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2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

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

Endorsed by: the European Stroke Organization (ESO)

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The Addenda and Questions and Answers companion documents of these guidelines are available at: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of

For the Web Addenda which include background information and detailed discussion of the data that have provided the basis for the recommendations see https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehx095#supplementary-data

Click here to access the corresponding chapter in ESC CardioMed - Section 49 Peripheral arterial diseases.

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Keywords Guidelines • Peripheral arterial diseases • Carotid artery disease • Vertebral artery disease • Upper extremity artery disease • Mesenteric artery disease • Renal artery disease • Lower extremity artery disease • Multisite artery disease

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Abbreviations and acronyms

AAA	Abdominal aorta aneurysm
ABI	Ankle-brachial index
ACAS	Asymptomatic Carotid Atherosclerosis Study
ACEIs	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ACSRS	Asymptomatic carotid atherosclerosis risk of stroke
ACST	Asymptomatic Carotid Surgery Trial
ACT	Asymptomatic Carotid Trial
AF	Atrial fibrillation
AMERICA	Aggressive detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis
ARBs	Angiotensin-receptor blockers
ARR	Absolute risk reduction
ASTRAL	Angioplasty and stenting for renal artery lesions
BASIL	Bypass versus angioplasty in severe ischaemia of the leg

BEST-CLI	Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia
BMT	Best medical therapy
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CAPTURE	Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Rare Events
CARESS	Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis
CASPAR	Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial disease
CAS	Carotid artery stenting
CCA	Common carotid artery
CEA	Carotid endarterectomy
CFA	Common femoral artery
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CI	Confidence interval
CKD	Chronic kidney disease
CLEVER	Claudication: exercise versus endoluminal revascularization
CLTI	Chronic limb-threatening ischaemia
CMI	Chronic mesenteric ischaemia
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CPG	Committee for Practice Guidelines
CPB	Cardiopulmonary bypass
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CTA	Computed tomography angiography
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
ECG	Electrocardiogram
ECST	European Carotid Surgery Trial
EPD	Embolus protection device
ESC	European Society of Cardiology
ESO	European Stroke Organisation;
ESVS	European Society of Vascular Surgery
EUCLID	Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease
EVA-3S	Endarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis
EVT	Endovascular therapy
ExT	Exercise therapy
FMD	Fibromuscular dysplasia
GSV	Great saphenous vein
HDL-C	High-density lipoprotein cholesterol
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HITS	High-intensity transient signal
HOPE	Heart Outcomes Prevention Trial
HR	Hazard ratio
IC	Intermittent claudication
ICA	Internal carotid artery
ICD	Implantable cardioverter defibrillator
ICSS	International Carotid Stenting Study
INR	International normalized ratio
INVEST	INternational VErapamil-SR/Trandolapril Study
LDL-C	Low-density lipoprotein cholesterol
LEAD	Lower extremity artery disease
LV	Left ventricular
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MR CLEAN	MultiCenter Randomized Clinical Trial of Ischemic Stroke in the Netherlands
MRI	Magnetic resonance imaging
MSAD	Multisite artery disease
MWD	Maximal walking distance
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NNH	Number needed to harm
NNT	Number needed to treat
NOAC	Non-vitamin K oral anticoagulant
OAC	Oral anticoagulation
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
OR	Odds ratio
PADs	Peripheral arterial diseases
PCI	Percutaneous coronary intervention
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54
PRODIGY	PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hYperplasia study
PTA	Percutaneous transluminal angioplasty
QOL	Quality of life
RAAS	Renin–angiotensin–aldosterone system
RAD	Renal artery disease
RAS	Renal artery stenosis
RCT	Randomized clinical trial
REACH	Reduction of Atherothrombosis for Continued Health
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	Relative risk
RRI	Renal resistive index

SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SAPT	Single antiplatelet therapy
SBP	Systolic blood pressure
SFA	Superficial femoral artery
SPACE	Stent Protected Angioplasty versus Carotid Endarterectomy
STAR	Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function
TAMARIS	Efficacy and Safety of XRP0038/NV1FGF in Critical Limb Ischaemia Patients With Skin Lesions
TAVI	Transcatheter aortic valve implantation
TBI	Toe-brachial index
$TcPO_2$	Transcutaneous oxygen pressure
TIA	Transient ischaemic attack
TTE	Transthoracic echocardiography
UEAD	Upper extremity artery disease
VA	Vertebral artery
VAST	Vertebral Artery Stenting Trial
VHD	Valvular heart disease
VKA	Vitamin K antagonist
WD	Walking distance
WIfI	Wound, ischaemia and foot infection

1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), by the European Society of Vascular Surgery (ESVS) and by the European Stroke Organization (ESO), as well as by other societies and organisations. 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 (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). 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, including representation from the ESVS and ESO 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 management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the ESVS and ESO. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that 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 were notified to the ESC and updated. The Task Force received its entire financial support from the ESC and ESVS without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by ESVS- and ESO-appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG and ESVS for publication in the European Heart Journal and in the European Journal of Vascular and

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.

Endovascular Surgery. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines in collaboration with ESVS also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC Website and hosted on the EHJ Website. The National Societies of the ESC are encouraged to endorse, translate and implement all 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, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines developed in collaboration with ESVS fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. 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

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

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

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

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

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

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

General recommendations on the management of patients with peripheral arterial diseases

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

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

What is new in the 2017 PAD Guidelines?

CHANGE IN RECOMMENDATIONS

2011	2017
Carotid Artery Disease	
EPDs in carotid stenting	
Asymptomatic 60–99% carotid stenosis	
• Surgery for all	• Surgery for high stroke risk[116]
• Stenting as an alternative	• Stenting in high surgery risk[129, 135-137]
	• Stenting in average surgical risk
Upper Extremity Artery Disease	
Revascularization for symptomatic subclavian artery stenosis	
Subclavian stenosis revascularization	
• Endovascular first	• Stenting or surgery
Revascularization for asymptomatic subclavian stenosis in patients with/planned for CABG	
Renal Artery Disease	
Stenting for symptomatic atherosclerotic stenosis >60%[229,231,232]	
Lower Extremity Artery Disease	
Aorto-iliac lesions	
• Primary endovascular therapy for "TASC-D"	• Surgery for aorto-iliac or aorto-bi-femoral occlusions
	• Endovascular as an alternative in experienced centres
Infra-popliteal lesions	
• Endovascular first	• Bypass using GSV
	• Endovascular therapy[320-326]

2017 NEW RECOMMENDATIONS

All Peripheral Arterial Diseases (PADs)

- Screening for heart failure (BNP, TTE)
- Stable PADs + other conditions requiring anticoagulants (e.g. AF): anticoagulation alone[91]

Carotid Artery disease

- Coronary angiography before elective carotid surgery[383]
- Routine prophylactic revascularization of asymptomatic carotid 70-99% stenosis in patients undergoing CABG

Mesenteric Artery Disease

- D-dimers to rule out acute mesenteric ischaemia
- No delay for re-nutrition in case of symptomatic CMI

Renal Artery Disease

- Fibromusuclar dysplasia: balloon angioplasty with bailout stenting

Lower Extremity Artery Disease (LEAD)

- Statins to improve walking distance[30,278]
- LEAD + AF: Anticoagulation if CHADS-VASc >2
- Angiography in CLTI with below-the-knee lesions
- Duplex screening for AAA[258, 259]
- In case of CABG: screen LEAD with ABI, limit vein harvesting if LEAD
- Screening for LEAD in CAD patients[366–368, 375–379]
- Screening for LEAD in HF patients
- Clopidogrel preferred over aspirin[a]
- Antiplatelet therapy in isolated[b] asymptomatic LEAD[66, 67]

I IIa IIb III

2017 NEW / REVISED CONCEPTS

PADs in general:
- "Vascular Team" for a multidisciplinary management.
- Best medical therapy: drugs and non pharmalogical interventions for optimal outcome. A specific chapter addresses antithrombotic therapies in different PADs presentations, including when anticoagulants are needed.

Carotid disease:
- Risk stratification for asymptomatic carotid disease.
- In patients undergoing CABG, revascularization of severe carotid stenosis is not systematic.

Lower extremity artery disease:
- Masked LEAD should be individualized from asymptomatic disease.
- Modern management of claudication: statins and (supervised) exercise therapy always prescribed, even after revascularization. In this context, the benefit from "vaso-active" drugs to improve walking distance is uncertain.
- "Chronic limb-threatening ischaemia (CLTI)" defines the most severe form of LEAD. Beyond ischaemia, wound and infection should be evaluated to stratify the amputation risk (new WIfI classification). TASC classification excluded from the guidelines.
- Beyond concomitant CAD, patients with PADs have often other cardiac conditions (e.g. HF, AF). The major scenarios have been addressed in a specific new chapter.

AAA = abdominal aorta aneurysm; ABI = ankle-brachial index; AF = atrial fibrillation; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting surgery; CAD = coronary artery disease; CLTI = chronic limb-threatening ischaemia; EPD = embolic protection devices; HF = heart failure; GSV = great saphenous vein; TASC = Trans-Atlantic InterSociety Consensus; TTE = transthoracic echocardiography.

[a]Recent data from COMPASS trial need further analyses and will be addressed in the future.

[b]Without any other clinical condition requiring antiplatelet therapy.

3. Epidemiology and risk factors

Key messages

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

3.1 Epidemiology

The epidemiology of different patterns of PADs is presented in the Web addenda 3.1. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

3.2 Risk factors

Although different localizations of PADs share common major risk factors for atherosclerosis, the impact of those and/or available evidence differ per arterial site. See Web addenda 3.2.

3.3 Prognosis

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

Beyond the risk of cerebrovascular events, patients with CAD are also at risk for myocardial infarction (MI) and cardiac death.[3] In a systematic review of 17 studies including 11 391 patients with >50% asymptomatic carotid stenosis, 63% of late deaths were related to cardiac events, with a mean cardiac-related mortality rate of 2.9%/year.[4]

Many studies have shown an increased risk of mortality, CV mortality and morbidity (MI, stroke) in patients with symptomatic or asymptomatic LEAD, even after adjustment for conventional risk factors.[5] An ankle-brachial index (ABI) ≤0.90 is associated with more than doubling of the 10-year rates of coronary events, CV mortality and total mortality.[6] After 5 years, 20% of patients with intermittent claudication (IC) present an MI or stroke and mortality is 10–15%.[7]

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

4. General aspects

Key messages

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

4.1 Diagnostic approach

4.1.1 Clinical history

Personal and family clinical history should always be assessed. Family history includes CAD, cerebrovascular disease, aortic aneurysm as well as LEAD.[8–10] Clinical history includes the evaluation of CV risk factors and comorbidities as well as a review of the symptoms related to different vascular territories (see Web Table 1). Lifestyle habits, dietary patterns, walking performances and physical activity need to be systematically interrogated. Physical activity should be assessed.[11] Questionnaires and functional status provide reasonably accurate outcome measures. They may be useful for determining the impairment level and selection of appropriate care.[12,13] The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

4.1.2 Clinical examination

Although physical examination alone is of relatively poor sensitivity and reproducibility, a systematic approach is mandatory (see Web Table 2). Beyond their diagnostic importance, clinical signs have a prognostic value. Individuals with carotid bruits have twice the risk of MI and CV death as compared with those without.[14] Interarm blood pressure (BP) asymmetry (≥15 mmHg) is a marker of vascular disease risk and death.[15] A femoral bruit is an independent marker for ischaemic cardiac events.[16]

4.1.3 Laboratory testing

Investigations should progress from the 'minimal' biological assessment[17] to complementary laboratory tests if necessary (outlined in Web Table 3).

4.1.4 Diagnostic methods for PADs

4.1.4.1 Ankle-brachial index

The ABI is a non-invasive tool useful for the diagnosis and surveillance of LEAD. It is also a strong marker of generalized atherosclerosis and CV risk (see *Table 3*). An ABI ≤0.90 is associated on average with a 2- to 3-fold increased risk of total and CV death. An ABI >1.40 represents arterial stiffening (medial arterial calcification) and is also associated with a higher risk of CV events and mortality.[6,18] It is more prevalent in elderly patients, mostly in those with diabetes or chronic kidney disease (CKD). When added to a risk score, ABI enables the risk estimation to be upgraded in one-third and one-fifth of 'low-risk' women and men, respectively.[6] It is a valid method of CV risk assessment in diverse ethnic groups, independent of risk factors.[18] In contrast to coronary calcium score and carotid intima-media thickness, ABI is inexpensive and minimally time consuming. Good training is mandatory.

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

4.1.4.2 Duplex ultrasound

Duplex ultrasound (DUS) is often a first step in the vascular workup both for screening and diagnosis. DUS includes B-mode echography, pulsed-wave, continuous, colour and power Doppler modalities to detect and localize vascular lesions and quantify their extent and severity through velocity criteria. More recent techniques, such as flow imaging or live three-dimensional (3D) echography, as well as the use

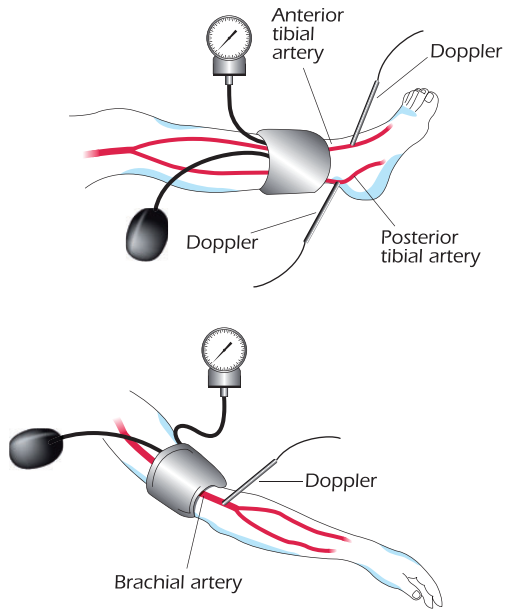
Table 3 The Ankle-Brachial Index

1. Who should have an ABI measurement in clinical practice?

- **Patients with clinical suspicion for LEAD:**
  - Lower extremities pulse abolition and/or arterial bruit
  - Typical intermittent claudication or symptoms suggestive for LEAD
  - Non-healing lower extremity wound
- **Patients at risk for LEAD because of the following clinical conditions:**
  - Atherosclerotic diseases: CAD, any PADs
  - Other conditions: AAA, CKD, heart failure
- **Asymptomatic individuals clinically-free but at-risk for LEAD:**
  - Men and women aged >65 years
  - Men and women aged <65 years classified at high CV risk according the ESC Guidelines[a]
  - Men and women aged >50 years with family history for LEAD

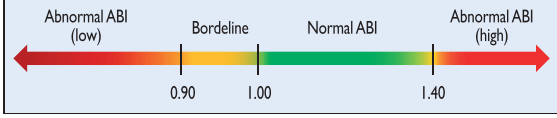
2. How to measure the ABI?

In supine position, with cuff placed just above the ankle, avoiding wounded zones. After a 5–10 minute rest, the SBP is measured by a Doppler probe (5–10 MHz) on the posterior and the anterior tibial (or dorsal pedis) arteries of each foot and on the brachial artery of each arm. Automated BP cuffs are mostly not valid for ankle pressure and may display overestimated results in case of low ankle pressure. The ABI of each leg is calculated by dividing the highest ankle SBP by the highest arm SBP.



3. How to interpret the ABI?

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



AAA = abdominal aorta aneurysm; ABI = ankle-brachial index; BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; ESC = European Society of Cardiology; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; SBP = systolic blood pressure. [a]Subjects with: markedly elevated single risk factors; diabetes mellitus (except for young people with type 1 diabetes without other major risk factors); a calculated SCORE ≥5% and <10%.

of ultrasound contrast agents, further improve DUS performances, although their use is still limited. DUS can detect subclinical artery disease (e.g. carotid plaque), which is important for CV risk assessment.[17]

4.1.4.3 Digital subtraction angiography

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

4.1.4.4 Computed tomography angiography

Multidetector computed tomography angiography (CTA) has a short examination time with reduced motion and respiration artefacts while imaging vessels and organs. Advantages of CTA include rapid non-invasive acquisition, wide availability, high resolution and 3D reformatting. Similar to DSA and magnetic resonance angiography (MRA), CTA displays a 'roadmap' of the vascularization, essential for determining interventional strategies (lesion localization and severity, upstream/downstream status). The drawbacks of CTA include the lack of functional and haemodynamic data, exposure to radiation and the use of iodinated contrast agents, which should be limited in the case of CKD, with precautions in case of allergies. Nephrotoxicity can be limited by minimizing contrast agent volume and ensuring adequate hydration before and after imaging. The benefit of acetylcysteine to limit nephrotoxicity is uncertain.[19,20] Recent studies have suggested that statins or sodium bicarbonate could prevent contrast agent nephrotoxicity.[21,22] Further research is required.

4.1.4.5 Magnetic resonance angiography

MRA is used for peripheral artery imaging using contrast (i.e. gadolinium) and non-contrast techniques (i.e. phase contrast and time-of-flight sequences). These latter techniques have inferior resolution and are susceptible to artefacts, limiting their interpretation. They are a valuable alternative for use in patients with mild to moderate CKD. Compared with CTA, MRA does not need iodine contrast and has higher soft tissue resolution; however, motion artefacts are more frequent and contraindications include pacemakers and implantable cardioverter defibrillators (ICDs) [except magnetic resonance imaging (MRI)-conditional and compatible pacemakers, ICDs and leads], claustrophobia and severe CKD. In the latter case, the risk of nephrogenic systemic fibrosis following gadolinium administration should not be underestimated.[23] Vascular calcifications, potentially affecting revascularization procedures, can be underestimated. Endovascular stents are not evaluable by MRI.

4.2 Treatment approach

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

The second aspect of management in these patients is related to their increased risk of any CV event (see **section 3.2**). General CV prevention is of the utmost importance and management should be multidisciplinary. Best medical therapy (BMT) includes CV risk factor management, including best pharmacological therapy, as well as non-pharmacological measures such as smoking cessation, healthy diet, weight loss and regular physical exercise.[24,25] The pharmacological

component of BMT includes antihypertensive, lipid-lowering and antithrombotic drugs. In diabetic patients, optimal glucose level control should be obtained as recommended.[26]

4.2.1 Smoking cessation

A body of evidence supports the benefits of smoking cessation in reducing CV events and mortality, especially in patients with cerebrovascular disease and LEAD.[27,28] Management and support for smoking cessation was extensively addressed in the 2016 ESC guidelines on CV disease prevention.[25] Passive smoking should be assessed and prevented.[29]

4.2.2 Lipid-lowering drugs

All patients with PADs should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to < 1.8 mmol/L (<70 mg/dL) or decreased by ≥ 50% if the initial LDL-C level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).[25] In observational studies and limited randomized clinical trials (RCTs) in patients with LEAD (from asymptomatic to severe cases), statin therapy has been shown to cause reductions in all-cause mortality and CV events.[30–32] In the Reduction of Atherothrombosis for Continued Health (REACH) registry, among patients with LEAD, statin use was associated with a 17% decrease in adverse CV events rates.[33] Even in the most advanced stages of disease, statin therapy is associated with lower 1-year rates of mortality and major CV adverse events.[34] Combination treatment with ezetimibe in selected patients is also beneficial.[35] In a randomized trial, bezafibrate showed no benefit over placebo to reduce coronary and cerebrovascular events in patients with LEAD.[36] In those with CAD, statins reduce the stroke risk.[37,38] Recently the Fourier trial demonstrated the additional benefits of evolocumab, a monoclonal antibody inhibiting the proprotein convertase subtilisin/kexin type 9 to reduce CV events in patients with atherosclerotic disease over statins alone.[39] The results were consistent in the subgroup of 1505 patients with LEAD alone. Further results are awaited.

4.2.3 Antithrombotic drugs

Antiplatelet agents are used for secondary prevention of CV events in patients with symptomatic PADs. The evidence is mostly available in patients with LEAD and cerebrovascular disease (see **chapter 5**).

4.2.4 Antihypertensive drugs

Lowering systolic blood pressure (SBP) reduces CV events.[40] According to the current ESC/European Society of Hypertension guidelines,[41] a target BP < 140/90 mmHg is recommended except in patients with diabetes, for whom a diastolic blood pressure ≤85 mmHg is considered safe. In patients with LEAD, this is mainly based on data from the INternational VErapamil-SR/Trandolapril (INVEST) study.[42] Caution should be exercised to avoid an SBP decrease below 110–120 mmHg, since a J-shape relationship between SBP and CV events has been reported in that trial in LEAD patients.[42] In old and frail patients, these levels should be achieved only if well tolerated, without orthostatic hypotension.[43,44] In patients with PADs, an appropriate lifestyle and salt intake (<5–6 g/day) are recommended.[45] Diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are all suitable for antihypertensive treatment, as monotherapy or in different combinations. In the INVEST study, no difference in CV outcomes was found between the verapamil plus trandolapril strategy vs. the atenolol plus hydrochlorothiazide strategy.[42] Some classes may be preferred according to comorbidities.[41]

The Heart Outcomes Prevention Trial (HOPE) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) have shown that ACEIs and ARBs significantly reduce CV events in patients with PADs.[46,47] According to these trials, ACEIs or ARBs are recommended for secondary prevention, even in patients with chronic limb-threatening ischaemia (CLTI). In this subgroup of patients, the use of ACEIs or ARBs is associated with decreased major adverse cardiovascular events (MACEs) and mortality without any effect on limb outcomes.[48]

Importantly, beta-blockers are not contraindicated in patients with LEAD, as they do not alter walking capacity in patients with mild to moderate LEAD.[49] In an observational study, patients with LEAD and prior MI and taking beta-blockers had a significant 53% coronary events risk decrease at 32 months.[50] Nevertheless, they should be carefully prescribed to patients with CLTI.

Recommendations in patients with peripheral arterial diseases: best medical therapy

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with PADs.[27,28]	I	B
Healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.[31,32]	I	A
In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by ≥ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).[25]	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.[51]	I	C[d]
In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg.[41,42,52]	I	A
ACEIs or ARBs should be considered as first-line therapy[c] in patients with PADs and hypertension.[47,53]	IIa	B

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; LDL-C = low-density lipoprotein cholesterol; PADs = peripheral arterial diseases.
[a]Class of recommendation.
[b]Level of evidence.
[c]Calcium channel blockers should be proposed in black individuals.
[d]Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding sections.

5. Antithrombotic drugs in peripheral arterial diseases

Key messages

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

Antiplatelet therapy is part of BMT for symptomatic PADs (see **chapter 4**). The specific issues about CAD and LEAD are addressed here. The question of DAPT after endovascular therapy in other territories as well as the sensitive issue of PADs patients requiring anticoagulation [e.g. with concomitant atrial fibrillation (AF)] are also addressed. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

5.1 Antithrombotic treatment in carotid artery disease

5.1.1 Single antiplatelet therapy

While the benefit of SAPT for preventing stroke in asymptomatic patients with carotid artery stenosis >50% is not evidenced through an RCT, lifelong low-dose aspirin should be part of BMT to reduce the risk of stroke and other CV events,[54] as these patients are also at twice the risk of MI.[14] In symptomatic extracranial carotid stenosis, antiplatelet monotherapy is recommended.[54,55] Clopidogrel (75 mg/day) is an alternative in patients with aspirin intolerance.[51]

5.1.2 Dual antiplatelet therapy

In the randomized Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, asymptomatic CAD was an inclusion criteria in 7% of patients enrolled. No benefit was observed between DAPT vs. SAPT.[56] The Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study, conducted in 108 patients, demonstrated that DAPT vs. aspirin reduced silent cerebral micro-emboli by 37% after 7 days.[57] No life-threatening intracranial or major bleeding was observed, but the sample size was small. For these reasons,

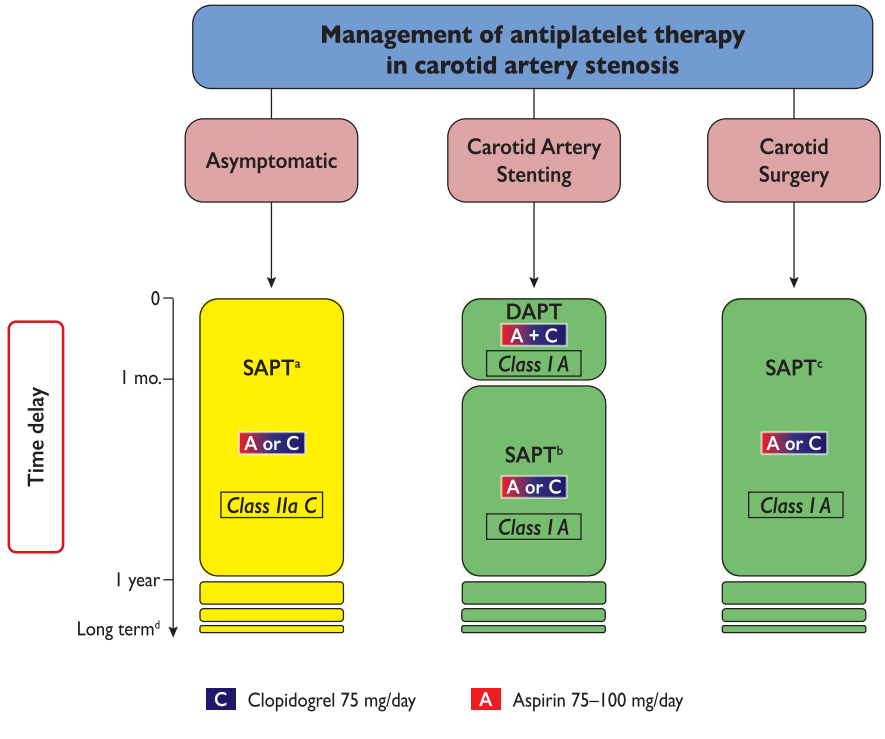


Figure 1 Management of antithrombotic treatment in patients with carotid artery stenosis. DAPT = dual antiplatelet therapy, a daily combination of aspirin (75–100 mg) and clopidogrel (75 mg); CAS = carotid artery stenting; SAPT = single antiplatelet therapy; TIA = transient ischaemic attack.
[a]At the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

DAPT may be considered within 24 h of a minor ischaemic stroke or transient ischaemic attack (TIA) and may be continued for 1 month in patients treated conservatively.[58]

DAPT is recommended in patients undergoing CAS. Two small RCTs comparing aspirin alone with DAPT for CAS were terminated prematurely due to high rates of stent thrombosis and neurological events in the aspirin-alone group.[59,60] These data were obtained at 30 days. Most events were procedure related. The optimal duration of DAPT following CAS is unknown. Recent studies showing late brain lesions on diffusion-weighted MRI after CAS question whether DAPT beyond the first month may be required.[61] However, potential risks include haemorrhagic transformation in patients with recent stroke and intracranial bleeding in patients at risk of reperfusion injury following revascularization. DAPT may be prolonged beyond 1 month after CAS in the presence of recent (<12 months) MI and low bleeding risk **(Figure 1)**.[62]

5.2 Antithrombotic therapy in lower extremity artery disease

Antiplatelet agents are used in patients with LEAD to prevent limb-related and general CV events. A number of antiplatelet strategies are available, but their specific indications remain unclear.[63] One study compared clopidogrel with aspirin[51] and two studies compared clopidogrel plus aspirin to aspirin alone.[64,65] No specific trial addressed the role of antiplatelet agents in the full spectrum of LEAD (asymptomatic, IC and CLTI). Also, the Task Force is aware of the premature halting of the COMPASS trial for 'overwhelming' efficacy. The trial compared rivaroxaban monotherapy (5 mg twice a day) with dual therapy (aspirin plus rivaroxaban 2.5 mg twice a day) and with aspirin monotherapy in 27 402 patients with CAD or LEAD. As the data were neither presented nor published at the time of guideline printing, the Task Force was unable to address these results and their potential clinical consequences. Hence the Task Force will consider the results when they become available, as well as the option for an update if necessary.

5.2.1 Single antiplatelet therapy

Two trials, one in a general population (with ABI <0.95)[66] and another in diabetic patients (with ABI <1.0)[67], found no benefit from aspirin in subclinical LEAD.

In symptomatic LEAD, the strongest evidence in favour of aspirin to protect against MACE (combining non-fatal MI and stroke with CV death) comes from the Antithrombotic Trialists Collaboration.[54] In 6200 patients with IC, aspirin significantly reduced MACE vs. controls (6.4 vs. 7.9%). Another meta-analysis of RCTs comparing aspirin to placebo in patients with LEAD (symptomatic or asymptomatic) showed a non-significant reduction in MACE {relative risk [RR] 0.75 [95% confidence interval (CI) 0.48–1.18]}.[68] No significant benefit was found within the individual components except for a reduction in non-fatal stroke [RR 0.64 (95% CI 0.42–0.99)].[68] In a post hoc analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, at 3 years, clopidogrel was superior to aspirin in the subgroup of patients with clinical LEAD (n = 6452), with significant reductions in CV mortality [hazard ratio (HR) 0.76 (95% CI 0.64–0.91)] and MACE [HR 0.78 (95% CI 0.65–0.93)], with similar benefit in the subgroup of LEAD patients with diabetes.[51] In the randomized Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease (EUCLID) trial, ticagrelor was compared to clopidogrel in 13 885 patients ≥50 years of age with symptomatic LEAD.[69] The trial failed to show any difference regarding MACE [HR 1.02 (95% CI 0.92–1.13)] or major bleeding [HR 1.10 (95% CI 0.84–1.43)].

5.2.2 Dual and triple antiplatelet therapy

So far, data proving the superiority of DAPT (with clopidogrel) over aspirin alone to reduce CV events in patients with LEAD are lacking.[63] In the subgroup of patients with LEAD enrolled in the CHARISMA trial (n = 3906), DAPT led to a reduction in MI [HR 0.63 (95% CI 0.42–0.95)], with a neutral effect on all the other vascular events, at the cost of increased severe, fatal or moderate bleeding [HR 1.99 (95% CI 1.69–2.34)].[65] Because of the post hoc nature of this analysis and the negative results of the overall trial, these findings need confirmation.

Vorapaxar, a protease-activated receptor-1 inhibitor, was tested vs. placebo on top of standard antiplatelet therapy in secondary prevention in patients with clinical LEAD (n = 3787).[70] Vorapaxar did not reduce the risk of MACE [HR 0.94 (95% CI 0.78–1.14)] but significantly reduced the risk of acute limb ischaemia [HR 0.58 (95% CI 0.39–0.86)] and peripheral revascularization [HR 0.84 (95% CI 0.73–0.97)].[70] This benefit was observed irrespective of the underlying mechanism of acute limb ischaemia, including surgical graft thrombosis and native vessel thrombosis.[71] These beneficial effects were counterbalanced by an increased risk of bleeding [HR 1.62 (95% CI 1.21–2.18)].

5.2.3 Antithrombotic therapy after lower-extremity bypass grafting

Antiplatelet agents are mostly used after peripheral percutaneous revascularization, while warfarin has a small role (*Figure 2*). No conclusive data are yet available for direct oral thrombin and factor Xa inhibitors.[72]

5.2.3.1 Aspirin vs. placebo

In a meta-analysis of 952 patients, graft patency was significantly improved with aspirin (with or without dipyridamole) vs. placebo (HR 0.42, P = 0.01).[72] Notably, at any of the time points, this effect was not observed for venous grafts alone but for prosthetic grafts (at 12 months: OR 0.19, P < 0.00001). Amputation, survival and bleeding rates were similar.

5.2.3.2 Aspirin vs. oral anticoagulation

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, no difference in graft patency was found between aspirin (or aspirin/dipyridamole) and vitamin K antagonist (VKA) over 2 years of follow-up [HR 0.64 (95% CI 0.25–1.63)].[73] There was no difference in mortality [OR 1.02 (95% CI 0.83–1.26)] or amputation [OR 0.99 (95% CI 0.75–1.30)]. Major bleeding risk doubled with VKA [with high target international normalized ratios (INRs) > 3].[73] There were significantly fewer venous bypass occlusions under VKA vs. aspirin [HR 0.69 (95% CI 0.51–0.94)]. In another study, the addition of warfarin to aspirin failed to show any improvement in graft patency vs. aspirin alone, with a 2-fold increased risk of major bleeding.[74] DAPT has been compared with VKA plus clopidogrel (n = 341) in femoro-popliteal bypass, with marginal benefit on graft failure, more bleeding and no effect on MACE.[75]

5.2.3.3. Aspirin vs. dual antiplatelet therapy

Among the 851 patients with below-the-knee bypass grafting enrolled in the Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial disease (CASPAR) randomized controlled trial, no

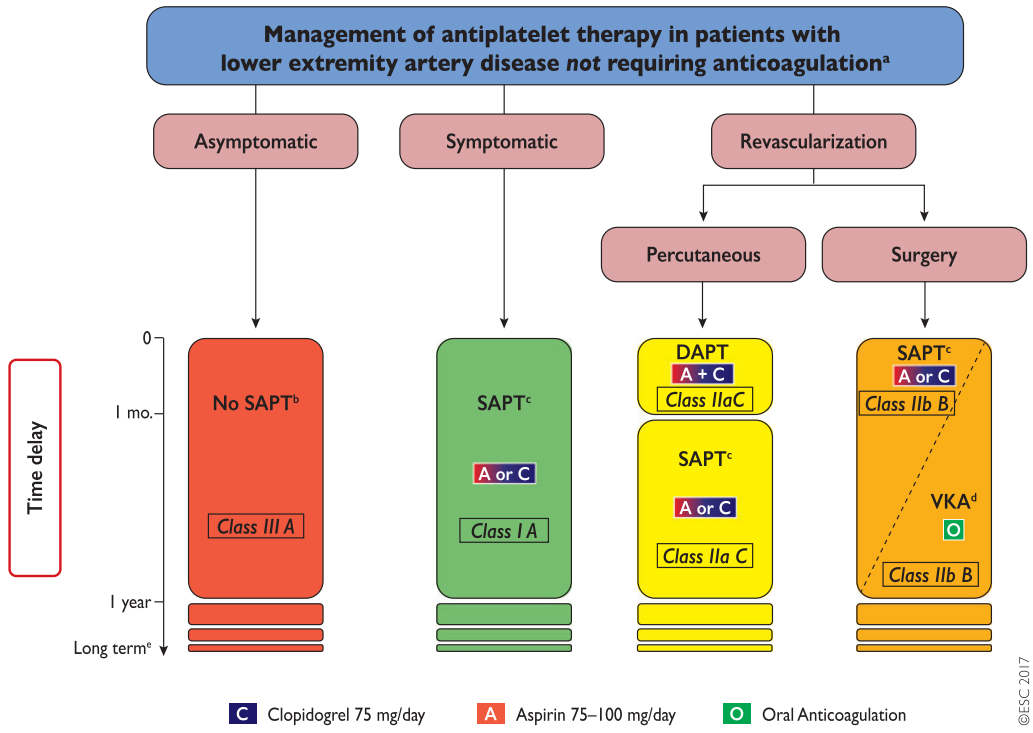


Figure 2 Antiplatelet therapy in patients with lower extremity artery disease. DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.
[a]e.g. concomitant AF or mechanical valve prosthesis.
[b]SAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease).
[c]DAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel diseasein diabetic patients with incomplete revascularization.
[d]Evidence is weak and bleeding doubles as compared to SAPT.
[e]Stands for as long as it is well tolerated.

difference between aspirin plus placebo vs. aspirin plus clopidogrel was found regarding the occurrence of index graft occlusion or revascularization, above-ankle amputation of the affected limb or death [HR 0.98 (95% CI 0.78–1.23)].[64] In the pre-specified subgroup of patients with a prosthetic graft, the primary efficacy endpoint was reduced in DAPT patients vs. aspirin alone [HR 0.65 (95% CI 0.45–0.95)] with a significant interaction according to the type of graft (venous vs. prosthetic). There was no statistically significant difference in the incidence of primary events when a venous graft was used [HR 1.25 (95% CI 0.94–1.67)]. Although total bleeding was more frequent on DAPT [HR 2.65 (95% CI 1.69–4.15)], there was no significant difference regarding severe or fatal bleeding (2.1 vs. 1.2%).

5.2.4 Antithrombotic drugs after endovascular therapy for lower extremity artery disease

DAPT is currently recommended for at least 1 month after intervention, irrespective of the stent type (bare metal vs. drug eluting). In the Zilver PTX randomized trial comparing provisional drug-eluting stents to bare-metal stents, DAPT was mandated for 2 months.[76] In the IN.PACT SFA trial, half of the patients were on DAPT at 1 year.[77] Stenting below-the-knee arteries is often followed by a longer period of DAPT, but no specific evidence is available. Anticoagulation has been prospectively tested after percutaneous infra-inguinal revascularization. Vascular patency was not improved, while bleeding was significantly increased.[78]

5.2.5 Patients with lower extremity artery disease and concomitant coronary artery disease

In patients with CAD, the coexistence of LEAD is associated with a worse prognosis irrespective of the clinical presentation. It has a direct impact on the duration and type of antiplatelet therapy regimen, in particular when there is a prior history of coronary stenting or acute coronary syndrome (ACS). The coexistence of LEAD in patients with CAD may be an argument for prolonged DAPT. The PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hYperplasia (PRODIGY) trial tested DAPT duration after ACS. Prolonged (24 months) vs. short (6 months) DAPT conveyed a lower risk of the primary efficacy endpoint, a composite of death, MI or cerebrovascular accidents, in patients with LEAD [HR 0.54 (95% CI 0.31–0.95)] but not in those without [HR 1.28 (95% CI 0.92–1.77)]. A significant interaction ($P = 0.01$) suggests specific benefits only in patients with concomitant LEAD.[79] In the Prevention of

Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, the addition of ticagrelor 90 mg twice a day or 60 mg twice a day on top of low-dose aspirin in stable patients with prior MI (1–3 years) was investigated.[80] Among patients with known LEAD (5% of the entire population), ticagrelor (pooled doses) reduced significantly the risk of major adverse limb outcomes (acute limb ischaemia and peripheral revascularization) [HR 0.65 (95% CI 0.44–0.95)]. In addition, in patients with LEAD, ticagrelor showed the greatest benefit, with an absolute risk reduction (ARR) of 4.1% [number needed to treat (NNT) = 25] for MACE and an absolute excess of major bleeding of 0.12% [number needed to harm (NNH) = 834].[81] Therefore, long-term ticagrelor on top of low-dose aspirin may be considered in LEAD patients with prior MI (<3 years).

DAPT duration in these settings should follow the current guidelines.[82] In LEAD patients who underwent infra-inguinal percutaneous revascularization, DAPT may be prolonged beyond 1 month when there is a prior history (<1 year) of ACS and/or percutaneous coronary intervention (PCI) (*Figure 2*). Yearly reassessment of DAPT should be considered according to the patient's clinical status.

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

AF is frequent in patients with LEAD, with a worse outcome as compared to those without AF (see **section 12.3**).[83,84] Although evidence is scarce to support a specific antithrombotic regimen in patients with LEAD and an indication for oral anticoagulation (OAC), the first step is to reassess the indication for OAC. OAC should be continued only if a compelling indication exists (e.g. paroxysmal, persistent or permanent AF with a Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category (CHA_2DS_2-VASc) score ≥2; mechanical heart valve; recent or a history of recurrent deep venous thrombosis or pulmonary embolism). Importantly, LEAD accounts for 1 point in the CHA_2DS_2-VASC score and can shift the indication for OAC. A post hoc analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial reported a significant interaction for major and non-major clinically relevant bleeding in patients with LEAD (n = 839) treated with rivaroxaban vs. warfarin [HR 1.40 (95% CI 1.06–1.86)] compared to patients

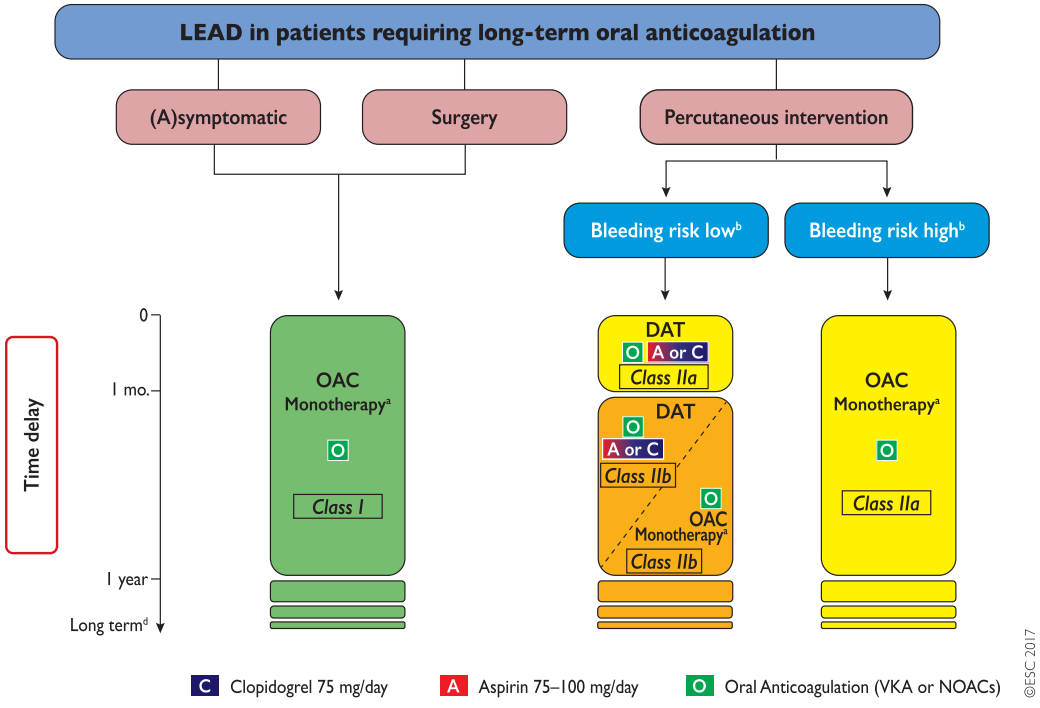


Figure 3 Antithrombotic therapy in patients with LEAD requiring oral anticoagulation. ACS = acute coronary syndrome; CAD = coronary artery disease; CLTI: chronic limb-threatening ischaemia; DAT = dual antithrombotic therapy; LEAD = lower extremity artery disease; NOACs = non-vitamin K oral anticoagulants; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]DAT may be considered in high ischaemic rick patients defined as prior stent thrombosis, acute limb ischaemia on OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization).
[b]Compared to the risk for stroke/CLTI due to stent/graft occlusion.
[c]Stands for as long as it is well tolerated.

without LEAD [HR 1.03 (95% CI 0.95–1.11); interaction $P = 0.037$].[85] Additional studies are needed.

The duration of combined therapy should be as limited as possible (1 month), depending on the clinical indication and bleeding risk.[82,83] The addition of an antiplatelet treatment may depend on concomitant CAD and the need for LEAD endovascular revascularization. With the exception of below-the-knee stenting or complex lesions at very high risk of thrombosis, triple therapy (i.e. aspirin, clopidogrel and an anticoagulant) is discouraged in this setting. The proposed treatment algorithm taking into account the management strategy and bleeding risk is shown in *Figure 3*. Gastric protection with a proton pump inhibitor is recommended and the dose intensity of OAC should be carefully monitored with a target INR of 2.0–2.5 in patients treated with VKA, with the exception of individuals with mechanical prosthetic valves in the mitral position. In patients treated with non-vitamin K oral anticoagulants (NOACs), the lowest dose in approval studies for stroke prevention should be applied when combined with antiplatelet therapy.[83,86]

5.4 Antithrombotic therapy after endovascular therapy in other territories

See Web addenda 5.4.

Recommendations on antithrombotic therapy in patients with peripheral arterial diseases

Recommendations	Class[a]	Level[b]
Carotid artery disease		
In patients with symptomatic carotid stenosis, long-term SAPT is recommended (87).	I	A
DAPT with aspirin and clopidogrel is recommended for at least 1 month after CAS (60).	I	B
In patients with asymptomatic >50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low.[c]	IIa	C
Lower extremities artery disease		
Long-term SAPT is recommended in symptomatic patients.[51,54,68]	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization.[72]	I	C
SAPT is recommended after infra-inguinal bypass surgery.[72,88,89]	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.[51,69]	IIb	B
Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass.[73]	IIb	B
DAPT with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation.	IIa	C
DAPT with aspirin and clopidogrel may be considered in below-the-knee bypass with a prosthetic graft.[64]	IIb	B
Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD.[66, 67]	III	A
Antithrombotic therapy for PADs patients requiring oral anticoagulant		
In patients with PADs and AF, OAC:[83,90]		
• is recommended when the CHA_2DS_2-VASc score is ≥ 2	I	A
• should be considered in all other patients.	IIa	B
In patients with PADs who have an indication for OAC (e.g. AF or mechanical prosthetic valve), oral anticoagulants alone should be considered.[91]	IIa	B
After endovascular revascularization, aspirin or clopidogrel should be considered in addition to OAC for at least 1 month if the bleeding risk is low compared with the risk of stent/graft occlusion.	IIa	C
After endovascular revascularization, OAC alone should be considered if the bleeding risk is high compared with the risk of stent/graft occlusion.	IIa	C
OAC and SAPT may be considered beyond 1 month in high ischaemic risk patients or when there is another firm indication for long-term SAPT.	IIb	C

AF = atrial fibrillation; CAS = carotid artery stenosis; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category; DAPT = dual antiplatelet therapy; LEAD = lower extremity artery disease; OAC = oral anticoagulation; PADs = peripheral arterial diseases; SAPT = single antiplatelet therapy.

CHA_2DS_2-VASc score is calculated as follows: congestive heart failure history (1 point), hypertension (1 point), age >75 years (2 points), diabetes mellitus (1 point), stroke or TIA or arterial thromboembolic history (1 point), vascular disease history (1 point), age 65–74 years (1 point), sex category (1 point if female).

[a]Class of recommendation.

[b]Level of evidence.

[c]With the exception of patients with an indication for long-term OAC.

[d]Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multisite artery diseases).

6. Extracranial carotid and vertebral artery disease

Key messages

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

6.1 Carotid artery disease

6.1.1 Definition

The different presentation modes of cerebrovascular events are detailed in Web Table 4.[92] This chapter primarily deals with stroke secondary to carotid and vertebral artery disease but not cardioembolism. carotid artery stenosis refers to a ≥ 50% stenosis of the extracranial internal carotid artery (ICA), with stenosis severity estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (Web Figure 1).[93] According to the definitions in major trials, carotid stenosis is defined as 'symptomatic' if associated with symptoms in the preceding 6 months and 'asymptomatic' if no prior symptoms can be identified or when symptoms occurred >6 months ago. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

6.1.2 Diagnosis

6.1.2.1 Clinical evaluation

The different presentation modes of cerebrovascular events are presented in the Web addenda 6.1.2.1.

6.1.2.2 Imaging

In patients with TIA/stroke, urgent imaging of the brain and supra-aortic vessels is mandatory. DUS is usually the first-line carotid imaging modality to assess extracranial ICA stenoses. It includes Doppler velocity measurements and ratios for accurate evaluation of stenosis severity. Multiple criteria should be used for reliable estimation of stenosis. Further details are presented in a recent consensus document.[94]

Plaque morphological evaluation using MRI or DUS (echolucency, intraplaque haemorrhage, surface irregularity) may identify patients with asymptomatic stenoses at higher risk of ipsilateral ischaemic stroke. Other markers are silent infarction on CT/MRI and the detection of spontaneous embolization using transcranial Doppler monitoring.[95–97] Combining DUS with transcranial Doppler and/or transcranial colour-coded DUS enables a more thorough assessment of intracranial stenoses and an evaluation of impaired cerebrovascular reserve.[98]

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

Recommendations for imaging of extracranial carotid arteries

Recommendations	Class[a]	Level[b]
DUS (as first-line imaging), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.[99]	I	B
When CAS is being considered, it is recommended that any DUS study be followed by either MRA or CTA to evaluate the aortic arch as well as the extra- and intracranial circulation.[99]	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated by either MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).[99]	I	B

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

6.1.3. Treatment

6.1.3.1 Medical therapy

The medical management of patients with carotid disease is detailed in **chapters 4** and **5**.

6.1.3.2 Open surgery

6.1.3.2.1 Technical aspects. Details about the technical performance of CEA (type of anaesthesia, patching, shunting and other details) are summarized in the Web addenda 6.1.3.2.1.

6.1.3.2.2 Postoperative outcomes. Several studies have identified prognostic factors and markers for an increased risk of stroke after CEA. See Web addenda 6.1.3.2.2.

6.1.3.3 Endovascular techniques

CAS is a potentially less invasive alternative to CEA, with a low risk of cranial nerve injury, wound complications and/or neck haematoma, but it is vulnerable to access complications. CAS offers advantages over CEA in the presence of a 'hostile neck' (previous radiation, recurrent stenosis), contralateral recurrent laryngeal nerve palsy or in the case of challenging surgical access [very high ICA lesions, proximal common carotid artery (CCA) lesions], though not necessarily with a lower risk of perioperative stroke. Patients at higher risk for suffering perioperative cardiac complications may benefit from CAS in order to reduce perioperative MI (more common after CEA).[100] In a subgroup analysis from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the 4-year mortality was significantly higher [HR 3.40 (95% CI 1.67–6.92)] in patients suffering a perioperative MI.[100]

6.1.3.3.1 Carotid stenting: technical aspects. 6.1.3.3.1.1 Criteria associated with increased difficulty for carotid artery stenting

See Web addenda 6.1.3.3.1.1.

6.1.3.3.1.2 Embolic protection devices

The rationale for cerebral protection devices is supported by the presence of embolic material in distal filters,[101] but their use remains controversial. Using diffusion-weighted MRI, studies have reported lower rates of cerebral embolization with a proximal embolus protection device (EPD), but none was powered to address clinical outcomes.[102–106] A meta-analysis of 24 studies observed that EPD use was associated with a lower risk of perioperative stroke (RR 0.59; $P < 0.001$).[107] A pooled analysis of RCTs also reported significantly lower rates of perioperative stroke/death (RR 0.57), favouring EPD.[108] The benefit of EPDs was also evident in a prospective registry of 1455 patients: in those treated with EPD, in-hospital death/stroke rates were at 2.1% vs. 4.9% in patients treated without EPD ($P = 0.004$).[109] The best results within RCTs were seen in the CREST and the Asymptomatic Carotid Trial (ACT-1), where cerebral protection was mandatory and CAS practitioners were trained in its use.[110] In contrast, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial observed lower ipsilateral stroke rates in CAS patients without EPD (6.2%) vs. with EPD (8.3%).[111] Given the lack of high-quality data, the revised recommendation in these guidelines is based on a broad consensus that protection devices should be considered when performing CAS.

Recommendation on the use of embolic protection device during carotid stenting

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

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

6.1.3.3.2 Carotid artery stenting: operator experience and outcome. Evidence suggests that experience plays a role in CAS outcomes.[112,113] See Web addenda 6.1.3.3.2.

6.1.4 Management of carotid artery disease

6.1.4.1 Asymptomatic carotid artery disease

6.1.4.1.1 Open surgery vs. medical therapy. The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST-1) compared CEA with medical therapy in asymptomatic patients with 60–99% carotid stenosis.[114–116] In ACAS, 5-year rates of ipsilateral stroke/death under CEA vs. medical therapy were 5.1% vs. 11.0%, respectively ($P = 0.0001$, NNT = 18). The 10-year risk of 'any' stroke rates were 13.4% vs. 17.9%, respectively ($P = 0.009$, NNT = 22). ACST-1 reported 5-year rates of any stroke of 6.4% vs. 11.8%, respectively ($P < 0.0001$, NNT = 19). Fatal/disabling stroke rates were 3.5% vs. 6.1%, respectively ($P = 0.004$, NNT = 38). In a combined analysis of both trials, CEA conferred less benefit in women at 5 years.[117] At 10 years, however, ACST-1[115] reported that females gained a small but significant benefit following CEA (ARR 5.8%, $P = 0.05$). However, both trials are now rather dated. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person-years in studies completing recruitment before 2000, compared with 1.0/100 person-years during the 2000–2010 period ($P < 0.001$).[118] A 60–70% decline in annual stroke rates was also observed in medically treated patients in both trials over the recruitment period from 1995 to 2010.[114–116,119]

Despite the small but significant benefit favouring CEA over medical therapy, the ARR in stroke was only 4.6% at 10 years, indicating that 95% of asymptomatic patients ultimately underwent unnecessary interventions.[97,115] There is a need to target revascularization in a subgroup of patients with clinical and/or imaging features that may make them higher risk for stroke on BMT[97] (*Table 4*). Pending the

Table 4 Features associated with increased risk of stroke in patients with asymptomatic carotid stenosis treated medically (for details see Web Table 5

Clinical[a]	• Contralateral TIA/stroke[121]
Cerebral imaging	• Ipsilateral silent infarction[122]
Ultrasound imaging	• Stenosis progression (> 20%)[123] • Spontaneous embolization on transcranial Doppler (HITS)[124] • Impaired cerebral vascular reserve[125] • Large plaques[b][126] • Echolucent plaques[96] • Increased juxta-luminal black (hypoechogenic) area[127]
MRA	• Intraplaque haemorrhage[128] • Lipid-rich necrotic core

HITS = high intensity transient signal; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.
[a]Age is not a predictor of poorer outcome.
[b]More than 40 mm^2 on digital analysis.

development of better algorithms for patient selection, the presence of one or more of these clinical or imaging features might be useful for selecting patients for revascularization.

Importantly, ACST found no evidence that age >75 years at baseline was associated with any ipsilateral stroke reduction at 5 or 10 years. Additionally, the stenosis severity cannot be a criterion for stratifying late stroke risk. In a meta-analysis of 41 studies, ipsilateral stroke in patients with 50–69% and 70–99% stenosis were at 1.9 and 2.1/100 person-years, respectively (*p* value).[118] Neither the ACAS nor ACST found any evidence that stenosis severity or contralateral occlusion increased late stroke risk.[114,115,120]

6.1.4.1.2 Carotid revascularization: surgery vs. stenting. Five RCTs compared CEA with CAS in 'average risk for CEA' asymptomatic patients (Web Table 6), while SPACE-2 also included a third limb for BMT. The two biggest RCTs (CREST and ACT-1) requested exclusively experienced interventionists. In ACT-1, the 2.9% rate of death/stroke after CAS fell within the 3% accepted risk. Because of the learning curve associated with CAS, as well as it being performed in small numbers by multiple specialties,[129] there are concerns as to whether the death/stroke rates reported for CAS in these trials can be replicated in 'real-world' practice. While some national CAS registries have published death/stroke rates within 3%,[130,131] others have reported wide variations in practice. In a review of 19 381 CAS procedures in a registry, there was a 4-fold variation regarding in-hospital death/stroke despite adjusting for case mix.[129] A systematic review in large administrative dataset registries (>1.5 million procedures) suggested that 40% of registries reported death/stroke rates after CAS >3% in asymptomatic patients, while 14% reported death/stroke rates >5%.[132] In some large registries the median annual number of CAS procedures in asymptomatic patients may only be one or two,[133] which is known to be associated with higher rates of perioperative stroke/death.[134]

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized symptomatic and asymptomatic patients deemed 'high risk for surgery' to either CEA or CAS (using EPDs routinely).[135] High surgical risk was defined as clinically significant cardiac disease, severe pulmonary disease, contralateral ICA occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy, recurrent stenosis after CEA and age >80 years. The primary endpoint (30-day death/stroke/MI and/or death or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% of CAS patients and 20.1% of CEA patients ($P = 0.053$). At 3 years, major ipsilateral stroke (CAS 1.3% vs. CEA 3.3%), minor ipsilateral stroke (6.1% vs. 3.0%) and repeat revascularization (3.0% vs. 7.1%) were not statistically different.[136] However, 71% of SAPPHIRE patients were asymptomatic, in whom the 30-day rate of death/stroke after CAS was 5.8% vs. 6.1% after CEA,[135] both beyond the recommended 3%. If these procedural risk levels reflect contemporary practice, most 'high-risk for surgery' asymptomatic patients would be better treated medically.

Recommendations for management of asymptomatic carotid artery disease

Recommendations	Class[a]	Level[b]
In 'average surgical risk' patients with an asymptomatic 60–99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years.[116]	IIa	B
In asymptomatic patients who have been deemed 'high risk for CEA'[d] and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years.[135,136]	IIa	B
In 'average surgical risk' patients with an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[d] that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years.[110,129,132,137]	IIb	B

BP = blood pressure, CAS = carotid artery stenting, CEA = carotid endarterectomy.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 4* and Web Table 5.
[d]Age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

6.1.4.2 Symptomatic carotid artery disease

6.1.4.2.1 Open surgery. In a meta-analysis of all symptomatic patients randomized within NASCET and the European Carotid Surgery Trial (ECST), those with a NASCET 0–49% stenosis gained no benefit from surgery. CEA conferred a 7.8% ARR for stroke at 5 years in patients with 50–69% stenoses (NNT = 13). The maximum benefit was seen in patients with 70–99% ICA stenoses, where the ARR for stroke was 15.6% (NNT = 6).[138]

A number of clinical/imaging features are associated with an increased rate of late stroke in symptomatic patients with 50–99% stenoses if treated medically: increasing age (especially >75 years),

symptoms within 14 days, male sex, hemispheric (vs. retinal) symptoms, cortical (vs. lacunar) stroke, increasing number of medical comorbidities, irregular stenoses, increasing stenosis severity, contralateral occlusion, tandem intracranial stenoses and a failure to recruit intracranial collaterals.[139]

A meta-analysis from ECST and NASCET showed that when CEA was performed within 14 days in patients with 50–69% stenoses, the ARR for stroke at 5 years was 14.8% (NNT = 7). The ARR declined to 3.3% when the delay was 2–4 weeks (NNT = 30) and 2.5% when the delay was 4–12 weeks (NNT = 40). Beyond 12 weeks, no strokes were prevented by CEA. In patients with 70–99% stenoses who underwent CEA within 14 days, the ARR for stroke at 5 years was 23.0% (NNT = 4), falling to 15.9% where delays were 2–4 weeks (NNT = 6) and 7.9% for delays of 4–12 weeks (NNT = 13). When performed beyond 12 weeks, the ARR was 7.4% at 5 years (NNT = 14).[117,139] Women appeared to gain almost no benefit from CEA when performed beyond 4 weeks.[117,138,139]

The risk of stroke is high within the first days after TIA. The early risk of stroke in patients with 50–99% ICA stenoses ranged from 5 to 8% within 48 h after TIA, up to 17% by 72 h, 8–22% by 7 days and 11–25% at 14 days.[139]

There is controversy over whether CEA can be performed safely within the first 48 h after symptom onset. The Swedish Registry (n = 2596 CEAs) reported that when CEA was performed within the first 48 h, 11.5% died or suffered a stroke as compared with a procedural risk of < 5% when done any time afterwards.[140] In contrast, the UK national audit (n = 23 235 CEAs) reported that when CEA was performed within 48 h, the rate of death/stroke was much lower than observed in Sweden (3.7%). Thereafter, procedural risks were <2%.[141] A similarly low risk of death/stroke (3.0%) was observed in

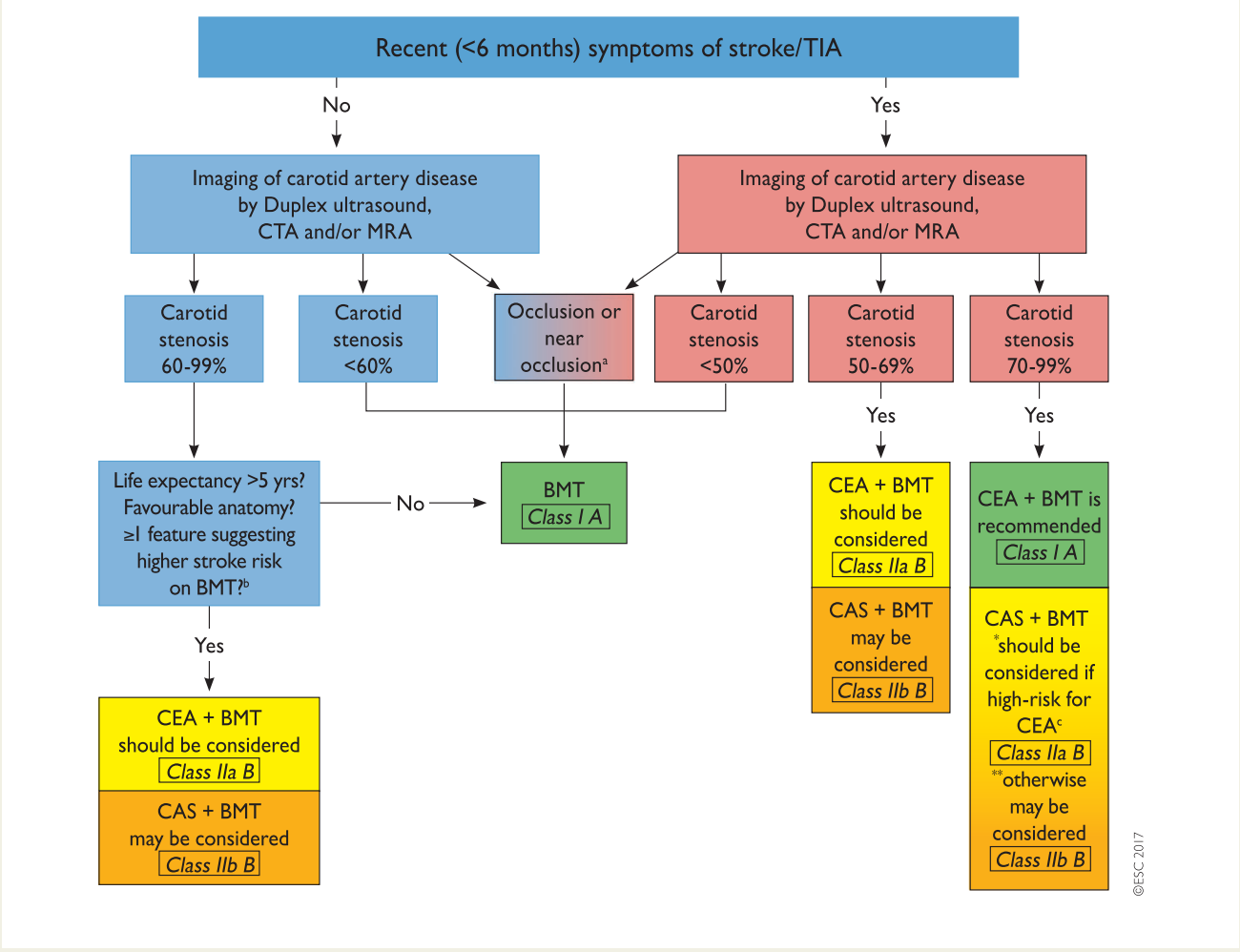


Figure 4 Management of extracranial carotid artery disease. BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.
[a]With post-stenotic internal carotid artery narrowed to the point of near occlusion.
[b]See Table 4.
[c]Age > 80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

Germany when CEA was performed in < 48 h.[142] These registries suggest that CEA can be performed safely in the first 7 days after TIA/minor stroke onset. However, not all patients will benefit from urgent revascularization. There may be an increased risk of haemorrhagic transformation within a recent area of infarction. Higher-risk patients include those with acute carotid occlusion or a persisting major neurological deficit, an area of middle cerebral artery infarction exceeding one-third, evidence of pre-existing parenchymal haemorrhage and evidence of impaired consciousness.

A meta-analysis of five randomized trials has shown that emergency endovascular treatment of acute ischaemic stroke (mechanical thrombectomy and/or intra-arterial thrombolysis) was associated with 2.22 times greater odds of a better functional outcome compared with those randomized to medical management. Endovascular therapy was not associated with a modified risk of symptomatic intracerebral hemorrhage.[143] In the MultiCenter Randomized Clinical Trial of Ischemic Stroke in the Netherlands (MR CLEAN), 13% of patients underwent simultaneous CAS, but no data were specifically provided on its procedural risk.[144]

6.1.4.2.2 Endovascular therapy vs. open surgery. The 30-day outcomes in four large contemporary RCTs comparing CEA with CAS are detailed in Web Table 7. Overall, the risk of 'any stroke' and 'death/stroke' was ~50% higher following CAS, primarily because CAS was associated with a significantly higher rate of minor stroke. Although the CREST reported that the majority of minor perioperative strokes resolved by 6 months,[145,146] it was also reported that any type of perioperative stroke was associated with a 3-fold poorer long-term survival,[146] similar to the poorer 4-year survival observed in patients suffering a perioperative MI.[100]

In a meta-analysis of 13 RCTs (80% involving symptomatic patients), CAS was associated with an increased risk of any stroke but a decreased risk of perioperative MI and cranial nerve injury.[147] In a Cochrane review (16 RCTs, 7572 patients), CAS was associated with higher periprocedural death/stroke, especially in patients >70 years of age, but with significantly lower risks for MI, cranial nerve injury and haematoma.[148]

In an individual-based meta-analysis, patients undergoing CEA within 7 days of symptoms had a 2.8% risk of stroke/death compared with 9.4% after CAS. Patients undergoing CEA 8–14 days after symptom onset had a 3.4% risk of stroke/death compared with 8.6% after CAS.[149] In the CREST, CAS performed within 14 days of symptom onset incurred a 5.6% rate of death/stroke compared with 2.6% after CEA. In symptomatic patients undergoing an intervention at 15–60 days, CAS was associated with a 6.1% risk of death/stroke compared with 2.3% after CEA.[150]

A meta-analysis[151] of 30-day death/stroke rates after CEA and CAS involving symptomatic patients randomized within the CREST, Endarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), SPACE and International Carotid Stenting Study (ICSS) (Web Table 8) reported significantly higher rates of perioperative stroke in patients >70 years of age undergoing CAS. In contrast, age had little effect on CEA outcomes. The increase in perioperative stroke in elderly CAS patients may be due to a greater burden of aortic arch disease. Beyond the 30-day perioperative period, long-term data suggest that outcomes after CAS are almost identical to those after CEA.[152,153] Henceforth the predicted magnitude of the 30-day risk will largely determine whether CEA or CAS is preferable in individual patients. Importantly, in a recent systematic review, 72% of registries reported 30-day death/stroke rates after CAS exceeding the 6% recommended risk threshold in patients with symptomatic ICA stenosis.[132]

An algorithm for managing TIA/minor stroke patients with carotid disease is presented in *Figure 4*.

Recommendations on revascularization in patients with symptomatic carotid disease*

Recommendations	Class[a]	Level[b]
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is < 6%.[138,147]	I	A
CEA should be considered in symptomatic patients with 50–69% carotid stenoses, provided the documented procedural death/stroke rate is < 6%.[138,147]	IIa	A
In recently symptomatic patients with a 50–99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them 'high risk for CEA', CAS should be considered, provided the documented procedural death/stroke rate is < 6%.[135,145,152]	IIa	B
When revascularization is indicated in 'average surgical risk' patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is < 6%.[152,153]	IIb	B
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.[138,154,155]	I	A
Revascularization is not recommended in patients with a < 50% carotid stenosis.[138]	III	A

*Stroke or TIA occurring within 6 months.

6.2 Vertebral artery disease

6.2.1 Definition and natural history

Up to 20% of ischaemic cerebrovascular events involving the posterior circulation are related to vertebral artery disease.[156] For further details see Web addenda 6.2.1.

6.2.2 Imaging

CTA/MRA have a higher sensitivity (94%) and specificity (95%) than DUS (sensitivity 70%).[157] Vertebral ostial stenoses are overestimated by MRA,[158] while CTA underestimates the degree and prevalence of ostial vertebral artery stenoses. Despite these limitations, DSA is rarely required for diagnostic purposes. However, DSA may be necessary in patients with symptomatic vertebral artery disease who are potentially candidates for revascularization. In patients with known vertebral artery stenoses, it is reasonable to use DUS to assess stenosis progression and to follow patients after revascularization therapies.

6.2.3 Management of vertebral artery disease

Although no prospective RCTs have evaluated different drug therapies in patients with vertebral artery disease, aspirin (or clopidogrel if aspirin is not tolerated) and statins are recommended irrespective of symptoms (see **chapters 4** and **5**). Most patients with asymptomatic vertebral artery disease do not require any revascularization.

In patients with ischaemic events despite antiplatelet therapy, revascularization may be considered. Surgery of extracranial vertebral stenoses (with transposition to CCA, trans-subclavian vertebral endarterectomy, distal venous bypass) can be performed with low stroke/death rates in experienced surgical teams.[159,160] However, in centres with limited expertise with complex vertebral artery reconstructions, open surgery has been mostly replaced by endovascular interventions. A systematic review identified 993 patients who were mostly symptomatic, 72% of whom had ostial vertebral stenoses. Overall, 980 were treated with stent implantation with a technical success rate of 99.3% and a 30-day stroke rate of 1.1%. At 24 months, 1.1% had suffered a recurrent vertebrobasilar stroke. Restenosis rates at 24 months were 11% in patients treated with drug-eluting stents and 30% if bare-metal stents were used.[161]

The Vertebral Artery Stenting Trial (VAST)[162] randomized patients with vertebrobasilar symptoms within the preceding 30 days and an extra- or intracranial vertebral artery stenosis >50% to stenting plus BMT (n = 57) or BMT alone (n = 58). The VAST was suspended after recruiting 115 patients, because of regulatory issues. Thirty-day vertebrobasilar stroke or death occurred in 5% of patients randomized to stenting and 2% in the medical arm. At 3 years, 12% of stented patients had recurrent vertebrobasilar stroke compared with 7% in the medical arm. These results do not support routine endovascular interventions for symptomatic vertebral artery stenoses unless symptoms recur despite optimal medical therapy.

Recommendations for management of vertebral artery stenoses

Recommendations	Class[a]	Level[b]
In patients with symptomatic extracranial vertebral artery stenoses, revascularization may be considered for lesions ≥50% in patients with recurrent ischaemic events despite optimal medical management.[159,160,162]	IIb	B
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C

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

7. Upper extremity artery disease

Key messages

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

General data, natural history and clinical examination are presented in Web addenda 7.1, 7.2 and 7.3 and Web Table 9. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

7.4 Diagnostic methods

7.4.1 Duplex ultrasound

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

7.4.2 Computed tomography angiography

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

7.4.3 Magnetic resonance angiography

MRA provides both functional and morphological information useful to distinguish anterograde from retrograde perfusion and to estimate stenosis severity.

7.4.4 Digital subtraction angiography

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

7.4.5 Positron emission tomography

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

7.5 Treatment

Risk factor control and BMT are recommended in all patients with symptomatic upper extremity artery disease (UEAD) to reduce CV risk.[163] Revascularization is indicated in symptomatic patients with TIA/stroke, coronary subclavian steal syndrome, ipsilateral haemodialysis access dysfunction or impaired quality of life (QOL). Revascularization should be considered in asymptomatic patients with planned coronary artery bypass grafting (CABG) using the internal mammary artery, those with ipsilateral haemodialysis access, as well as asymptomatic patients with significant bilateral subclavian stenosis/occlusion for adequate BP surveillance. For revascularization, both endovascular and surgical procedures are available. There are no RCTs comparing endovascular vs. open repair. The risk of severe complications, including vertebrobasilar stroke, is low with both approaches. The post-procedural stroke rate is reported at 2.6% for endovascular therapy[164] and 0.9–2.4% after open surgery.[164–166]

7.5.1 Endovascular treatment

Percutaneous angioplasty for subclavian arterial stenosis is often used with stenting. There is no conclusive evidence to determine whether stenting is more effective than balloon angioplasty.[167] In a systematic review (544 patients) comparing both options, stenting was superior to angioplasty alone, with a higher patency rate at 1 year indicated by the absence of events.[168] Technical success of endovascular therapy is 100% when treating stenosis and 80–95% when treating occlusions. Similar results were reported for endovascular therapy of the innominate artery.[169] In heavily calcified ostial lesions, in addition to an easier placement, balloon-expandable stents give more radial force than nitinol stents. Mid-term patency (≥24 months) following subclavian endovascular therapy is 70–85%.[170]

7.5.2 Open surgery

An endovascular approach is often the default strategy. However, in selected patients with low operative risk, with subclavian artery occlusion or after endovascular therapy failure, surgical subclavian–carotid transposition is safe with good long-term patency results (5-year patency 96%).[166] Carotid–subclavian bypass surgery with a prosthetic graft showed long-term benefit with low operative mortality and morbidity rates, especially in patients with extensive disease or re-occlusion after stenting (5-year patency 97%).[171] Other options are extrathoracic extra-anatomic bypass procedures (axillo-axillary, carotid–axillary or carotid–carotid bypass).[172,173] The transthoracic approach is an option in patients with multivessel disease involving the aortic arch and several supra-aortic vessels.[165]

7.5.3 Medical therapy

In symptomatic patients with contraindications for endovascular therapy or open surgery, prostanoid infusion or thoracic sympathectomy may be considered.[174]

Recommendations on the management of subclavian artery stenosis

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

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

8. Mesenteric artery disease

Key messages

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

This section covers acute and chronic occlusion of the mesenteric arteries. Chronic mesenteric artery disease is related to atherosclerosis as well as non-atherosclerotic conditions. For further information refer to the recently published ESVS Guidelines.[175] The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

8.1 Acute mesenteric ischaemia

8.1.1 Diagnosis

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

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

Although D-dimer is highly sensitive, it lacks specificity. There are no other reliable plasma markers for acute mesenteric ischaemia.[176–178] In a meta-analysis, the pooled sensitivity for D-dimer was 96%, with a specificity of 40%.[179] Lactate is metabolized effectively by the liver, explaining why it does not serve as an early warning. Lactate is elevated only after bowel gangrene has developed.[179]

Plain abdominal X-ray is not specific. If normal, it does not exclude the diagnosis. High-resolution CTA is a major breakthrough for the timely diagnosis of acute mesenteric ischaemia. It should be performed in arterial and venous phases, with 1 mm slices. The diagnostic accuracy for CTA in diagnosing acute superior mesenteric artery occlusion is excellent. In a meta-analysis the pooled estimated sensitivity was 94% and the specificity was 95%. Asking the radiologist specifically about occlusion of the mesenteric arteries improves diagnostic accuracy.[180] Elevated creatinine levels are common but should not contraindicate CTA in the case of clinical suspicion. CT examination of the bowel (venous phase) may show wall thickening, dilatation, intestinal pneumatosis, portal venous air, mesenteric oedema or ascites. There is no role for ultrasound or invasive angiography in diagnosing acute mesenteric ischaemia. MRA is seldom available outside of office hours, explaining why its diagnostic accuracy has not been investigated in this setting.

8.1.2 Treatment

Most patients with an acute occlusion of the superior mesenteric artery require immediate revascularization to survive. Approximately 20–30% can survive with bowel resection only, especially with distal embolism.[181] In other cases, revascularization must be attempted. Whether revascularization or bowel inspection (with possible resection) should be performed first is controversial. Data suggest that revascularization should be attempted first, unless there is serious peritonitis and septic shock.[175]

Another controversy is whether open surgery or endovascular therapy of the occluded superior mesenteric artery should be attempted first.[182–185] Hybrid intervention is an alternative, with retrograde operative mesenteric stenting, where the superior mesenteric artery is punctured in the open abdomen, followed by stenting.[186] In the absence of RCTs, evidence is based on prospective registries.[182,184,187,188] In the case of embolic occlusion, open and endovascular revascularizations seem to do equally well, whereas with thrombotic occlusion, endovascular therapy is associated with lower mortality and bowel resection rates. The principles of damage control surgery[189] are important to follow when treating these frail patients. This concept focuses on saving life by restoring normal physiology as quickly as possible, thus avoiding unnecessary time-consuming procedures.[189] Although laparotomy is not mandatory after endovascular therapy in these patients with acute bowel ischaemia, it is often necessary to inspect the bowel. In this setting, second-look laparotomy is also indicated after open revascularization.[184,190] Intra-arterial catheter thrombolysis of the superior mesenteric artery has been reported with good results. Severe bleeding complications were uncommon, except when intestinal mucosal gangrene was present.[191]

Recommendations on the management of acute mesenteric ischaemia

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended.[179]	I	C
In patients with suspicion of acute mesenteric ischaemia, the measurement of D-dimer should be considered to rule out the diagnosis.[177–179]	IIa	B
Treatment		
In patients with acute thrombotic occlusion of the superior mesenteric artery, endovascular therapy should be considered as first-line therapy for revascularization.[182,184,187,188]	IIa	B
In patients with acute embolic occlusion of the superior mesenteric artery, both endovascular and open surgery therapy should be considered.[182,184,187,188]	IIa	B

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

8.2 Chronic mesenteric artery disease

Chronic mesenteric artery disease includes stenosis or chronic occlusion of the coeliac trunk or the mesenteric arteries. Its prevalence increases with age, especially in the presence of other atherosclerotic diseases and abdominal aortic aneurysms (AAAs). In patients with an AAA and LEAD, significant stenosis (mostly asymptomatic) of at least one of the three arteries was detected in 40% and 27%, respectively.[192]

8.2.1 Diagnosis

8.2.1.1 Clinical examination

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

8.2.1.2 Imaging

DUS is often the imaging tool of first choice. This investigation requires great skill and should be performed in specialized centres. Diagnostic criteria have been suggested, although without consensus.[193,194] When a decision to treat CMI is made, an anatomical mapping of the lesions is needed, mostly using CTA. There is no study comparing CTA with MRA or DSA, the latter offering the advantages of mapping the flow and enabling post-stenotic pressure measurements.

8.2.1.3 Functional assessments

See Web addenda 8.2.1.3.

8.2.2 Treatment

There is no indication for prophylactic revascularization in patients with asymptomatic disease. In symptomatic CMI, it is not recommended to delay revascularization in order to improve the nutritional status. Delayed revascularization has been associated with clinical deterioration, bowel infarction and sepsis from catheter-related complications.[195] The number of mesenteric revascularizations has increased 10-fold over the last decade as the result of increased recognition and imaging and the use of endovascular therapy as a less invasive treatment.[188] In most centres, angioplasty and stenting have become the first option, reserving open surgery for patients with failed endovascular therapy. Data from the USA show lower postoperative mortality after endovascular therapy [OR 0.20 (95% CI 0.17–0.24)].[188,196] Open mesenteric bypass, however, offers improved patency, lower re-intervention rates and better freedom from recurrent symptoms.[188,197] In the absence of RCTs it is not possible to issue a recommendation favouring open surgery or endovascular therapy as first-line therapy. Both alternatives should be discussed case by case by a multidisciplinary team.

Another controversy is whether one or two vessels (superior mesenteric and/or coeliac artery) should be treated. Two retrospective studies showed a non-significant trend towards lower recurrence rates with two-vessel stenting.[198,199] Another study reported similar recurrence rates at 2 years.[200] Balloon angioplasty has been replaced by primary stenting in most centres. Regarding the choice between bare-metal or covered stents to treat superior mesenteric artery stenosis, in one non-randomized study of 225 patients,[201] covered stents were associated with lower restenosis and symptom recurrence rates and fewer re-interventions (10% vs. 50%).

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

8.3 Secondary prevention

Following acute mesenteric arterial occlusion, lifelong medical treatment should be considered, including lifestyle changes and BMT for atherosclerosis (see **chapter 4**). After embolic occlusion, treatment of the source of embolus and/or lifelong anticoagulation therapy should be considered.[202] After treatment of CMI, antiplatelet therapy is indicated.[1] The potential benefit of DAPT is unknown.

Recommendations for management of chronic mesenteric artery disease

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected CMI, DUS is recommended as the first-line examination.[193,194]	I	C
In patients with suspected CMI, occlusive disease of a single mesenteric artery makes the diagnosis unlikely and a careful search for alternative causes should be considered.[192,203]	IIa	C
Treatment		
In patients with symptomatic multivessel CMI, revascularization is recommended.[192,195]	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.[192,195]	III	C

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

9. Renal artery disease

Key messages

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

9.1 Introduction

RAD is generally considered when renal artery stenosis (RAS) is ≥ 60%, although additional functional assessment by haemodynamic criteria is advisable. The prevalence of RAD increases with advancing age and is mostly related to atherosclerosis. It is associated with male gender, hypertension, smoking, diabetes mellitus, CKD, aorto-iliac occlusive disease and CAD.[204] It may be present in 5–10% of the general population, with a higher prevalence in high-risk populations.[205] Approximately 20% have bilateral disease or a single functioning kidney may be affected. Less frequent causes of RAD are fibromuscular dysplasia (FMD)[206] and arteritis. The former is the most frequent cause of RAD in young hypertensive patients (especially in women). The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

9.2 Clinical presentation

Clinical signs include resistant hypertension, unexplained renal failure and, uncommonly, flash pulmonary oedema (*Table 5*). RAD promotes hypertension and subsequent CV disease, while atherosclerotic disease may in turn cause RAD. The filtration capacity loss in the ischaemic kidney may be due to either hypoperfusion or recurrent micro-embolism. Renal hypoperfusion causes a BP increase secondary to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), which may be important for the risk of CV complications.[207] With unilateral RAS, the contralateral kidney increases sodium excretion and there is no sodium retention or volume overload. In patients with severe bilateral RAS or unilateral RAS in a single functioning kidney, renal failure and flash pulmonary oedema can occur.[208]

Table 5 Clinical situations raising suspicion for renal artery disease

Onset of hypertension before the age of 30 years
Onset of severe hypertension after the age of 55 years, when associated with CKD or heart failure
Hypertension and abdominal bruit
Rapid and persistent worsening of previously controlled hypertension
Resistant hypertension (i.e. other secondary form unlikely and target not achieved despite four drug classes including a diuretic and a mineralocorticoid-receptor antagonist in appropriate doses)
Hypertensive crisis (i.e. acute renal failure, acute heart failure, hypertensive encephalopathy, or grade 3–4 retinopathy)
New azotaemia or worsening of renal function after treatment with RAAS blockers
Unexplained atrophic kidney or discrepancy in kidney size, or unexplained renal failure
Flash pulmonary oedema

CKD = chronic kidney disease; RAAS = renin-angiotensin-aldosterone system.

9.3 Natural history

See Web addenda 9.3.

9.4 Diagnostic strategy

Patients with a clinical suspicion of RAS (*Table 5*) should undergo a diagnostic evaluation including physical examination, exclusion of other potential causes of secondary hypertension and ambulatory (or home) BP measurement.

DUS is the first-line imaging modality to screen for significant (≥60%) stenosis,[205,207,209,210] although it may overestimate the degree of stenosis. It can be repeated to assess stenosis progression and its haemodynamic consequences (e.g. flow velocity and vascular resistance). Peak systolic velocity in the main renal artery shows the best sensitivity (85%) and specificity (92%) to identify angiographically significant stenoses.[211] Thus criteria other than peak systolic velocity should be used to support the diagnosis.[210,211] The renal resistive index (RRI) may help to identify more severe RAS and provide additional information on patient response to intervention.[207,210] Further information regarding the RRI is available in Web addenda 9.4. Renal DUS requires experience and may be difficult in overweight subjects. Other limitations include failure to visualize the entire renal artery and missing the highest peak systolic velocity tracing. Accessory renal arteries may be missed.

Multidetector CTA and MRA (with or without gadolinium) show equally high sensitivities (64–100% and 94–97%) and specificities (92–98% and 85–93%) for detection of significant RAS.[212,213] CTA provides higher spatial resolution, but usual limitations should always be considered. Gadolinium-enhanced MRA provides excellent characterization of renal arteries, the surrounding vessels, renal mass and even renal excretion function. It tends to overestimate the stenosis severity. It is less useful in patients with renal artery stents, because of artefacts. DSA remains the gold standard for the diagnosis of RAS.[209,212] Since the correlation between the angiographic stenosis and the haemodynamic impact is poor, a major advantage of DSA is the possibility to measure the pressure gradient across the lesion, which is especially useful for moderate stenosis. A systolic pressure gradient >20 mmHg or a resting pressure ratio distal to the stenosis <0.90 is considered to confirm significant stenosis in symptomatic patients.[214] Renal artery fractional flow reserve measured during maximum hyperaemia induced by papaverine, dopamine or acetylcholine is an alternative method to assess the stenosis severity, which might predict the clinical response to intervention.[207] Due to the potential risks with invasive procedures, angiography is generally limited to visualization and quantification of the stenosis before vascular intervention. It is also indicated when clinical suspicion is high and the results of non-invasive examinations are inconclusive.[205,212] Renal scintigraphy, plasma renin measurements before and after ACEI provocation and venous renin measurements are no longer considered for the diagnosis of atherosclerotic RAD.[204,205]

Recommendations for diagnostic strategies for renal artery disease

Recommendations	Class[a]	Level[b]
DUS (as first-line), CTA[c] and MRA[d] are recommended imaging modalities to establish a diagnosis of RAD.[204,212]	I	B
DSA may be considered to confirm a diagnosis of RAD when clinical suspicion is high and the results of non-invasive examinations are inconclusive.[212,215]	IIb	C
Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD.[204]	III	C

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

9.5 Prognosis

Life expectancy is reduced in patients with RAD without end-stage CKD, as they mostly die from an acute CV event.[205,216] Patients who progress to end-stage CKD have even higher mortality rates.[217]

9.6 Treatment

9.6.1 Medical therapy

Risk assessment, lifestyle management and medical treatment should follow current ESC guidelines.[25,41,218] Most antihypertensive drugs (ACEIs, ARBs, calcium channel blockers, beta-blockers and diuretics) are effective for treating hypertension and may lead to slowing of the progression of renal disease.[219,220] Most patients with significant RAS tolerate ACEIs or ARBs without difficulty. In large observational studies, ACEIs and ARBs have shown benefits in reducing mortality and morbidity in patients with RAD.[220–222] However, these drugs can reduce glomerular capillary hydrostatic pressure enough to cause a transient decrease in glomerular filtration rate and raise serum creatinine, warranting caution and close follow-up. These drugs may be introduced in the case of bilateral RAS and when the lesion affects a single functioning kidney, provided that the patients are very carefully monitored.[219,221] Optimal BP in the setting of RAD is unknown. It has been hypothesized that severe RAS might require higher BP to maintain adequate blood flow across the stenosis; however, very low rates of progressive renal failure in medically managed patients argue against such a strategy.

Statins are associated with improved survival, slower lesion progression and reduced restenosis risk after renal stenting.[223,224] Antiplatelet therapy should be part of BMT.

9.6.2 Revascularization

9.6.2.1 Impact on blood pressure control, renal function and survival

Uncontrolled trials have reported improved BP control in resistant hypertensive patients following renal stenting,[225,226] but previous[227] and three recent major RCTs (Web Table 10) showed no difference between endovascular therapy and BMT other than a minor reduction in antihypertensive medications after revascularization (2.96 vs. 3.18 drugs).[228–231] Data do not support a benefit of stenting based on the degree of stenosis, haemodynamic significance of the lesion or higher pre-treatment BP.[230]

Regarding renal function, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial reported no benefit from endovascular therapy over BMT.[227] Progressive renal failure occurred in 16.8% in the endovascular therapy group vs. 18.9% in the BMT group ($P = 0.34$) and permanent renal replacement therapy occurred in 3.5% vs. 1.7%, respectively ($P = 0.11$). Renal artery dissection was reported in 2.4% of the endovascular therapy group. The two other RCTs showed similar findings even in the highest risk groups, including severe kidney ischaemia and impaired or rapidly decreasing kidney function. There was no advantage for revascularization with regard to CV morbidity and mortality.[229,231,232]

9.6.2.2 Revascularization in specific indications

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

9.6.2.2.1 Renal artery disease due to fibromuscular dysplasia. The prevalence of renal FMD is considered to be < 1% in the general population[233] and more common in women than men by a ratio of 9:1. Renovascular hypertension is the most common clinical presentation of FMD. Revascularization of FMD-related lesions should be recommended only in cases of symptomatic FMD with signs of organ ischaemia.[206] Renal balloon angioplasty is the first-line revascularization technique and stenting should be considered in the management of dissection or balloon angioplasty failure.[234–236] In a meta-analysis (47 studies for endovascular therapy, 1616 patients; 23 studies for open surgery, 1014 patients), major complication rates and mortality rates were lower in the case of endovascular therapy (6.3% and 0.9% vs. 15.4% and 1.2%, respectively).[236] Therefore, open surgery should be reserved for the management of stenosis associated with complex aneurysms, complex lesions (arterial bifurcation or branches) or endovascular therapy failure.[206]

9.6.2.2.2 Renal artery disease in flash pulmonary oedema or congestive heart failure. Patients with sudden onset or 'flash' pulmonary oedema or congestive heart failure predominantly with preserved left ventricular function may be candidates for endovascular therapy,[208,237–239] although a subanalysis of the CORAL trial was not conclusive.[229]

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

9.6.2.3 Technical considerations for revascularization
See Web addenda 9.6.2.3.

Recommendations for treatment strategies for renal artery disease

Recommendations	Class[a]	Level[b]
Medical therapy		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral RAS.[219–222,240]	I	B
Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with renal artery disease.	I	C
ACEIs/ARBs may be considered in bilateral severe RAS and in the case of stenosis in a single functioning kidney, if well-tolerated and under close monitoring.[219,221]	IIb	B
Revascularization		
Routine revascularization is not recommended in RAS secondary to atherosclerosis.[229,231,232]	III	A
In cases of hypertension and/or signs of renal impairment related to renal arterial fibromuscular dysplasia, balloon angioplasty with bailout stenting should be considered.[234–236]	IIa	B
Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema.[229,237,238]	IIb	C
In the case of an indication for revascularization, surgical revascularization should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure or during open aortic surgery.[241–243]	IIa	B

ACEIs = angiotensin-converting enzyme inhibitor; ARBs = angiotensin-receptor blockers; RAS = renal artery stenosis.
[a]Class of recommendation.
[b]Level of evidence.

10. Lower extremity artery disease

Key messages

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

10.1. Clinical presentation and natural history

LEAD has several different presentations, categorized according to the Fontaine or Rutherford classifications (*Table 6*). Even with a similar extent and level of disease progression, symptoms and their intensity may vary from one patient to another. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

Most patients are asymptomatic, detected either by a low ABI (<0.90) or pulse abolition. Among these, a subset may have severe disease without symptoms, which can be related to their incapacity to walk enough to reveal symptoms (e.g. heart failure) and/or reduced pain sensitivity (e.g. diabetic neuropathy). This subgroup should be qualified as 'masked LEAD'. In a study of 460 patients with LEAD, one-third of asymptomatic patients were unable to walk more than six blocks, corresponding to this concept.[244] These patients were older, more often women, with higher rates of neuropathy and multiple comorbidities. While all asymptomatic patients are at increased risk of CV events, the subgroup with masked LEAD is also at high risk of limb events. This situation explains how a subset of patients presents a specific path with 'asymptomatic' disease shifting rapidly to severe LEAD. A typical presentation is an elderly patient with several comorbidities who presents with toe necrosis after a trivial wound (e.g. after aggressive nail clipping). It is important to identify these patients to educate them about foot protection. Hence, prior to the estimation of pain when walking, a clinical assessment of walking ability is necessary, and clinical examination should also look for neuropathy. LEAD can also be clinically masked in one leg when the other one has more disabling disease.

In symptomatic patients, the most typical presentation is IC. The Edinburgh Claudication Questionnaire is a standardized method to screen and diagnose typical IC.[245]

CLTI is defined by the presence of ischaemic rest pain, with or without tissue loss (ulcers, gangrene) or infection. When present,

Table 6 Clinical stages of lower extremity artery disease

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

arterial ulcers are usually painful and are often complicated by local infection and inflammation. When pain is absent, peripheral neuropathy should be considered. While CLTI is a clinical diagnosis, it is often associated with an ankle pressure <50 mmHg or toe pressure <30 mmHg.[246] Investigation of the microcirculation [i.e. transcutaneous oxygen pressure ($TcPO_2$)] is helpful in some cases of medial calcinosis.

Regular clinical examination is important in elderly patients, especially diabetic patients.[247] Early recognition of tissue loss and referral to a vascular specialist is mandatory to improve limb salvage. Primary major amputation rates in patients unsuitable for revascularization are high (20–25%).[248] CLTI is also a marker for generalized, severe atherosclerosis, with a 3-fold increased risk of MI, stroke and vascular death as compared to patients with IC.[246,248]

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

Regarding the natural history, in a recent meta-analysis,[249] most patients with IC present increased 5-year cumulative CV-related morbidity of 13% vs. 5% in the reference population. Regarding the limb risk, at 5 years, 21% progress to CLTI, of whom 4–27% have amputations.[246]

10.2 Diagnostic tests

10.2.1 Ankle-brachial index

The ABI is the first diagnostic step after clinical examination (see **chapter 4**). An ABI ≤0.90 has 75% sensitivity and 86% specificity to diagnose LEAD.[250] Its sensitivity is poorer in patients with diabetes or end-stage CKD because of medial calcification.[251] Patients with borderline ABI (0.90–1.00) need further diagnostic tests (*Table 3* and **chapter 4**). When clinically suspected, a normal ABI (>0.90) does not definitely rule out the diagnosis of LEAD; further post-exercise ABI and/or DUS are necessary. In case of a high ABI (>1.40) related to medial calcification, alternative tests such as toe pressure, toe-brachial index (TBI) or Doppler waveform analysis of ankle arteries are useful. Along with DUS, ABI can be used during patient follow-up. It is also a good tool for stratifying the CV risk (see **chapter 4**).[6]

Recommendations for ankle-brachial index measurement

Recommendations	Class[a]	Level[b]
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.[250,251]	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated.[252]	I	C

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

10.2.2 Treadmill test

The treadmill test (usually using the Strandness protocol at a speed of 3 km/h and 10% slope) is an excellent tool for objective functional assessment and unmasking moderate stenosis, as well as for exercise rehabilitation follow-up. It is also helpful when the ischaemic origin of limb pain is uncertain. The test is stopped when the patient is unable to walk further because of pain, defining maximal walking distance (WD). A post-exercise ankle SBP decrease >30 mmHg or a post-exercise ABI decrease >20% are diagnostic for LEAD.[251]

10.2.3 Imaging methods

10.2.3.1 Ultrasound

DUS provides extensive information on arterial anatomy and haemodynamics. It must be combined with ABI measurement. It presents 85–90% sensitivity and >95% specificity to detect stenosis >50%.[253] A normal DUS at rest should be completed by a post-exercise test when iliac stenosis is suspected, because of lower sensitivity. DUS is operator dependent and good training is mandatory. DUS does not present as a roadmap the entire vasculature. Another imaging technique is usually required when revascularization is considered. DUS is also important to address vein quality for bypass substitutes. It is the method of choice for routine follow-up after revascularization.

10.2.3.2 Computed tomography angiography

In a meta-analysis, the reported sensitivity and specificity of CTA to detect aorto-iliac stenoses >50% were 96% and 98%, respectively, with similar sensitivity (97%) and specificity (94%) for the femoro-popliteal region.[254] The main advantages are visualization of calcifications, clips, stents, bypasses and concomitant aneurysms. Beyond general limitations (radiation, nephrotoxicity and allergies), pitfalls are severe calcifications (impeding the appreciation of stenosis, mostly in distal arteries).

10.2.3.3 Magnetic resonance angiography

The sensitivity and specificity of MRA are ~95% for diagnosing segmental stenosis and occlusion. However, MRA tends to overestimate the degree of stenosis.[255] It cannot visualize arterial calcifications, useful for the estimation of stenosis severity in highly calcified lesions. This is a limitation for selection of the anastomotic site of surgical bypass. The visualization of steel stents is poor. In expert centres, MRA has a higher diagnostic accuracy for tibial arteries than DUS and CTA.

10.2.3.4 Digital subtraction angiography

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

10.2.3.5 Cardiovascular screening in patients with LEAD

Patients with LEAD often have other concomitant arterial lesions, including other PADs and AAA. See Web addenda 10.2.3.5 and **chapter 11**.

10.2.4 Other tests

Toe systolic BP, TBI and $TcPO_2$ are useful in patients with medial calcinosis and incompressible arteries. For further details see Web addenda 10.2.4.

Recommendations on imaging in patients with lower extremity artery disease

Recommendations	Class[a]	Level[b]
DUS is indicated as a first-line imaging method to confirm LEAD lesions.[253]	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.[254–257]	I	C
Data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to a treatment decision.[246]	I	C
DUS screening for AAA should be considered.[258,259]	IIa	C

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

10.3 Medical treatment

The therapeutic options addressed here are those to improve limb symptoms or salvage. Treatments proposed to reduce other CV events and mortality are addressed in **chapter 4**.

General prevention strategies can improve limb events. Smoking cessation provides the most noticeable improvement in WD when combined with regular exercise, especially when lesions are located below the femoral arteries. In patients with IC, the natural history is deteriorated by ongoing tobacco use, with increased risk of amputation.[25,260]

Several studies have shown that statins significantly improve the CV prognosis of patients with IC or CLTI.[30,34] Additionally, several meta-analyses have shown a relevant improvement in pain-free and maximal WD with the use of statins.[30,261] It is suggested that statins could limit adverse limb events in patients with LEAD.[33]

In subjects with hypertension, calcium antagonists or ACEIs/ARBs should be preferred because of their potential in peripheral arterial dilatation. A meta-analysis[262] showed improved maximal and pain-free WD when using an ACEI over placebo; however, two of six RCT reports have been recently withdrawn because of unreliable data, and the meta-analysis of the remaining studies is inconclusive.[263] The benefit of verapamil in improving WD in LEAD has been shown in a randomized study.[264] Because of comorbidities such as heart failure, beta-blockers are indicated in some patients with LEAD. Studies have shown that beta-blockers, in particular nebivolol, are safe in patients with IC without negative effects on WD.[49] Metoprolol and nebivolol have been compared in a double-blind RCT including 128 beta-blocker-naive patients with IC and hypertension.[265] After a 48-week treatment period, both drugs were well tolerated and decreased BP equally. In both groups, maximal WD improved significantly. Nebivolol showed an advantage, with significant improvement in pain-free WD [+34% ($P < 0.003$) vs. +17% for metoprolol ($P < 0.12$)]. In a single-centre study of 1873 consecutive CLTI patients who received endovascular therapy, those treated with other beta-blockers did not have a poorer clinical outcome.[266] In a multicentre registry of 1273 patients hospitalized for severe LEAD (of whom 65% had CLTI and 28% were on beta-blocker therapy), death and amputation rates did not differ among those with vs. without beta-blocker.[267]

10.4 Revascularization options: general aspects

See Web addenda 10.4.

10.5 Management of intermittent claudication

10.5.1 Exercise therapy

In patients with IC, exercise therapy (ExT) is effective and improves symptoms and QOL and increases maximal WD. In 30 RCTs including 1816 patients with stable leg pain, ExT improved maximal WD on a treadmill by almost 5 min compared with usual care.[268] Pain-free and maximal WD were increased on average by 82 and 109 m, respectively. Improvement was observed up to 2 years. Moreover, ExT improved QOL. Exercise did not improve ABI. Whether ExT reduces CV events and improves life expectancy is still unclear. Supervised ExT is more effective than unsupervised ExT.[11,269]

In 14 trials with participants assigned to either supervised ExT or unsupervised ExT (1002 participants), lasting from 6 weeks to 12 months, maximal and pain-free WD increased by almost 180 m in favour of supervised ExT. These benefits remained at 1 year. Most studies use programmes of at least 3 months, with a minimum of 3 h/week, with walking to the maximal or submaximal distance. Long-term benefits of ExT are less clear and largely depend on patient compliance. Supervised ExT is safe and routine cardiac screening beforehand is not required.[270] It is also more cost effective than unsupervised ExT,[271] but it is not reimbursed or available everywhere. Although home-based walking ExT is not as effective as supervised ExT, it is a useful alternative, with positive effects on QOL and functional walking capacity vs. walking advice alone.[272,273] Alternative exercise modes (e.g. cycling, strength training and upper-arm ergometry) may be useful when walking exercise is not an option for patients, as these have also been shown to be effective.[274] ExT is impossible in patients with CLTI but can be considered after successful revascularization.[275,276]

10.5.2 Pharmacotherapy to decrease walking impairment

Some antihypertensive drugs (e.g. verapamil),[264] statins,[277,278] antiplatelet agents and prostanoids (prostaglandins I2 and E1)[279] have some favourable effects on WD and leg functioning (see above). Other pharmacological agents claim to increase WD in patients with IC without other effects on CV health. The drugs mostly studied are cilostazol, naftidrofuryl, pentoxifylline, buflomedil, carnitine and propionyl-L-carnitine.[261,280] However, objective documentation of such an effect is limited. The beneficial effects on WD, if any, are generally mild to moderate, with large variability.[261] Also, the incremental benefit of these treatments in addition to ExT and statins is unknown. For further details see Web addenda 10.5.2.

10.5.3 Revascularization for intermittent claudication

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

10.5.3.1 Aorto-iliac lesions

Isolated aorto-iliac lesions are a common cause of claudication. In the case of short stenosis/occlusion (<5 cm) of iliac arteries, endovascular therapy gives good long-term patency (≥90% over 5 years) with a low risk of complications.[281] In cases of ilio-femoral lesions, a hybrid procedure is indicated, usually endarterectomy or bypass at the femoral level combined with endovascular therapy of iliac arteries, even with long occlusions. If the occlusion extends to the infrarenal aorta, covered endovascular reconstruction of an aortic bifurcation can be considered. In a small series, 1- and 2-year primary patency was 87% and 82%, respectively.[282] If the occlusion comprises the aorta up to the renal arteries and iliac arteries, aorto-bifemoral bypass surgery is indicated in fit patients with severe life-limiting claudication.[283] In these extensive lesions, endovascular therapy may be an option, but it is not free of perioperative risk and long-term occlusion. In the absence of any other alternative, extra-anatomic bypass (e.g. axillary to femoral bypass) may be considered.

10.5.3.2 Femoro-popliteal lesions

Femoro-popliteal lesions are common in claudicants. If the circulation to the profunda femoral artery is normal, there is a good possibility that the claudication will be relieved with ExT and intervention is mostly unnecessary. If revascularization is needed, endovascular therapy is the first choice in stenosis/occlusions <25 cm. If the occlusion/stenosis is > 25 cm, endovascular recanalization is still possible, but better long-term patency is achieved with surgical bypass, especially when using the great saphenous vein (GSV). No head-to-head trials comparing endovascular therapy and surgery are yet available. In the Zilver-PTX trial, the 5-year primary patency with conventional and drug-eluting stents was 43% and 66%, respectively.[76] The 5-year patency after above-the-knee femoro-popliteal bypass is > 80% with GSV and 67% with prosthetic conduits.[284] The challenge of endovascular therapy is the long-term patency and durability of stents in the femoro-popliteal region, where the artery is very mobile. Several new endovascular solutions, such as atherectomy devices, drug-eluting balloons and new stent designs, have been shown to improve long-term patency.

10.5.4 Management strategy for intermittent claudication

Several studies have demonstrated the efficacy of endovascular therapy and open surgery on symptom relief, WD and QOL in claudicants. However, these interventions have limited durability and may be associated with mortality and morbidity. Thus they should be restricted to patients who do not respond favourably to ExT (e.g. after a 3-month period of ExT) or when disabling symptoms substantially alter daily life activities. A systematic review of 12 trials (1548 patients) comparing medical therapy, ExT, endovascular therapy and open surgery in claudicants showed that, compared with the former, each of the three other alternatives was associated with improved WD, claudication symptoms and QOL.[285] Compared with endovascular therapy, open surgery may be associated with longer hospital stays and higher complication rates but results in more durable patency. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial randomized 111 patients with IC and aorto-iliac lesions to BMT alone or in combination with supervised ExT or stenting.[286] At 6 months, changes in maximal WD were greatest with supervised ExT, while stenting provided greater improvement in peak walking time than BMT alone. At 18 months the difference in terms of peak walking time was not statistically different between supervised EXT and stenting.[286] The management of patients with intermittent claudication is summarized in *Figure 5*.

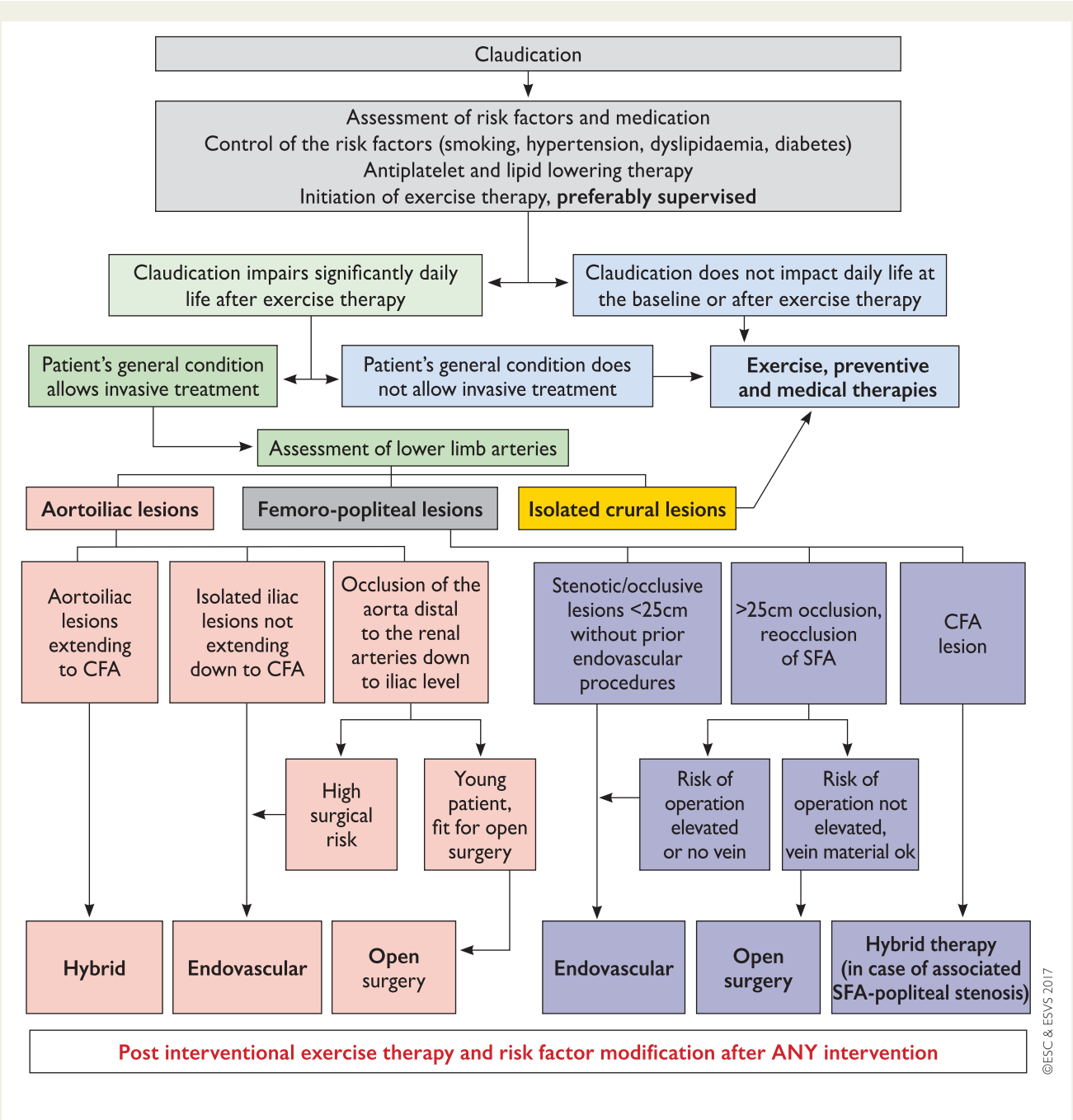


Figure 5 Management of patients with intermittent claudication[a]. CFA = common femoral artery; SFA = superficial femoral artery.
[a]Related to atherosclerotic lower extremity artery disease (LEAD).

Recommendations for the management of patients with intermittent claudication

Recommendations	Class[a]	Level[b]
On top of general prevention, statins are indicated to improve walking distance.[30,278]	I	A
In patients with intermittent claudication:		
• supervised exercise training is recommended[273,287–289]	I	A
• unsupervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
When daily life activities are compromised despite exercise therapy, revascularization should be considered.	IIa	C
When daily life activities are is severely compromised, revascularization should be considered in association with exercise therapy.[288,290]	IIa	B

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

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

Recommendations	Class[a]	Level[b]
An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions.[291]	I	C
In patients fit for surgery, aorto-(bi)femoral bypass should be considered in aorto-iliac occlusions.[281,292,293]	IIa	B
An endovascular-first strategy should be considered in long and/or bilateral lesions in patients with severe comorbidities.[288,294,295]	IIa	B
An endovascular-first strategy may be considered for aorto-iliac occlusive lesions if done by an experienced team and if it does not compromise subsequent surgical options.[76,281–283,286]	IIb	B
Primary stent implantation rather than provisional stenting should be considered.[294–296]	IIa	B
Open surgery should be considered in fit patients with an aortic occlusion extending up to the renal arteries.	IIa	C
In the case of ilio-femoral occlusive lesions, a hybrid procedure combining iliac stenting and femoral endarterectomy or bypass should be considered.[297–300]	IIa	C
Extra-anatomical bypass may be indicated for patients with no other alternatives for revascularization.[301]	IIb	C

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

Recommendations on revascularization of femoro-popliteal occlusive lesions[c]

Recommendations	Class[a]	Level[b]
An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions.[302,303]	I	C
Primary stent implantation should be considered in short (i.e. <25 cm) lesions.[304,305]	IIa	A
Drug-eluting balloons may be considered in short (i.e. <25 cm) lesions.[77,306–310]	IIb	A
Drug-eluting stents may be considered for short (i.e. <25 cm) lesions.[302,303,311]	IIb	B
Drug-eluting balloons may be considered for the treatment of in-stent restenosis.[312,313]	IIb	B
In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. ≥25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is > 2 years.[314]	I	B
The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass.[284,315]	I	A
When above-the-knee bypass is indicated, the use of a prosthetic conduit should be considered in the absence of any autologous saphenous vein.[284]	IIa	A
In patients unfit for surgery, endovascular therapy may be considered in long (i.e. ≥25 cm) femoro-popliteal lesions.[312]	IIb	C

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

10.6 Chronic limb-threatening ischaemia

This entity includes clinical patterns with a threatened limb viability related to several factors. In contrast to the former term 'critical limb ischaemia', severe ischaemia is not the only underlying cause. Three issues must be considered with the former terminology of critical limb ischaemia. First, 'critical' implies that treatment is urgent to avoid limb loss, while some patients can keep their legs for long periods of time even in the absence of revascularization.[316] Second, the increasing predominance of diabetes in these situations, present in 50–70% of cases, presents mostly as neuro-ischaemic diabetic foot ulcers. Third, the risk of amputation not only depends on the severity of ischaemia, but also the presence of a wound and infection. This explains why ankle or toe pressures, measured to address LEAD severity, are not a definition component of CLTI.

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

A new classification system (WIfI) has been proposed as the initial assessment of all patients with ischaemic rest pain or wounds.[317] The target population for this system includes any patient with

- ischaemic rest pain, typically in the forefoot with objectively confirmed haemodynamic studies (ABI <0.40, ankle pressure <50 mmHg, toe pressure <30 mmHg, $TcPO_2$ <30 mmHg),
- diabetic foot ulcer,
- non-healing lower limb or foot ulceration ≥2 weeks duration or
- gangrene involving any portion of the foot or lower limb.

The three primary factors that constitute and contribute to the risk of limb threat are wound (W), ischaemia (I) and foot infection (fI).

Each factor is graded into four categories (0 = none, 1 = mild, 2 = moderate, 3 = severe). *Table 7* shows the coding and clinical staging according to the WIfI classification. Web Figure 2 provides an estimation of the amputation risk according the WIfI classification. The management of patients with CLTI should consider the three components of this classification system. Revascularization should always be discussed, as its suitability is increased with more severe stages (except stage 5).

10.6.2 Management of patients with chronic limb-threatening ischaemia

The management of patients with CLTI is summarized in *Figure 6*. All patients with CLTI must have BMT with correction of risk factors (see **section 9.3**). In those with diabetes, glycaemic control is particularly important for improved limb-related outcomes, including lower rates of major amputation and increased patency after infrapopliteal revascularization.[318,319] Proper wound care must be started immediately, as well as the use of adapted footwear, treatment of concomitant infection and pain control.

10.6.2.1 Revascularization

Revascularization should be attempted as much as possible.[246,320–322] So far, only one randomized trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, has directly compared endovascular therapy to open surgery in CLTI patients.[323] At 2 years there was no significant difference between endovascular therapy and surgery regarding amputation-free survival. In survivors after 2 years, bypass surgery was associated with improved survival (on average 7 months, $P = 0.02$) and amputation-free survival (6 months,

Table 7 Assessment of the risk of amputation: the WIFI classification (for further details see Mills *et al*[317])

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or $TcPO_2$
	0	≥0.80	> 100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fI (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		
Example: A 65-year-old male diabetic patient with gangrene of the big toe and a <2 cm rim of cellulitis at the base of the toe, without any clinical/biological sign of general infection/inflammation, whose toe pressure is at 30 mmHg would be classified as Wound 2, Ischaemia 2, foot Infection 1 (WIfI 2-2-1). The clinical stage would be 4 (high risk of amputation). The benefit of revascularization (if feasible) is high, also depending on infection control.				

ABI = ankle-brachial index; TcPO2 = transcutaneous oxygen pressure.

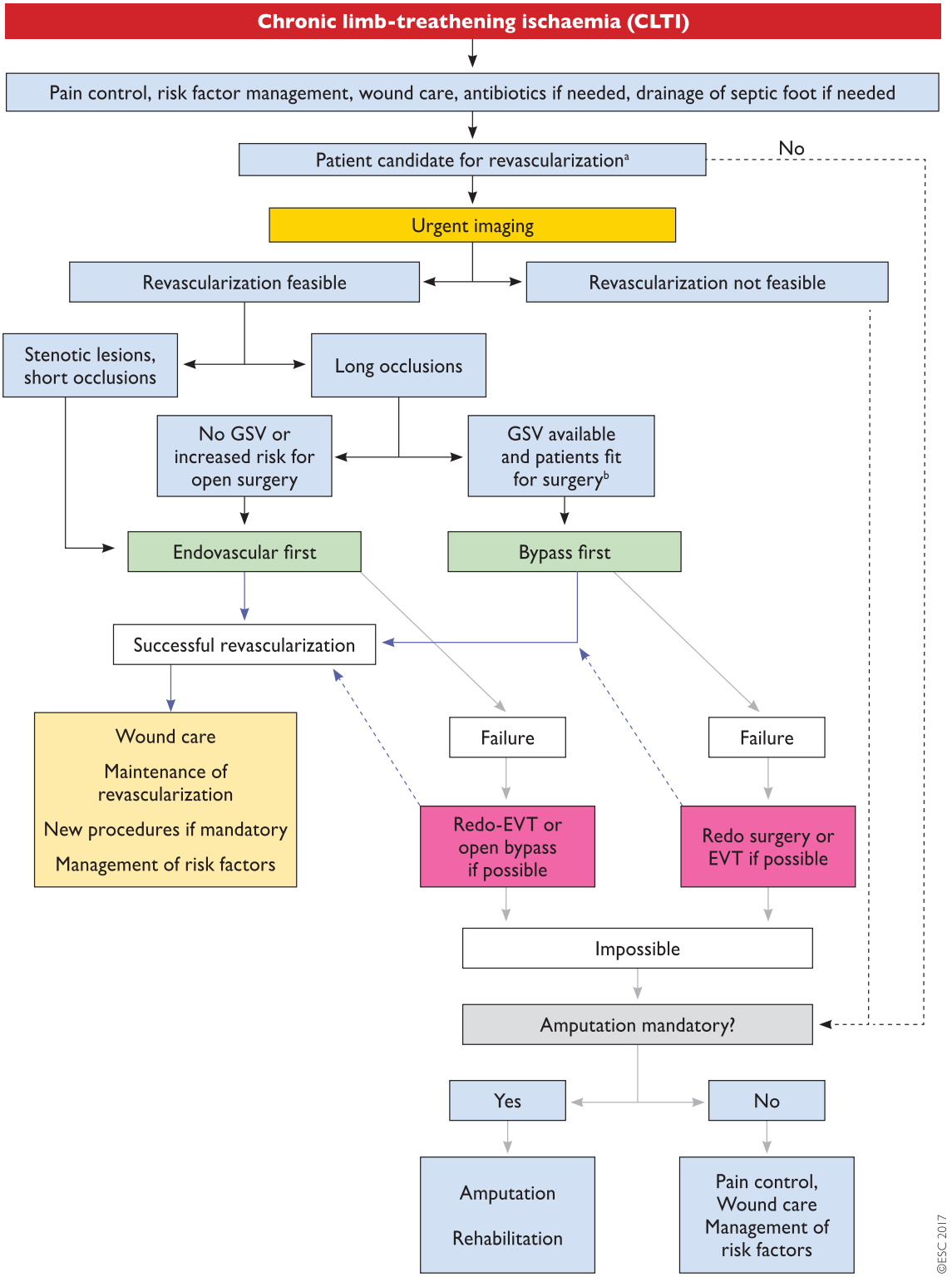


Figure 6 Management of patients with chronic limb-threatening ischaemia. EVT= endovascular therapy; GSV = great saphenous vein.
[a]In bedridden, demented and/or frail patients, primary amputation should be considered.
[b]In the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff.

$P = 0.06$).[314] These data are challenged by more recent endovascular therapy techniques. So far, drug-eluting balloons in below-the-knee disease have shown no superiority over plain balloon angioplasty.[324] The results of two ongoing RCTs, BASIL-2 and Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI), are awaited.[325,326] Meanwhile, in each anatomical region, both revascularization options should be individually discussed.

10.6.2.1.1 Aorto-iliac disease. CLTI is almost never related to isolated aorto-iliac disease, and downstream lesions are often concomitant. In addition to CTA and/or MRA, complete DSA down to the plantar arches is required for proper arterial network assessment and procedure planning.[327] Hybrid procedures (e.g. aorto-iliac stenting and distal bypass) should be encouraged in a one-step modality when necessary.

10.6.2.1.2 Femoro-popliteal disease. CLTI is unlikely to be related to isolated SFA lesions; usually femoro-popliteal involvement combined with aorto-iliac or below-the-knee disease is found. In up to 40% of cases, inflow treatment is needed.[324] The revascularization strategy should be judged on lesion complexity. If endovascular therapy is chosen first, landing zones for potential bypass grafts should be preserved. When bypass surgery is decided, the bypass should be as short as possible, using the saphenous vein.

10.6.2.1.3 Infra-popliteal disease. Extended infra-popliteal artery disease is mainly seen in diabetic patients, often associated with SFA lesions (inflow disease). Full-leg DSA down to the plantar arches is mandatory to explore all revascularization options.[327] In stenotic lesions and short occlusions, endovascular therapy can be the first choice. In long occlusions of crural arteries, bypass with an autologous vein gives superior long-term patency and leg survival. If the patient has increased risk for surgery or does not have an autologous vein, endovascular therapy can be attempted. The decision of revascularization should also consider the angiosome concept, targeting the ischaemic tissues. For further details, see Web addenda 10.6.2.1.3.1.

Recommendations on revascularization of infra-popliteal occlusive lesions

Recommendations	Class[a]	Level[b]
In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage.[320–326]	I	C
For revascularization of infra-popliteal arteries:		
• bypass using the great saphenous vein is indicated	I	A
• endovascular therapy should be considered.[320–326]	IIa	B

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

10.6.3 Spinal cord stimulation

See Web addenda 10.6.3.

10.6.4 Stem cell and gene therapy

Angiogenic gene and stem cell therapy are still being investigated, with insufficient evidence in favour of these treatments.[328–330] For further details see Web addenda 10.6.4.

10.6.5 Amputation

10.6.5.1 Minor amputation

In case of CLTI, minor amputation (up to the forefoot level) is often necessary to remove necrotic tissues with minor consequences on patient's mobility. Revascularization is needed before amputation to improve wound healing. Foot $TcPO_2$ and toe pressure can be useful to delineate the amputation zone (see **section 10.2.4**).

10.6.5.2 Major amputation

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

Secondary amputation should be performed when revascularization has failed and re-intervention is no longer possible or when the limb continues to deteriorate because of infection or necrosis despite patent graft and optimal management. In any case, infragenicular amputation should be preferred, because the knee joint allows better mobility with a prosthesis. For bedridden patients, femoral amputation may be the best option.

Recommendations on the management of chronic limb-threatening ischaemia

Recommendations	Class[a]	Level[b]
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.[317]	I	C
In patients with CLTI, assessment of the risk of amputation is indicated.[317]	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended.[318,319]	I	C
For limb salvage, revascularization is indicated whenever feasible.[314]	I	B
In CLTI patients with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularization.	IIa	C
In patients with CLTI, stem cell/gene therapy is not indicated.[328]	III	B

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

10.7 Acute limb ischaemia

Acute limb ischaemia is caused by an abrupt decrease in arterial perfusion of the limb. Potential causes are artery disease progression, cardiac embolization, aortic dissection or embolization, graft thrombosis, thrombosis of a popliteal aneurysm or cyst, popliteal artery entrapment syndrome, trauma, phlegmasia cerulea dolens, ergotism, hypercoagulable states and iatrogenic complications related to vascular procedures. Limb viability is threatened and prompt management is needed for limb salvage.

Once the clinical diagnosis is established, treatment with unfractionated heparin should be given, along with appropriate analgesia.[246,331] The emergency level and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficits. The clinical categories are presented in *Table 8*.

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

Different revascularization modalities can be applied, including percutaneous catheter–directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy) and surgical thrombectomy, bypass and/or arterial repair. The strategy will depend on the presence of a neurological deficit, ischaemia duration, its localization, comorbidities, type of conduit (artery or graft) and therapy-related risks and outcomes. Owing to reduced morbidity and mortality, endovascular therapy is often preferred, especially in patients with severe comorbidities. Thrombus extraction, thrombo-aspiration and surgical thrombectomy are indicated in the case of neurological deficit, while catheter-directed thrombolytic therapy is more appropriate in less severe cases without neurological deficit. The modern concept of the combination of intra-arterial thrombolysis and catheter-based clot removal is associated with 6-month amputation rates of < 10%.[246] Systemic thrombolysis has no role in the treatment of patients with acute limb ischaemia.

Based on RCTs, there is no clear superiority of local thrombolysis vs. open surgery on 30-day mortality or limb salvage.[333] After thrombus removal, the pre-existing arterial lesion should be treated by endovascular therapy or open surgery. Lower extremity four-compartment fasciotomies should be performed in patients with long-lasting ischaemia to prevent a post-reperfusion compartment syndrome. The management of acute limb ischaemia is summarized in *Figure 7*.

Table 8 Clinical categories of acute limb ischaemia[332]

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

Recommendations for the management of patients presenting with acute limb ischaemia

Recommendations	Class[a]	Level[b]
In the case of neurological deficit, urgent revascularization is indicated.[246,331,c]	I	C
In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision.[246,331]	I	C
Heparin and analgesics are indicated as soon as possible.[246,331]	I	C

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

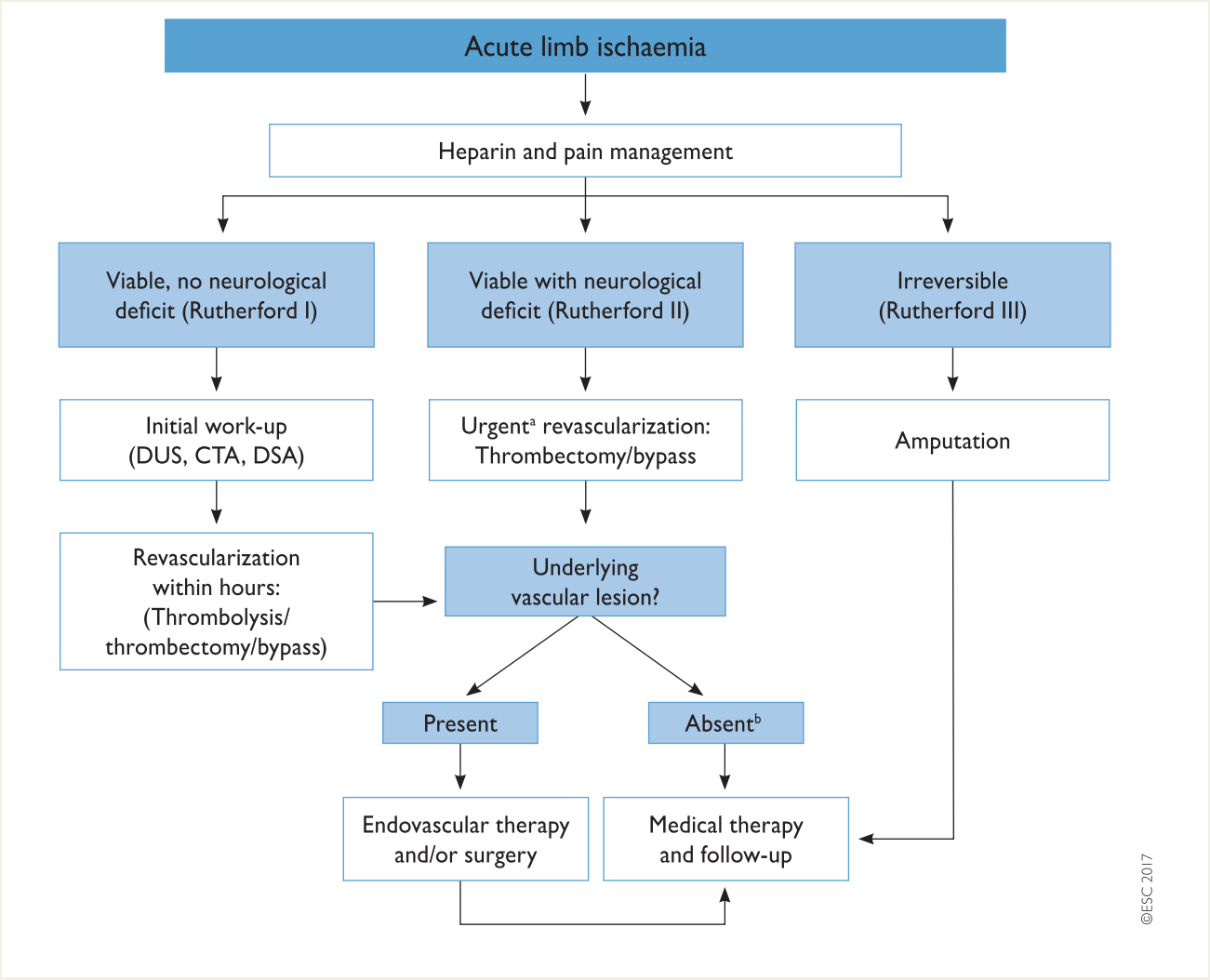


Figure 7 Management of acute limb ischaemia. CTA = computed tomography angiography; DSA = digital subtraction ultrasound; DUS = duplex ultrasound.
[a]Imaging should not delay revascularization.
[b]Specific etiological work-up is necessary (cardiac, aorta).

10.8 Blue toe syndrome

Another particular clinical presentation is blue toe syndrome. This is characterized by a sudden cyanotic discoloration of one or more toes. It is usually due to embolic atherosclerotic debris from the proximal arteries. For further details see Web addenda 10.8.

11. Multisite artery disease

Key messages

- Multisite artery disease (MSAD) is common in patients with atherosclerotic involvement in one vascular bed, ranging from 10 to 15% in patients with CAD to 60 to 70% in patients with severe carotid stenosis or LEAD.
- MSAD is invariably associated with worse clinical outcomes; however, screening for asymptomatic disease in additional vascular sites has not been proven to improve prognosis.
- In patients with any presentation of PADs, clinical assessment of symptoms and physical signs of other localizations and/or CAD is necessary, and in case of clinical suspicion, further tests may be planned.
- Systematic screening for asymptomatic MSAD is not indicated for any presentation of PADs, as it would not consistently lead to a modification of management strategy. It may be interesting in some cases for risk stratification (e.g. an antiplatelet therapy strategy beyond 1 year in patients who benefited from coronary stenting for ACS).
- In some situations the identification of asymptomatic lesions may affect patient management. This is the case for patients undergoing CABG, where ABI measurement may be considered,

especially when saphenous vein harvesting is planned, and carotid screening should be considered in a subset of patients at high risk of CAD.
- In patients scheduled for CABG with severe carotid stenoses, prophylactic carotid revascularization should be considered in recently symptomatic cases and may be considered in asymptomatic cases after multidisciplinary discussion.
- In patients planned for carotid artery revascularization for asymptomatic stenosis, preoperative coronary angiography for detection (and revascularization) of CAD may be considered.

Multisite artery disease (MSAD) is defined by the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories. Subclinical plaques are beyond the scope of this document. While patients with MSAD are regularly encountered in clinical practice, robust data on the management of these patients are scarce. For the management of these patients, clinical status and comorbidities should be considered, in addition to the lesion sites. Generally the treatment strategy should be decided case by case within a multidisciplinary team and should focus first on the symptomatic vascular site. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

11.1 Multisite artery disease: epidemiology and impact prognosis

Among 3.6 million American volunteers for a systematic ultrasound screening for LEAD, CAD and AAA, the proportion of subjects with two or more localizations increased with age, from 0.04% at 40–50 years to 3.6% at 81–90 years.[334] *Figure 8* summarizes the prevalence of MSAD when atherosclerotic disease is diagnosed in one territory.

Although several studies have demonstrated that patients with MSAD have a significantly worse clinical outcome as compared with patients with single vascular site disease, the only RCT designed to assess the impact on prognosis of systematic screening for MSAD in patients with high-risk CAD (three-vessel CAD and/or with an ACS at age >75 years) failed to prove any significant benefit.[344] The Aggressive detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis (AMERICA) trial randomized 521 patients to a proactive strategy (total-body DUS and ABI measurement associated with intensive medical therapy) or to conventional strategy (no screening for asymptomatic MSAD and standard medical therapy); at the 2-year follow-up, the primary composite endpoint, including death, any ischaemic event leading to rehospitalization or any evidence of organ failure, occurred in 47.4% and 46.9% of patients, respectively ($P > 0.2$).[344] Hence the clinical benefit of systematic screening for asymptomatic MSAD in patients with known atherosclerotic disease appears questionable.

11.2 Screening for and management of multisite artery disease

11.2.1 Peripheral arterial diseases in patients presenting with coronary artery disease

11.2.1.1 Carotid artery disease in patients scheduled for coronary artery bypass grafting

Web Table 11 details the epidemiology of CAD and the incidence of stroke among patients undergoing isolated CABG (without synchronous/staged CEA).[341] In another study, unilateral 50–99% carotid stenosis was found in 11% of patients, bilateral 50–99% stenosis in 5.6% and unilateral occlusion in 1.3%.[345]

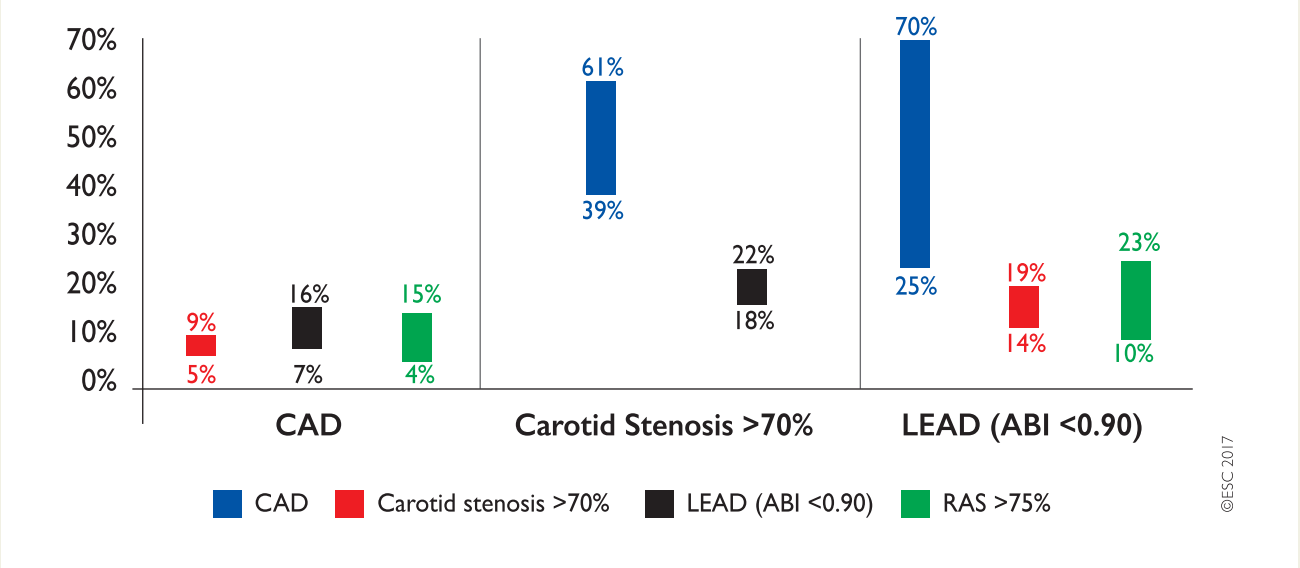


Figure 8 Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease.[51, 335–343] The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g. in patients with CAD, 5 - 9% of cases have concomitant carotid stenosis >70%). ABI = ankle-brachial index; CAD = coronary artery disease; LEAD = lower extremity artery disease; RAS = renal artery stenosis.

Ischaemic stroke after CABG is multifactorial, including aortic embolism during manipulation, cannulation/decannulation and graft anastomosis to the ascending aorta; platelet aggregation during cardiopulmonary bypass (CPB) and hypercoagulable states; carotid embolization; postoperative AF and haemodynamic instability, especially in patients with impaired cerebral vascular reserve.[346]

The impact of asymptomatic carotid stenosis on stroke risk after CABG is modest, except for bilateral stenoses or unilateral occlusion. In a systematic review, 86% of postoperative strokes were not attributed to carotid disease. Carotid stenosis appears as a marker of severe aortic atherosclerosis and stroke risk rather than the direct cause. Conversely, a history of prior stroke/TIA is a significant risk factor for post-CABG stroke.[341,347–349] Evidence of the benefits of prophylactic revascularization of asymptomatic carotid stenoses in all CABG candidates to reduce perioperative stroke is lacking. The decision to perform CEA/CAS in these patients should be made by a multidisciplinary team. It may be reasonable to restrict prophylactic carotid revascularization to patients at highest risk of postoperative stroke, i.e. patients with severe bilateral lesions or a history of prior stroke/TIA.[341,348–350]

The timing and the modality of carotid revascularization (CEA or CAS) are controversial and should be individualized based on clinical presentation, level of emergency and severity of carotid and coronary artery diseases. Web Table 12 details the results of meta-analyses evaluating outcomes following different scenarios. No specific strategy is clearly safer. A recent RCT did not report lower stroke rate for off-pump vs. on-pump surgery.[351]

The two-staged CEA strategies provide higher risk of periprocedural MI if the carotid artery is revascularized first and a trend towards increased cerebral risk if CABG is performed first. In a recent RCT in patients with unilateral asymptomatic carotid stenosis, CABG followed by CEA was the worst strategy, with a higher 90-day stroke and death rate compared with CABG with previous or synchronous CEA (8.8% vs. 1.0%; $P = 0.02$).[352]

The higher risk of cerebral embolization from aortic arch plaques may explain why CAS is not associated with lower procedural risks. If CAS is performed before elective CABG, the need for DAPT usually delays cardiac surgery for at least 4 weeks, exposing the patient to the risk of MI between the staged CAS and CABG (0–1.9%).[353,354] Some authors performed CAS immediately prior to CABG and reported low death/stroke rates.[355] Among 132 patients with same-day CAS plus cardiac surgery, the in-hospital stroke rate was 0.75%, while 5- and 10-year freedom from neurological events was 95% and 85%, respectively.[356] In a single-centre propensity-matched analysis of 350 patients undergoing carotid revascularization within 90 days before cardiac surgery, staged CAS plus cardiac surgery and combined CEA plus cardiac surgery had similar early outcomes (death/stroke/MI), whereas staged CEA plus cardiac surgery incurred the highest risk, driven by interstage MI. Beyond 1 year, patients with either staged or combined CEA plus cardiac surgery had a 3-fold higher rate of MACE compared with patients undergoing staged CAS plus cardiac surgery.[357] However, staged CAS plus cardiac surgery entails an increased bleeding risk during CABG (if performed within the DAPT period).

Two studies suggest that limiting DUS to patients with at least one risk factor (age >70 years, history of cerebrovascular disease, presence of a carotid bruit, multivessel CAD or LEAD) identifies all patients with carotid stenosis >70%, reducing the total number of scans by 40%.[338,358] However, a study comparing patients undergoing a preoperative carotid scan before cardiac surgery with those without screening reported no difference in perioperative mortality and stroke.[345] But only 12% of those with severe carotid stenosis underwent synchronous CABG plus CEA. Hence routine carotid DUS identifies only the minority of patients who will develop perioperative stoke, without clearly evidenced benefit of prophylactic carotid revascularization. Carotid DUS is indicated in patients with recent (<6 months) stroke/TIA. No carotid imaging is indicated when CABG is urgent, unless neurological symptoms occurred in the previous 6 months.

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

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, DUS is recommended in patients with a recent (<6 months) history of TIA/stroke.[345,358]	I	B
In patients with no recent (<6 months) history of TIA/stroke, DUS may be considered in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD or carotid bruit.[345,358]	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C

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

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

Recommendations	Class[a]	Level[b]
It is recommended that the indication (and, if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients with a recent (<6 months) history of TIA/stroke who are scheduled for CABG:		
• Carotid revascularization should be considered in patients with 50–99% carotid stenosis.[359,360]	IIa	B
• Carotid revascularization with CEA should be considered as the first choice in patients with 50–99% carotid stenosis.[359,360]	IIa	B
• Carotid revascularization is not recommended in patients with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG:		
• Routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.[350]	III	B
• Carotid revascularization may be considered in patients with bilateral 70–99% carotid stenoses or 70–99% carotid stenosis + contralateral occlusion.[350]	IIb	B
• Carotid revascularization may be considered in patients with a 70–99% carotid stenosis in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke[c] in order to reduce stroke risk beyond the perioperative period.	IIb	C

CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 4*.

11.2.1.2 Carotid artery stenosis in other coronary artery disease patients (without coronary artery bypass grafting)

The available data regarding the prevalence of carotid stenosis in these patients and the lack of evidence of any effect on outcome lead to the conclusion that carotid screening is not indicated in patients with CAD other than in candidates for CABG. For further details refer to Web addenda 11.2.1.2.

11.2.1.3. Renal artery disease in patients presenting with coronary artery disease

In the absence of any proof of benefit, systematic screening for RAS in patients with CAD cannot be recommended. For further details refer to Web addenda 11.2.1.3. As in other patients, the indications for imaging renal arteries are presented in *Table 5*.

11.2.1.4 Lower extremity artery disease in patients with coronary artery disease

LEAD often coexists with CAD (*Figure 8*). It is often asymptomatic or masked by limiting angina and/or dyspnoea. LEAD (ABI < 0.90) is present in 13–16% of patients who have CAD at coronary angiography.[361,362] Left main coronary artery stenosis and multivessel CAD were independent predictors. Patients with LEAD exhibit more extensive, calcified and progressive coronary atherosclerosis.[363]

The coexistence of LEAD in CAD patients has been consistently associated with worse outcome, although it is unclear whether LEAD is a marker or a cause of cardiac adverse events.[364,365] In the 3-year follow-up of the PEGASUS trial, patients with concomitant LEAD had adjusted 2-fold increased rates of all-cause death, CV death, stroke and MACE.[81] In ACS registries, in-hospital mortality, acute heart failure and recurrent ischaemia rates were significantly higher (up to 5-fold) in subjects with LEAD.[340,343] In a pooled analysis of 19 867 patients enrolled in RCTs on PCI, 8% had clinical LEAD, identified as an independent predictor of mortality at 30 days (HR 1.67), 6 months (HR 1.76) and 1 year (HR 1.46).[366] Concomitant LEAD (clinical or subclinical) is also associated with worse outcome in patients undergoing CABG.[367,368]

In patients with CAD who have concomitant LEAD, strict risk factor control is mandatory, although no specific recommendations exist, as compared with CAD patients without MSAD. In a post hoc analysis of the CHARISMA trial, DAPT with aspirin and clopidogrel was associated with a significant decrease in non-fatal MI compared with aspirin alone,[65] at a cost of increased minor bleeding. The potential benefits of DAPT in these patients need further confirmation.

In LEAD patients requiring coronary revascularization, the treatment of CAD is usually prioritized, except in the case of CLTI. Whether PCI or CABG should be favoured to treat CAD in patients with LEAD is controversial.[369,370] In the case of PCI, radial artery access should be favoured. If the femoral approach is necessary, pre-interventional assessment of the iliac and common femoral arteries should be performed to minimize the risk of ischaemia/embolization and to identify the best location for arterial puncture, since access site complications are more frequent in these patients, particularly when closure devices are used.[371] In patients undergoing CABG with advanced LEAD, the GSV should be spared whenever possible; later success of peripheral arterial revascularization is strongly dependent on the availability of sufficient autologous venous segments.[372] Also, saphenous vein harvesting may be associated with wound healing delays in severe LEAD. This justifies the screening for LEAD prior to use of the saphenous vein as bypass material, at least by clinical examination and/or ABI. CPB during CABG causes a mean arterial pressure drop and loss of pulsatile flow, entailing the risk of worsening CLTI. When off-pump CABG is not feasible, maintaining an adequate mean arterial pressure and monitoring peripheral oxygen

saturation in CLTI patients are strongly advisable during CPB. Postoperatively, active clinical surveillance is needed to diagnose in a timely fashion the compartment syndrome potentially caused by ischaemia–reperfusion injury during CPB. The coexistence of LEAD, even asymptomatic, may upset cardiac rehabilitation.[373]

Screening for LEAD by means of ABI could represent a non-invasive and inexpensive method for prognostic stratification of patients. However, the AMERICA trial failed to demonstrate the benefit of a proactive strategy of MSAD screening in patients.[344] However, the trial was small, with some limitations. It does not exclude a role for screening for asymptomatic LEAD in CAD patients for prognostic stratification. Importantly, in patients with severe CAD, the presence of symptomatic or asymptomatic LEAD is associated with a high probability (almost 20%) of carotid stenosis.[374]

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

	Class[a]	Level[b]
In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention.[365]	I	C
In patients with LEAD undergoing CABG, sparing the autologous great saphenous vein for potential future use for surgical peripheral revascularization should be considered.	IIa	C
In patients undergoing CABG and requiring saphenous vein harvesting, screening for LEAD should be considered.	IIa	C
In patients with CAD, screening for LEAD by ABI measurement may be considered for risk stratification.[340,343,344,366–368,375–379]	IIb	B

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

11.2.2. Coronary artery disease in patients presenting with peripheral arterial diseases

11.2.2.1. Coronary artery disease in patients with carotid artery stenosis

In a study including 276 patients with non-cardioembolic ischaemic stroke/TIA, coronary CTA detected coronary stenosis (>50%) in 18% of cases. The prevalence was 4-fold higher in the case of carotid stenosis >50%.[380] In a prospective investigation of 390 patients undergoing elective CAS, systematic coronary angiography found coronary artery stenosis ≥70% in 61% of cases.[381]

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

In an RCT, 426 patients planned for CEA and without a history of CAD and normal electrocardiogram (ECG) and cardiac ultrasound were randomized to either systematic coronary angiography (with subsequent revascularization) or no coronary angiography.[382] Significant CAD was found (and treated) before CEA in 39% of those randomized to angiography, with no postoperative MI, vs. 2.9% in the no-angiography group ($P = 0.01$). Importantly, PCI delayed CEA by a median of 4 days (range 1–8 days), without neurological events and without bleeding complications in patients on DAPT. At 6 years, patients allocated to systematic coronary angiography had a lower rate of MI (1.4% vs. 15.7%; $P < 0.01$) and improved survival (95% vs. 90%; $P < 0.01$).[383] Hence routine preoperative coronary angiography may be considered in patients undergoing elective CEA.

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

	Class[a]	Level[b]
In patients undergoing elective CEA, preoperative CAD screening, including coronary angiography, may be considered.[382,383]	IIb	B

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

11.2.2.2 Coronary artery disease in patients undergoing vascular surgery of lower limbs

In patients undergoing surgery for LEAD, the probability of significant concomitant CAD at coronary angiography is ∼50–60%.[384–386] For the management of these patients, aortic and major vascular surgery are classified as 'high risk' for cardiac complications, with an expected 30-day MACE rate (cardiac death and MI) >5%.[387] The management of CAD in patients requiring vascular surgery should be based on the 2014 ESC/ESA Guidelines on non-cardiac surgery.[387]

11.2.2.3 Coronary artery disease in patients with lower extremity artery disease not undergoing vascular surgery

At least one-third of patients with LEAD have a history and/or ECG signs of CAD, while two-thirds have an abnormal stress test and up to 70% present at least single-vessel disease at coronary angiography.[69,388] The prevalence of CAD is 2- to 4-fold higher in patients with LEAD vs. those without. In the Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter (CONFIRM) registry, among 7590 patients with LEAD without a history and symptoms of heart disease, the prevalence of obstructive CAD at coronary CTA was 25%.[389] In the REACH registry, 57% of the participants with LEAD also suffered from CAD.[390] The severity of LEAD is related to the prevalence of associated CAD; up to 90% of patients presenting with CLTI also have CAD.

There is no evidence that the presence of CAD directly influences limb outcomes in LEAD patients; however, in the CONFIRM registry, obstructive CAD was associated with an annual mortality rate of 1.6% vs. 0.7% in the absence of severe CAD.[389]

Table 9 Indication for screening of associated atherosclerotic disease in additional vascular territories

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

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CABG = coronary artery bypass grafting; CAD = coronary artery disease; CAS: carotid artery stenting; CEA = coronary endarterectomy; CKD = chronic kidney disease; ECG = electrocardiogram; LEAD = lower extremity artery disease; NR = no recommendation (not enough evidence to support systematic screening); TIA = transient ischaemic attack; U = uncertain.

[a]Especially when venous harvesting is planned for bypass.

[b]In patients with symptomatic cerebrovascular disease.

[c]In patients with asymptomatic carotid disease and: age ≥ 70 years, multivessel CAD, associated LEAD or carotid bruit.

[d]Screening with ECG is recommended in all patients and with imaging stress testing in patients with poor functional capacity and more than two of the following: history of CAD, heart failure, stroke or TIA, CKD, diabetes mellitus requiring insulin therapy.

The presence of CAD in patients with LEAD may require coronary revascularization, depending on the severity and urgency of LEAD symptoms. Risk factor modification and medical treatment recommended for CAD also apply to LEAD.[391] Screening for CAD in LEAD patients may be useful for risk stratification, as morbidity and mortality are mainly cardiac. Non-invasive screening can be performed by stress testing or coronary CTA, but there is no evidence of improved outcomes in LEAD patients with systematic screening for CAD.

11.2.3 Other peripheral localizations in patients with peripheral arterial diseases

11.2.3.1 Carotid artery stenosis in patients with lower extremity artery disease

Carotid stenosis is frequent in patients with LEAD (*Figure 8*), but there is no evidence that the presence of CAS would influence lower limb outcomes. The presence of CAD is a marker of worse CV prognosis.[392] For more details see Web addenda 11.2.3.1.

11.2.3.2 Renal artery disease in patients with lower extremity artery disease

While RAS is frequently discovered incidentally during imaging for LEAD, it requires specific intervention. Opinions on whether atherosclerotic RAD could be a marker of worse CV prognosis in LEAD patients are conflicting.[335,393] The only report looking also at limb outcome found no prognostic alteration in the case of concomitant RAS.[335] Systematic screening for RAS in patients with LEAD cannot be recommended, as the therapeutic value of renal artery stenting is questionable (see **chapter 9**).

For more details see Web addenda 11.2.3.2.

12. Cardiac conditions in peripheral arterial diseases

Key messages

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

12.1 Introduction

Cardiac diseases are frequent in patients with PADs. The simultaneous presence of PADs and CAD is addressed in **chapter 11**. Here we address the most important issues related to PADs patients with coexisting heart failure, AF and valvular heart disease (VHD). Such coexistence may carry important prognostic and

therapeutic implications and often needs a multidisciplinary approach. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

12.2 Heart failure and peripheral arterial diseases

There are multiple pathways linking LEAD and heart failure (Web Figure 3). Together with diabetes, smoking and other risk factors, inflammation may be one of the common factors leading to the development of heart failure in PADs patients.[394] Data on the coexistence of the two conditions are generally limited to subjects with heart failure and LEAD.

LEAD is associated with increased risk for incident heart failure. It is often associated with overt atherosclerosis involving CAD, which may cause subsequent heart failure.[53] Also, elevated aortic stiffness increases left ventricular (LV) afterload and high pulse pressure impairs coronary blood flow, resulting in hypertension, LV hypertrophy, diastolic dysfunction and ultimately heart failure.[395,396] Importantly, skeletal muscle involvement and deconditioning in LEAD may affect heart failure severity.[397,398] On the other hand, functional limitation due to heart failure is likely to mask symptoms of LEAD, causing underestimation of the number of patients with both conditions.

12.2.1 Epidemiology

Overall, LV dysfunction and heart failure are more frequent in patients with PADs. The evidence is mostly presented in patients with LEAD. See Web addenda 12.2.1.

12.2.2. Heart failure in patients with peripheral arterial diseases

Despite the high prevalence and incidence of heart failure in patients with PADs, outcome data for this group are very limited. It is most likely, however, that this combination is associated with increased CV morbidity and mortality. Evaluation of LV function in PADs may be of value for better risk stratification for future CV events and comprehensive management of patients' CV diseases.[399] This is particularly important when an intermediate- or high-risk vascular intervention is planned.[387] The primary assessment should include medical history, physical examination and resting ECG. In case of any abnormalities suggestive of heart failure, transthoracic echocardiography (TTE) or measurement of natriuretic peptides should be undertaken.[400] Natriuretic peptides are particularly useful in patients with a poor echocardiographic window and in those with diastolic dysfunction.[401] In patients with LEAD, heart failure may be associated with reduced patency after endovascular therapy.[402] TTE and natriuretic peptides can also be proposed in patients with claudication, even if no revascularization is planned.

12.2.3 Peripheral arterial diseases in patients with heart failure

Observational studies and meta-analyses consistently show that the presence of LEAD in heart failure patients is an independent predictor of hospitalizations and mortality.[376–379,403] In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, LEAD was reported in ~7% of patients with heart failure and LV ejection fraction <35% and was associated with an increased risk of all-cause hospitalization and mortality (HR 1.31, P = 0.011).[376] Other studies reported an increased risk for progressive heart failure (HR 1.35, P = 0.03), all-cause mortality (HR 1.36, P < 0.001)[404] and CV mortality (HR 1.31, P = 0.02).[405] Among hospitalized patients with heart failure, the prevalence of subclinical (ABI ≤0.90) and symptomatic LEAD was 19% and 7%, respectively, and was associated with increased cardiac and all-cause mortality.[378] Therefore, in heart failure patients, screening for PADs may be considered.

Finally, flash pulmonary oedema may be due to severe RAS (see **section 9.2**). Therefore, in patients with this condition, testing for RAS may be considered.

12.3 Peripheral arterial diseases and atrial fibrillation

12.3.1 General considerations

Ageing is a strong risk factor for AF[406] and PADs, thus a frequent coexistence of the two conditions is expected. In an analysis from the Cardiovascular Health Study, LEAD was associated with a higher risk of AF (HR 1.52, P < 0.01).[407]

Despite a considerable variability in BP due to the beat-to-beat variability in stroke volume, ABI appears to be a reliable method to detect unknown LEAD in patients with AF.[408] In patients with AF receiving anticoagulant treatment, abnormal ABI was an independent predictor of all-cause death and major bleeding complications.[409]

Among 41 882 patients hospitalized for LEAD, the prevalence of AF was 13%.[406] Those with AF tend to be older, more often hypertensive, female and with diabetes, CKD, CAD and/or heart failure than patients in sinus rhythm. LEAD was overall more severe in patients with AF as assessed by the Rutherford classification. In-hospital complications, including renal failure, MI, stroke, infections and death, occurred more frequently in the presence of AF. In other studies, AF associated with LEAD was an independent predictor of stroke, amputation and death.[410,411] In the REACH registry, AF was present in 10% of patients with LEAD.[84] Compared with patients without AF, the two-year CV and all-cause mortality was higher, 7.7% and 5.6% vs. 2.5% and 1.6%, respectively (P < 0.001 for both). Those with AF also had higher incidences of heart failure, unstable angina and severe bleeding.

12.3.2 Antithrombotic treatment in patients with atrial fibrillation

Except for recent stenting, patients with PADs and AF should mostly be on OACs alone. See **section 5.3**.

12.4 Peripheral arterial diseases and valvular heart disease

PADs are common among patients with VHD, especially among the elderly with symptomatic aortic stenosis. The presence of LEAD is captured within the scores used to predict outcome after cardiac surgery.[412] Among patients with symptomatic aortic stenosis not eligible for surgical aortic valve replacement, the prevalence of LEAD is as high as 40%.[413–415] It often coexists with other manifestations of systemic atherosclerosis, including CAD and cerebrovascular disease. This has an impact on patient care with respect to the timing of coronary revascularization, if needed,[366] and the vascular access site for transcatheter aortic

valve implantation (TAVI).[416] Systematic CT scan imaging of the aorta, including all major peripheral arteries, has become the standard of care in patients eligible for TAVI.

12.5 Peripheral arterial diseases and vascular access site for cardiac interventions

Patient evaluation for the presence of LEAD and UEAD is pivotal for access site choice in patients eligible for TAVI and their diagnosis has a great impact on clinical outcome after TAVI because of the increased rate of peri- and post-procedural complications.[417,418] The presence of LEAD or UEAD is an independent predictor of mortality following TAVI with both percutaneous and surgical access, independent of the occurrence of vascular complications.[417,419] The use of low-profile devices for TAVI and alternative access sites, such as direct aortic, carotid or subclavian, may also reduce vascular complications.

Acute limb ischaemia is a complication of intra-aortic balloon pump insertion in the setting of cardiogenic shock or in the prophylaxis of low output syndrome. LEAD is a major risk factor for this complication and preliminary iliac artery stenting with the use of an unsheathed device may avoid such complications.[420] These complications are also common in LV assist device recipients, where sheaths are usually larger, resulting in higher 30-day mortality in patients with LEAD.[421] The added risk of underlying LEAD is not clearly established in that particular setting and deserves additional investigations. These patients often need lower limb revascularization and surgical vascular closure when weaned off LV assist devices.

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

Recommendations	Class[a]	Level[b]
PADs and heart failure		
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation.	I	C
In patients with symptomatic PADs, screening for heart failure with TTE and/or natriuretic peptides assessment should be considered.	IIa	C
Screening for LEAD may be considered in patients with heart failure.	IIb	C
Testing for renal artery disease may be considered in patients with flash pulmonary oedema.	IIb	C
PADs and atrial fibrillation[c]		
In patients with LEAD and atrial fibrillation, oral anticoagulation:[83]		
• is recommended with a CHA_2DS_2-VASc score ≥2	I	A
• should be considered in all other patients.	IIa	B
PADs and valvular heart disease		
Screening for LEAD and UEAD is indicated in patients undergoing TAVI or other structural interventions requiring an arterial approach.	I	C

CHA_2DS_2VASC = Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; TAVI = transcatheter aortic valve implantation; TTE = transthoracic echocardiography; UEAD = upper extremity artery disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]For more detail please refer to **chapter 5**.

13. Gaps in evidence

Rapid changes in therapeutic techniques create the situation in which clinical practice tends to follow technical developments without evidence from RCTs. In addition, RCTs often yield conflicting results because of technical evolution. Moreover, PADs may involve multiple sites, creating a large number of clinical scenarios to investigate. All these contribute to the broad spectrum of gaps in evidence, of which the most relevant are listed in *Table 10*. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

Table 10 Main gaps in evidence in the management of patients with peripheral arterial diseases

Epidemiology
Data on epidemiology of PADs in Europe are scarce.
Important challenges are associated with PADs in women. This group has classically been underrepresented in research studies. Therefore, several sex-related challenges regarding diagnosis and management issues should be acknowledged.
Carotid artery disease
The benefits of new antiplatelet drugs for the management of asymptomatic carotid artery disease should be assessed by RCTs.
A multifactorial and standardized score is necessary to stratify the risk of stroke in patients with asymptomatic carotid artery stenosis, to determine the subgroup who may benefit from revascularization, in addition to best medical therapy.
The efficacy of embolic protection devices during CAS has not been studied in adequately powered RCTs, and the available evidence is conflicting.
The optimal duration of dual antiplatelet therapy after CAS is not well established.
The timing of carotid revascularization in the acute phase of stroke after intra-cerebral thrombolysis/thrombectomy is not yet defined and should be investigated.
Vertebral artery disease
Almost no data are available on the comparison between surgical and endovascular revascularization in symptomatic patients.
Upper extremity artery disease
Little is known about the natural course in upper extremity artery disease.
Almost no data are available on the long-term clinical benefit of revascularization (and the optimal mode) of symptomatic subclavian artery stenosis/occlusion.
Optimal duration for DAPT after subclavian artery stenting is unknown.
Mesenteric artery disease
The potential benefits of prophylactic revascularization for asymptomatic mesenteric artery disease involving multiple vessels needs investigations.
In case of symptomatic mesenteric artery disease, no data are available on the potential benefit of covered vs. bare stents.
Optimal duration for DAPT after mesenteric stenting is unknown.
Renal artery disease
The role of renal artery stenting for patients with pulmonary flash oedema remains to be demonstrated by RCT.
Appropriate treatment of in-stent renal artery restenosis is not yet defined.
Risk stratification would be necessary to clarify whether a subgroup of patients with RAS may benefit from renal revascularization. In case of renal stenting, optimal duration for DAPT is unknown.
Lower extremity artery disease
The role of drug-eluting stents and drug-eluting balloons in superficial femoral artery and below-the-popliteal artery interventions has to be established.
Optimal treatment for popliteal artery stenosis needs to be addressed.
Clinical studies on self-expanding stents, drug-coated balloons and drug-eluting stents for below-the-knee interventions in patients with CLTI should include amputation-free survival, wound healing and quality of life in addition to standard-patency outcomes.
Optimal duration of DAPT after stenting, as well as the potential benefit of its long-term use in patients with CLTI, should be further investigated.
The rationale of the angiosome concept to decide on modality of revascularization in patients with CLTI remains to be demonstrated.
There is a need to develop European registries for patients with LEAD in order to provide "real world" assessment of clinical outcomes and practices.
There is a need to validate improved classification systems for CLTI that incorporate wound, ischaemia and foot infection such as the WIfI classification.
Multisite artery disease
Whether the screening for other sites of atherosclerosis (e.g. CAD) in patients with PADs may improve their outcome needs further investigation.
Cardiac conditions in patients with PADs
The impact of heart failure screening and treatment and its impact on outcome of patients with PADs requires further investigations.
The optimal strategy of antithrombotic treatment in patients with atrial fibrillation and PADs requires specific RCTs.

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

14. To do and not to do messages from the Guidelines

Recommendations	Class[a]	Level[b]
General recommendations on the management of patients with PADs		
In healthcare centres, it is recommended to set up a multidisciplinary Vascular Team to make decisions for the management of patients with PADs.	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases.	I	C
Recommendations in patients with PADs: best medical therapy		
Smoking cessation is recommended in all patients with PADs.	I	B
A healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.	I	A
In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by ≥ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C[c]
In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg.	I	A
Recommendations on antithrombotic therapy in patients with PADs		
In patients with symptomatic carotid stenosis, long-term SAPT is recommended.	I	A
Dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least 1 month after CAS.	I	B
Long-term SAPT is recommended in symptomatic patients.	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization.	I	C
SAPT is recommended after infra-inguinal bypass surgery.	I	A
Because of the lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD.	III	A
In patients with PADs and AF, OAC is recommended when the CHA_2DS_2-VASc score is ≥ 2	I	A
Recommendations for imaging of extracranial carotid arteries		
DUS (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.	I	B
When CAS is being considered, it is recommended that any DUS study be followed either by MRA or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation.	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated either by MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).	I	B
Recommendations on revascularization in patients with symptomatic carotid disease[e]		
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is < 6%.	I	A
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.	I	A
Revascularization is not recommended in patients with a < 50% carotid stenosis.	III	A

Continued

Recommendations for management of vertebral artery stenoses		
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C
Recommendations on the management of acute mesenteric ischaemia		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended.	I	C
Recommendations for management of chronic mesenteric artery disease		
In patients with suspected CMI, DUS is recommended as the first-line examination.	I	C
In patients with symptomatic multivessel CMI, revascularization is recommended.	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.	III	C
Recommendations for diagnostic strategies for RAD		
DUS (as first-line), CTA[f] and MRA[g] are recommended imaging modalities to establish a diagnosis of RAD.	I	B
Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD.	III	C
Recommendations for treatment strategies for RAD		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral renal artery stenosis.	I	B
Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with RAD.	I	C
Routine revascularization is not recommended in renal artery stenosis secondary to atherosclerosis.	III	A
Recommendations for ABI measurement		
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated.	I	C
Recommendations on imaging in patients with LEAD		
DUS is indicated as a first-line imaging method to confirm LEAD lesions.	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.	I	C
The data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to a treatment decision.	I	C
Recommendations for the management of patients with intermittent claudication		
On top of general prevention, statins are indicated to improve walking distance.	I	A
In patients with intermittent claudication, supervised exercise training is recommended.	I	A
In patients with intermittent claudication, non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Recommendations on revascularization of aorto-iliac occlusive lesions[h]		
An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions.	I	C
Recommendations on revascularization of femoro-popliteal occlusive lesions[g]		
An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions.	I	C
In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. ≥25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is > 2 years.	I	B
The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass.	I	A

Continued

Recommendations on revascularization of infra-popliteal occlusive lesions		
In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage.	I	C
For revascularization of infra-popliteal arteries, bypass using the great saphenous vein is indicated.	I	A
Recommendations on the management of CLTI		
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.	I	C
In patients with CLTI, assessment of the risk of amputation is indicated.	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended.	I	C
For limb salvage, revascularization is indicated whenever feasible.	I	B
In patients with CLTI, stem cell/gene therapy is not indicated.	III	B
Recommendations for the management of patients presenting with acute limb ischaemia		
In the case of neurological deficit, urgent revascularization is indicated.[i]	I	C
In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision.	I	C
Heparin and analgesics are indicated as soon as possible.	I	C
Recommendations on screening for carotid disease in patients undergoing CABG surgery		
In patients undergoing CABG, DUS is recommended in patients with a recent (<6 months) history of TIA/stroke.	I	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C
Recommendations on the management of carotid stenosis in patients undergoing CABG surgery		
It is recommended that the indication (and, if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with a recent (<6 months) history of TIA/stroke, carotid revascularization is not recommended in those with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG, routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.	III	B
Recommendations for screening and management of concomitant LEAD and CAD		
In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention.	I	C
Recommendations on the management of cardiac conditions associated with PADs		
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation.	I	C
In patients with LEAD and atrial fibrillation, OAC is recommended with a CHA_2DS_2-VASc score ≥2.	I	A
Screening for LEAD and UEAD is indicated in patients undergoing TAVI or other structural interventions requiring an arterial approach.	I	C

ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CLTI = chronic limb-threatening ischaemia; CMI = chronic mesenteric ischaemia; CTA = computed tomography angiography; DUS = duplex ultrasound; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography; OAC = oral anticoagulation; PADs = peripheral arterial diseases; RAD = renal artery disease; SAPT = single antiplatelet therapy; TAVI = transcatheter aortic valve implantation; TIA = transient ischaemic attack; UEAD = upper extremity artery disease. CHA_2DS_2-VASc score is calculated as follows: congestive heart failure history (1 point), hypertension (1 point), age >75 years (2 points), diabetes mellitus (1 point), stroke/TIA or arterial thromboembolic history (1 point), vascular disease history (1 point), age 65–74 years (1 point), sex category (1 point if female).

[a]Class of recommendation.

[b]Level of evidence.

[c]Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding sections.

[d]Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multisite artery diseases).

[e]Stroke or TIA occurring within 6 months.

[f]When eGFR is ≥ 60 mL/min.

[g]When eGFR is ≥ 30 mL/min.

[h]These recommendations apply for patients with intermittent claudication and severe chronic limb ischaemia.

[i]In this case, imaging should not delay intervention.

15. Web addenda and companion document

All Web figures and Web tables are available at the European Heart Journal online and also via the ESC Web site at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of

The questions and answers companion document for these guidelines is available via this same link.

16. Appendix

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