

Editor's Choice — 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)

Victor Aboyans^{a,*}, Jean-Baptiste Ricco^{a,*}, Marie-Louise E.L. Bartelink^a, Martin Björck^a, Marianne Brodmann^a, Tina Cohnert^a, Jean-Philippe Collet^a, Martin Czerny^a, Marco De Carlo^a, Sebastian Debus^a, Christine Espinola-Klein^a, Thomas Kahan^a, Serge Kownator^a, Lucia Mazzolai^a, A. Ross Naylor^a, Marco Roffi^a, Joachim Röther^a, Muriel Sprynger^a, Michal Tendera^a, Gunnar Tepe^a, Maarit Venermo^a, Charalambos Vlachopoulos^a, Ileana Desormais^a

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](http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of) companion documents of these guidelines are available at: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of

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

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.

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oxfordjournals.org).

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines 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 and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

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

^b **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^c (The Netherlands), Victoria Delgado (The Netherlands), Florian Dick^c (Switzerland), Cetin Erol (Turkey), Marc Ferrini (France), Stavros Kakkos^c (Greece/UK), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Jes Lindholt^c (Denmark), Heinrich Mattle^d (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^c (Spain), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain)

^{*} 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: +33 5 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

^c Representing the European Society for Vascular Surgery (ESVS)

^d Representing the European Stroke Organisation (ESO)

1078-5884/© 2017 European Society of Cardiology. Published by Oxford University Press and Elsevier Limited on behalf of European Society for Vascular Surgery. All rights reserved.

The article has been co-published with permission in the *European Heart Journal* [DOI: 10.1093/eurheartj/ehx095] on behalf of the European Society of Cardiology and *European Journal of Vascular and Endovascular Surgery* [DOI: 10.1016/j.ejvs.2017.07.018] on behalf of the European Society for Vascular Surgery. All rights reserved in respect of *European Heart Journal*, © European Society of Cardiology 2017. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citations can be used when citing this article.

<http://dx.doi.org/10.1016/j.ejvs.2017.07.018>

Document Reviewers^b, Petr Widimsky, Philippe Kolh, Stefan Agewall, Héctor Bueno, Antonio Coca, Gert J. De Borst, Victoria Delgado, Florian Dick, Cetin Erol, Marc Ferrini, Stavros Kakkos, Hugo A. Katus, Juhani Knuuti, Jes Lindholt, Heinrich Mattle, Piotr Pieniazek, Massimo Francesco Piepoli, Dierk Scheinert, Horst Sievert, Iain Simpson, Jakub Sulzenko, Juan Tamargo, Lale Tokgozoglul, Adam Torbicki, Nikolaos Tsakountakis, José Tuñón, Melina Vega de Ceniga, Stephan Windecker, Jose Luis Zamorano

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	307
1. Preamble	309
2. Introduction	310
3. Epidemiology and risk factors	312
3.1. Epidemiology	312
3.2. Risk factors	312
3.3. Prognosis	312
4. General aspects	312
4.1. Diagnostic approach	312
4.1.1. Clinical history	312
4.1.2. Clinical examination	312
4.1.3. Laboratory testing	313
4.1.4. Diagnostic methods for PADs	313
4.2. Treatment approach	314
4.2.1. Smoking cessation	314
4.2.2. Lipid-lowering drugs	314
4.2.3. Antithrombotic drugs	314
4.2.4. Antihypertensive drugs	314
5. Antithrombotic drugs in PADs	315
5.1. Antithrombotic treatment in carotid artery disease	315
5.1.1. Single antiplatelet therapy	315
5.1.2. Dual antiplatelet therapy	315
5.2. Antithrombotic therapy in lower extremity artery disease	316
5.2.1. Single antiplatelet therapy	316
5.2.2. Dual and triple antiplatelet therapy	317
5.2.3. Antithrombotic therapy after lower-extremity bypass grafting	317
5.2.4. Antithrombotic drugs after endovascular therapy for lower extremity artery disease	317
5.2.5. Patients with lower extremity artery disease and concomitant coronary artery disease	317
5.3. Antithrombotic therapy in lower extremity artery disease patients requiring long-term oral anticoagulant	318
5.4. Antithrombotic therapy after endovascular therapy in other territories	319
6. Extracranial carotid and vertebral artery disease	320
6.1. Carotid artery disease	320
6.1.1. Definition	320
6.1.2. Diagnosis	321
6.1.3. Treatment	321
6.1.4. Management of carotid artery disease	322
6.2. Vertebral artery disease	326
6.2.1. Definition and natural history	326
6.2.2. Imaging	326
6.2.3. Management of vertebral artery disease	326
7. Upper extremity artery disease	326
7.4. Diagnostic methods	326
7.4.1. Duplex ultrasound	326
7.4.2. Computed tomography angiography	326
7.4.3. Magnetic resonance angiography	327
7.4.4. Digital subtraction angiography	327
7.4.5. Positron emission tomography	327
7.5. Treatment	327
7.5.1. Endovascular treatment	327
7.5.2. Open surgery	327
7.5.3. Medical therapy	327
8. Mesenteric artery disease	328
8.1. Acute mesenteric ischaemia	328
8.1.1. Diagnosis	328
8.1.2. Treatment	328
8.2. Chronic mesenteric artery disease	329
8.2.1. Diagnosis	329
8.2.2. Treatment	329
8.3. Secondary prevention	329
9. Renal artery disease	330

9.1.	Introduction	330
9.2.	Clinical presentation	330
9.3.	Natural history	330
9.4.	Diagnostic strategy	330
9.5.	Prognosis	331
9.6.	Treatment	331
9.6.1.	Medical therapy	331
9.6.2.	Revascularization	332
10.	Lower extremity artery disease	333
10.1.	Clinical presentation and natural history	333
10.2.	Diagnostic tests	334
10.2.1.	Ankle-brachial index	334
10.2.2.	Treadmill test	334
10.2.3.	Imaging methods	334
10.2.4.	Other tests	334
10.3.	Medical treatment	335
10.4.	Revascularization options: general aspects	335
10.5.	Management of intermittent claudication	335
10.5.1.	Exercise therapy	335
10.5.2.	Pharmacotherapy to decrease walking impairment	335
10.5.3.	Revascularization for intermittent claudication	336
10.5.4.	Management strategy for intermittent claudication	336
10.6.	Chronic limb-threatening ischaemia	337
10.6.1.	Chronic limb-threatening ischaemia severity and risk stratification: the Wlfl classification	337
10.6.2.	Management of patients with chronic limb-threatening ischaemia	339
10.6.3.	Spinal cord stimulation	341
10.6.4.	Stem cell and gene therapy	341
10.6.5.	Amputation	341
10.7.	Acute limb ischaemia	341
10.8.	Blue toe syndrome	342
11.	Multisite artery disease	343
11.1.	Multisite artery disease: epidemiology and impact prognosis	343
11.2.	Screening for and management of multisite artery disease	344
11.2.1.	Peripheral arterial diseases in patients presenting with coronary artery disease	344
11.2.2.	Coronary artery disease in patients presenting with peripheral arterial diseases	346
11.2.3.	Other peripheral localizations in patients with peripheral arterial diseases	347
12.	Cardiac conditions in peripheral arterial diseases	348
12.1.	Introduction	348
12.2.	Heart failure and peripheral arterial diseases	348
12.2.1.	Epidemiology	348
12.2.2.	Heart failure in patients with peripheral arterial diseases	348
12.2.3.	Peripheral arterial diseases in patients with heart failure	349
12.3.	Peripheral arterial diseases and atrial fibrillation	349
12.3.1.	General considerations	349
12.3.2.	Antithrombotic treatment in patients with atrial fibrillation	349
12.4.	Peripheral arterial diseases and valvular heart disease	349
12.5.	Peripheral arterial diseases and vascular access site for cardiac interventions	349
13.	Gaps in evidence	350
14.	To do and not to do messages from the Guidelines	351
	Web addenda and companion document	354
	Appendix	354
	References	354

ABBREVIATIONS AND ACRONYMS

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

BEST-CLI	Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia	EVA-3S	Enderarterectomy vs Stenting in Patients with Symptomatic Severe Carotid Stenosis
BMT	best medical therapy	EVT	endovascular therapy
BP	blood pressure	ExT	exercise therapy
CABG	coronary artery bypass grafting	FMD	fibromuscular dysplasia
CAD	coronary artery disease	GSV	great saphenous vein
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events	HDL-C	high-density lipoprotein cholesterol
CAPTURE	Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Rare Events	HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
CARESS	Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis	HITS	high-intensity transient signal
CASPAR	Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial disease	HOPE	Heart Outcomes Prevention Trial
CAS	carotid artery stenting	HR	hazard ratio
CCA	common carotid artery	IC	intermittent claudication
CEA	carotid endarterectomy	ICA	internal carotid artery
CFA	common femoral artery	ICD	implantable cardioverter defibrillator
CHA ₂ DS 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	ICSS	International Carotid Stenting Study
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance	INR	international normalized ratio
CI	confidence interval	INVEST	INternational VErapamil-SR/Trandolapril Study
CKD	chronic kidney disease	LDL-C	low-density lipoprotein cholesterol
CLEVER	Claudication: exercise versus endoluminal revascularization	LEAD	lower extremity artery disease
CLTI	Chronic limb-threatening ischaemia	LV	left ventricular
CMI	chronic mesenteric ischaemia	MACE	major adverse cardiovascular event
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter	MI	myocardial infarction
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions	MRA	magnetic resonance angiography
CPB	cardiopulmonary bypass	MR CLEAN	MultiCenter Randomized Clinical Trial of Ischemic Stroke in the Netherlands
CPG	Committee for Practice Guidelines	MRI	magnetic resonance imaging
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial	MSAD	multisite artery disease
CTA	computed tomography angiography	MWD	maximal walking distance
CV	cardiovascular	NASCET	North American Symptomatic Carotid Endarterectomy Trial
DAPT	dual antiplatelet therapy	NNH	number needed to harm
DES	drug eluting stent	NNT	number needed to treat
DSA	digital subtraction angiography	NOAC	non-vitamin K oral anticoagulant
DUS	duplex ultrasound	OAC	oral anticoagulation
ECG	electrocardiogram	ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
ECST	European Carotid Surgery Trial	OR	odds ratio
EPD	embolus protection device	PADs	peripheral arterial diseases
ESC	European Society of Cardiology	PCI	percutaneous coronary intervention
ESO	European Stroke Organisation	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
ESVS	European Society of Vascular Surgery	PRODIGY	PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hyperplasia study
EUCLID	Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease	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	STAR	Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function
REACH	Reduction of Atherothrombosis for Continued Health	TAMARIS	Efficacy and Safety of XRP0038/NV1FGF in Critical Limb Ischaemia Patients With Skin Lesions
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	TAVI	transcatheter aortic valve implantation
RR	relative risk	TBI	toe-brachial index
RRI	renal resistive index	TcPO ₂	transcutaneous oxygen pressure
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy	TIA	transient ischaemic attack
SAPT	single antiplatelet therapy	TTE	transthoracic echocardiography
SBP	systolic blood pressure	UEAD	upper extremity artery disease
SFA	superficial femoral artery	VA	vertebral artery
SPACE	Stent Protected Angioplasty versus Carotid Endarterectomy	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*.

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.

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 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 utmost 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.

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}

What is new in the 2017 PAD Guidelines?

CHANGE IN RECOMMENDATIONS 2011	2017	2017 NEW RECOMMENDATIONS	
Carotid Artery Disease		All Peripheral Arterial Diseases (PADs)	
EPDs in carotid stenting		• Screening for heart failure (BNP, TTE)	
Asymptomatic 60–99% carotid stenosis		• Stable PADs + other conditions requiring anticoagulants (e.g. AF): anticoagulation alone ⁹¹	
• Surgery for all	• Surgery for high stroke risk ¹¹⁶	Carotid Artery disease	
• Stenting as an alternative	• Stenting in high surgery risk ^{129, 135-137}	• Coronary angiography before elective carotid surgery ³⁸³	
	• Stenting in average surgical risk	• Routine prophylactic revascularization of asymptomatic carotid 70-99% stenosis in patients undergoing CABG	
Upper Extremity Artery Disease		Mesenteric Artery Disease	
Revascularization for symptomatic subclavian artery stenosis		• D-dimers to rule out acute mesenteric ischaemia	
Subclavian stenosis revascularization		• No delay for re-nutrition in case of symptomatic CMI	
• Endovascular first	• Stenting or surgery	Renal Artery Disease	
Revascularization for asymptomatic subclavian stenosis in patients with/planned for CABG		• Fibromuscular dysplasia: balloon angioplasty with bailout stenting	
Renal Artery Disease		Lower Extremity Artery Disease (LEAD)	
Stenting for symptomatic atherosclerotic stenosis >60% ^{229,231,232}		• Statins to improve walking distance ^{30,278}	
Lower Extremity Artery Disease		• LEAD + AF: Anticoagulation if CHADS-VASc >2	
Aorto-iliac lesions		• Angiography in CLTI with below-the-knee lesions	
• Primary endovascular therapy for "TASC-D"	• Surgery for aorto-iliac or aorto-bi-femoral occlusions	• Duplex screening for AAA ^{258, 259}	
	• Endovascular as an alternative in experienced centres	• In case of CABG: screen LEAD with ABI, limit vein harvesting if LEAD	
Infra-popliteal lesions		• Screening for LEAD in CAD patients ^{366-368, 375-379}	
• Endovascular first	• Bypass using GSV	• Screening for LEAD in HF patients	
	• Endovascular therapy ³²⁰⁻³²⁶	• Clopidogrel preferred over aspirin ^a	
		• Antiplatelet therapy in isolated ^b asymptomatic LEAD ^{66, 67}	
I	IIa	IIb	III
2017 NEW / REVISED CONCEPTS			
<p>PADs in general:</p> <ul style="list-style-type: none"> • "Vascular Team" for a multidisciplinary management. • Best medical therapy: drugs and non pharmacological interventions for optimal outcome. A specific chapter addresses antithrombotic therapies in different PADs presentations, including when anticoagulants are needed. 		<p>Lower extremity artery disease:</p> <ul style="list-style-type: none"> • 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 VwfI 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. 	
<p>Carotid disease:</p> <ul style="list-style-type: none"> • Risk stratification for asymptomatic carotid disease. • In patients undergoing CABG, revascularization of severe carotid stenosis is not systematic. 			

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.

^aRecent data from COMPASS trial need further analyses and will be addressed in the future.

^bWithout any other clinical condition requiring antiplatelet therapy.

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.

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](#).

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}

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 assessment¹⁷ 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 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

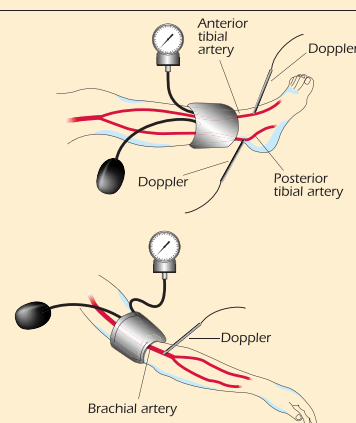
Table 3. The Ankle-Brachial Index.

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 $\geq 5\%$ and $<10\%$.

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 acetyl-cysteine 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 $\geq 50\%$ 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.

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.

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 pa-

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}	Ia	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 PADs

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

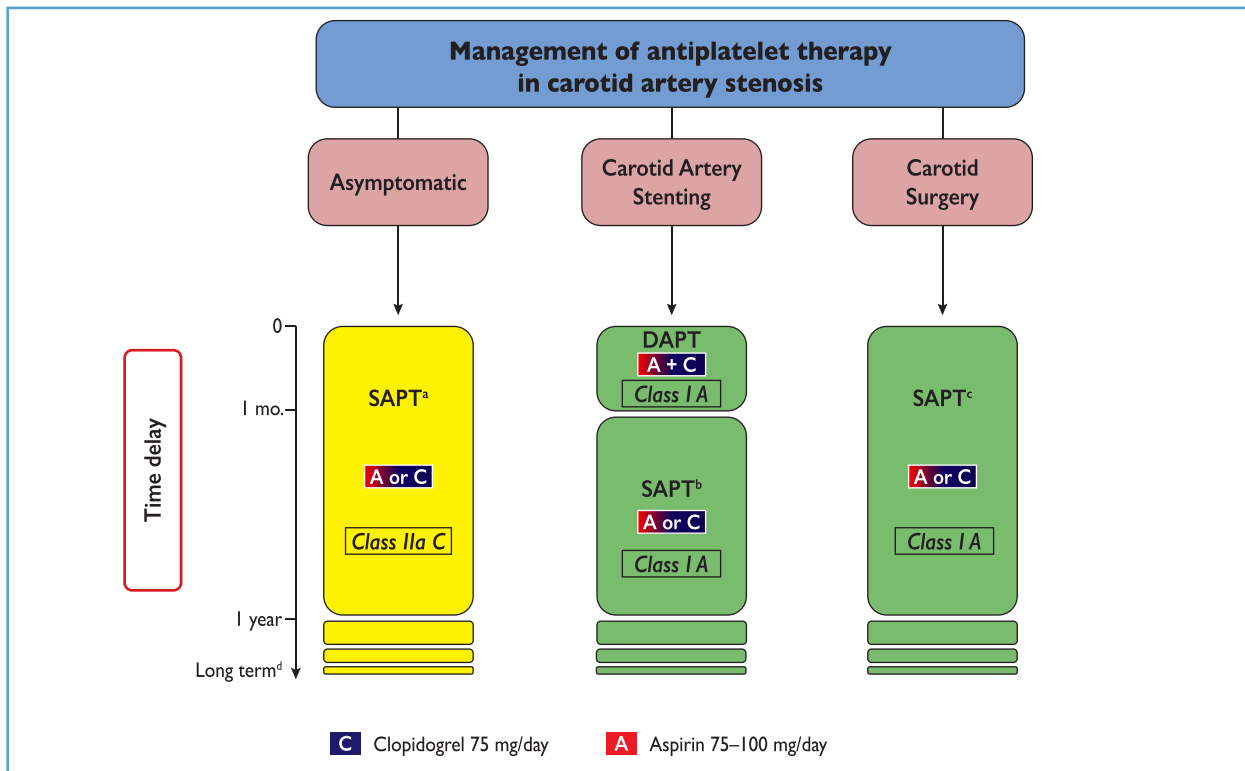
tients enrolled. No benefit was observed between DAPT vs. SAPT.⁵⁶ The Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study, conducted in 108 patients, demonstrated that DAPT vs. aspirin reduced silent cerebral micro-emboli by 37% after 7 days.⁵⁷ No life-threatening intracranial or major bleeding was observed, but the sample size was small. For these reasons, 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

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.



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.

^aAt the exception of patient at very high bleeding risk.

^bDAPT 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.

^cIn 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.

^dStands for as long as it is well tolerated.

Figure 1. Management of antithrombotic treatment in patients with carotid artery stenosis.

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 aspirin⁵¹ 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

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 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%).

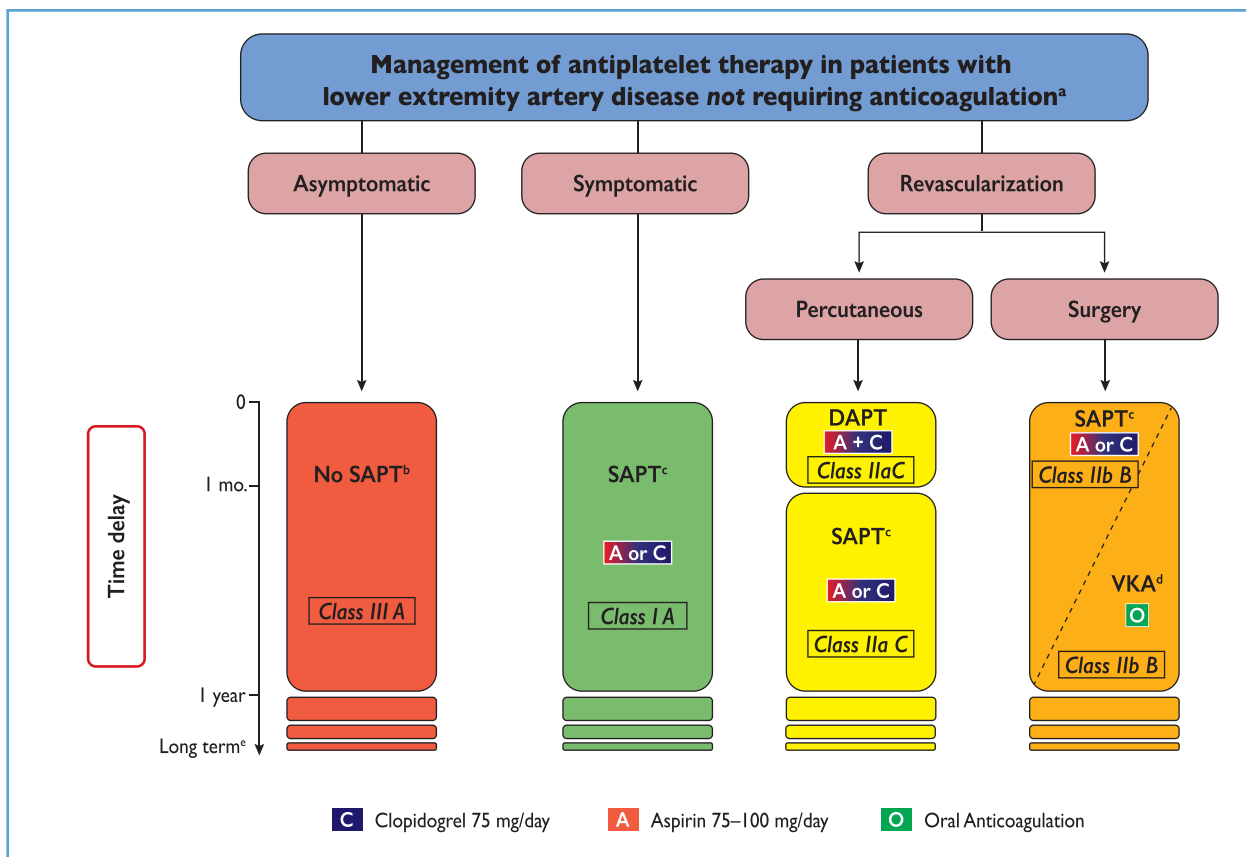
5.2.4. Antithrombotic drugs after endovascular therapy for lower extremity artery disease. DAPT is currently recommended for at least 1 month after intervention, irrespective of the stent type (bare metal vs. drug eluting). In the Zilver PTX randomized trial comparing provisional drug-eluting stents 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

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.



DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.

^ae.g. concomitant AF or mechanical valve prosthesis.

^bSAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease).

^cDAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization.

^dEvidence is weak and bleeding doubles as compared to SAPT.

^eStands for as long as it is well tolerated.

Figure 2. Antiplatelet therapy in patients with lower extremity artery disease.

(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

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

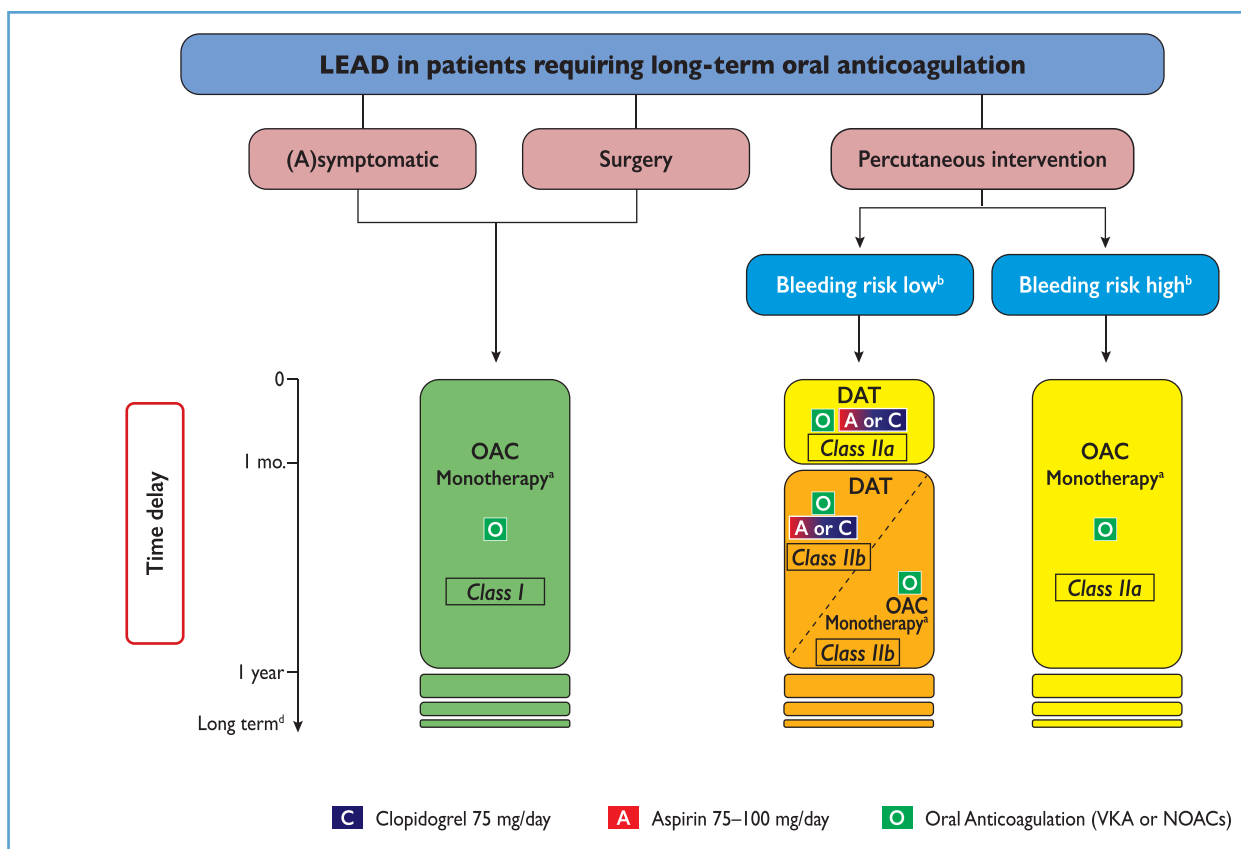
to reassess the indication for OAC. OAC should be continued only if a compelling indication exists (e.g. paroxysmal, persistent or permanent AF with a Congestive heart failure, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category (CHA₂DS₂-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 CHA₂DS₂-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 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.



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.

^aDAT may be considered in high ischaemic risk 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).

^bCompared to the risk for stroke/CLTI due to stent/graft occlusion.

^dStands for as long as it is well tolerated.

Figure 3. Antithrombotic therapy in patients with LEAD requiring oral anticoagulation.

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 ₂ DS 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; CHA₂DS₂-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.

CHA₂DS₂-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 $\geq 50\%$ 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.

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.

6.1.2. 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

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-1¹¹⁵ 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 BMT⁹⁷ ([Table 4](#)). Pending the development of better algorithms for patient selection, the presence of one or more of these clinical or imaging features might be useful for selecting patients for revascularization.

Importantly, ACST found no evidence that age >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}

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	<ul style="list-style-type: none"> • Contralateral TIA/stroke¹²¹
Cerebral imaging	<ul style="list-style-type: none"> • Ipsilateral silent infarction¹²²
Ultrasound imaging	<ul style="list-style-type: none"> • Stenosis progression (> 20%)¹²³ • Spontaneous embolization on transcranial Doppler (HITS)¹²⁴ • Impaired cerebral vascular reserve¹²⁵ • Large plaques^{b 126} • Echolucent plaques⁹⁶ • Increased juxta-luminal black (hypoechoic) area¹²⁷
MRA	<ul style="list-style-type: none"> • Intraplaque haemorrhage¹²⁸ • Lipid-rich necrotic core

HITS = high intensity transient signal; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.

^a Age is not a predictor of poorer outcome.

^b More than 40 mm² on digital analysis.

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.

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%

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.

(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 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

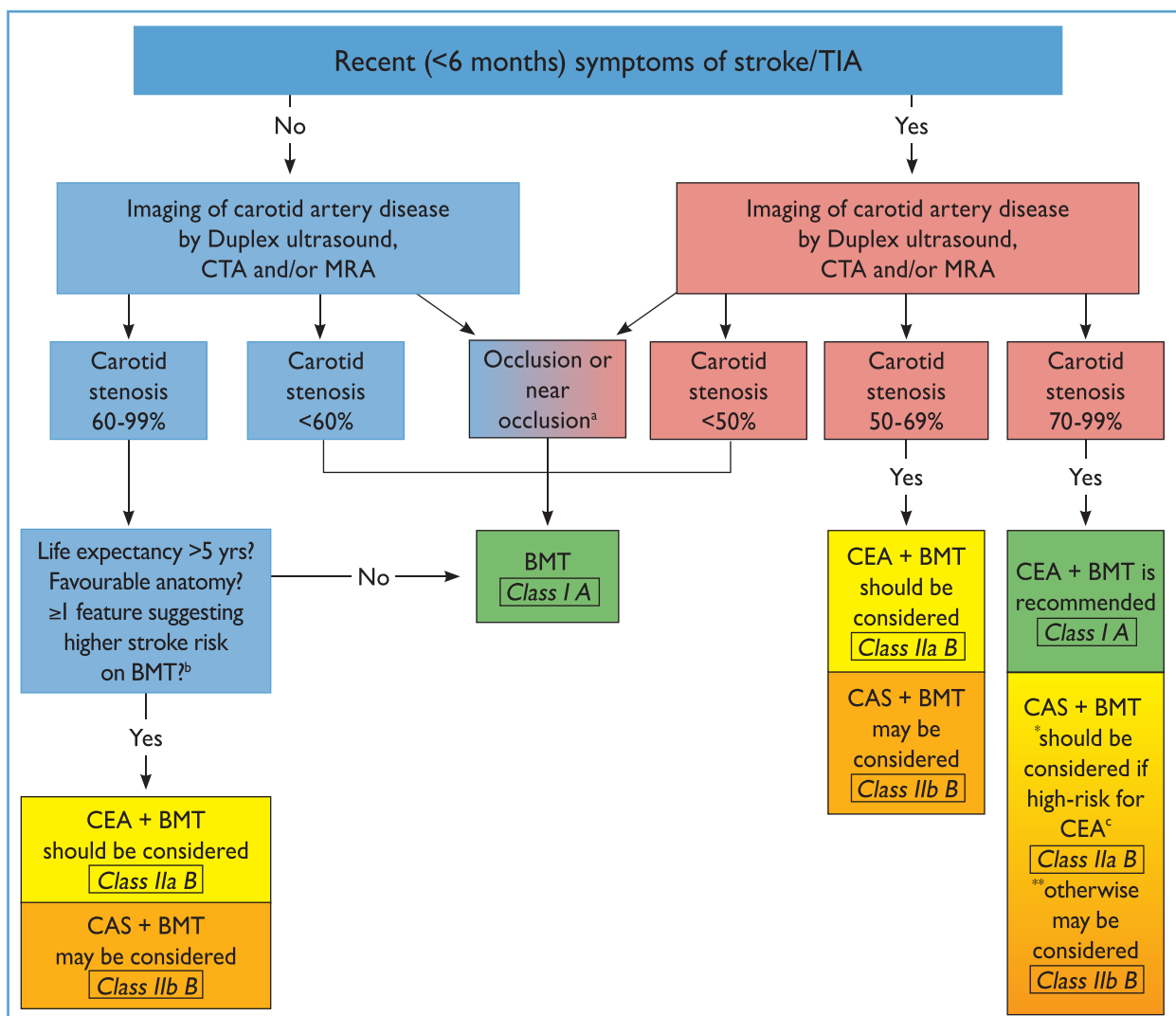
The 30-day outcomes in four large contemporary RCTs comparing CEA with CAS are detailed in [Web Table 7](#). Overall, the risk of ‘any stroke’ and ‘death/stroke’ was ~50% higher following CAS, primarily because CAS was associated with a significantly higher rate of minor stroke. Although the CREST reported 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-analysis¹⁵¹ 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](#).



BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.

^aWith post-stenotic internal carotid artery narrowed to the point of near occlusion.

^bSee Table 4.

^cAge > 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.

Figure 4. Management of extracranial carotid artery disease.

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.

^a Class of recommendation.

^b Level of evidence.

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](#).

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 $\geq 50\%$ 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.

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.

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](#).

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 antegrade 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 therapy¹⁶⁴ 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 extra-thoracic 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

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 surgery¹⁸⁹ 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 $\geq 60\%$, 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).

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 ($\geq 60\%$) 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 diag-

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.

nosis.^{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

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 previous²²⁷ 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 population²³³ 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.

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, arterial ulcers are usually painful and are often complicated by local infection and inflammation. When pain is absent, peripheral neuropathy should be considered. While CLTI is a clinical diagnosis, it is often associated with an ankle pressure <50 mmHg or toe pressure <30 mmHg.²⁴⁶ Investigation of the microcirculation [i.e. transcutaneous oxygen pressure (TcPO₂)] is helpful in some cases of medial calcinosis.

Table 6. Clinical stages of lower extremity artery disease.

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

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.

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

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

Clinical examination is fundamental but the diagnosis must be confirmed by objective tests. Pulse palpation should be systematic. Abdominal and/or groin auscultation

is poorly sensitive. In severe cases, inspection may show foot pallor in a resting leg, with extended recoloration time (>2 s) after finger pressure.

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

10.2. Diagnostic tests

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

Recommendations for ankle-brachial index measurement

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

ABI = ankle-brachial index; LEAD = lower extremity artery disease.

^a Class of recommendation.

^b Level of evidence.

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

10.2.3. Imaging methods

10.2.3.1. Ultrasound. DUS provides extensive information on arterial anatomy and haemodynamics. It must be combined with ABI measurement. It presents 85–90% sensitivity and >95% specificity to detect stenosis >50%.²⁵³ A normal DUS at rest should be completed by a post-exercise test

when iliac stenosis is suspected, because of lower sensitivity. DUS is operator dependent and good training is mandatory. DUS does not present as a roadmap the entire vasculature. Another imaging technique is usually required when revascularization is considered. DUS is also important to address vein quality for bypass substitutes. It is the method of choice for routine follow-up after revascularization.

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

10.2.3.3. Magnetic resonance angiography. The sensitivity and specificity of MRA are ~95% for diagnosing segmental stenosis and occlusion. However, MRA tends to overestimate the degree of stenosis.²⁵⁵ It cannot visualize arterial calcifications, useful for the estimation of stenosis severity in highly calcified lesions. This is a limitation for selection of the anastomotic site of surgical bypass. The visualization of steel stents is poor. In expert centres, MRA

has a higher diagnostic accuracy for tibial arteries than DUS and CTA.

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

10.2.3.5. Cardiovascular screening in patients with LEAD. Patients with LEAD often have other concomitant arterial lesions, including other PADs and AAA. See [Web addenda 10.2.3.5](#) and [chapter 11](#).

10.2.4. Other tests. Toe systolic BP, TBI and TcPO₂ are useful in patients with medial calcinosis and incompressible arteries. For further details see [Web addenda 10.2.4](#).

Recommendations on imaging in patients with lower extremity artery disease

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

AAA = abdominal aorta aneurysm; CTA = computed tomography angiography; DUS = duplex ultrasound; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography.

^a Class of recommendation.

^b Level of evidence.

10.3. Medical treatment

The therapeutic options addressed here are those to improve limb symptoms or salvage. Treatments proposed to reduce other CV events and mortality are addressed in [chapter 4](#). General prevention strategies can improve limb events. Smoking cessation provides the most noticeable improvement in WD when combined with regular exercise, especially when lesions are located below the femoral arteries. In patients with IC, the natural history is deteriorated by ongoing tobacco use, with increased risk of amputation.^{25,260}

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

In subjects with hypertension, calcium antagonists or ACEIs/ARBs should be preferred because of their potential in peripheral arterial dilatation. A meta-analysis²⁶² showed improved maximal and pain-free WD when using an ACEI over placebo; however, two of six RCT reports have been recently withdrawn because of unreliable data, and the meta-analysis of the remaining studies is inconclusive.²⁶³ The benefit of verapamil in improving WD in LEAD has been shown in a randomized study.²⁶⁴ Because of comorbidities such as heart failure, beta-blockers are indicated in some patients with LEAD. Studies have shown that beta-blockers, in particular nebivolol, are safe in patients with IC without negative effects on WD.⁴⁹ Metoprolol and nebivolol have been compared in a double-blind RCT including 128 beta-blocker-naïve patients with IC and hypertension.²⁶⁵ After a 48-week treatment period, both drugs were well tolerated and decreased BP equally. In both groups, maximal WD improved significantly. Nebivolol showed an advantage, with significant improvement in pain-free WD [+34% ($P < 0.003$) vs. +17% for metoprolol ($P < 0.12$)]. In a single-centre study of 1873 consecutive CLTI patients who received endovascular therapy, those treated with other beta-blockers did not have a poorer clinical outcome.²⁶⁶ In a multicentre registry of 1273 patients hospitalized for severe LEAD (of whom 65% had CLTI and 28% were on beta-blocker therapy), death and amputation rates did not differ among those with vs. without beta-blocker.²⁶⁷

10.4. Revascularization options: general aspects

See [Web addenda 10.4](#).

10.5. Management of intermittent claudication

10.5.1. Exercise therapy. In patients with IC, exercise therapy (ExT) is effective and improves symptoms and QOL and increases maximal WD. In 30 RCTs including 1816 patients with stable leg pain, ExT improved maximal WD on a treadmill by almost 5 min compared with usual care.²⁶⁸ Pain-free and maximal WD were increased on average by 82 and 109 m, respectively. Improvement was observed up to 2 years. Moreover, ExT improved QOL. Exercise did not improve ABI. Whether ExT reduces CV events and improves life expectancy is still unclear. Supervised ExT is more effective than unsupervised ExT.^{11,269} In 14 trials with participants assigned to either supervised ExT or unsupervised ExT (1002 participants), lasting from 6 weeks to 12 months, maximal and pain-free WD increased by almost 180 m in favour of supervised ExT. These benefits remained at 1 year. Most studies use programmes of at least 3 months, with a minimum of 3 h/week, with walking to the maximal or submaximal distance. Long-term benefits of ExT are less clear and largely depend on patient compliance. Supervised ExT is safe and routine cardiac screening beforehand is not required.²⁷⁰ It is also more cost effective than unsupervised ExT,²⁷¹ but it is not reimbursed or available everywhere. Although home-based walking ExT is not as effective as supervised ExT, it is a useful alternative, with positive effects on QOL and functional walking capacity vs. walking advice alone.^{272,273} Alternative exercise modes (e.g. cycling, strength training and upper-arm ergometry) may be useful when walking exercise is not an option for patients, as these have also been shown to be effective.²⁷⁴ ExT is impossible in patients with CLTI but can be considered after successful revascularization.^{275,276}

10.5.2. Pharmacotherapy to decrease walking impairment.

Some antihypertensive drugs (e.g. verapamil),²⁶⁴ statins,^{277,278} antiplatelet agents and prostanoids (prostaglandins I₂ and E₁)²⁷⁹ have some favourable effects on WD and leg functioning (see above). Other pharmacological agents claim to increase WD in patients with IC without other effects on CV health. The drugs mostly studied are cilostazol, naftidrofuryl, pentoxifylline, buflomedil, carnitine and propionyl-L-carnitine.^{261,280} However, objective documentation

of such an effect is limited. The beneficial effects on WD, if any, are generally mild to moderate, with large variability.²⁶¹ Also, the incremental benefit of these treatments in addition to ExT and statins is unknown. For further details see [Web addenda 10.5.2](#).

10.5.3. Revascularization for intermittent claudication. The anatomical location and extension of arterial lesions has an impact on revascularization options.

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

10.5.3.2. Femoro-popliteal lesions. Femoro-popliteal lesions are common in claudicants. If the circulation to the profunda femoral artery is normal, there is a good possibility that the claudication will be relieved with ExT and intervention is mostly unnecessary. If revascularization is needed, endovascular therapy is the first choice in stenosis/occlusions <25 cm. If the occlusion/stenosis is >25 cm, endovascular recanalization is still possible, but better long-term patency is achieved with surgical bypass, especially when using the great saphenous vein (GSV). No head-to-head trials comparing endovascular therapy and

surgery are yet available. In the Zilver-PTX trial, the 5-year primary patency with conventional and drug-eluting stents was 43% and 66%, respectively.⁷⁶ The 5-year patency after above-the-knee femoro-popliteal bypass is >80% with GSV and 67% with prosthetic conduits.²⁸⁴ The challenge of endovascular therapy is the long-term patency and durability of stents in the femoro-popliteal region, where the artery is very mobile. Several new endovascular solutions, such as atherectomy devices, drug-eluting balloons and new stent designs, have been shown to improve long-term patency.

10.5.4. Management strategy for intermittent claudication.

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

Recommendations for the management of patients with intermittent claudication

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

^a Class of recommendation.

^b Level of evidence.

Recommendations on revascularization of aorto-iliac occlusive lesions^c

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

^a Class of recommendation.

^b Level of evidence.

^c These recommendations apply for patients with intermittent claudication and severe chronic limb ischaemia.

Recommendations on revascularization of femoro-popliteal occlusive lesions^c

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

^a Class of recommendation.

^b Level of evidence.

^c These recommendations apply for patients with intermittent claudication and severe chronic limb ischaemia.

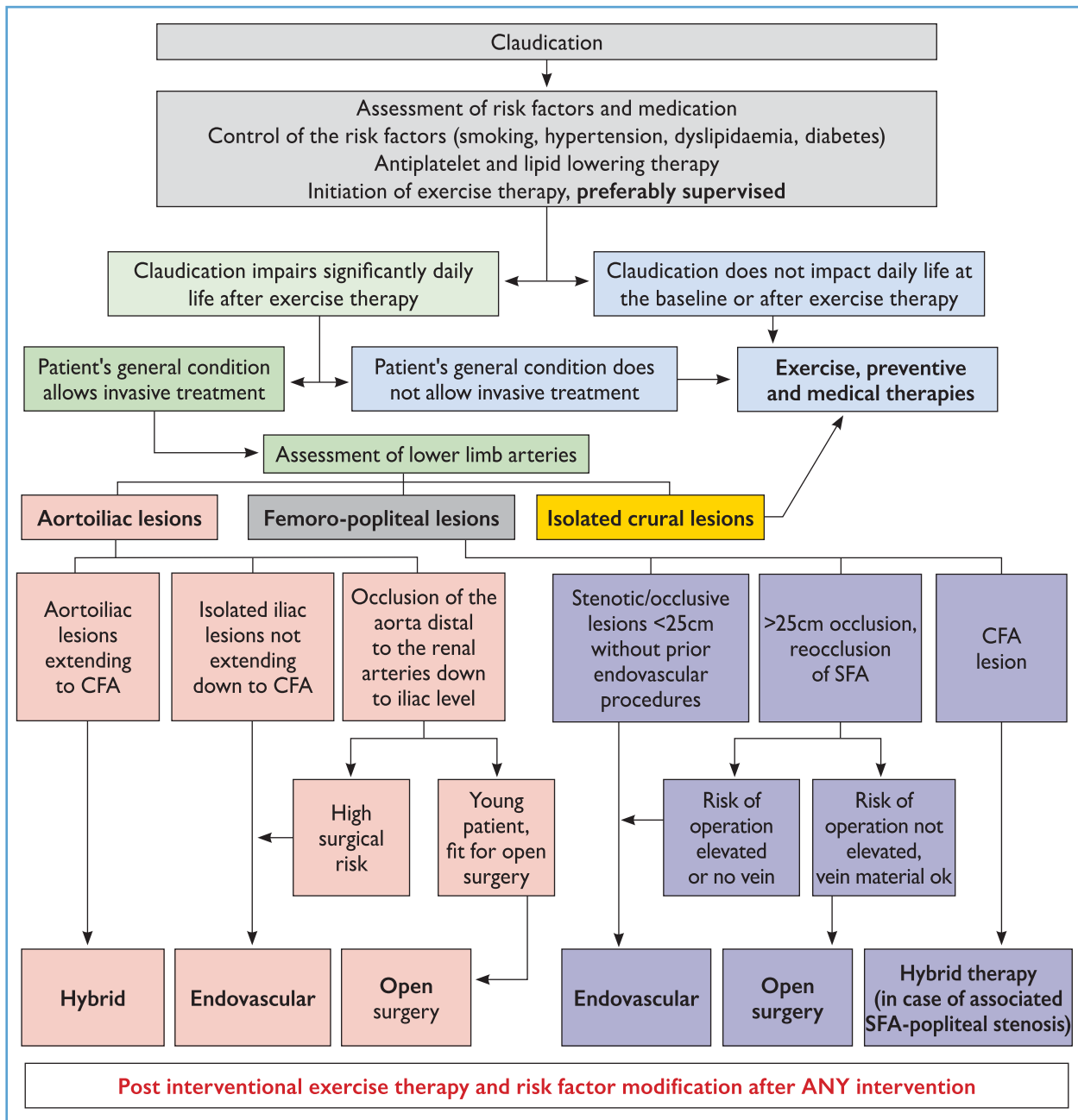
10.6. Chronic limb-threatening ischaemia

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

presence of a wound and infection. This explains why ankle or toe pressures, measured to address LEAD severity, are not a definition component of CLTI.

10.6.1. Chronic limb-threatening ischaemia severity and risk stratification: the WIfI classification. A new classification system (WIfI) has been proposed as the initial assessment of all patients with ischaemic rest pain or wounds.³¹⁷ The target population for this system includes any patient with

- ischaemic rest pain, typically in the forefoot with objectively confirmed haemodynamic studies (ABI <0.40, ankle pressure <50 mmHg, toe pressure <30 mmHg, TcPO₂ <30 mmHg),



CFA = common femoral artery; SFA = superficial femoral artery.

*Related to atherosclerotic lower extremity artery disease (LEAD).

Figure 5. Management of patients with intermittent claudication.^a

- diabetic foot ulcer,
- non-healing lower limb or foot ulceration ≥ 2 weeks duration or
- gangrene involving any portion of the foot or lower limb.

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

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

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

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

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

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

10.6.2. Management of patients with chronic limb-threatening ischaemia.

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

10.6.2.1. Revascularization. Revascularization should be attempted as much as possible.^{246,320–322} So far, only one randomized trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, has directly compared endovascular therapy to open surgery in CLTI patients.³²³ At 2 years there was no significant difference between endovascular therapy and surgery regarding amputation-free survival. In survivors after 2 years, bypass surgery was associated with improved survival (on average 7 months, $P = 0.02$) and amputation-free survival (6 months, $P = 0.06$).³¹⁴ These data are challenged by more recent endovascular therapy techniques. So far, drug-eluting balloons in below-the-knee disease have shown no superiority over plain balloon angioplasty.³²⁴ The results of two ongoing RCTs, BASIL-2 and Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI), are awaited.^{325,326} Meanwhile, in each anatomical region, both revascularization options should be individually discussed.

10.6.2.1.1. Aorto-iliac disease

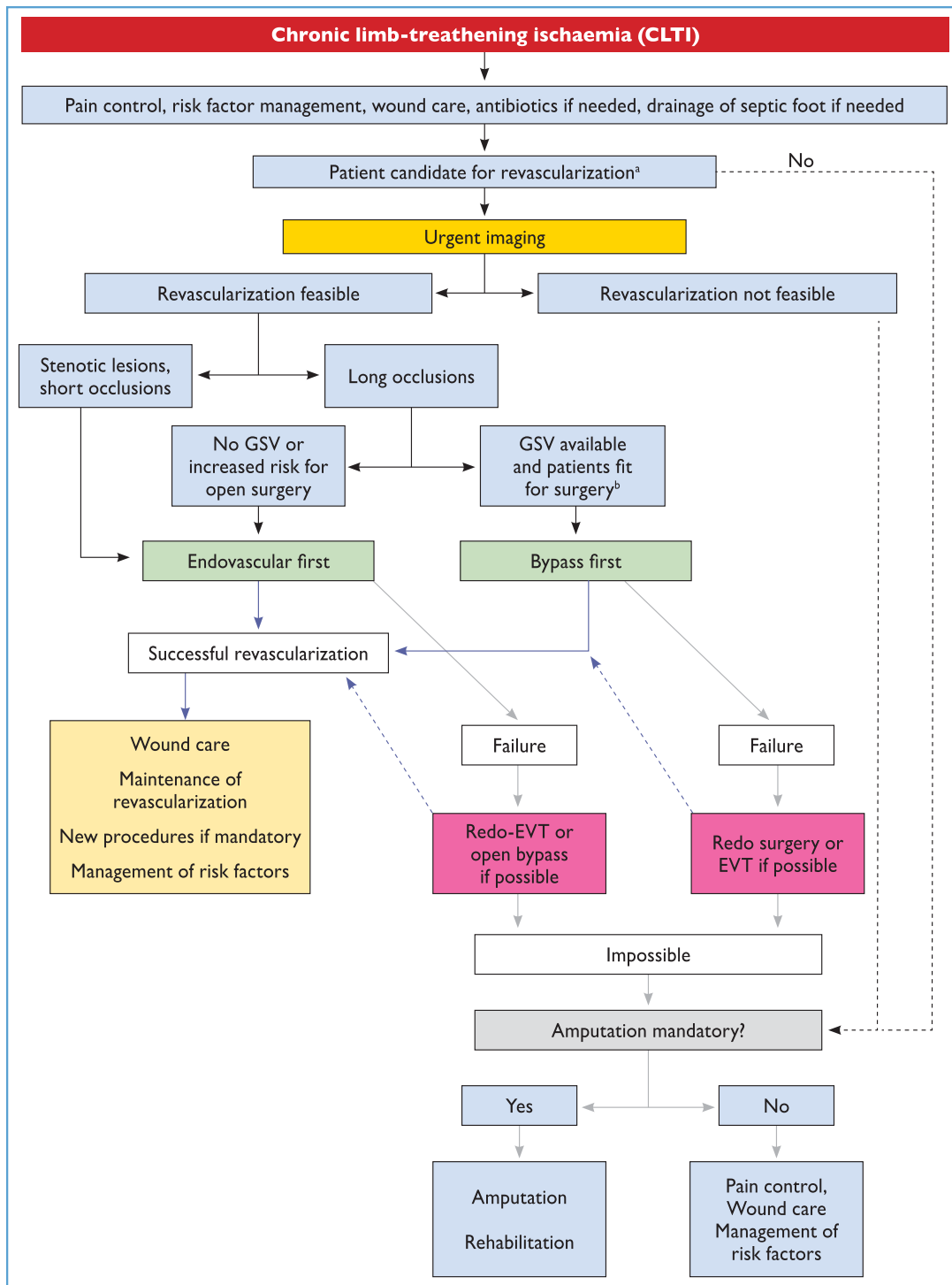
CLTI is almost never related to isolated aorto-iliac disease, and downstream lesions are often concomitant. In addition to CTA and/or MRA, complete DSA down to the plantar arches is required for proper arterial network assessment and procedure planning.³²⁷ Hybrid procedures (e.g. aorto-iliac stenting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

10.6.2.1.2. Femoro-popliteal disease

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

10.6.2.1.3. Infra-popliteal disease

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



EVT= endovascular therapy; GSV = great saphenous vein.

^aIn bedridden, demented and/or frail patients, primary amputation should be considered.

^bIn the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff.

Figure 6. Management of patients with chronic limb-threatening ischaemia.

Recommendations on revascularization of infra-popliteal occlusive lesions

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

CLTI = chronic limb threatening ischaemia.

^a Class of recommendation.

^b Level of evidence.

10.6.3. Spinal cord stimulation

See [Web addenda 10.6.3](#).

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

10.6.5. Amputation

10.6.5.1. Minor amputation. In case of CLTI, minor amputation (up to the forefoot level) is often necessary to remove necrotic tissues with minor consequences on patient's mobility. Revascularization is needed before amputation to improve wound healing. Foot TcPO₂ and toe pressure can be useful to delineate the amputation zone (see section 10.2.4).

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

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

appropriate analgesia.^{246,331} The emergency level and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficits. The clinical categories are presented in [Table 8](#).

Table 8. Clinical categories of acute limb ischaemia.³³²

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

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

Different revascularization modalities can be applied, including percutaneous catheter-directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy) and surgical thrombectomy, bypass and/or arterial repair. The strategy will depend on the presence of a neurological deficit, ischaemia duration, its localization, comorbidities, type of conduit (artery or graft) and therapy-related risks and outcomes. Owing to reduced morbidity and mortality, endovas-

Recommendations on the management of chronic limb-threatening ischaemia

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

CLTI = chronic limb-threatening ischaemia.

^a Class of recommendation.

^b Level of evidence.

10.7. Acute limb ischaemia

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

Once the clinical diagnosis is established, treatment with unfractionated heparin should be given, along with

cular therapy is often preferred, especially in patients with severe comorbidities. Thrombus extraction, thrombo-aspiration and surgical thrombectomy are indicated in the case of neurological deficit, while catheter-directed thrombolytic therapy is more appropriate in less severe cases without neurological deficit. The modern concept of the combination of intra-arterial thrombolysis and catheter-based clot removal is associated with 6-month amputation rates of <10%.²⁴⁶ Systemic thrombolysis has no role in the treatment of patients with acute limb ischaemia.

Based on RCTs, there is no clear superiority of local thrombolysis vs. open surgery on 30-day mortality or limb salvage.³³³

After thrombus removal, the pre-existing arterial lesion should be treated by endovascular therapy or open surgery. Lower extremity four-compartment fasciotomies should be performed in patients with long-lasting ischaemia to prevent a post-reperfusion compartment syndrome. The management of acute limb ischaemia is summarized in [Figure 7](#).

10.8. Blue toe syndrome

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

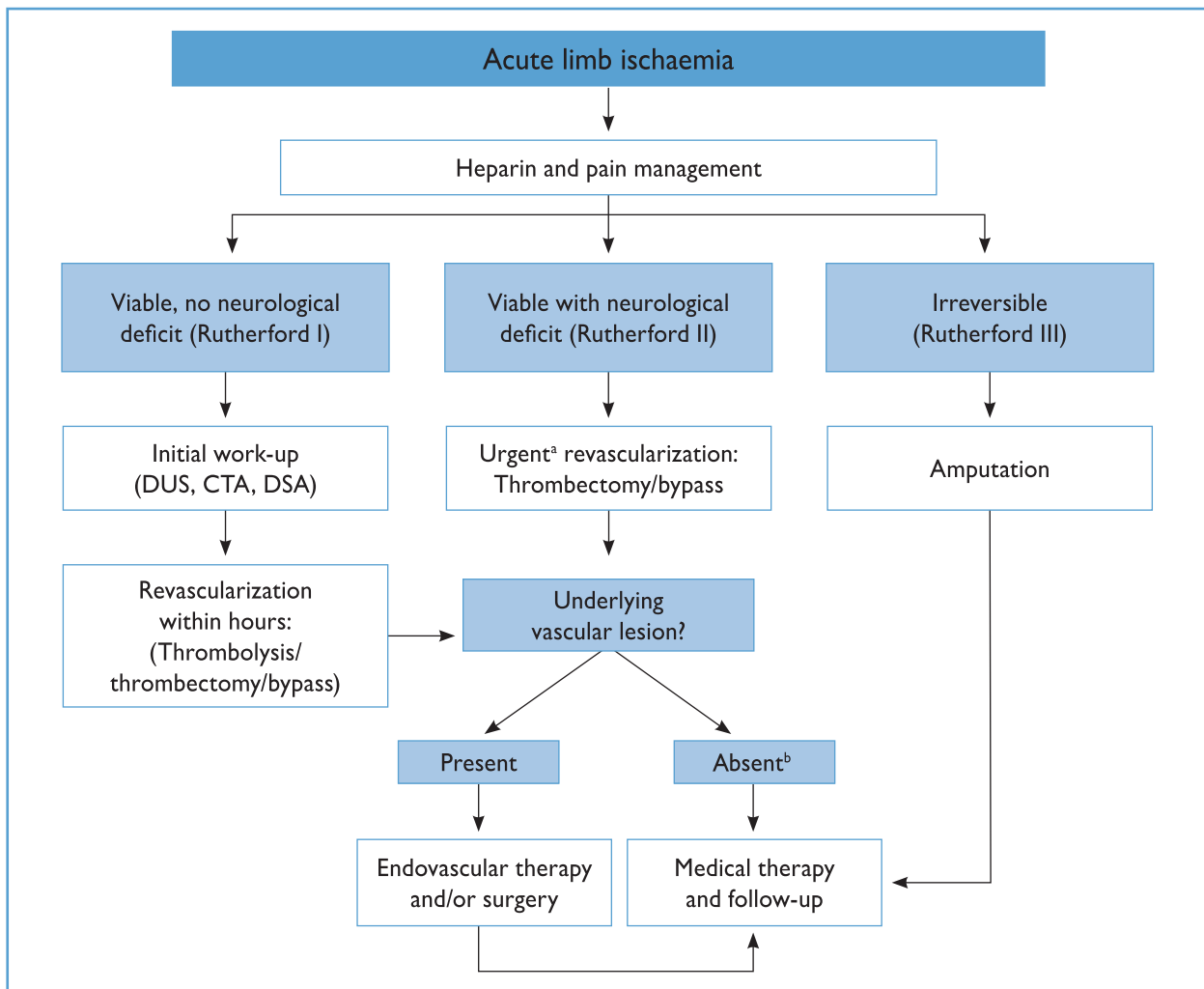
Recommendations for the management of patients presenting with acute limb ischaemia

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

^a Class of recommendation.

^b Level of evidence.

^c In this case, imaging should not delay intervention.



CTA = computed tomography angiography; DSA = digital subtraction ultrasound; DUS = duplex ultrasound.

^aImaging should not delay revascularization.

^bSpecific etiological work-up is necessary (cardiac, aorta).

Figure 7. Management of acute limb ischaemia.

11. MULTISITE ARTERY DISEASE

Key messages

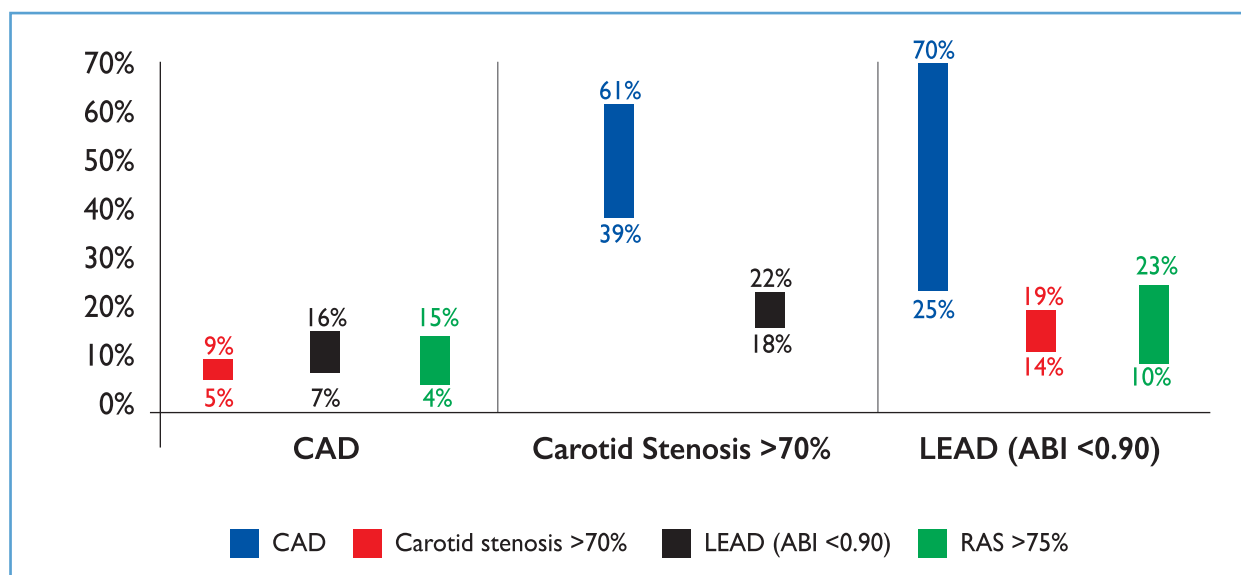
- Multisite artery disease (MSAD) is common in patients with atherosclerotic involvement in one vascular bed, ranging from 10 to 15% in patients with CAD to 60 to 70% in patients with severe carotid stenosis or LEAD.
- MSAD is invariably associated with worse clinical outcomes; however, screening for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

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

11.1. Multisite artery disease: epidemiology and impact prognosis

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

Although several studies have demonstrated that patients with MSAD have a significantly worse clinical outcome as compared with patients with single vascular site disease, the only RCT designed to assess the impact on prognosis of systematic screening for MSAD in patients with high-risk CAD (three-vessel CAD and/or with an ACS at age >75 years) failed to prove any significant benefit.³⁴⁴ The Aggressive detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis (AMERICA) trial randomized 521 patients to a proactive strategy (total-body DUS and ABI measurement associated with intensive medical therapy) or to conventional strategy (no screening for asymptomatic



The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g. in patients with CAD, 5–9% of cases have concomitant carotid stenosis >70%).

ABI = ankle-brachial index; CAD = coronary artery disease; LEAD = lower extremity artery disease; RAS = renal artery stenosis.

Figure 8. Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease.^{51,335–343}

MSAD and standard medical therapy); at the 2-year follow-up, the primary composite endpoint, including death, any ischaemic event leading to rehospitalization or any evidence of organ failure, occurred in 47.4% and 46.9% of patients, respectively ($P > 0.2$).³⁴⁴ Hence the clinical benefit of systematic screening for asymptomatic MSAD in patients with known atherosclerotic disease appears questionable.

11.2. Screening for and management of multisite artery disease

11.2.1. Peripheral arterial diseases in patients presenting with coronary artery disease

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

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

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

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

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

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

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

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

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

CABG = coronary artery bypass grafting; DUS = duplex ultrasound; LEAD = lower extremity artery disease; TIA = transient ischaemic attack.

^a Class of recommendation.

^b Level of evidence.

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

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

CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy.

^a Class of recommendation.

^b Level of evidence.

^c See Table 4.

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

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

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

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

11.2.1.4. Lower extremity artery disease in patients with coronary artery disease.

LEAD often coexists with CAD ([Figure 8](#)). It is often asymptomatic or masked by limiting angina and/or dyspnoea. LEAD (ABI < 0.90) is present in 13–16% of patients who have CAD at coronary angiography.^{361,362} Left main coronary artery stenosis and

multivessel CAD were independent predictors. Patients with LEAD exhibit more extensive, calcified and progressive coronary atherosclerosis.³⁶³

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

In patients with CAD who have concomitant LEAD, strict risk factor control is mandatory, although no specific

recommendations exist, as compared with CAD patients without MSAD. In a post hoc analysis of the CHARISMA trial, DAPT with aspirin and clopidogrel was associated with a significant decrease in non-fatal MI compared with aspirin alone,⁶⁵ at a cost of increased minor bleeding. The potential benefits of DAPT in these patients need further confirmation.

In LEAD patients requiring coronary revascularization, the treatment of CAD is usually prioritized, except in the case of CLTI. Whether PCI or CABG should be favoured to treat CAD in patients with LEAD is controversial.^{369,370} In the case of PCI, radial artery access should be favoured. If the femoral approach is necessary, pre-interventional assessment of the iliac and common femoral arteries should be performed to minimize the risk of ischaemia/

compartment syndrome potentially caused by ischaemia–reperfusion injury during CPB. The coexistence of LEAD, even asymptomatic, may upset cardiac rehabilitation.³⁷³

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

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

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

ABI = ankle-brachial index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LEAD = lower extremity artery disease; TIA = transient ischaemic attack.

^a Class of recommendation.

^b Level of evidence.

embolization and to identify the best location for arterial puncture, since access site complications are more frequent in these patients, particularly when closure devices are used.³⁷¹ In patients undergoing CABG with advanced LEAD, the GSV should be spared whenever possible; later success of peripheral arterial revascularization is strongly dependent on the availability of sufficient autologous venous segments.³⁷² Also, saphenous vein harvesting may be associated with wound healing delays in severe LEAD. This justifies the screening for LEAD prior to use of the saphenous vein as bypass material, at least by clinical examination and/or ABI. CPB during CABG causes a mean arterial pressure drop and loss of pulsatile flow, entailing the risk of worsening CLTI. When off-pump CABG is not feasible, maintaining an adequate mean arterial pressure and monitoring peripheral oxygen saturation in CLTI patients are strongly advisable during CPB. Postoperatively, active clinical surveillance is needed to diagnose in a timely fashion the

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

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

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

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

from CAD.³⁹⁰ The severity of LEAD is related to the prevalence of associated CAD; up to 90% of patients presenting with CLTI also have CAD.

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

The presence of CAD in patients with LEAD may require coronary revascularization, depending on the severity and urgency of LEAD symptoms. Risk factor modification and medical treatment recommended for CAD also apply to LEAD.³⁹¹ Screening for CAD in LEAD patients may be useful for risk stratification, as morbidity and mortality are mainly cardiac. Non-invasive screening can be performed by stress testing or coronary CTA, but

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

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

CAD = coronary artery disease; CEA = carotid endarterectomy.

^a Class of recommendation.

^b Level of evidence.

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

11.2.2.3. Coronary artery disease in patients with lower extremity artery disease not undergoing vascular surgery. At least one-third of patients with LEAD have a history and/or ECG signs of CAD, while two-thirds have an abnormal stress test and up to 70% present at least single-vessel disease at coronary angiography.^{69,388} The prevalence of CAD is 2- to 4-fold higher in patients with LEAD vs. those without. In the Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter (CONFIRM) registry, among 7590 patients with LEAD without a history and symptoms of heart disease, the prevalence of obstructive CAD at coronary CTA was 25%.³⁸⁹ In the REACH registry, 57% of the participants with LEAD also suffered

there is no evidence of improved outcomes in LEAD patients with systematic screening for CAD.

11.2.3. Other peripheral localizations in patients with peripheral arterial diseases

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

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

For more details see [Web addenda 11.2.3.2](#).

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

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

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

^a Especially when venous harvesting is planned for bypass.

^b In patients with symptomatic cerebrovascular disease.

^c In patients with asymptomatic carotid disease and: age \geq 70 years, multivessel CAD, associated LEAD or carotid bruit.

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

12. CARDIAC CONDITIONS IN PERIPHERAL ARTERIAL DISEASES

Key messages

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

12.1. Introduction

Cardiac diseases are frequent in patients with PADs. The simultaneous presence of PADs and CAD is addressed in [chapter 11](#). Here we address the most important issues related to PADs patients with coexisting heart failure, AF and valvular heart disease (VHD). Such coexistence may carry important prognostic and therapeutic implications and often needs a multi-disciplinary approach.

12.2. Heart failure and peripheral arterial diseases

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

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

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

12.2.2. Heart failure in patients with peripheral arterial diseases. Despite the high prevalence and incidence of heart failure in patients with PADs, outcome data for this group are very limited. It is most likely, however, that this combination is associated with increased CV morbidity and mortality. Evaluation of LV function in PADs may be of value for better risk stratification for future CV events and comprehensive management of patients' CV diseases.³⁹⁹ This is particularly important when an intermediate- or

high-risk vascular intervention is planned.³⁸⁷ The primary assessment should include medical history, physical examination and resting ECG. In case of any abnormalities suggestive of heart failure, transthoracic echocardiography (TTE) or measurement of natriuretic peptides should be undertaken.⁴⁰⁰ Natriuretic peptides are particularly useful in patients with a poor echocardiographic window and in those with diastolic dysfunction.⁴⁰¹ In patients with LEAD, heart failure may be associated with reduced patency after endovascular therapy.⁴⁰² TTE and natriuretic peptides can also be proposed in patients with claudication, even if no revascularization is planned.

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

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

12.3. Peripheral arterial diseases and atrial fibrillation

12.3.1. General considerations. Ageing is a strong risk factor for AF⁴⁰⁶ and PADs, thus a frequent coexistence of the two conditions is expected. In an analysis from the Cardiovascular Health Study, LEAD was associated with a higher risk of AF (HR 1.52, $P < 0.01$).⁴⁰⁷

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

Among 41 882 patients hospitalized for LEAD, the prevalence of AF was 13%.⁴⁰⁶ Those with AF tend to be older, more often hypertensive, female and with diabetes, CKD, CAD and/or heart failure than patients in sinus rhythm. LEAD was overall more severe in patients with AF as assessed by the Rutherford classification. In-hospital complications, including renal failure, MI, stroke, infections and death, occurred more frequently in the presence of AF. In other studies, AF associated with LEAD was an independent predictor of stroke, amputation and death.^{410,411} In the

REACH registry, AF was present in 10% of patients with LEAD.⁸⁴ Compared with patients without AF, the two-year CV and all-cause mortality was higher, 7.7% and 5.6% vs. 2.5% and 1.6%, respectively ($P < 0.001$ for both). Those with AF also had higher incidences of heart failure, unstable angina and severe bleeding.

12.3.2. Antithrombotic treatment in patients with atrial fibrillation. Except for recent stenting, patients with PADs and AF should mostly be on OACs alone. See section 5.3.

12.4. Peripheral arterial diseases and valvular heart disease

PADs are common among patients with VHD, especially among the elderly with symptomatic aortic stenosis. The presence of LEAD is captured within the scores used to predict outcome after cardiac surgery.⁴¹² Among patients with symptomatic aortic stenosis not eligible for surgical aortic valve replacement, the prevalence of LEAD is as high as 40%.^{413–415} It often coexists with other manifestations of systemic atherosclerosis, including CAD and cerebrovascular disease. This has an impact on patient care with respect to the timing of coronary revascularization, if needed,³⁶⁶ and the vascular access site for transcatheter aortic valve implantation (TAVI).⁴¹⁶ Systematic CT scan imaging of the aorta, including all major peripheral arteries, has become the standard of care in patients eligible for TAVI.

12.5. Peripheral arterial diseases and vascular access site for cardiac interventions

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

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

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

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

CHA₂DS₂VASC = Congestive heart failure, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; TAVI = transcatheter aortic valve implantation; TTE = transthoracic echocardiography; UEAD = upper extremity artery disease.

^a Class of recommendation.

^b Level of evidence.

^c For more detail please refer to [chapter 5](#).

13. GAPS IN EVIDENCE

Rapid changes in therapeutic techniques create the situation in which clinical practice tends to follow technical developments without evidence from RCTs. In addition, RCTs often yield conflicting results because of technical

evolution. Moreover, PADs may involve multiple sites, creating a large number of clinical scenarios to investigate. All these contribute to the broad spectrum of gaps in evidence, of which the most relevant are listed in [Table 10](#).

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

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

Table 10-continued

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

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

14. TO DO AND NOT TO DO MESSAGES FROM THE GUIDELINES

Recommendations	Class ^a	Level ^b
General recommendations on the management of patients with PADs		
In healthcare centres, it is recommended to set up a multidisciplinary Vascular Team to make decisions for the management of patients with PADs.	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases.	I	C
Recommendations in patients with PADs: best medical therapy		
Smoking cessation is recommended in all patients with PADs.	I	B
A healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.	I	A
In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by ≥50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C ^c
In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg.	I	A
Recommendations on antithrombotic therapy in patients with PADs		
In patients with symptomatic carotid stenosis, long-term SAPT is recommended.	I	A
Dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least 1 month after CAS.	I	B
Long-term SAPT is recommended in symptomatic patients.	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization.	I	C

Recommendations	Class ^a	Level ^b
SAPT is recommended after infra-inguinal bypass surgery.	I	A
Because of the lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated ^d asymptomatic LEAD.	III	A
In patients with PADs and AF, OAC is recommended when the CHA ₂ DS ₂ -VASc score is ≥ 2	I	A
Recommendations for imaging of extracranial carotid arteries		
DUS (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.	I	B
When CAS is being considered, it is recommended that any DUS study be followed either by MRA or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation.	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated either by MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).	I	B
Recommendations on revascularization in patients with symptomatic carotid disease^e		
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is <6%.	I	A
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.	I	A
Revascularization is not recommended in patients with a <50% carotid stenosis.	III	A
Recommendations for management of vertebral artery stenoses		
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C
Recommendations on the management of acute mesenteric ischaemia		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended.	I	C
Recommendations for management of chronic mesenteric artery disease		
In patients with suspected CMI, DUS is recommended as the first-line examination.	I	C
In patients with symptomatic multivessel CMI, revascularization is recommended.	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.	III	C
Recommendations for diagnostic strategies for RAD		
DUS (as first-line), CTA ^f and MRA ^g are recommended imaging modalities to establish a diagnosis of RAD.	I	B
Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD.	III	C
Recommendations for treatment strategies for RAD		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral renal artery stenosis.	I	B
Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with RAD.	I	C
Routine revascularization is not recommended in renal artery stenosis secondary to atherosclerosis.	III	A
Recommendations for ABI measurement		
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated.	I	C
Recommendations on imaging in patients with LEAD		
DUS is indicated as a first-line imaging method to confirm LEAD lesions.	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.	I	C
The data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to a treatment decision.	I	C
Recommendations for the management of patients with intermittent claudication		
On top of general prevention, statins are indicated to improve walking distance.	I	A
In patients with intermittent claudication, supervised exercise training is recommended.	I	A
In patients with intermittent claudication, non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Recommendations on revascularization of aorto-iliac occlusive lesions^h		
An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions.	I	C
Recommendations on revascularization of femoro-popliteal occlusive lesions^g		
An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions.	I	C
In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. ≥ 25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is >2 years.	I	B
The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass.	I	A

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

ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CLTI = chronic limb-threatening ischaemia; CMI = chronic mesenteric ischaemia; CTA = computed tomography angiography; DUS = duplex ultrasound; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography; OAC = oral anticoagulation; PADs = peripheral arterial diseases; RAD = renal artery disease; SAPT = single antiplatelet therapy; TAVI = transcatheter aortic valve implantation; TIA = transient ischaemic attack; UEAD = upper extremity artery disease.

CHA₂DS₂-VASc score is calculated as follows: congestive heart failure history (1 point), hypertension (1 point), age >75 years (2 points), diabetes mellitus (1 point), stroke/TIA or arterial thromboembolic history (1 point), vascular disease history (1 point), age 65–74 years (1 point), sex category (1 point if female).

^a Class of recommendation.

^b Level of evidence.

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

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

^e Stroke or TIA occurring within 6 months.

^f When eGFR is ≥60 mL/min.

^g When eGFR is ≥30 mL/min.

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

ⁱ In this case, imaging should not delay intervention.

WEB ADDENDA AND COMPANION DOCUMENT

Supplementary figures, tables, a web addendum and PAD Section can be found at <http://dx.doi.org/10.1016/j.ejvs.2017.07.018>

APPENDIX

ESC Committee for Practice Guidelines (CPG):

Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), Héctor Bueno (Spain), Antonio Coca (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Veronica Dean (France), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Gerhard Hindricks (Germany), Bernard Jung (France), Peter Juni (Canada), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Patrizio Lancellotti (Belgium), Christophe Leclercq (France), Theresa McDonagh (UK), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russia), Iain A. Simpson (UK), Jose Luis Zamorano (Spain).

ESC National Cardiac Societies actively involved in the review process of the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases:

Armenia: Armenian Cardiologists Association, Parounak H. Zelveian; Austria: Austrian Society of Cardiology, Markus Haumer; Belarus: Belorussian Scientific Society of Cardiologists, Dzmitry Isachkin; Belgium: Belgian Society of Cardiology, Tine De Backer; Bosnia and Herzegovina: Association of Cardiologists of Bosnia and Herzegovina, Mirza Dilic; Bulgaria: Bulgarian Society of Cardiology, Ivo Petrov; Croatia: Croatian Cardiac Society, Majda Vrkic Kirhmajer; Czech Republic: Czech Society of Cardiology, Debora Karetova; Denmark: Danish Society of Cardiology, Eva Prescott; Egypt: Egyptian Society of Cardiology, Hamdy Soliman; Estonia: Estonian Society of Cardiology, Ants Paapstel; Finland: Finnish Cardiac Society, Kimmo Makinen; The Former Yugoslav Republic of Macedonia: Macedonian FYR Society of Cardiology, Slavco Tosev; France: French Society of Cardiology, Emmanuel Messas; Georgia: Georgian Society of Cardiology, Zurab Pagava; Germany: German Cardiac Society, Oliver J. Müller; Greece: Hellenic Society of Cardiology, Katerina K. Naka; Hungary: Hungarian Society of Cardiology, Zoltán Járai; Iceland: Icelandic Society of Cardiology, Thorbjorn Gudjonsson; Israel: Israel Heart Society, Michael Jonas; Italy: Italian Federation of Cardiology, Salvatore Novo; Kosovo: Kosovo Society of Cardiology, Pranvera Ibrahim; Kyrgyzstan: Kyrgyz Society of Cardiology, Olga Lunegova; Latvia: Latvian Society of Cardiology, Vilnis Dzerve; Lithuania: Lithuanian Society of Cardiology, Nerijus Misonis; Luxembourg: Luxembourg Society of Cardiology, Jean Beissel; Malta: Maltese Cardiac Society, Elton Pllaha; Morocco: Moroccan Society of Cardiology, Mustapha Taberkant; Norway: Norwegian Society of Cardiology, Torbjørn Bakken; Portugal: Portuguese Society of Cardiology, Rui Teles; Romania: Romanian Society of Cardiology, Daniel Lighezan; Russian Federation: Russian Society of Cardiology,

Alexandra Konradi; San Marino: San Marino Society of Cardiology, Marco Zavatta; Slovakia: Slovak Society of Cardiology, Juraj Madaric; Slovenia: Slovenian Society of Cardiology, Zlatko Fras; Spain: Spanish Society of Cardiology, Lorenzo Silva Melchor; Sweden: Swedish Society of Cardiology, Ulf Näslund; Switzerland: Swiss Society of Cardiology, Beatrice Amann-Vesti; United Kingdom: British Cardiovascular Society, Agu Obiekeze.

REFERENCES

- 1 Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2851–906.
- 2 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329–40.
- 3 Belcaro G, Nicolaides AN, Ramaswami G, Cesarone MR, De Sanctis M, Incandela L, et al. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study). *Atherosclerosis* 2001;**156**:379–87.
- 4 Giannopoulos A, Kakkos S, Abbott A, Naylor AR, Richards T, Mikhailidis DP, et al. Long-term mortality in patients with asymptomatic carotid stenosis: implications for statin therapy. *Eur J Vasc Endovasc Surg* 2015;**50**:573–82.
- 5 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509–26.
- 6 Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
- 7 Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;**94**:3026–49.
- 8 Valentine RJ, Guerra R, Stephan P, Scoggins E, Clagett GP, Cohen J. Family history is a major determinant of subclinical peripheral arterial disease in young adults. *J Vasc Surg* 2004;**39**:351–6.
- 9 Wassel CL, Loomba R, Ix JH, Allison MA, Denenberg JO, Criqui MH. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. *J Am Coll Cardiol* 2011;**58**:1386–92.
- 10 Khaleghi M, Isseh IN, Bailey KR, Kullo IJ. Family history as a risk factor for peripheral arterial disease. *Am J Cardiol* 2014;**114**:928–32.
- 11 Corra U, Piepoli MF, Carre F, Heuschmann P, Hoffmann U, Verschuren M, et al. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J* 2010;**31**:1967–74.

- 12 Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;**35**:1381–95.
- 13 Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993;**46**:153–62.
- 14 Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet* 2008;**371**:1587–94.
- 15 Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet* 2012;**379**:905–14.
- 16 Cournot M, Taraszkiwicz D, Cambou JP, Galinier M, Boccalon H, Hanaire-Broutin H, et al. Additional prognostic value of physical examination, exercise testing, and arterial ultrasonography for coronary risk assessment in primary prevention. *Am Heart J* 2009;**158**:845–51.
- 17 Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015;**241**:507–32.
- 18 Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010;**56**:1506–12.
- 19 Wu MY, Hsiang HF, Wong CS, Yao MS, Li YW, Hsiang CY, et al. The effectiveness of N-acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials. *Int Urol Nephrol* 2013;**45**:1309–18.
- 20 O'Sullivan S, Healy DA, Moloney MC, Grace PA, Walsh SR. The role of N-acetylcysteine in the prevention of contrast-induced nephropathy in patients undergoing peripheral angiography: a structured review and meta-analysis. *Angiology* 2013;**64**:576–82.
- 21 Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004;**291**:2328–34.
- 22 Akyuz S, Yaylak B, Altay S, Kasikcioglu H, Cam N. The role of statins in preventing contrast-induced acute kidney injury: a narrative review. *Angiology* 2015;**66**:701–7.
- 23 Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M. Gadolinium-based contrast agent accumulation and toxicity: an update. *AJNR Am J Neuroradiol* 2016;**37**:1192–8.
- 24 Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2007;**28**:2375–414.
- 25 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–81.
- 26 Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;**34**:3035–87.
- 27 Bullen C. Impact of tobacco smoking and smoking cessation on cardiovascular risk and disease. *Expert Rev Cardiovasc Ther* 2008;**6**:883–95.
- 28 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2224–60.
- 29 Morris PB, Ference BA, Jahangir E, Feldman DN, Ryan JJ, Bahrami H, et al. Cardiovascular effects of exposure to cigarette smoke and electronic cigarettes: clinical perspectives from the Prevention of Cardiovascular Disease Section Leadership Council and Early Career Councils of the American College of Cardiology. *J Am Coll Cardiol* 2015;**66**:1378–91.
- 30 Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;**4**:CD000123.
- 31 Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis. *Vascul Pharmacol* 2014;**63**:79–87.
- 32 Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007;**45**:645–54.
- 33 Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith Jr SC, Goto S, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;**35**:2864–72.
- 34 Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, et al. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol* 2014;**63**:682–90.
- 35 Murphy SA, Cannon CP, Blazing MA, Giugliano RP, White JA, Likhnygina Y, et al. Reduction in total cardiovascular events with ezetimibe/simvastatin post-acute coronary syndrome: the IMPROVE-IT Trial. *J Am Coll Cardiol* 2016;**67**:353–61.
- 36 Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002;**325**:1139.
- 37 Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;**35**:2902–9.
- 38 Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. *J Atheroscler Thromb* 2013;**20**:108–21.

- 39 Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–22.
- 40 Staessen JA, Thijs L, Gasowski J, Cells H, Fagard RH. Treatment of isolated systolic hypertension in the elderly: further evidence from the systolic hypertension in Europe (Syst-Eur) trial. *Am J Cardiol* 1998;**82**:20R–2R.
- 41 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;**31**:1281–12357.
- 42 Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril Study. *Hypertension* 2010;**55**:48–53.
- 43 Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
- 44 Cushman WC, Whelton PK, Fine LJ, Wright Jr JT, Reboussin DM, Johnson KC, et al. SPRINT trial results: latest news in hypertension management. *Hypertension* 2016;**67**:263–5.
- 45 World Health Organization. *Guideline: sodium intake for adults and children*. Geneva: World Health Organization; 2012 [reprinted 2014].
- 46 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
- 47 Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–59.
- 48 Armstrong EJ, Chen DC, Singh GD, Amsterdam EA, Laird JR. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. *Vasc Med* 2015;**20**:237–44.
- 49 Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev* 2013;**9**:CD005508.
- 50 Aronow WS, Ahn C. Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and symptomatic peripheral arterial disease. *Am J Cardiol* 2001;**87**:1284–6.
- 51 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
- 52 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
- 53 Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, et al. Impact of ramipril in patients with evidence of clinical or sub-clinical peripheral arterial disease. *Eur Heart J* 2004;**25**:17–24.
- 54 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
- 55 Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;**359**:1238–51.
- 56 Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;**49**:1982–8.
- 57 Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;**111**:2233–40.
- 58 Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;**369**:11–9.
- 59 Dalainas I, Nano G, Bianchi P, Stegheer S, Malacrida G, Tealdi DG. Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting. *Cardiovasc Intervent Radiol* 2006;**29**:519–21.
- 60 McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg* 2005;**29**:522–7.
- 61 Gensicke H, van der Worp HB, Nederkoorn PJ, Macdonald S, Gaines PA, van der Lugt A, et al. Ischemic brain lesions after carotid artery stenting increase future cerebrovascular risk. *J Am Coll Cardiol* 2015;**65**:521–9.
- 62 Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016;**37**:390–9.
- 63 Schmit K, Dolor RJ, Jones WS, Vemulapalli S, Hasselblad V, Subherwal S, et al. Comparative effectiveness review of antiplatelet agents in peripheral artery disease. *J Am Heart Assoc* 2014;**3**:e001330.
- 64 Belch JJ, Dormandy J, Biasi GM, Cairols M, Diehm C, Eikelboom B, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg* 2010;**52**:825–33.
- 65 Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. *Eur Heart J* 2009;**30**:192–201.
- 66 Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 2010;**303**:841–8.
- 67 Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;**337**:a1840.

- 68 Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA* 2009;**301**:1909–19.
- 69 Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;**376**:32–40.
- 70 Bonaca MP, Scirica BM, Creager MA, Olin J, Bounameaux H, Dellborg M, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. *Circulation* 2013;**127**:1522–9.
- 71 Bonaca MP, Gutierrez JA, Creager MA, Scirica BM, Olin J, Murphy SA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). *Circulation* 2016;**133**:997–1005.
- 72 Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2015;**2**:CD000535.
- 73 Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;**355**:346–51.
- 74 Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002;**35**:413–21.
- 75 Monaco M, Di Tommaso L, Pinna GB, Lillo S, Schiavone V, Stassano P. Combination therapy with warfarin plus clopidogrel improves outcomes in femoropopliteal bypass surgery patients. *J Vasc Surg* 2012;**56**:96–105.
- 76 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation* 2016;**133**:1472–83.
- 77 Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. *J Am Coll Cardiol* 2015;**66**:2329–38.
- 78 Dagher NN, Modrall JG. Pharmacotherapy before and after revascularization: anticoagulation, antiplatelet agents, and statins. *Semin Vasc Surg* 2007;**20**:10–4.
- 79 Franzone A, Piccolo R, Gargiulo G, Ariotti S, Marino M, Santucci A, et al. Prolonged vs short duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with or without peripheral arterial disease: a subgroup analysis of the PRODIGY randomized clinical trial. *JAMA Cardiol* 2016;**1**:795–803.
- 80 Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–800.
- 81 Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol* 2016;**67**:2719–28.
- 82 2017 Guidelines for DAPT (citation pending).
- 83 Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962.
- 84 Winkel TA, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, et al. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg* 2010;**40**:9–16.
- 85 Jones WS, Hellkamp AS, Halperin J, Piccini JP, Breithardt G, Singer DE, et al. Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF. *Eur Heart J* 2014;**35**:242–9.
- 86 Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;**17**:1467–507.
- 87 Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60.
- 88 Donaldson DR, Kester RC, Rajah SM, Hall TJ, Sreeharan N, Crow MJ. The influence of platelet inhibition on the patency of femoro-popliteal Dacron bypass grafts. *Vasc Endovasc Surg* 1985;**19**:224–30.
- 89 McCollum C, Alexander C, Kenchington G, Franks PJ, Greenhalgh R. Antiplatelet drugs in femoropopliteal vein bypasses: a multicenter trial. *J Vasc Surg* 1991;**13**:150–61.
- 90 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–67.
- 91 Lamberts M, Lip GY, Ruwald MH, Hansen ML, Ozcan C, Kristensen SL, et al. Antithrombotic treatment in patients with heart failure and associated atrial fibrillation and vascular disease: a nationwide cohort study. *J Am Coll Cardiol* 2014;**63**:2689–98.
- 92 Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:2064–89.
- 93 Donnan GA, Davis SM, Chambers BR, Gates PC. Surgery for prevention of stroke. *Lancet* 1998;**351**:1372–3.
- 94 Sprynger M, RF, Moonen M, Aboyans V, Edvardsen T, Alcantara M, et al. EACVI recommendations on echovascular imaging assessment of arterial diseases: Partim I, 2017 [in preparation].
- 95 Esposito-Bauer L, Saam T, Ghodrati I, Pelisek J, Heider P, Bauer M, et al. MRI plaque imaging detects carotid plaques with a high risk for future cerebrovascular events in asymptomatic patients. *PLoS One* 2013;**8**:e67927.
- 96 Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambone AE, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. *Stroke* 2015;**46**:91–7.
- 97 Naylor AR, Schroeder TV, Sillesen H. Clinical and imaging features associated with an increased risk of late stroke in patients with asymptomatic carotid disease. *Eur J Vasc Endovasc Surg* 2014;**48**:633–40.
- 98 Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, et al. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2004;**62**:1468–81.

- 99 Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technol Assess* 2006;**10**. iii–iv, ix–x, 1–182.
- 100 Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al. Myocardial infarction after carotid stenting and endarterectomy: results from the carotid revascularization endarterectomy versus stenting trial. *Circulation* 2011;**123**:2571–8.
- 101 Giannakopoulos TG, Moulakakis K, Sfyroeras GS, Avgerinos ED, Antonopoulos CN, Kakisis JD, et al. Association between plaque echogenicity and embolic material captured in filter during protected carotid angioplasty and stenting. *Eur J Vasc Endovasc Surg* 2012;43627–31.
- 102 Akkaya E, Vuruskan E, Gul ZB, Yildirim A, Pusuroglu H, Surgit O, et al. Cerebral microemboli and neurocognitive change after carotid artery stenting with different embolic protection devices. *Int J Cardiol* 2014;**176**:478–83.
- 103 Bijklic K, Wandler A, Hazizi F, Schofer J. The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. *J Am Coll Cardiol* 2012;**59**:1383–9.
- 104 Cano MN, Kambara AM, de Cano SJ, Pezzi Portela LA, Paes AT, Costa Jr JR, et al. Randomized comparison of distal and proximal cerebral protection during carotid artery stenting. *JACC Cardiovasc Interv* 2013;**6**:1203–9.
- 105 Montorsi P, Caputi L, Galli S, Ciceri E, Ballerini G, Agrifoglio M, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. *J Am Coll Cardiol* 2011;**58**:1656–63.
- 106 Stabile E, Esposito G. Operator's experience is the most efficient embolic protection device for carotid artery stenting. *Circ Cardiovasc Interv* 2013;**6**:496–7.
- 107 Garg N, Karagiorgos N, Pisimisis GT, Sohal DP, Longo GM, Johanning JM, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. *J Endovasc Ther* 2009;**16**:412–27.
- 108 Touze E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke* 2009;**40**:e683–93.
- 109 Zahn R, Ischinger T, Hochadel M, Zeymer U, Schmalz W, Treese N, et al. Carotid artery stenting in octogenarians: results from the ALKK Carotid Artery Stent (CAS) Registry. *Eur Heart J* 2007;**28**:370–5.
- 110 Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med* 2016;**374**:1011–20.
- 111 Jansen O, Fiehler J, Hartmann M, Bruckmann H. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. *Stroke* 2009;**40**:841–6.
- 112 Gray WA, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of site and operator characteristics on carotid artery stent outcomes: analysis of the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) clinical study. *JACC Cardiovasc Interv* 2011;**4**:235–46.
- 113 Nallamothu BK, Gurm HS, Ting HH, Goodney PP, Rogers MA, Curtis JP, et al. Operator experience and carotid stenting outcomes in Medicare beneficiaries. *JAMA* 2011;**306**:1338–43.
- 114 Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;**273**:1421–8.
- 115 Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;**376**:1074–84.
- 116 Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491–502.
- 117 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. *Stroke* 2004;**35**:2855–61.
- 118 Hadar N, Raman G, Moorthy D, O'Donnell TF, Thaler DE, Feldmann E, et al. Asymptomatic carotid artery stenosis treated with medical therapy alone: temporal trends and implications for risk assessment and the design of future studies. *Cerebrovasc Dis* 2014;**38**:163–73.
- 119 Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? *Eur J Vasc Endovasc Surg* 2009;**37**:625–32.
- 120 Baker WH, Howard VJ, Howard G, Toole JF. Effect of contralateral occlusion on long-term efficacy of endarterectomy in the Asymptomatic Carotid Atherosclerosis Study (ACAS). ACAS Investigators. *Stroke* 2000;**31**:2330–4.
- 121 Nicolaidis AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. *Eur J Vasc Endovasc Surg* 2005;**30**:275–84.
- 122 Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, et al. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg* 2009;**49**:902–9.
- 123 Kakkos SK, Nicolaidis AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg* 2014;**59**:956–67.
- 124 Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol* 2010;**9**:663–71.
- 125 King A, Serena J, Bornstein NM, Markus HS. Does impaired cerebrovascular reactivity predict stroke risk in asymptomatic carotid stenosis? A prospective substudy of the asymptomatic carotid emboli study. *Stroke* 2011;**42**:1550–5.
- 126 Nicolaidis AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg* 2010;**52**:1486–96.
- 127 Kakkos SK, Griffin MB, Nicolaidis AN, Kyriacou E, Sabetai MM, Tegos T, et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. *J Vasc Surg* 2013;**57**:609–18.
- 128 Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* 2013;**44**:3071–7.

- 129 Hawkins BM, Kennedy KF, Aronow HD, Nguyen LL, White CJ, Rosenfield K, et al. Hospital variation in carotid stenting outcomes. *JACC Cardiovasc Interv* 2015;**6**:858–63.
- 130 Kallmayer MA, Tsantilas P, Knappich C, Haller B, Storck M, Stadlbauer T, et al. Patient characteristics and outcomes of carotid endarterectomy and carotid artery stenting: analysis of the German mandatory national quality assurance registry – 2003 to 2014. *J Cardiovasc Surg (Torino)* 2015;**56**:827–36.
- 131 Werner N, Zeymer U, Hochadel M, Hauptmann KE, Jung J, Janicke I, et al. Fifteen-year experience with carotid artery stenting (from the carotid artery stenting-registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte). *Am J Cardiol* 2015;**115**:360–6.
- 132 Paraskevas KI, Kalmykov EL, Naylor AR. Stroke/death rates following carotid artery stenting and carotid endarterectomy in contemporary administrative dataset registries: a systematic review. *Eur J Vasc Endovasc Surg* 2016;**51**:3–12.
- 133 Choi JC, Johnston SC, Kim AS. Early outcomes after carotid artery stenting compared with endarterectomy for asymptomatic carotid stenosis. *Stroke* 2015;**46**:120–5.
- 134 Dua A, Romanelli M, Upchurch Jr GR, Pan J, Hood D, Hodgson KJ, et al. Predictors of poor outcome after carotid intervention. *J Vasc Surg* 2016;**64**:663–70.
- 135 Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;**351**:1493–501.
- 136 Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;**358**:1572–9.
- 137 Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;**42**:675–80.
- 138 Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107–16.
- 139 Naylor AR, Sillesen H, Schroeder TV. Clinical and imaging features associated with an increased risk of early and late stroke in patients with symptomatic carotid disease. *Eur J Vasc Endovasc Surg* 2015;**49**:513–23.
- 140 Stromberg S, Gelin J, Osterberg T, Bergstrom GM, Karlstrom L, Osterberg K. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke* 2012;**43**:1331–5.
- 141 Loftus IM, Paraskevas KI, Johal A, Waton S, Heikkila K, Naylor AR, et al. Delays to surgery and procedural risks following carotid endarterectomy in the UK National Vascular Registry. *Eur J Vasc Endovasc Surg* 2016;**52**:438–43.
- 142 Tsantilas P, Kuehnl A, Konig T, Breikreuz T, Kallmayer M, Knappich C, et al. Short time interval between neurologic event and carotid surgery is not associated with an increased procedural risk. *Stroke* 2016;**47**:2783–90.
- 143 Bush CK, Kurimella D, Cross LJ, Conner KR, Martin-Schild S, He J, et al. Endovascular treatment with stent-retriever devices for acute ischemic stroke: a meta-analysis of randomized controlled trials. *PLoS One* 2016;**11**:e0147287.
- 144 Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;**372**:11–20.
- 145 Brott TG, Hobson 2nd RW, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;**363**:11–23.
- 146 Hill MD, Brooks W, Mackey A, Clark WM, Meschia JF, Morrish WF, et al. Stroke after carotid stenting and endarterectomy in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Circulation* 2012;**126**:3054–61.
- 147 Economopoulos KP, Sergentanis TN, Tsvigoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. *Stroke* 2011;**42**:687–92.
- 148 Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev* 2012;**9**:CD000515.
- 149 Rantner B, Goebel G, Bonati LH, Ringleb PA, Mas JL, Fraedrich G. The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. *J Vasc Surg* 2013;**57**:619–26.
- 150 Meschia JF, Hopkins LN, Altafullah I, Wechsler LR, Stotts G, Gonzales NR, et al. Time from symptoms to carotid endarterectomy or stenting and perioperative risk. *Stroke* 2015;**46**:3540–2.
- 151 Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. *Lancet* 2016;**387**:1305–11.
- 152 Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2015;**385**:529–38.
- 153 Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med* 2016;**374**:1021–31.
- 154 Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379–87.
- 155 Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;**339**:1415–25.
- 156 Borhani Haghighi A, Edgell RC, Cruz-Flores S, Zaidat OO. Vertebral artery origin stenosis and its treatment. *J Stroke Cerebrovasc Dis* 2011;**20**:369–76.
- 157 Khan S, Cloud GC, Kerry S, Markus HS. Imaging of vertebral artery stenosis: a systematic review. *J Neural Neurosurg Psychiatry* 2007;**78**:1218–25.
- 158 Kumar Dundamadappa S, Cauley K. Vertebral artery ostial stenosis: prevalence by digital subtraction angiography, MR angiography, and CT angiography. *J Neuroimaging* 2013;**23**:360–7.
- 159 Berguer R, Flynn LM, Kline RA, Caplan L. Surgical reconstruction of the extracranial vertebral artery: management and outcome. *J Vasc Surg* 2000;**31**:9–18.
- 160 Kieffer E, Praquin B, Chiche L, Koskas F, Bahnini A. Distal vertebral artery reconstruction: long-term outcome. *J Vasc Surg* 2002;**36**:549–54.

- 161 Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. *Stroke* 2011;**42**:2212–6.
- 162 Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. *Lancet Neurol* 2015;**14**:606–14.
- 163 Aboyans V, Criqui MH, McDermott MM, Allison MA, Denenberg JO, Shadman R, et al. The vital prognosis of subclavian stenosis. *J Am Coll Cardiol* 2007;**49**:1540–5.
- 164 Klitfod L, Jensen LP. Treatment of chronic upper limb ischaemia is safe and results are good. *Dan Med J* 2014;**61**:A4859.
- 165 Daniel VT, Madenci AL, Nguyen LL, Eslami MH, Kalish JA, Farber A, et al. Contemporary comparison of supra-aortic trunk surgical reconstructions for occlusive disease. *J Vasc Surg* 2014;**59**:1577–82.
- 166 Duran M, Grottemeyer D, Danch MA, Grabitz K, Schelzig H, Sagban TA. Subclavian carotid transposition: immediate and long-term outcomes of 126 surgical reconstructions. *Ann Vasc Surg* 2015;**29**:397–403.
- 167 Burihan E, Soma F, Iared W. Angioplasty versus stenting for subclavian artery stenosis. *Cochrane Database Syst Rev* 2011;**10**:CD008461.
- 168 Chatterjee S, Nerella N, Chakravarty S, Shani J. Angioplasty alone versus angioplasty and stenting for subclavian artery stenosis—a systematic review and meta-analysis. *Am J Ther* 2013;**20**:520–3.
- 169 Huttli K, Nemes B, Simonffy A, Entz L, Berczi V. Angioplasty of the innominate artery in 89 patients: experience over 19 years. *Cardiovasc Intervent Radiol* 2002;**25**:109–14.
- 170 van de Weijer MA, Vonken EJ, de Vries JP, Moll FL, Vos JA, de Borst GJ. Technical and clinical success and long-term durability of endovascular treatment for atherosclerotic aortic arch branch origin obstruction: evaluation of 144 procedures. *Eur J Vasc Endovasc Surg* 2015;**50**:13–20.
- 171 Modarai B, Ali T, Dourado R, Reidy JF, Taylor PR, Burnand KG. Comparison of extra-anatomic bypass grafting with angioplasty for atherosclerotic disease of the supra-aortic trunks. *Br J Surg* 2004;**91**:1453–7.
- 172 Owens LV, Tinsley Jr EA, Criado E, Burnham SJ, Keagy BA. Extrathoracic reconstruction of arterial occlusive disease involving the supraaortic trunks. *J Vasc Surg* 1995;**22**:217–21.
- 173 Song L, Zhang J, Li J, Gu Y, Yu H, Chen B, et al. Endovascular stenting vs. extrathoracic surgical bypass for symptomatic subclavian steal syndrome. *J Endovasc Ther* 2012;**19**:44–51.
- 174 Lee AD, Agarwal S, Sadhu D. A 7-year experience with thoracoscopic sympathectomy for critical upper limb ischemia. *World J Surg* 2006;**30**:1644–7.
- 175 Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the European Society of Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2017;**53**:460–510.
- 176 Acosta S, Nilsson TK, Björck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. *Br J Surg* 2004;**91**:991–4.
- 177 Block T, Nilsson TK, Björck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. *Scand J Clin Lab Invest* 2008;**68**:242–8.
- 178 Matsumoto S, Sekine K, Funaoka H, Yamazaki M, Shimizu M, Hayashida K, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. *Br J Surg* 2014;**101**:232–8.
- 179 Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: a systematic review and meta-analysis. *Acad Emerg Med* 2013;**20**:1087–100.
- 180 Lehtimäki TT, Karkkainen JM, Saari P, Manninen H, Paajanen H, Vanninen R. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: review of 95 consecutive patients. *Eur J Radiol* 2015;**84**:2444–53.
- 181 Jrvinen O, Laurikka J, Salenius JP, Tarkka M. Acute intestinal ischaemia. A review of 214 cases. *Ann Chir Gynaecol* 1994;**83**:22–5.
- 182 Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black 3rd JH. Comparison of open and endovascular treatment of acute mesenteric ischemia. *J Vasc Surg* 2014;**59**:159–64.
- 183 Björck M, Orr N, Endean ED. Debate: Whether an endovascular-first strategy is the optimal approach for treating acute mesenteric ischemia. *J Vasc Surg* 2015;**62**:767–72.
- 184 Block TA, Acosta S, Björck M. Endovascular and open surgery for acute occlusion of the superior mesenteric artery. *J Vasc Surg* 2010;**52**:959–66.
- 185 Kalra M, Ryer EJ, Oderich GS, Duncan AA, Bower TC, Glociczki P. Contemporary results of treatment of acute arterial mesenteric thrombosis: has endovascular treatment improved outcomes? *Perspect Vasc Surg Endovasc Ther* 2012;**24**:171–6.
- 186 Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg* 2007;**45**:269–75.
- 187 Arthurs ZM, Titus J, Bannazadeh M, Eagleton MJ, Srivastava S, Sarac TP, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. *J Vasc Surg* 2011;**53**:698–704.
- 188 Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988–2006. *J Vasc Surg* 2009;**50**:341–8.
- 189 Rotondo MF, Schwab CW, McGonigal MD, Phillips 3rd GR, Fruchterman TM, Kauder DR, et al. ‘Damage control’: an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993;**35**:375–82.
- 190 Björck M, Acosta S, Lindberg F, Troeng T, Bergqvist D. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. *Br J Surg* 2002;**89**:923–7.
- 191 Björnsson S, Björck M, Block T, Resch T, Acosta S. Thrombolysis for acute occlusion of the superior mesenteric artery. *J Vasc Surg* 2011;**54**:1734–42.
- 192 Thomas JH, Blake K, Pierce GE, Hermreck AS, Seigel E. The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg* 1998;**27**:840–4.
- 193 van Petersen AS, Meerwaldt R, Kolkman JJ, Huisman AB, van der Palen J, van Bockel JH, et al. The influence of respiration on criteria for transabdominal duplex examination of the splanchnic arteries in patients with suspected chronic splanchnic ischemia. *J Vasc Surg* 2013;**57**:1603–11.
- 194 Zwolak RM, Fillinger MF, Walsh DB, LaBombard FE, Musson A, Darling CE, et al. Mesenteric and celiac duplex scanning: a validation study. *J Vasc Surg* 1998;**27**:1078–87.

- 195 Rheudasil JM, Stewart MT, Schellack JV, Smith 3rd RB, Salam AA, Perdue GD. Surgical treatment of chronic mesenteric arterial insufficiency. *J Vasc Surg* 1988;**8**:495–500.
- 196 Moghadamyeghaneh Z, Carmichael JC, Mills SD, Dolich MO, Pigazzi A, Fujitani RM, et al. Early outcome of treatment of chronic mesenteric ischemia. *Am Surg* 2015;**81**:1149–56.
- 197 Rawat N, Gibbons CP. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. *Ann Vasc Surg* 2010;**24**:935–45.
- 198 Peck MA, Conrad MF, Kwolek CJ, LaMuraglia GM, Paruchuri V, Cambria RP. Intermediate-term outcomes of endovascular treatment for symptomatic chronic mesenteric ischemia. *J Vasc Surg* 2010;**51**:140–7.
- 199 Silva JA, White CJ, Collins TJ, Jenkins JS, Andry ME, Reilly JP, et al. Endovascular therapy for chronic mesenteric ischemia. *J Am Coll Cardiol* 2006;**47**:944–50.
- 200 Malgor RD, Oderich GS, McKusick MA, Misra S, Kalra M, Duncan AA, et al. Results of single- and two-vessel mesenteric artery stents for chronic mesenteric ischemia. *Ann Vasc Surg* 2010;**24**:1094–101.
- 201 Oderich GS, Erdoes LS, Lesar C, Mendes BC, Glociczki P, Cha S, et al. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. *J Vasc Surg* 2013;**58**:1316–23.
- 202 Menke J, Luthje L, Kastrup A, Larsen J. Thromboembolism in atrial fibrillation. *Am J Cardiol* 2010;**105**:502–10.
- 203 Mensink PB, van Petersen AS, Geelkerken RH, Otte JA, Huisman AB, Kolkman JJ. Clinical significance of splanchnic artery stenosis. *Br J Surg* 2006;**93**:1377–82.
- 204 Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001;**344**:431–42.
- 205 Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**:e463–654.
- 206 Persu A, Giavarini A, Touze E, Januszewicz A, Sapoval M, Azizi M, et al. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens* 2014;**32**:1367–78.
- 207 Tafur-Soto JD, White CJ. Renal artery stenosis. *Cardiol Clin* 2015;**33**:59–73.
- 208 Messerli FH, Bangalore S, Makani H, Rimoldi SF, Allemann Y, White CJ, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *Eur Heart J* 2011;**32**:2231–5.
- 209 Jennings CG, Houston JG, Severn A, Bell S, Mackenzie IS, Macdonald TM. Renal artery stenosis-when to screen, what to stent? *Curr Atheroscler Rep* 2014;**16**:416.
- 210 Zeller T, Bonvini RF, Sixt S. Color-coded duplex ultrasound for diagnosis of renal artery stenosis and as follow-up examination after revascularization. *Catheter Cardiovasc Interv* 2008;**71**:995–9.
- 211 Williams GJ, Macaskill P, Chan SF, Karplus TE, Yung W, Hodson EM, et al. Comparative accuracy of renal duplex sonographic parameters in the diagnosis of renal artery stenosis: paired and unpaired analysis. *AJR Am J Roentgenol* 2007;**188**:798–811.
- 212 AbuRahma AF, Yacoub M. Renal imaging: duplex ultrasound, computed tomography angiography, magnetic resonance angiography, and angiography. *Semin Vasc Surg* 2013;**26**:134–43.
- 213 Tan KT, van Beek EJ, Brown PW, van Delden OM, Tijssen J, Ramsay LE. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. *Clin Radiol* 2002;**57**:617–24.
- 214 De Bruyne B, Manoharan G, Pijls NH, Verhamme K, Madaric J, Bartunek J, et al. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol* 2006;**48**:1851–5.
- 215 Drieghe B, Madaric J, Sarno G, Manoharan G, Bartunek J, Heyndrickx GR, et al. Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. *Eur Heart J* 2008;**29**:517–24.
- 216 Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int* 2001;**60**:1490–7.
- 217 Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis* 1994;**24**:622–9.
- 218 Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2999–3058.
- 219 Evans KL, Tuttle KR, Folt DA, Dawson T, Haller ST, Brewster PS, et al. Use of renin-angiotensin inhibitors in people with renal artery stenosis. *Clin J Am Soc Nephrol* 2014;**9**:1199–206.
- 220 Hackam DG, Duong-Hua ML, Mamdani M, Li P, Tobe SW, Spence JD, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *Am Heart J* 2008;**156**:549–55.
- 221 Chrysochou C, Foley RN, Young JF, Khavandi K, Cheung CM, Kalra PA. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;**27**:1403–9.
- 222 Losito A, Errico R, Santirosi P, Lupattelli T, Scalera GB, Lupattelli L. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. *Nephrol Dial Transplant* 2005;**20**:1604–9.
- 223 Hackam DG, Wu F, Li P, Austin PC, Tobe SW, Mamdani MM, et al. Statins and renovascular disease in the elderly: a population-based cohort study. *Eur Heart J* 2011;**32**:598–610.
- 224 Vashist A, Heller EN, Brown Jr EJ, Alhaddad IA. Renal artery stenosis: a cardiovascular perspective. *Am Heart J* 2002;**143**:559–64.
- 225 Chrysant GS, Bates MC, Sullivan TM, Bachinsky WB, Popma JJ, Peng L, et al. Proper patient selection yields significant and sustained reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: long-term results from the HERCULES trial. *J Clin Hypertens (Greenwich)* 2014;**16**:497–503.

- 226 Jaff MR, Bates M, Sullivan T, Popma J, Gao X, Zaugg M, et al. Significant reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: results from the HERCULES trial. *Catheter Cardiovasc Interv* 2012;**80**:343–50.
- 227 Nordmann AJ, Woo K, Parkes R, Logan AG. Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. *Am J Med* 2003;**114**:44–50.
- 228 Bavry AA, Kapadia SR, Bhatt DL, Kumbhani DJ. Renal artery revascularization: updated meta-analysis with the CORAL trial. *JAMA Intern Med* 2014;**174**:1849–51.
- 229 Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**:13–22.
- 230 Murphy TP, Cooper CJ, Matsumoto AH, Cutlip DE, Pencina KM, Jamerson K, et al. Renal artery stent outcomes: effect of baseline blood pressure, stenosis severity, and translesion pressure gradient. *J Am Coll Cardiol* 2015;**66**:2487–94.
- 231 Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953–62.
- 232 Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med* 2009;**150**:840–8.
- 233 Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. *Circulation* 2014;**129**:1048–78.
- 234 Davies MG, Saad WE, Peden EK, Mohiuddin IT, Naoum JJ, Lumsden AB. The long-term outcomes of percutaneous therapy for renal artery fibromuscular dysplasia. *J Vasc Surg* 2008;**48**:865–71.
- 235 Mousa AY, Campbell JE, Stone PA, Broce M, Bates MC, AbuRahma AF. Short- and long-term outcomes of percutaneous transluminal angioplasty/stenting of renal fibromuscular dysplasia over a ten-year period. *J Vasc Surg* 2012;**55**:421–7.
- 236 Trinquart L, Mounier-Vehier C, Sapoval M, Gagnon N, Plouin PF. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. *Hypertension* 2010;**56**:525–32.
- 237 Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrol Dial Transplant* 2010;**25**:813–20.
- 238 Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis* 2014;**63**:186–97.
- 239 van den Berg DT, Deinum J, Postma CT, van der Wilt GJ, Riksen NP. The efficacy of renal angioplasty in patients with renal artery stenosis and flash oedema or congestive heart failure: a systematic review. *Eur J Heart Fail* 2012;**14**:773–81.
- 240 Cianci R, Martina P, Borghesi F, di Donato D, Polidori L, Lai S, et al. Revascularization versus medical therapy for renal artery stenosis: antihypertensive drugs and renal outcome. *Angiology* 2011;**62**:92–9.
- 241 Abela R, Ivanova S, Lidder S, Morris R, Hamilton G. An analysis comparing open surgical and endovascular treatment of atherosclerotic renal artery stenosis. *Eur J Vasc Endovasc Surg* 2009;**38**:666–75.
- 242 Balzer KM, Neuschäfer S, Sagban TA, Grottemeyer D, Pfeiffer T, Rump LC, et al. Renal artery revascularization after unsuccessful percutaneous therapy: a single centre experience. *Langenbecks Arch Surg* 2012;**397**:111–5.
- 243 Balzer KM, Pfeiffer T, Rossbach S, Voiculescu A, Modder U, Godehardt E, et al. Prospective randomized trial of operative vs interventional treatment for renal artery ostial occlusive disease (RAOOD). *J Vasc Surg* 2009;**49**:667–74.
- 244 McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;**286**:1599–606.
- 245 Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992;**45**:1101–9.
- 246 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;**45**(Suppl. S):S5–67.
- 247 Abou-Zamzam Jr AM, Gomez NR, Molkara A, Banta JE, Teruya TH, Killeen JD, et al. A prospective analysis of critical limb ischemia: factors leading to major primary amputation versus revascularization. *Ann Vasc Surg* 2007;**21**:458–63.
- 248 Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015;**62**:1642–51.
- 249 Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016;**51**:395–403.
- 250 Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. *Can J Cardiol* 2013;**29**:492–8.
- 251 Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:2890–909.
- 252 Tehan PE, Santos D, Chuter VH. A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral artery disease. *Vasc Med* 2016;**21**:382–9.
- 253 Collins R, Cranny G, Burch J, Aguiar-Ibanez R, Craig D, Wright K, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. *Health Technol Assess* 2007;**11**:1–184.
- 254 Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 2009;**301**:415–24.
- 255 Menke J, Larsen J. Meta-analysis: accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. *Ann Intern Med* 2010;**153**:325–34.
- 256 Koelemay MJ, Lijmer JG, Stoker J, Legemate DA, Bossuyt PM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. *JAMA* 2001;**285**:1338–45.
- 257 Ouwendijk R, de Vries M, Stijnen T, Pattynama PM, van Sambeek MR, Buth J, et al. Multicenter randomized controlled trial of the costs and effects of noninvasive diagnostic imaging in patients with peripheral arterial disease: the DIPAD trial. *AJR Am J Roentgenol* 2008;**190**:1349–57.

- 258 Barba A, Estallo L, Rodriguez L, Baquer M, Vega de Ceniga M. Detection of abdominal aortic aneurysm in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg* 2005;**30**:504–8.
- 259 Giugliano G, Laurenzano E, Rengo C, De Rosa G, Brevetti L, Sannino A, et al. Abdominal aortic aneurysm in patients affected by intermittent claudication: prevalence and clinical predictors. *BMC Surg* 2012;**12**(Suppl. 1):S17.
- 260 Juergens JL, Barker NW, Hines Jr EA. Arteriosclerosis obliterans: review of 520 cases with special reference to pathogenic and prognostic factors. *Circulation* 1960;**21**:188–95.
- 261 Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg* 2009;**38**:463–74.
- 262 Shahin Y, Barnes R, Barakat H, Chetter IC. Meta-analysis of angiotensin converting enzyme inhibitors effect on walking ability and ankle brachial pressure index in patients with intermittent claudication. *Atherosclerosis* 2013;**231**:283–90.
- 263 Vlachopoulos C, Terentes-Printzios D, Aboyans V, Brodmann M, De Carlo M, Tousoulis D. Angiotensin converting enzyme inhibitors and walking distance: have we walked the whole distance? *Atherosclerosis* 2016;**252**:199–200.
- 264 Bagger JP, Helligsoe P, Randsbaek F, Kimose HH, Jensen BS. Effect of verapamil in intermittent claudication A randomized, double-blind, placebo-controlled, cross-over study after individual dose-response assessment. *Circulation* 1997;**95**:411–4.
- 265 Espinola-Klein C, Weisser G, Jagodzinski A, Savvidis S, Warnholtz A, Ostad MA, et al. Beta-blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial. *Hypertension* 2011;**58**:148–54.
- 266 Soga Y, Iida O, Takahara M, Hirano K, Suzuki K, Kawasaki D. Beta-blocker treatment does not worsen critical limb ischemia in patients receiving endovascular therapy. *J Atheroscler Thromb* 2015;**22**:481–9.
- 267 Mirault TGA, Cambou JP, Lacroix P, Aboyans V, Boulon C, Constans J, et al. Impact of beta-blockers on general and local outcome in patients hospitalized for lower extremity peripheral artery disease. The COPART Registry. *Medicine (Baltimore)* 2017;**96**:e5916.
- 268 Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2014;**7**:CD000990.
- 269 Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2013;**8**:CD005263.
- 270 Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg* 2015;**61**:512–8.
- 271 Birmingham SL, Sparrow K, Mullis R, Fox M, Shearman C, Bradbury A, et al. The cost-effectiveness of supervised exercise for the treatment of intermittent claudication. *Eur J Vasc Endovasc Surg* 2013;**46**:707–14.
- 272 Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. *Eur J Vasc Endovasc Surg* 2013;**46**:690–706.
- 273 Back M, Jivegard L, Johansson A, Nordanstig J, Svanberg T, Adania UW, et al. Home-based supervised exercise versus hospital-based supervised exercise or unsupervised walk advice as treatment for intermittent claudication: a systematic review. *J Rehabil Med* 2015;**47**:801–8.
- 274 Lauret GJ, Fakhry F, Fokkenrood HJ, Hunink MG, Teijink JA, Spronk S. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev* 2014;**7**:CD009638.
- 275 Jakubseviciene E, Vasiliauskas D, Velicka L, Kubilius R, Milinaviciene E, Vencloviene J. Effectiveness of a new exercise program after lower limb arterial blood flow surgery in patients with peripheral arterial disease: a randomized clinical trial. *Int J Environ Res Public Health* 2014;**11**:7961–76.
- 276 Kruidenier LM, Nicolai SP, Rouwet EV, Peters RJ, Prins MH, Teijink JA. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. *J Vasc Interv Radiol* 2011;**22**:961–8.
- 277 Gargiulo G, Giugliano G, Brevetti L, Sannino A, Schiattarella GG, Serino F, et al. Use of statins in lower extremity artery disease: a review. *BMC Surg* 2012;**12**(Suppl. 1):S15.
- 278 McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation* 2003;**107**:757–61.
- 279 Robertson L, Andras A. Prostanoids for intermittent claudication. *Cochrane Database Syst Rev* 2013;**4**:CD000986.
- 280 Stevens JW, Simpson E, Harnan S, Squires H, Meng Y, Thomas S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. *Br J Surg* 2012;**99**:1630–8.
- 281 Indes JE, Pfaff MJ, Farrokhyar F, Brown H, Hashim P, Cheung K, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. *J Endovasc Ther* 2013;**20**:443–55.
- 282 Grimme FA, Goverde PC, Verbruggen PJ, Zeebregts CJ, Reijnen MM. Editor's choice—first results of the covered endovascular reconstruction of the aortic bifurcation (CERAB) technique for aortoiliac occlusive disease. *Eur J Vasc Endovasc Surg* 2015;**50**:638–47.
- 283 Anderson JL, Antman EM, Harold JG, Jessup M, O'Gara PT, Pinto FJ, et al. Clinical practice guidelines on perioperative cardiovascular evaluation: collaborative efforts among the ACC, AHA, and ESC. *Circulation* 2014;**130**:2213–4.
- 284 Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature. *Eur J Vasc Endovasc Surg* 2004;**27**:357–62.
- 285 Malgor RD, Alahdab F, Elraiyah TA, Rizvi AZ, Lane MA, Prokop LJ, et al. A systematic review of treatment of intermittent claudication in the lower extremities. *J Vasc Surg* 2015;**61**(Suppl. 3):54s–73s.
- 286 Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation* 2012;**125**:130–9.
- 287 Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2006;**2**:CD005263.
- 288 Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and

- intermittent claudication: a randomized clinical trial. *JAMA* 2015;**314**:1936–44.
- 289 Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised vs unsupervised exercise for intermittent claudication: a systematic review and meta-analysis. *Am Heart J* 2015;**169**:924–37.
- 290 Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *Eur J Vasc Endovasc Surg* 2008;**36**:680–8.
- 291 Jongkind V, Akkersdijk GJ, Yeung KK, Wisselink W. A systematic review of endovascular treatment of extensive aortoiliac occlusive disease. *J Vasc Surg* 2010;**52**:1376–83.
- 292 Ballotta E, Lorenzetti R, Piatto G, Tolin F, Da Giau G, Toniato A. Reconstructive surgery for complex aortoiliac occlusive disease in young adults. *J Vasc Surg* 2012;**56**:1606–14.
- 293 Bredahl K, Jensen LP, Schroeder TV, Sillesen H, Nielsen H, Eiberg JP. Mortality and complications after aortic bifurcated bypass procedures for chronic aortoiliac occlusive disease. *J Vasc Surg* 2015;**62**:75–82.
- 294 Bosiers M, Deloose K, Callaert J, Maene L, Beelen R, Keirse K, et al. BRAVISSIMO: 12-month results from a large scale prospective trial. *J Cardiovasc Surg (Torino)* 2013;**54**:235–53.
- 295 Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions. *J Vasc Surg* 2011;**53**:1728–37.
- 296 Goode SDCT, Gaines PA. Randomized clinical trial of stents versus angioplasty for the treatment of iliac artery occlusions (STAG trial). *Br J Surg* 2013;**100**:1148–53.
- 297 Antoniou GA, Sfyroeras GS, Karathanos C, Achouhan H, Koutsias S, Vretzakis G, et al. Hybrid endovascular and open treatment of severe multilevel lower extremity arterial disease. *Eur J Vasc Endovasc Surg* 2009;**38**:616–22.
- 298 Dosluoglu HH, Lall P, Cherr GS, Harris LM, Dryjski ML. Role of simple and complex hybrid revascularization procedures for symptomatic lower extremity occlusive disease. *J Vasc Surg* 2010;**51**:1425–35.
- 299 Kavanagh CM, Heidenreich MJ, Albright JJ, Aziz A. Hybrid external iliac selective endarterectomy surgical technique and outcomes. *J Vasc Surg* 2016;**64**:1327–34.
- 300 Matsagkas M, Kouvelos G, Arnaoutoglou E, Papa N, Labropoulos N, Tassiopoulos A. Hybrid procedures for patients with critical limb ischemia and severe common femoral artery atherosclerosis. *Ann Vasc Surg* 2011;**25**:1063–9.
- 301 Crawford JD, Perrone KH, Wong VW, Mitchell EL, Azarbal AF, Liem TK, et al. A modern series of acute aortic occlusion. *J Vasc Surg* 2014;**59**:1044–50.
- 302 Lammer J, Zeller T, Hausegger KA, Schaefer PJ, Gschwendtner M, Mueller-Huelsbeck S, et al. Sustained benefit at 2 years for covered stents versus bare-metal stents in long SFA lesions: the VIASTAR trial. *Cardiovasc Intervent Radiol* 2015;**38**:25–32.
- 303 Lammer J, Zeller T, Hausegger KA, Schaefer PJ, Gschwendtner M, Mueller-Huelsbeck S, et al. Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viabahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). *J Am Coll Cardiol* 2013;**62**:1320–7.
- 304 Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. *J Endovasc Ther* 2012;**19**:1–9.
- 305 Schillinger M, Sabeti S, Dick P, Amighi J, Mlekusch W, Schlager O, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. *Circulation* 2007;**115**:2745–9.
- 306 Liistro F, Grotti S, Porto I, Angioli P, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). *JACC Cardiovasc Interv* 2013;**6**:1295–302.
- 307 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015;**373**:145–53.
- 308 Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation* 2015;**131**:495–502.
- 309 Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwald U, Beregi JP, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 2008;**358**:689–99.
- 310 Werk M, Albrecht T, Meyer DR, Ahmed MN, Behne A, Dietz U, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv* 2012;**5**:831–40.
- 311 Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. *J Vasc Surg* 2013;**58**:386–95.
- 312 Scheinert D, Werner M, Scheinert S, Paetzold A, Banning-Eichenseer U, Piorkowski M, et al. Treatment of complex atherosclerotic popliteal artery disease with a new self-expanding interwoven nitinol stent: 12-month results of the Leipzig SUPERA popliteal artery stent registry. *JACC Cardiovasc Interv* 2013;**6**:65–71.
- 313 Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. *J Am Coll Cardiol* 2012;**59**:16–23.
- 314 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. *J Vasc Surg* 2010;**51**(Suppl. 5):52s–68s.
- 315 Arvela E, Venermo M, Soderstrom M, Alback A, Lepantalo M. Outcome of infrainguinal single-segment great saphenous vein bypass for critical limb ischemia is superior to alternative autologous vein bypass, especially in patients with high operative risk. *Ann Vasc Surg* 2012;**26**:396–403.
- 316 Brass EP, Anthony R, Dormandy J, Hiatt WR, Jiao J, Nakanishi A, et al. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia. *J Vasc Surg* 2006;**43**:752–9.
- 317 Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery

- Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI). *J Vasc Surg* 2014;**59**:220–234.e2.
- 318 Singh S, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, et al. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med* 2014;**19**:307–14.
- 319 Takahara M, Kaneto H, Iida O, Gorogawa S, Katakami N, Matsuoka TA, et al. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. *Diabetes Care* 2010;**33**:2538–42.
- 320 Dominguez 3rd A, Bahadorani J, Reeves R, Mahmud E, Patel M. Endovascular therapy for critical limb ischemia. *Expert Rev Cardiovasc Ther* 2015;**13**:429–44.
- 321 Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. *J Endovasc Ther* 2009;**16**(2 Suppl. 2):31–62.
- 322 Manzi M, Palena L, Cester G. Endovascular techniques for limb salvage in diabetics with crural and pedal disease. *J Cardiovasc Surg (Torino)* 2011;**52**:485–92.
- 323 Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005;**366**:1925–34.
- 324 Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 2014;**64**:1568–76.
- 325 Menard MT, Farber A. The BEST-CLI trial: a multidisciplinary effort to assess whether surgical or endovascular therapy is better for patients with critical limb ischemia. *Semin Vasc Surg* 2014;**27**:82–4.
- 326 Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, et al. Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials* 2016;**17**:11.
- 327 Teraa M, Conte MS, Moll FL, Verhaar MC. Critical limb ischemia: current trends and future directions. *J Am Heart Assoc* 2016;**5**:e002938.
- 328 Belch J, Hiatt WR, Baumgartner I, Driver IV, Nikol S, Norgren L, et al. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet* 2011;**377**:1929–37.
- 329 Moazzami K, Moazzami B, Roohi A, Nedjat S, Dolmatova E. Local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischaemia. *Cochrane Database Syst Rev* 2014;**12**:CD008347.
- 330 Peeters Weem SM, Teraa M, de Borst GJ, Verhaar MC, Moll FL. Bone marrow derived cell therapy in critical limb ischemia: a meta-analysis of randomized placebo controlled trials. *Eur J Vasc Endovasc Surg* 2015;**50**:775–83.
- 331 Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;**133**(Suppl. 6):815s–43s.
- 332 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;**26**:517–38.
- 333 Berridge DC, Kessel D, Robertson I. Surgery versus thrombolysis for acute limb ischaemia: initial management. *Cochrane Database Syst Rev* 2002;**3**:CD002784.
- 334 Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol* 2013;**61**:1736–43.
- 335 Aboyans V, Desormais I, Magne J, Morange G, Mohty D, Lacroix P. Renal Artery stenosis in patients with peripheral artery disease: prevalence, risk factors and long-term prognosis. *Eur J Vasc Endovasc Surg* 2016;**53**:380–5.
- 336 Aboyans V. Polyvascular disease: definition, epidemiology, relevance. In: Lanzer P, editor. *PanVascular Medicine*. 2nd ed. Berlin: Springer; 2015. p. 4779–810.
- 337 Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2009;**37**:262–71.
- 338 Durand DJ, Perler BA, Roseborough GS, Grega MA, Borowicz Jr LM, Baumgartner WA, et al. Mandatory versus selective preoperative carotid screening: a retrospective analysis. *Ann Thorac Surg* 2004;**78**:159–66 [discussion 159–66].
- 339 Fowkes FG, Low LP, Tuta S, Kozak J. Ankle-brachial index and extent of atherothrombosis in 8891 patients with or at risk of vascular disease: results of the international AGATHA study. *Eur Heart J* 2006;**27**:1861–7.
- 340 Mukherjee D, Eagle KA, Kline-Rogers E, Feldman LJ, Juliard JM, Agnelli G, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). *Am J Cardiol* 2007;**100**:1–6.
- 341 Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Surg* 2002;**23**:283–94.
- 342 Steinvil A, Sadeh B, Arbel Y, Justo D, Belei A, Borenstein N, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011;**57**:779–83.
- 343 Subherwal S, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2012;**5**:541–9.
- 344 Collet JP, Cayla G, Ennezat PV, Leclercq F, Cuisset T, Elhadad S, et al; for the AMERICA Investigators. Systematic detection of polyvascular disease combined with aggressive secondary prevention in patients presenting with severe coronary artery disease: the randomized AMERICA Study [submitted].
- 345 Lin JC, Kabbani LS, Peterson EL, Masabni K, Morgan JA, Brooks S, et al. Clinical utility of carotid duplex ultrasound prior to cardiac surgery. *J Vasc Surg* 2016;**63**:710–4.
- 346 Masabni KRS, Blackstone EH, Gornik HL, Sabik 3rd JF. Does preoperative carotid stenosis screening reduce perioperative stroke in patients undergoing coronary artery bypass grafting? *J Thorac Cardiovasc Surg* 2015;**149**:1253–60.
- 347 Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: an updated systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2011;**41**:607–24.
- 348 Schoof J, Lubahn W, Baeumer M, Kross R, Wallesch CW, Koziar A, et al. Impaired cerebral autoregulation distal to

- carotid stenosis/occlusion is associated with increased risk of stroke at cardiac surgery with cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2007;**134**:690–6.
- 349 Stamou SC, Hill PC, Dangas G, Pfister AJ, Boyce SW, Dullum MK, et al. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. *Stroke* 2001;**32**:1508–13.
- 350 Naylor AR. Delay may reduce procedural risk, but at what price to the patient? *Eur J Vasc Endovasc Surg* 2008;**35**:383–91.
- 351 Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med* 2012;**366**:1489–97.
- 352 Illuminati G, Ricco JB, Calio F, Pacile MA, Miraldi F, Frati G, et al. Short-term results of a randomized trial examining timing of carotid endarterectomy in patients with severe asymptomatic unilateral carotid stenosis undergoing coronary artery bypass grafting. *J Vasc Surg* 2011;**54**:993–9.
- 353 Randall MS, McKeivitt F, Cleveland TJ, Gaines PA, Venables GS. Is there any benefit from staged carotid and coronary revascularization using carotid stents? A single-center experience highlights the need for a randomized controlled trial. *Stroke* 2006;**37**:435–9.
- 354 Van der Heyden JSM, Bal ET, Ernst JM, Ackerstaff RG, Schaap J, Kelder JC, et al. Staged carotid angioplasty and stenting followed by cardiac surgery in patients with severe asymptomatic carotid artery stenosis: early and long-term results. *Circulation* 2007;**116**:2036–342.
- 355 Versaci F, Del Giudice C, Scafuri A, Zeitani J, Gandini R, Nardi P, et al. Sequential hybrid carotid and coronary artery revascularization: immediate and mid-term results. *Ann Thorac Surg* 2007;**84**:1508–13.
- 356 Chiariello LNP, Pellegrino A, Saitto G, Chiariello GA, Russo M, Zeitani J, et al. Simultaneous carotid artery stenting and heart surgery: expanded experience of hybrid surgical procedures. *Ann Thorac Surg* 2015;**99**:1291–7.
- 357 Shishehbor MH, Venkatachalam S, Sun Z, Rajeswaran J, Kapadia SR, Bajzer C, et al. A direct comparison of early and late outcomes with three approaches to carotid revascularization and open heart surgery. *J Am Coll Cardiol* 2013;**62**:1948–56.
- 358 Aboyans V, Lacroix P. Indications for carotid screening in patients with coronary artery disease. *Presse Med* 2009;**38**:977–86.
- 359 Naylor AR, Cuffe RL, Rothwell PM, Bell PR. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg* 2003;**25**:380–9.
- 360 Paraskevas KI, Nduwayo S, Saratzis AN, Naylor AR. Carotid stenting prior to coronary bypass surgery: an updated systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2017;**53**:309–19.
- 361 Imori Y, Akasaka T, Ochiai T, Oyama K, Tobita K, Shishido K, et al. Co-existence of carotid artery disease, renal artery stenosis, and lower extremity peripheral arterial disease in patients with coronary artery disease. *Am J Cardiol* 2014;**113**:30–5.
- 362 Kim EKSP, Yang JH, Song YB, Hahn JY, Choi JH, Gwon HC, et al. Peripheral artery disease in Korean patients undergoing percutaneous coronary intervention: prevalence and association with coronary artery disease severity. *J Korean Med Sci* 2013;**28**:87–92.
- 363 Hussein AAUK, Wolski K, Kapadia S, Schoenhagen P, Tuzcu EM, Nissen SE, et al. Peripheral arterial disease and progression of coronary atherosclerosis. *J Am Coll Cardiol* 2011;**57**:1220–5.
- 364 Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. The Coronary Artery Surgery Study (CASS) Investigators. *J Am Coll Cardiol* 1994;**23**:1091–5.
- 365 Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. *Vasc Med* 2013;**18**:176–84.
- 366 Saw J, Bhatt DL, Moliterno DJ, Brener SJ, Steinhubl SR, Lincoff AM, et al. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. *J Am Coll Cardiol* 2006;**48**:1567–72.
- 367 Aboyans V, Lacroix P, Postil A, Guilloux J, Rolle F, Cornu E, et al. Subclinical peripheral arterial disease and incompressible ankle arteries are both long-term prognostic factors in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol* 2005;**46**:815–20.
- 368 Rihal CS, Sutton-Tyrrell K, Guo P, Keller NM, Jandova R, Sellers MA, et al. Increased incidence of periprocedural complications among patients with peripheral vascular disease undergoing myocardial revascularization in the bypass angioplasty revascularization investigation. *Circulation* 1999;**100**:171–7.
- 369 Hlatky MA, Boothroyd DB, Baker L, Kazi DS, Solomon MD, Chang TI, et al. Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. *Ann Intern Med* 2013;**158**:727–34.
- 370 Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;**381**:639–50.
- 371 Dencker D, Pederson F, Engstrom T, Kober L, Hojberg S, Nielsen MB, et al. Major femoral vascular access complications after coronary diagnostic and interventional procedures: a Danish register study. *Int J Cardiol* 2016;**202**:604–8.
- 372 Neufang A, Dorweiler B, Espinola-Klein C, Savvidis S, Doemland M, Schotten S, et al. Outcomes of complex femorodistal sequential autologous vein and biologic prosthesis composite bypass grafts. *J Vasc Surg* 2014;**60**:1543–53.
- 373 Spronk S, White JV, Ryjewski C, Rosenblum J, Bosch JL, Hunink MG. Invasive treatment of claudication is indicated for patients unable to adequately ambulate during cardiac rehabilitation. *J Vasc Surg* 2009;**49**:1217–25.
- 374 Aboyans V, Lacroix P, Guilloux J, Rolle F, Le Guyader A, Cautres M, et al. A predictive model for screening cerebrovascular disease in patient undergoing coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg* 2005;**4**:90–5.
- 375 Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;**385**:2465–76.
- 376 Jones WS, Clare R, Ellis SJ, Mills JS, Fischman DL, Kraus WE, et al. Effect of peripheral arterial disease on functional and clinical outcomes in patients with heart failure (from HF-AC-TION). *Am J Cardiol* 2011;**108**:380–4.

- 377 Inglis SC, Bebhuk J, Al-Suhaim SA, Case J, Pfeffer MA, Solomon SD, et al. Peripheral artery disease and outcomes after myocardial infarction: an individual-patient meta-analysis of 28,771 patients in CAPRICORN, EPEHESUS, OPTIMAAL and VALIANT. *Int J Cardiol* 2013;**168**:1094–101.
- 378 Nakamura Y, Kunii H, Yoshihisa A, Takiguchi M, Shimizu T, Yamauchi H, et al. Impact of peripheral artery disease on prognosis in hospitalized heart failure patients. *Circ J* 2015;**79**:785–93.
- 379 van Straten AH, Firanescu C, Soliman Hamad MA, Tan ME, ter Woorst JF, Martens EJ, et al. Peripheral vascular disease as a predictor of survival after coronary artery bypass grafting: comparison with a matched general population. *Ann Thorac Surg* 2010;**89**:414–20.
- 380 Calvet D, Touze E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. *Circulation* 2010;**121**:1623–9.
- 381 Hofmann R, Kypta A, Steinwender C, Kerschner K, Grund M, Leisch F. Coronary angiography in patients undergoing carotid artery stenting shows a high incidence of significant coronary artery disease. *Heart* 2005;**91**:1438–41.
- 382 Illuminati G, Ricco JB, Greco C, Mangieri E, Calio F, Ceccanei G, et al. Systematic preoperative coronary angiography and stenting improves postoperative results of carotid endarterectomy in patients with asymptomatic coronary artery disease: a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2010;**39**:139–45.
- 383 Illuminati G, Schneider F, Greco C, Mangieri E, Schiariti M, Tanzilli G, et al. Long-term results of a randomized controlled trial analyzing the role of systematic pre-operative coronary angiography before elective carotid endarterectomy in patients with asymptomatic coronary artery disease. *Eur J Vasc Endovasc Surg* 2015;**49**:366–774.
- 384 Vidakovic R, Schouten O, Kuiper R, Hoeks SE, Flu WJ, van Kuijk JP, et al. The prevalence of polyvascular disease in patients referred for peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2009;**38**:435–40.
- 385 Hur DJ, Kizilgul M, Aung WW, Roussillon KC, Keeley EC. Frequency of coronary artery disease in patients undergoing peripheral artery disease surgery. *Am J Cardiol* 2012;**110**:736–40.
- 386 Ishihara T, Iida O, Tosaka A, Soga Y, Sakamoto Y, Hirano K, et al. Severity of coronary artery disease affects prognosis of patients with peripheral artery disease. *Angiology* 2013;**64**:417–22.
- 387 Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol* 2014;**31**:517–73.
- 388 Gallino A, Aboyans V, Diehm C, Cosentino F, Stricker H, Falk E, et al. Non-coronary atherosclerosis. *Eur Heart J* 2014;**35**:1112–9.
- 389 Cho I, Chang H, Sung JM, Pencina MJ, Lin FY, Dunning AM, et al. CONFIRM Investigators. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). *Circulation* 2012;**126**:304–13.
- 390 Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. CRUSADE Investigators. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J* 2009;**30**:1195–202.
- 391 Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
- 392 Sirimarco G, Amarenco P, Labreuche J, Touboul PJ, Alberts M, Goto S, et al. REACH Registry Investigators. Carotid atherosclerosis and risk of subsequent coronary event in outpatients with atherothrombosis. *Stroke* 2013;**44**:373–9.
- 393 Amighi J, Schlager O, Haumer M, Dick P, Mlekusch W, Loewe C, et al. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. *Eur J Clin Invest* 2009;**39**:784–92.
- 394 Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000;**102**:3060–7.
- 395 Kahan T. The importance of myocardial fibrosis in hypertensive heart disease. *J Hypertens* 2012;**30**:685–7.
- 396 O'Rourke MF, Safar ME, Dzau V. The Cardiovascular Continuum extended: aging effects on the aorta and microvasculature. *Vasc Med* 2010;**15**:461–8.
- 397 Duscha BD, Annex BH, Green HJ, Phippen AM, Kraus WE. Deconditioning fails to explain peripheral skeletal muscle alterations in men with chronic heart failure. *J Am Coll Cardiol* 2002;**39**:1170–4.
- 398 Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation* 1992;**85**:1364–73.
- 399 Hedberg P, Hammar C, Selmeryd J, Viklund J, Leppert J, Hellberg A, et al. Left ventricular systolic dysfunction in outpatients with peripheral atherosclerotic vascular disease: prevalence and association with location of arterial disease. *Eur J Heart Fail* 2014;**16**:625–32.
- 400 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
- 401 Yamasaki S, Izawa A, Shiba Y, Tomita T, Miyashita Y, Koyama J, et al. Presence of diastolic dysfunction in patients with peripheral artery disease. *Angiology* 2013;**64**:540–3.
- 402 Meltzer AJ, Shrikhande G, Gallagher KA, Aiello FA, Kahn S, Connolly P, et al. Heart failure is associated with reduced patency after endovascular intervention for symptomatic peripheral arterial disease. *J Vasc Surg* 2012;**55**:353–62.
- 403 Inglis SC, Hermis A, Shehab S, Newton PJ, Lal S, Davidson PM. Peripheral arterial disease and chronic heart failure: a dangerous mix. *Heart Fail Rev* 2013;**18**:457–664.
- 404 Inglis SC, McMurray JJ, Bohm M, Schaufelberger M, van Veldhuisen DJ, Lindberg M, et al. Intermittent claudication as a predictor of outcome in patients with ischaemic systolic heart failure: analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure trial (CORONA). *Eur J Heart Fail* 2010;**12**:698–705.

- 405 Ahmed MI, Aronow WS, Criqui MH, Aban I, Love TE, Eichhorn EJ, et al. Effects of peripheral arterial disease on outcomes in advanced chronic systolic heart failure: a propensity-matched study. *Circ Heart Fail* 2010;**3**:118–24.
- 406 Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–5.
- 407 Griffin WF, Salahuddin T, O'Neal WT, Soliman EZ. Peripheral arterial disease is associated with an increased risk of atrial fibrillation in the elderly. *Europace* 2016;**18**:794–8.
- 408 Aboyans V, Lacroix P, Echahidi N, Mohty D. Ankle-brachial index in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2014;**63**:1456–7.
- 409 Gallego P, Roldan V, Marin F, Jover E, Manzano-Fernandez S, Valdes M, et al. Ankle brachial index as an independent predictor of mortality in anticoagulated atrial fibrillation. *Eur J Clin Invest* 2012;**42**:1302–8.
- 410 O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Peripheral arterial disease and risk of atrial fibrillation and stroke: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2014;**3**:e001270.
- 411 Wasmer K, Unrath M, Kobe J, Malyar NM, Freisinger E, Meyborg M, et al. Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease. *Int J Cardiol* 2015;**199**:223–8.
- 412 euroSCORE interactive calculator. <http://www.euroscore.org/calc.html>.
- 413 Gilard M, Eltchaninoff H, Lung B, Donzeau-Gouge P, Chevreul K, Fajadet J, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;**366**:1705–15.
- 414 Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–607.
- 415 Skelding KA, Yakubov SJ, Kleiman NS, Reardon MJ, Adams DH, Huang J, et al. Transcatheter aortic valve replacement versus surgery in women at high risk for surgical aortic valve replacement (from the CoreValve US High Risk Pivotal Trial). *Am J Cardiol* 2016;**118**:560–6.
- 416 Aronow WS. Peripheral arterial disease in the elderly. *Clin Interv Aging* 2007;**2**:645–54.
- 417 Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**371**:967–8.
- 418 Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–98.
- 419 Sinning JM, Horack M, Grube E, Gerckens U, Erbel R, Eggebrecht H, et al. The impact of peripheral arterial disease on early outcome after transcatheter aortic valve implantation: results from the German Transcatheter Aortic Valve Interventions Registry. *Am Heart J* 2012;**164**:102–10.
- 420 Erdogan HB, Goksedef D, Erentug V, Polat A, Bozbuga N, Mansuroglu D, et al. In which patients should sheathless IABP be used? An analysis of vascular complications in 1211 cases. *J Card Surg* 2006;**21**:342–6.
- 421 Ohman JW, Vemuri C, Prasad S, Silvestry SC, Jim J, Geraghty PJ. The effect of extremity vascular complications on the outcomes of cardiac support device recipients. *J Vasc Surg* 2014;**59**:1622–7.