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 arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS)

Aboyans, Victor; Ricco, Jean-Baptiste; et al; ESC Scientific Document Group

DOI: https://doi.org/10.1093/eurheartj/ehx095

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 763–821
doi:10.1093/eurheartj/ehx095

ESC GUIDELINES

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)

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

Authors/Task Force Members: Victor Aboyans* (ESC Chairperson) (France), Jean-Baptiste Ricco*[1] (Co-Chairperson) (France), Marie-Louise E. L. Bartelink (The Netherlands), Martin Björck[1] (Sweden), Marianne Brodmann (Austria), Tina Cohnert[1] (Austria), Jean-Philippe Collet (France), Martin Czerny (Germany),

* Corresponding authors: Victor Aboyans, Department of Cardiology CHRU Dupuytren Limoges, 2 Avenue Martin Luther King, 87042 Limoges, France. Tel: +33 5 55 05 63 10, Fax: +335 55 05 63 34, Email: vaboyans@live.fr. Jean-Baptiste Ricco, Department of Vascular Surgery, University Hospital, rue de la Miletrie, 86021 Poitiers, France. Tel: +33 549443846, Fax: +33 5 49 50 05 50, Email: jeanbaptistericco@gmail.com

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies (NCS) document reviewers: listed in the Appendix

[1]Representing the European Society for Vascular Surgery (ESVS)

[2]Representing the European Stroke Organisation (ESO)

ESC entities having participated in the development of this document:
Associations: European Association of Preventive Cardiology (EAPC), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI).
Councils: Council for Cardiology Practice (CCP), Council on Cardiovascular Primary Care (CCPC), Council on Hypertension (CHT).
Working Groups: Atherosclerosis and Vascular Biology, Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Peripheral Circulation, Thrombosis.

Marco De Carlo (Italy), Sebastian Debus[1] (Germany), Christine Espinola-Klein (Germany), Thomas Kahan (Sweden), Serge Kownator (France), Lucia Mazzolai (Switzerland), A. Ross Naylor[1] (UK), Marco Roffi (Switzerland), Joachim Röther[2] (Germany), Muriel Sprynger (Belgium), Michal Tendera (Poland), Gunnar Tepe (Germany), Maarit Venermo[1] (Finland), Charalambos Vlachopoulos (Greece), Ileana Desormais (France)

Document Reviewers: Petr Widimsky (ESC Review Coordinator) (Czech Republic), Philippe Kolh (ESVS Review Coordinator) (Belgium), Stefan Agewall (Norway), Héctor Bueno (Spain), Antonio Coca (Spain), Gert J. De Borst[1] (The Netherlands), Victoria Delgado (The Netherlands), Florian Dick[1] (Switzerland), Cetin Erol (Turkey), Marc Ferrini (France), Stavros Kakkos[1] (Greece/UK), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Jes Lindholt[1] (Denmark), Heinrich Mattle[2] (Switzerland), Piotr Pieniazek (Poland), Massimo Francesco Piepoli (Italy), Dierk Scheinert (Germany), Horst Sievert (Germany), Iain Simpson (UK), Jakub Sulzenko (Czech Republic), Juan Tamargo (Spain), Lale Tokgozoglu (Turkey), Adam Torbicki (Poland), Nikolaos Tsakountakis (Greece), José Tuñón (Spain), Melina Vega de Ceniga[1] (Spain), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain)

The disclosure forms of all experts involved in the development of these guidelines are available on the ESC website http://www.escardio.org/guidelines.

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

SD 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.

Online publish-ahead-of-print 26 August 2017

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

Table of contents

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

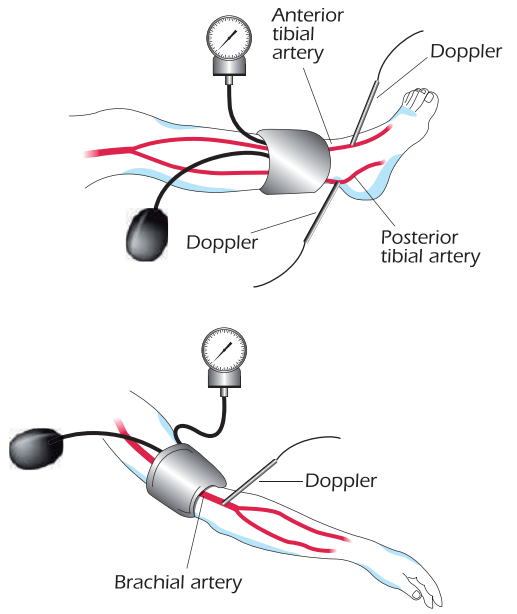
Table 3 The Ankle-Brachial Index

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

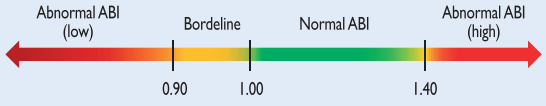
2. How to measure the ABI?

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,

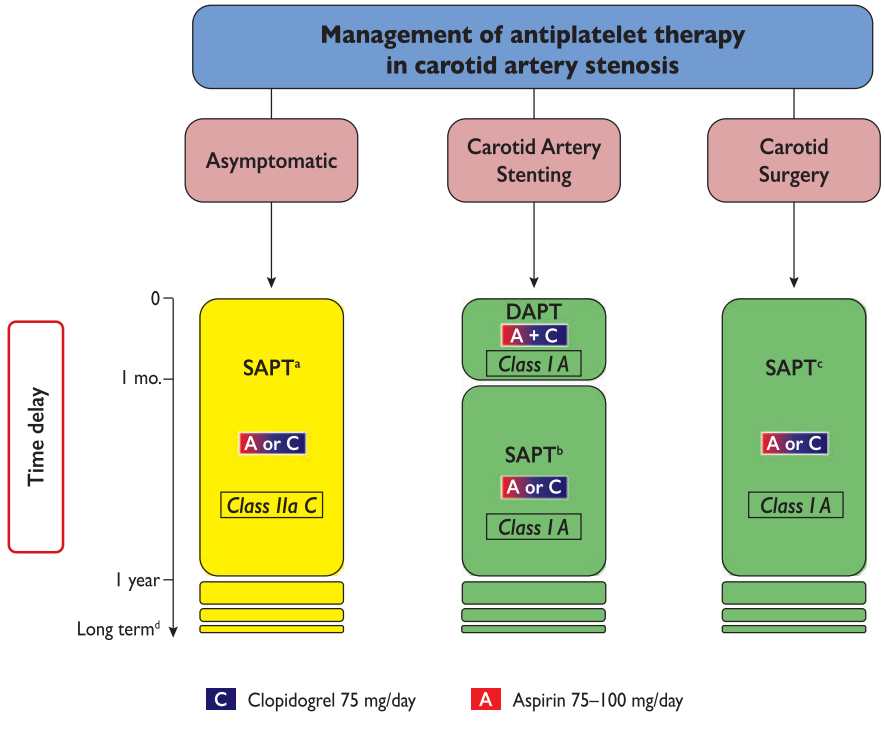


Figure 1 Management of antithrombotic treatment in patients with carotid artery stenosis. DAPT = dual antiplatelet therapy, a daily combination of aspirin (75–100 mg) and clopidogrel (75 mg); CAS = carotid artery stenting; SAPT = single antiplatelet therapy; TIA = transient ischaemic attack.
[a]At the 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

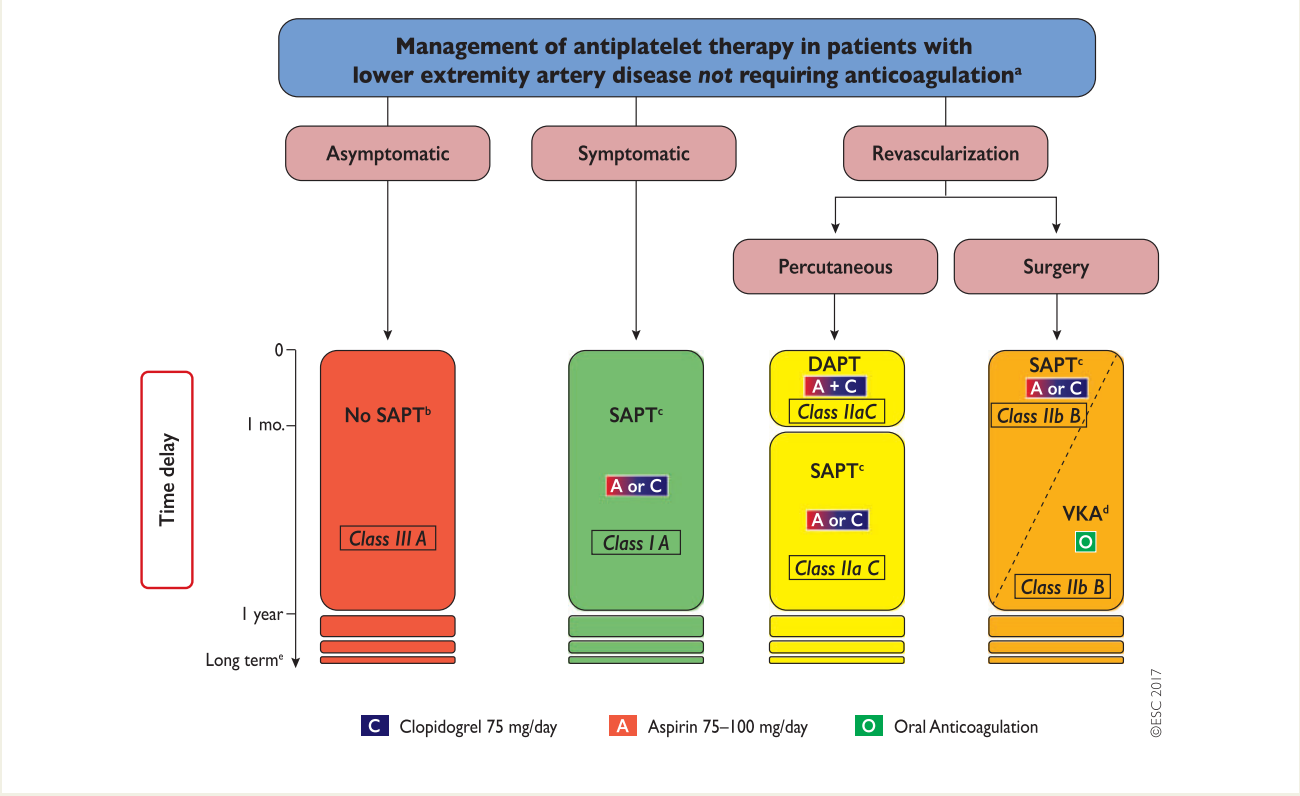


Figure 2 Antiplatelet therapy in patients with lower extremity artery disease. DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.
[a]e.g. concomitant AF or mechanical valve prosthesis.
[b]SAPT should be considered if there is another concomitant atherosclerotic 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

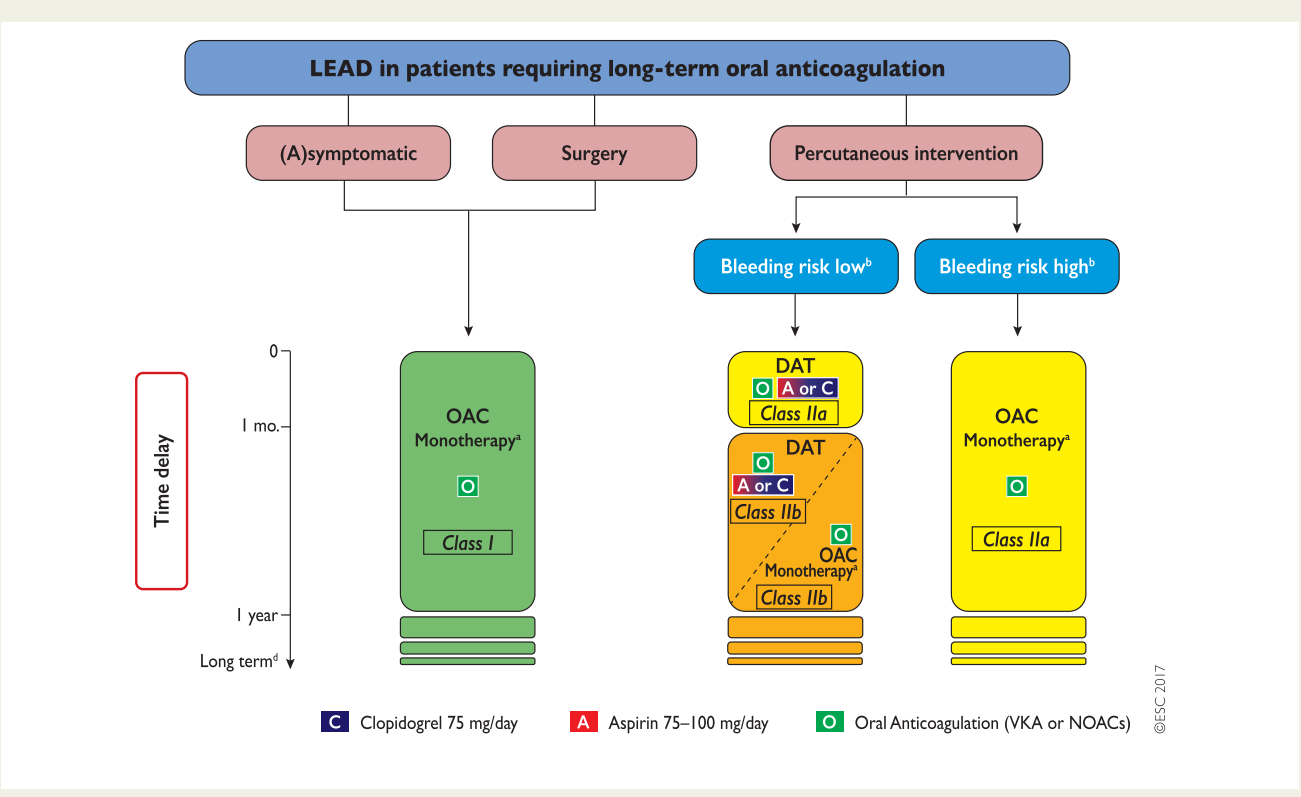


Figure 3 Antithrombotic therapy in patients with LEAD requiring oral anticoagulation. ACS = acute coronary syndrome; CAD = coronary artery disease; CLTI: chronic limb-threatening ischaemia; DAT = dual antithrombotic therapy; LEAD = lower extremity artery disease; NOACs = non-vitamin K oral anticoagulants; 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

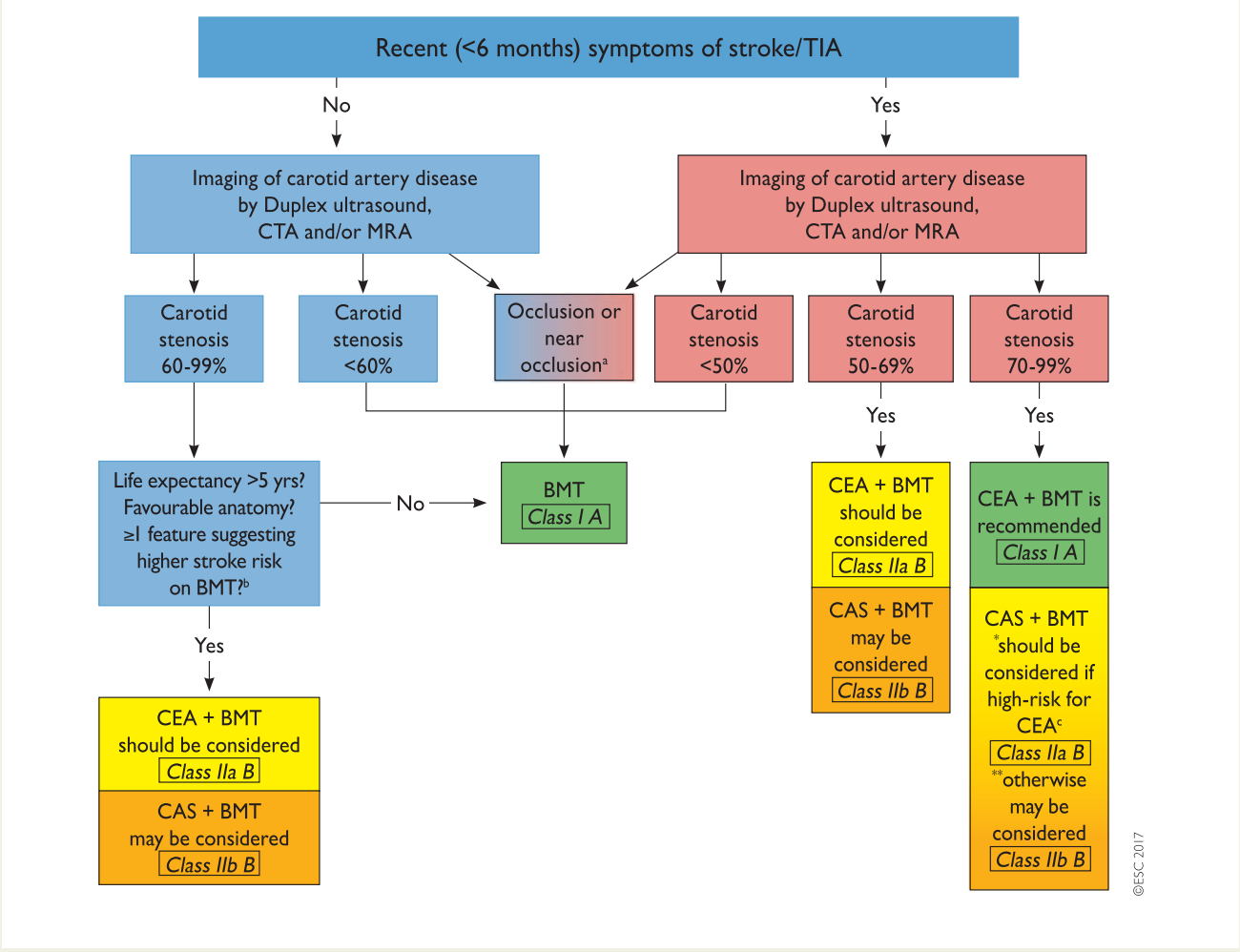


Figure 4 Management of extracranial carotid artery disease. BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.
[a]With post-stenotic internal carotid artery 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,