *in situ* venous bypasses for the leg.

4.6.3.2 Screening for and management of coronary artery disease in patients with peripheral artery disease

Management of CAD in patients presenting with carotid disease and LEAD is addressed below.

4.6.3.2.1 Screening for and management of coronary artery disease in patients presenting with carotid artery disease

Few studies have systematically used coronary angiography to define the frequency of asymptomatic CAD in patients with carotid disease. In a landmark study performed over two decades ago, haemodynamically relevant CAD was demonstrated in 40% of 200 patients while only 6% had absence of disease at angiography.[398] In a recent prospective investigation in 390 patients undergoing elective CAS, systematic coronary angiography showed the presence of one-, two-, and three-vessel disease and left main stenoses in 17, 15, 22, and 7% of patients, respectively. Only 39% of the patients with significant coronary artery stenoses had cardiac symptoms.[399]

Recommendations for management of patients with LEAD and concomitant CAD

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with unstable CAD, vascular surgery should be postponed and CAD treated first, except when vascular surgery cannot be delayed due to a life- or limb-threatening condition.	I	C	-
The choice between CABG and PCI should be individualized, taking into consideration the clinical presentation of CAD and LEAD, and comorbidities.	I	C	-
In the case of LEAD in patients with stable CAD, clopidogrel should be considered as an alternative to aspirin for the long-term antiplatelet therapy.	IIa	B	38
In patients with CAD, screening for LEAD by ABI measurement should be considered.	IIa	C	-
Prophylactic myocardial revascularization before high-risk vascular surgery may be considered in stable patients if they have persistent signs of extensive ischaemia or are at high cardiac risk.	IIb	B	47, 395-397

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ABI = ankle–brachial index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LEAD = lower extremity artery disease; PCI = percutaneous coronary intervention.

The only study involving the management of patients undergoing CEA randomized 426 patients with no history of coronary disease and with normal cardiac ultrasound and electrocardiography into two groups, namely systematic coronary angiography and (if needed) revascularization, or no coronary angiography.[400] No post-operative myocardial ischaemic events were observed among patients undergoing coronary angiography, while nine events were observed in the no-angiography group ($P = 0.01$).

In conclusion, patients with carotid stenosis have a high prevalence of CAD—even in the absence of cardiac symptoms—and are at risk of cardiovascular events. While CEA is considered as an intermediate-risk procedure, the cardiac risk associated with carotid revascularization may be lower with stenting than with endarterectomy.[79,98] With respect to screening with coronary angiography and, if needed, coronary revascularization, before vascular surgery, the results of the four available randomized trials[395–397,400]—none of them large-scale—have led to conflicting results, and no firm recommendation can be made at this point for patients undergoing carotid revascularization.

4.6.3.2.2 Screening for and management of coronary artery disease in patients presenting with lower extremity artery disease

4.6.3.2.2.1 Patients with lower extremity artery disease undergoing surgery

This topic has been addressed extensively in the ESC guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.[47] Briefly, the goals of pre-operative screening are to ensure that the perioperative period is free of adverse cardiac events and to identify PAD patients with a poor long-term prognosis in whom treatment and risk factor modification may improve their outcome.

In LEAD patients, screening offers the opportunity to initiate timely medication for secondary prevention of atherosclerotic disease; this improves both direct post-operative outcome and long-term survival. Factors that need to be considered in LEAD patients for screening, include:

(i) Emergency surgery: chronic cardiovascular medication should be continued during the procedure, and patients should be referred for surgery without delay.
(ii)Unstable cardiac conditions: deferral of the procedure and treatment of the underlying cardiovascular disease is recommended.
(iii) Whether cardiovascular medications for secondary prevention of atherosclerosis (β-blockers, statins, ACE inhibitors, aspirin) are needed.
(iv) Whether work-up for the presence and extent of CAD is warranted.
(v) How the results of the work-up will alter perioperative management.

The first step is to identify unstable cardiac conditions (ACS, arrhythmias, decompensated heart failure, severe valvular disease) that require immediate treatment. Patients with LEAD have a high risk for CAD: in a study of >1000 patients, only 8% had a normal angiogram.[401] Therefore, secondary prevention for atherosclerotic complications is recommended before high-risk surgery, including a low-dose, titrated β-blocker, statins, and aspirin. In patients with reduced left ventricular function, ACE inhibitors are recommended, according to the ESC guidelines.[47] Overall, the second step is to assess the level of surgical risk. However, peripheral vascular surgery is classified as high-risk surgery. The third step is to assess functional capacity. If the patient can achieve four or more metabolic equivalents without symptoms, then it is acceptable to proceed with surgery. Patients who have a functional capacity of less than four metabolic equivalents are at higher risk. A metabolic equivalent of less than four is equivalent to the inability to climb two flights of stairs or to run a short distance. Obviously, for patients with lower extremity arterial insufficiency, this might not always be possible to assess. In patients with a low functional capacity, the cardiac risk of the procedure should be considered (*Table 11*).

Three randomized studies including patients with LEAD addressed the role of prophylactic coronary revascularization in stable patients scheduled for vascular surgery. The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first to compare optimal medical therapy with revascularization (by either CABG or PCI) in patients with stable ischaemic heart disease prior to major vascular surgery.[396] Of 5859 patients screened, 510 were randomized. Patients were included on the basis of a combination of cardiovascular risk factors and the detection of ischaemia on non-invasive testing. There was no difference in the primary endpoint of mortality at 2.7 years after randomization: 22% in the revascularization group vs. 23% in the no-intervention group. In addition, no difference in the rate of perioperative myocardial infarction was detected (12% vs. 14%, respectively). As a limitation, only a small proportion (8.9%) of screened patients were randomized, and patients with left main coronary disease were excluded by design from randomization.

DECREASE-V was a pilot study that applied a precise screening methodology and a more contemporary perioperative medical management.[397] Patients at high risk for surgery underwent dobutamine stress echocardiography or nuclear stress testing, and in the presence of extensive ischaemia were randomized to either revascularization or no revascularization. β-Blocker therapy was initiated and aspirin was continued during surgery in all patients. All patients ($n = 101$) had had a previous myocardial infarction, 51% had ongoing angina, and 47% had congestive heart failure. Three-vessel or left main disease was present in 75% of cases and 43% had an ejection fraction of ≤35%. Both groups showed a very high 30-day death or myocardial infarction rate at 30 days (43% for revascularization vs. 33% for no revascularization; $P =$ not significant) and at 1 year (44% vs. 43%, respectively). The fact that all patients who were randomly assigned to the revascularization arm were compelled to undergo revascularization may have increased the risk associated with revascularization in patients with anatomy unsuitable for PCI and at high risk for CABG.[397]

A third study involved 208 consecutive patients scheduled for elective surgical treatment of major vascular disease who were at moderate to high cardiac risk for surgery. The patients were randomized to mandatory pre-operative coronary angiography and revascularization, if needed, or a selective strategy arm in which angiography was performed only if indicated based on the results

Table 11 Cardiac risk stratification for non-cardiac surgical procedures

High (reported cardiac risk often more than 5%)
Aortic and other major vascular surgery
Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1%–5%)
Intraperitoneal and intrathoracic surgery
Carotid endarterectomy
Head and neck surgery
Orthopaedic surgery
Prostate surgery
Low (reported cardiac risk generally less than 1%)
Endoscopic procedures
Superficial procedures
Cataract surgery
Breast surgery
Ambulatory surgery

From Poldermans *et al.*, with permission.[47]

of non-invasive tests.[395] The revascularization rates were 58% and 40% ($P = 0.01$), respectively. The in-hospital major adverse cardiovascular event rate did not differ between the two groups, but at a mean follow-up of 58 months patients subject to the systematic strategy of pre-operative coronary angiography had a statistically significant benefit in terms of freedom from major cardiovascular events as well as of survival.

LEAD patients scheduled for intermediate-risk surgery can be referred for surgery without additional testing for CAD. In patients scheduled for high-risk surgery, the number of cardiac risk factors should be assessed: angina pectoris, myocardial infarction, stroke or TIA, renal dysfunction (creatinine >177 μmol/L; 2 mg/dL), heart failure, and diabetes mellitus. In patients with three or more risk factors, additional cardiac testing for the presence and extent of CAD is recommended, if this will change management. In selected cases one might also consider additional cardiac testing as a means of patient counselling. If cardiac stress testing shows no or only mild stress-inducible myocardial ischaemia, additional invasive testing is not recommended. Again, all patients should be prescribed statins, low-dose titration of β-blockers before surgery, and aspirin; and those with systolic dysfunction should have ACE inhibitors. Patients with extensive stress-inducible myocardial ischaemia present a very difficult group. Optimal medical treatment including β-blockers and statins will not provide sufficient cardioprotection. However, pre-operative prophylactic coronary revascularization is not generally associated with an improved perioperative outcome in this patient population. An individualized approach should be carried out for these patients, taking into account the very high cardiac risk of the planned surgical procedure and the possible harms of not performing surgery (i.e. risk of rupture in patients with abdominal aortic aneurysm). If it is decided to perform pre-operative revascularization after multidisciplinary consultation, it must be realized that the vascular surgical procedure should be postponed for ≥14 days for balloon angioplasty, for 3 months for bare-metal coronary stent placement, and for 12 months for drug-eluting coronary stent placement.[47]

In summary, perioperative cardiovascular complications are common in LEAD patients and result in significant morbidity following non-cardiac surgery. All patients require pre-operative screening to identify and minimize immediate and future risk, with a careful focus on known CAD or risks for CAD and functional capacity. The 2009 ESC guidelines[47] are clear that non-invasive and invasive testing should be limited to circumstances in which results will clearly affect patient management or in which testing would otherwise be indicated. β-Blockers, statins, and aspirin therapy should be continued in patients already on therapy and should be started in PAD patients undergoing intermediate- or high-risk surgery.

4.6.3.2.2.2 Patients with non-surgical lower extremity artery disease

Beyond the specific situation where a patient with LEAD will undergo vascular surgery, the goal of screening for CAD is to identify LEAD patients with a poor long-term prognosis in whom treatment and risk factor modification may improve their outcome. The co-existence of significant vascular lesions in different sites is a common feature of atherosclerosis, a systemic disease that can affect virtually any of the arterial vessels.[384,402–404] The importance of prompt diagnosis and treatment of CAD has been repeatedly underscored. Half of patients with LEAD die from cardiovascular complications, and as early as 1 year after diagnosis; cardiovascular mortality rates are 3.7-fold higher than in patients without LEAD.[405] One-third of PAD patients have significant CAD lesions. Of interest, asymptomatic CAD is usually independently associated with traditional risk factors but also with the severity and extent of non-surgical LEAD.

The pending question is whether such identification may improve clinical outcomes in patients who are already in secondary prevention programmes. Of importance, stable atherosclerotic patients without previous ischaemic events experienced significantly more events in the case of multisite artery disease,[406] but this does not preclude any prognostic improvement in the case of prophylactic coronary revascularization. Screening asymptomatic CAD in patients with LEAD would be interesting if it leads to a different management from the one proposed for LEAD patients without CAD. Asymptomatic CAD in patients with LEAD is by definition stable, a situation in which coronary revascularization is controversial, given the negative results of the Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[407] which failed to demonstrate the superiority of coronary revascularization over optimal medical therapy. However, this trial excluded situations in which revascularization was considered as necessary, especially patients with a poor ejection fraction and those with left main coronary artery stenosis >50%. These situations are not infrequent in patients with severe and extended LEAD, which is frequently associated with multisite artery disease. In the absence of any specific trial in LEAD patients, the screening and management of CAD may be considered after a multidisciplinary discussion for each case.

5. Gaps in evidence

Solid evidence is still needed in many aspects of the management of PAD. In numerous situations, adequate trials are lacking and sometimes the management of PAD is extrapolated from data regarding CAD. In the field of interventional therapy, rapid changes in available therapeutic techniques create the situation in which clinical practice tends to follow technical developments without evidence from randomized trials. In addition, the randomized studies often yield conflicting results because of technical evolution and growth in the participants' experience. Moreover, PAD may involve multiple sites, creating a large number of clinical scenarios that are difficult to investigate in a systematic way. All of these aspects contribute to the broad spectrum of gaps in evidence, of which the most relevant are listed below.

Carotid artery disease

(i) The benefits of statins in patients with symptomatic carotid stenosis derive from the subgroup analysis of the SPARCL trial; the treatment goals for LDL cholesterol levels cannot be clearly defined. Even fewer data are available on the benefits of statins in asymptomatic carotid stenosis.

(ii) The benefits of other preventive therapies, i.e. antiplatelet drugs and ACE inhibitors, are not well assessed in carotid

disease, especially in the case of carotid plaque with non-significant stenosis, which is the most frequent situation.

(iii) The benefits of CEA in asymptomatic patients were proven in RCTs performed before the modern era of cardiovascular prevention, when medical therapy was almost non-existent and patients >80 years of age were excluded; thus, both CEA and CAS need to be evaluated against current optimal medical therapy in asymptomatic carotid stenosis, with a particular focus on elderly patients.

(iv) The efficacy of EPDs during CAS has not been studied in adequately powered RCTs, and the available evidence is conflicting.

(v) The optimal duration of dual antiplatelet therapy after CAS is not well established.

Vertebral artery disease

(i) Almost no data are available on the clinical benefit of revascularization of symptomatic VA stenosis, and on the comparison between surgical and endovascular revascularization.

Upper extremity artery disease

(i) Almost no data are available on the clinical benefit of revascularization of symptomatic subclavian artery stenosis/occlusion, and on the comparison between surgical and endovascular revascularization.

(ii) Little is known about the natural course in UEAD.

Mesenteric artery disease

(i) No data are available on the comparison between surgical and endovascular revascularization for symptomatic mesenteric artery disease.

(ii) No data are available on the potential benefits of revascularization for asymptomatic mesenteric artery disease involving two or more main visceral vessels.

Renal artery disease

(i) Large-size trials are still necessary to clarify the potential benefits of RAS in patients with different clinical presentations of renal artery disease.

(ii) Appropriate treatment of in-stent renal artery restenosis is not yet defined, although several trials are under way.

Lower extremity artery disease

(i) The benefits of statins in LEAD patients derive mainly from small studies or from subgroup analyses of large RCTs focused on CAD patients; thus, the treatment goals for LDL cholesterol levels in LEAD patients cannot be defined clearly.

(ii) Data on the benefits of the combination of 'supervised exercise training' and medical therapy are lacking.

(iii) Data on the potential benefit of endovascular revascularization over supervised exercise for intermittent claudication are limited.

(iv) The role of primary stenting vs. provisional stenting in aortoiliac disease needs to be evaluated.

(v) In the superficial femoral artery, the role of primary stenting in TASC II type C lesions, the potential benefit of covered stents for long superficial femoral artery occlusions, and the optimal treatment of in-stent restenosis need to be investigated.

(vi) The role of drug-eluting stents and drug-eluting balloons in superficial femoral artery and below-the-knee interventions has to be established.

(vii) Optimal treatment for popliteal artery stenosis needs to be addressed.

(viii) The role of self-expanding stents for below-the-knee interventions is unclear.

(ix) Benefits and/or adverse effects of β-blockers in CLI must be further evaluated.

(x) Optimal duration of dual antiplatelet therapy after LEAD stenting, as well as potential benefit of long-term dual antiaggregation therapy in patients with advanced CLI should be further investigated.

(xi) The role of gene or stem cell therapy in CLI needs further studies.

Multisite disease

(i) The need for prophylactic carotid revascularization in patients with asymptomatic carotid stenosis scheduled for CABG is still unclear.

(ii) The preferred timing of CABG associated with carotid revascularization (synchronous or staged) is still unclear.

(iii) If future studies confirm the benefits of carotid revascularization in patients undergoing CABG, the optimal treatment method (CAS vs. CEA) should be determined.

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