

## CLINICAL PRACTICE GUIDELINE DOCUMENT

# European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication<sup>☆</sup>

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<https://doi.org/10.1016/j.ejvs.2023.08.067>

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## ABBREVIATIONS

ABI	Ankle Brachial Index
BMS	Bare Metal Stent
CAD	Coronary Artery Disease
CI	Confidence Interval
CLTI	Chronic Limb Threatening Ischaemia
CR	Cardiac Rehabilitation
CTA	Computed Tomography Angiography
CV	Cardiovascular
DAPT	Dual Antiplatelet Therapy
DCB	Drug Coated Balloon
DES	Drug Eluting Stent
DSA	Digital Subtraction Angiography
ePTFE	expanded PolyTetraFluoroEthylene
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
GSC	Guidelines Steering Committee
GWC	Guideline Writing Committee
HBET	Home Based Exercise Therapy
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IC	Intermittent Claudication
INR	International Normalised Ratio
MACE	Major Adverse Cardiovascular Events
MALE	Major Adverse Limb Events
MRA	Magnetic Resonance Angiography
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PTA	Percutaneous Transluminal Angioplasty
PROM	Patient Reported Outcome Measure

QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RR	Risk Ratio
SET	Supervised Exercise Therapy
TBI	Toe Brachial Index
TP	Toe Pressure

## STUDY ACRONYMS

AMERICA	The Active detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis
BATTLE	Bare Metal Stent Versus Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate Length Femoropopliteal Lesions
BIOLUX P-II	BIOTRONIK's First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularisation of infrapopliteal arteries
CANVAS	CANagliflozin cardioVascular Assessment Study
CAPRIE	Clopidogrel versus vs.Aspirin in Patients at Risk of Ischaemic Events
CASPAR	Clopidogrel and AcetylSalicylic acid in bypass surgery for Peripheral ARterial disease
CASTLE	Cilostazol:A STudy in Long-term Effects
CAVASIC	Comparison and Evaluation of Cardiac Biomarkers in Patients with Intermittent Claudication

CLEVER	Claudication:Exercise Vs. Endoluminal Revascularisation	MIRROR	Management of peripheral arterial interventions with mono or dual antiplatelet therapy
COBEST	Covered Versus vs. Balloon Expandable Stent Trial	SAMSON	Self-Assessment Method for Statin side-effects Or Nocebo
DANCAVAS	the Danish Cardiovascular Screening trial	PANDORA	Prevalence of peripheral Arterial disease in patients with a non-high cardiovascular disease risk, with No overt vascular Diseases nOR diAbetes mellitus
DAPA-CKD	Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease trial	POPADAD	Prevention Of Progression of Arterial Disease And Diabetes
DAPA-HF	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	PARTNERS	PAD Awareness, Risk, and Treatment: NEw Resources for Survival
DECLARE-TIMI	Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes	ODYSSEY	Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome
DISCOVER	Dutch Iliac Stent trial:COVERed balloon-expandable versus vs.uncovered balloon-expandable stents in the common iliac artery	STAG	Stents versus vs.angioplasty for the treatment of iliac artery occlusions
BOA	Bypass Oral anticoagulants or Aspirin	SUPER	Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction
EMINENT	Trial Comparing ELUVIA Versus vs.Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery	VIVA	Viborg Vascular Trial
EMPA-REG	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes	VIBRANT	VIABAHN endoprosthesis versus vs.bare nitinol stent implantation for complex superficial femoral artery occlusive disease
OUTCOME	Empagliflozin in Heart Failure with a Preserved Ejection Fraction	VIASTAR	Viabahn endoprosthesis with PROPATEN bioactive surface versus vs.bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease
EMPEROR	Ticagrelor versus vs. Clopidogrel in Symptomatic Peripheral Artery Disease	VOYAGER	Rivaroxaban in Peripheral Artery Disease after Revascularisation
EUCLID	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk	PAD	YUKON-drug-eluting Stent Below The Knee
FOURIER	German Epidemiological Trial on Ankle Brachial Index	ZILVERPASS	ZILVER PTX Stent versus vs.Bypass Surgery in Femoropopliteal Lesions
GET ABI	Heart Outcomes Prevention Evaluation	ZILVER PTX	Zilver PTX randomised trial of paclitaxel-eluting stents for femoropopliteal artery disease
HOPE	Heart Protection Study		
HPS	The Nord-Trøndelag Health Survey		
HUNT	Self-Expanding Versus vs.Balloon-Expandable Stents for Iliac Artery Occlusive Disease		
ICE	Invasive revascularisation or not in intermittent claudication		
IRONIC			

## 1. INTRODUCTION

### 1.1. Purpose, terminology, and definitions

The European Society for Vascular Surgery (ESVS) continuously develops clinical practice guidelines for patients with vascular diseases. This is the first guideline that specifically covers the diagnosis and treatment of patients with atherosclerotic lower extremity peripheral arterial disease (PAD, see also [section 2.1](#)) falling within the following clinical stages: (1) asymptomatic lower limb PAD (Rutherford grade 0/Fontaine stage I); and (2) intermittent claudication (IC, Rutherford grade I–III/Fontaine stage IIa and IIb).

Thus, the management of patients with chronic limb threatening ischaemia (CLTI) falls outside the primary purpose of this guideline, as the management of such patients is already covered by other recent guidelines from the Society.<sup>1</sup> Throughout the guideline, the term lower limb PAD refers to both aforementioned patient categories, whereas the terms

asymptomatic PAD and IC are used where a certain section or recommendation only applies to that particular subcategory. Within the context of this guideline, the term PAD includes atherosclerotic disease from the infrarenal aorta to the toes.

The primary aim of the guideline is to assist clinicians and patients in their selection of an optimal diagnostic and therapeutic pathway for PAD during patient centred shared decision making. A secondary aim is to contribute to an aligned management and research process of the disease across European countries and globally. Both the diagnostic and the therapeutic landscapes have evolved markedly within the PAD space during recent years with the introduction of new diagnostic modalities, imaging protocols, and therapeutic options. These include increased understanding and utilisation of non-interventional treatment options such as exercise therapy and secondary preventive pharmacotherapy and continuous advancements in endovascular therapeutic options that are becoming available to an

increasing number of PAD patients. The scope of this guideline is to provide comprehensive, evidence based and clear recommendations on as many as possible of the different steps and decisions that fall within the clinical PAD patient management process.

The term patient as used in the guideline is all encompassing, including people of all sex identities, and in general, these guidelines apply to adults over the age of 18 years. The clinician responsible for a PAD patient's care will also differ by country, and will among others include vascular surgeons, angiologists, cardiologists, interventional radiologists, vascular physicians, primary care physicians, and exercise rehabilitation specialists. The guidelines were therefore developed by a multidisciplinary group of specialists in the field (see [Appendix B](#)) to promote a high standard of care based on the highest quality evidence available. This guideline should not be considered as a legal standard of care. The document provides guidance and support, and the choice of therapy will ultimately depend on the individual patient and treatment setting and fall within the responsibility of the treating physician. All ESVS guidelines, including app based smartphone and tablet versions, can be downloaded free of charge from the ESVS website (<https://www.esvs.org/journal/guidelines/>).

## 1.2. Methodology

The AGREE reporting standards for clinical practice guidelines were used throughout the guideline process and the AGREE II checklist is included as supplementary material ([Appendix A](#)).<sup>2</sup> The development of these guidelines also followed the principal steps suggested for the ESVS guidelines development cycle, and was further informed by the ESVS Clinical Practice Guideline Development Scheme.<sup>3</sup>

**1.2.1. Writing committee.** Members of the Guideline Writing Committee (GWC) were selected by the guideline chairs in collaboration with the ESVS Guideline Steering Committee (GSC) to represent an expert clinician group deeply involved in the management of PAD. This included representation from the disciplines of vascular surgery, angiology, physiotherapy, and vascular medicine ([Appendix A](#)). Members of the GWC have provided annual disclosure statements regarding relationships which might be perceived as conflicts of interest. These are available from ESVS headquarters upon request ([info@esvs.org](mailto:info@esvs.org)). Members of the GWC received no financial support from any pharmaceutical, medical device, or industry body to develop these guidelines. Videoconference software support along with travel and accommodation costs for mandatory meetings to develop the guideline were funded by the ESVS. The ESVS GSC was responsible for undertaking the review process which also included several independent external experts outside of the ESVS organisation. The final version was checked and approved by all members of both the GWC and the GSC.

**1.2.2. Patients' representatives and public involvement.** Following the completion of the second draft of the guideline on 15 January 2022, the GWC sent out the

Guideline draft for review by the Swedish Heart and Lung Association (<https://www.hjart-lung.se/om-oss/about-us/>); a non-profit Swedish national patient organisation formed in 1939 that strives to improve the quality of life for persons with cardiovascular and lung diseases and works to ensure that patients with heart, vascular, and lung disease receive the care they need. This organisation was invited to review and provide comments from the patient and public perspectives on the full guideline content. After reading through the guideline document the response received stated that, as the organisation does not have medically trained personnel, neither among elected representatives nor civil servants, they could not comment on the specific medical content of the guidelines. They, however, welcomed the work done by the ESVS to design a compilation of knowledge, and in the guidelines propose the best possible care and treatment, based on science and clinical experience. Overall, the guideline content received a positive opinion from the patient organisation.

### 1.2.3. Definition of clinically relevant issues and Guideline Writing Committee decision process.

The GWC held an introductory meeting on 23 and 24 June 2021 by video conference, where the list of topics and author assignments was determined by consensual agreement. The GWC met monthly by videoconference to discuss the writing process and any ongoing issues. After the first draft was completed and internally reviewed, the GWC met again on 21 and 22 April 2022 to review and approve the wording and content of each recommendation. If any of the GWC members disagreed with the content of a particular recommendation during this meeting, an open vote was held (where all GWC members participated and had the same voting rights) where a simple majority decision was decisive for acceptance of the recommendation.

### 1.2.4. Literature search.

Detailed search strategies for the different topic specific sections of the guideline are available in Supplementary material. Members of the GWC performed literature searches in Medline/PubMed, Embase, and the Cochrane Library from inception up to the date specified in the search for peer reviewed publications. Hand searching of included references was also performed. As per the ESVS guideline development process cycle, all systematic literature searches were last updated in November 2022 when the GWC worked with the first revision of the guideline draft. The last literature search was done in July 2023.

Selection of studies for inclusion was based on the titles and abstracts of retrieved studies. The selection process followed the pyramid of evidence with systematic review and meta-analysis of randomised trials at the top, followed by individual randomised trials, meta-analysis of observational studies, and finally observational studies. Case reports, abstracts, and *in vitro* studies were excluded leaving expert opinion at the base of the pyramid. Other guideline documents were considered only if they applied a systematic approach for literature searches and or produced their own meta-analyses of existing literature. For [section 3.3](#)

**Table 1.** Levels of evidence adapted from the European Society of Cardiology evidence grading system.

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

where no suitable systematic review or consensus document was available, an extensive DELPHI expert consensus process on the use of patient reported outcome measures was arranged and published separately to support this part of the guideline.<sup>4</sup> For section 6.4 of the guidelines where there was no appropriate systematic review and meta-analysis available, such a study was performed by members of the GWC.<sup>5</sup> The studies that underpin each recommendation are shown directly in the individual recommendation table, and further details are given for each in more comprehensive tables of evidence Supplementary material.

**1.2.5. Evidence and recommendations criteria.** The European Society of Cardiology (ESC) system was used for grading the level of evidence and the accompanying class of each recommendation. For each guideline recommendation, the level of evidence was graded from A to C (Table 1) with A being the highest. The strength (class) of each recommendation was graded from I to III with I as the strongest (Table 2). The class II subcategory was also further subcategorised into IIa and IIb based on an overall assessment of the strength and robustness of available evidence alongside concurrent clinical experience and expert consensus opinion within the GWC.

**Table 2.** Class of recommendations from the European Society of Cardiology evidence grading system.

Class	Definition	Wording
I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful, effective	is recommended
IIa	Conflicting evidence and or divergence of opinion about the usefulness or efficacy of the given treatment or procedure: weight of evidence or opinion is in favour of usefulness or efficacy	should be considered
IIb	Conflicting evidence and or divergence of opinion about the usefulness or efficacy of the given treatment or procedure: usefulness or efficacy is less well established by evidence or opinion	may be considered
III	Evidence or general agreement that a given treatment or procedure is not useful or effective and in some cases may be harmful	is not recommended, should not be done

**1.2.6. Areas covered by other European Society for Vascular Surgery guidelines and overlap.** This is the first ESVS guideline focusing on asymptomatic PAD and IC. However, the ESC/ESVS 2017 Guidelines on the Diagnosis and Treatment of PAD included several relevant sections and recommendations that potentially overlap with this guideline.<sup>6</sup> Furthermore, this guideline does not cover acute lower limb PAD presentations, as these are already covered by the ESVS 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia.<sup>7</sup> The ESVS 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases contains comprehensive recommendations on antithrombotic therapies for both asymptomatic PAD and IC patients, and the recommendations from that guideline are aligned with this as far as possible; however, an updated literature search was done on this topic to account for potential new evidence that may have emerged following the publication of the antithrombotic guideline. When this guideline changes or updates a previous recommendation from any of these previous guidelines, it is discussed in the relevant section, and all changed or updated recommendations are also briefly summarised below (Table 3).

**1.2.7. The revision process.** The guideline document underwent a formal external expert peer review process and was additionally reviewed and approved by the ESVS GSC as well as by the editors of the *European Journal of Vascular and Endovascular Surgery*. Non-European reviewers were also invited to enhance global reach and relevance. This document was reviewed over three rounds by 23 reviewers, including 14 members of GSC (with a review coordinator) and nine external reviewers, of whom 20 were from Europe, two from the USA, and one from Australia. All reviewers assessed all versions, and the final version of this document was approved by the ESVS GSC on 9 August.

**1.2.8. Update plan.** It is the aim of the ESVS to revise these guidelines when important new evidence emerges, or in accordance with the ESVS guideline update policy that is applicable to all guidelines.

**1.2.9. Economic aspects.** According to the data of the Organisation for Economic Co-operation and Development (OECD) (<https://data.oecd.org/healthres/health-spending.htm>), the annual total health spending per capita in EU member states varies widely between 1842 US dollars in Bulgaria and 6347 US dollars in Germany (Fig. 1). This emphasises the marked challenge of comparing health economic aspects between European countries. Hence, it is beyond the scope of these guidelines to provide comprehensive detail on the health economics of different PAD management strategies and treatments, as both resource allocation to different PAD treatments and cost thresholds for use and reimbursement vary between countries. However, in scenarios where existing evidence does not support a clear advantage of a certain treatment strategy over another, the health economic aspects are briefly discussed within the relevant sections of this guideline. Relevant areas where proper health economy studies are suitable or

**Table 3.** Brief overview of differences between previous cardiovascular guideline recommendations and this guideline.

Guideline	Year of printed publication	Recommendation in previous guidelines	ESVS lower limb PAD and intermittent claudication guideline recommendation	Reasons for differences
Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease	2022	We suggest against routine PAD testing for inferring global cardiovascular risk, in patients without symptoms of PAD, who have clinically symptomatic atherosclerosis in another vascular territory (Weak Recommendation; Moderate quality evidence).	<i>Recommendation 4:</i> For clinically asymptomatic individuals at increased risk of lower limb peripheral arterial disease, focused screening for peripheral arterial disease with ankle brachial index measurements based on the lowest recorded ankle pressure may be considered, to support secondary prevention strategies. (Iib, B)	They suggest against screening in patients who already manifested atherosclerotic symptoms from other vascular territories than the legs (and thus are already considered having a high cardiovascular risk).
European Society for Vascular Medicine (ESVM) Guideline on Peripheral Arterial Disease	2019	It is recommended that patients with diabetes should be screened for PAD (Class I Level B)	<i>Recommendation 4:</i> For clinically asymptomatic individuals at increased risk of lower limb peripheral arterial disease, focused screening for peripheral arterial disease with ankle brachial index measurements based on the lowest recorded ankle pressure may be considered, to support secondary prevention strategies. (Iib, B)	They recommend PAD screening only for patients with diabetes whereas the ESVS guideline suggest focused screening in a broader high risk population (see <a href="#">section 3.1.1.2</a> ).
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)	2018	In patients with coronary artery disease, screening for lower extremity atherosclerotic disease (LEAD) by ABI measurement may be considered for risk stratification. (Iib, B) Screening for LEAD may be considered in patients with heart failure. (Iib, C)	<i>Recommendation 4:</i> For clinically asymptomatic individuals at increased risk of lower limb peripheral arterial disease, focused screening for peripheral arterial disease with ankle brachial index measurements based on the lowest recorded ankle pressure may be considered, to support secondary prevention strategies. (Iib, B)	They recommend PAD screening only for patients with manifest coronary artery disease or heart failure whereas this guideline suggests focused screening in a broader high risk population (see <a href="#">section 3.1.1.2</a> ).
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)	2018	Measurement of the ABI is indicated as a first line non-invasive test for screening and diagnosis of lower extremity atherosclerotic disease (LEAD). (Class 1 Level C)	<i>Recommendation 5:</i> The ankle brachial index is recommended as the appropriate test to establish the diagnosis of lower limb peripheral arterial disease. (I, B)	Current evidence level supports upgrading from level C to B, based on two review studies, one systematic Cochrane review, one meta-analysis, and one clinical trial (see <a href="#">section 3.1.3.1</a> )
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	Recommendation 2.1 We recommend using the ABI as the first line non-invasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease. When the ABI is borderline or normal (> 0.9) and symptoms of claudication are suggestive, we recommend an exercise ABI. (Grade 1 Level A)	<i>Recommendation 5:</i> The ankle brachial index is recommended as the appropriate test to establish the diagnosis of lower limb peripheral arterial disease. (I, B)	Current evidence level supports a downgrading from level A to B. (see <a href="#">section 3.1.3.1</a> )

Continued

Table 3-continued

Guideline	Year of printed publication	Recommendation in previous guidelines	ESVS lower limb PAD and intermittent claudication guideline recommendation	Reasons for differences
European Society for Vascular Medicine (ESVM) Guideline on Peripheral Arterial Disease	2019	Measurement of the ABI by non-invasive measurements using Doppler occlusion pressure is indicated as an appropriate test to verify PAD. (Class 1 Level C)	<i>Recommendation 5:</i> The ankle brachial index is recommended as the appropriate test to establish the diagnosis of lower limb peripheral arterial disease. (I, B)	Current evidence level supports upgrading from level C to B, based on two review studies, one systematic Cochrane review, one meta-analysis and one clinical trial (see <a href="#">section 3.1.3.1</a> )
European Society for Vascular Medicine (ESVM) Guideline on Peripheral Arterial Disease	2019	It is recommended that ABI values $\leq 0.9$ are evidence of significant PAD. (Class I Level B)	<i>Recommendation 6:</i> It is recommended that an ankle brachial index cutoff value at $\leq 0.9$ is used for lower limb peripheral arterial disease diagnosis, and that a value $\geq 1.4$ be considered inconclusive. (I, C)	A cutoff value has been added for incompressible ankle arteries (ABI $\geq 1.4$ ) which led to an overall downgrading of evidence to level C. No references are provided in support of the level B evidence level in the ESVM guideline.
European Society for Vascular Medicine (ESVM) Guideline on Peripheral Arterial Disease	2019	It is recommended that the ABI score with the highest ankle artery pressure value is to be used for the calculation of ABI. (Class I Level C)	<i>Recommendation 7:</i> When the ankle brachial index is used to estimate the severity of lower limb peripheral arterial disease in symptomatic patients or is being used during follow up after revascularisation, it is recommended to be calculated by dividing the highest systolic pressure at the ankle level by the highest systolic arm pressure. (I, B)	The recommendation has been upgraded to level B based on two observational studies and one review. The level C evidence statement suggested by ESVM refers to the scientific statement from the American Heart Association. (Aboyans <i>et al. Circulation</i> 2012) that in turn suggested a Grade I Level A recommendation.
Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease	2022	We recommend smoking cessation interventions ranging from intensive counselling, nicotine replacement therapy, bupropion, varenicline, and sometimes nicotine e-cigarettes (Strong Recommendation; High quality Evidence).	<i>Recommendation 22:</i> For patients with lower limb peripheral arterial disease who smoke, counselling as part of intensive smoking cessation intervention is recommended. (I, B) <i>Recommendation 23:</i> For patients with lower limb peripheral arterial disease who smoke, varenicline, either alone or in combination with nicotine replacement therapy, is recommended as the first line pharmacological smoking cessation treatment due to its higher effectiveness as compared to other pharmacological alternatives. (I, B)	We considered the current evidence base differently, especially for bupropion. We also considered the potential harm of e-cigarettes (see <a href="#">chapter 4.1.1.1</a> )
Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease	2022	Statin add on therapies (ezetimibe and or PCSK-9 inhibitors) if receiving maximally tolerated dose of statin therapy and the low density lipoprotein cholesterol is $\geq 1.8$ mmol/L, non-high density lipoprotein cholesterol $\geq 2.4$ mmol/L or apolipoprotein B 100 $\geq 0.7$ mg/dL.	<i>Recommendation 32:</i> For patients with lower limb peripheral arterial disease, it is recommended to reduce the low density lipoprotein cholesterol concentrations to $< 1.4$ mmol/L ( $< 55$ mg/dL) and decrease it by $\geq 50\%$ if baseline values are within 55–110 mg/dL. (I, B)	We recommended a slightly lower low density lipoprotein cholesterol threshold, although we recognise that the current evidence for a lower threshold is mainly based on heterogeneous cohorts and was mainly driven by positive data from recent trials on PCSK-9 inhibitors.

Continued



Table 3-continued

Guideline	Year of printed publication	Recommendation in previous guidelines	ESVS lower limb PAD and intermittent claudication guideline recommendation	Reasons for differences
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice	2021	Considered to be at high risk: Documented atherosclerotic cardiovascular disease (ASCVD), clinical or unequivocal on imaging. Documented clinical ASCVD includes previous AMI, ACS, coronary revascularisation and other arterial revascularisation procedures, stroke and TIA, aortic aneurysm and PAD. Symptomatic or asymptomatic lower extremity atherosclerotic disease (LEAD) (ABI < 0.90) is associated with a doubling of the 10 year rate of coronary events, CV mortality, and total mortality.	<i>Recommendation 44</i> For patients with lower limb peripheral arterial disease, even if asymptomatic, it is recommended to consider an ankle brachial index $\leq 0.9$ or $\geq 1.4$ a risk enhancing factor for a cardiovascular event and for an increased all cause mortality. (I, A)	The ESC document classifies PAD as a documented ASCVD, and further emphasises the high cardiovascular risk associated with PAD. In our document we have suggested a diagnostic method for PAD which is not given in the ESC guideline.
European Society for Vascular Medicine (ESVM) Guideline on Peripheral Arterial Disease	2019	It is recommended that recognition be given that patients with PAD have a high risk of vascular events in other vascular beds, and as such these patients should always be considered very high risk for further events. (Class I Level A) and It is recommended that ABI values $\leq 0.9$ are evidence of significant PAD (Class I Level B)	<i>Recommendation 44:</i> For patients with lower limb peripheral arterial disease, even if asymptomatic, it is recommended to consider an ankle brachial index $\leq 0.9$ or $\geq 1.4$ a risk enhancing factor for a cardiovascular event and for an increased all cause mortality. (I, A)	The two quoted recommendations from ESVM together provide a similar message to recommendation 43 in this guideline.
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	<i>Recommendation 5.5</i> We recommend the selective use of BMS or covered stents for aorto-iliac angioplasty for common iliac artery or external iliac artery occlusive disease, or both, due to improved technical success and patency. (Grade 1 Level B)	<i>Recommendation 55:</i> For patients with disabling intermittent claudication undergoing revascularisation, primary bare metal stenting is recommended over primary balloon angioplasty for iliac artery occlusions due to the lower risk of distal embolisation. (I, B)	We have also considered the risk of distal embolisation when performing balloon angioplasty on iliac artery occlusions why we did not recommend selective use of stents for iliac artery occlusions. We also considered the results from the recently published DISCOVER trial that did not show any benefit of covered vs. uncovered stents in the common iliac artery (see <a href="#">chapter 6.4</a> ).
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	<i>Recommendation 5.6</i> We recommend the use of covered stents for treatment of AIOD in the presence of severe calcification or aneurysmal changes where the risk of rupture may be increased after unprotected dilation. (Grade 1 Level C)	<i>Recommendation 57:</i> For patients with disabling intermittent claudication undergoing revascularisation who have Trans-Atlantic Inter-Society Consensus Document II C/D iliac lesions, covered stent placement may be considered over bare metal stents due to higher patency rates. (Iib, B)	Our recommendation more precisely targets complex (i.e., TASC II C and D) aorto-iliac lesions, where the risk of vessel rupture is substantially higher. We also considered the results of the recently published DISCOVER trial that did not show any treatment benefit for covered vs. uncovered stents in the common iliac position (see <a href="#">chapter 6.4</a> ).

Continued

Table 3-continued				
Guideline	Year of printed publication	Recommendation in previous guidelines	ESVS lower limb PAD and intermittent claudication guideline recommendation	Reasons for differences
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)	2018	Recommendations on revascularisation of femoropopliteal occlusive lesions: Primary stent implantation should be considered in short (i.e., < 25 cm) lesions. (Class IIa Level A)	<i>Recommendation 65:</i> For patients with disabling intermittent claudication undergoing revascularisation, primary bare metal stenting is not recommended over balloon angioplasty with provisional stenting in femoropopliteal lesions due to the unfavourable secondary patency rates in patients with in stent re-stenosis. (III, C)	We have also considered the meta-analysis of Koeckerling <i>et al.</i> , demonstrating lack of long term target lesion revascularisation benefits from primary stenting compared with balloon angioplasty (see <a href="#">chapter 6.4</a> ).
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)	2018	Recommendations on revascularisation of femoropopliteal occlusive lesions: Drug eluting stents may be considered for short (i.e., < 25 cm) lesions. (Class IIb Level B)	<i>Recommendation 66:</i> For patients with disabling intermittent claudication undergoing revascularisation, selective drug eluting stent placement should be considered if femoropopliteal plain balloon angioplasty leads to suboptimal results i.e., residual stenosis or dissection. (IIa, B)	We have considered the recent meta-analysis of Koeckerling <i>et al.</i> that only reported transient efficacy benefits for primary over provisional stenting in femoropopliteal arteries. We also considered the recently published EMINENT trial that reported superior 12 month primary patency rates for drug eluting stents vs. bare metal stents in femoropopliteal lesions (see <a href="#">chapter 6.4</a> ).
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	<i>Recommendation 5.18</i> For intermediate length lesions (5–15 cm) in the SFA, we recommend the adjunctive use of self expanding nitinol stents (with or without paclitaxel) to improve the midterm patency of angioplasty. (Grade 1 Level B)	<i>Recommendation 66:</i> For patients with disabling intermittent claudication undergoing revascularisation, selective drug eluting stent placement should be considered if femoropopliteal plain balloon angioplasty leads to suboptimal results i.e., residual stenosis or dissection. (IIa, B)	We have considered the recent meta-analysis of Koeckerling <i>et al.</i> that only reported transient efficacy benefits for primary over provisional stenting in femoropopliteal arteries. We also considered the recently published EMINENT trial that reported superior 12 month primary patency rates for drug eluting stents vs. bare metal stents in femoropopliteal lesions (see <a href="#">chapter 6.4</a> ).

Displayed differences between recommendations in this guideline and other contemporary guidelines have been colour-coded in the table when they differ in terms of either the Class or the Level of Evidence. PAD = peripheral artery disease; PCSK-9 = proprotein convertase subtilisin-kexin type 9; IC = intermittent claudication; SFA = superficial femoral artery; AIOD = aorto-iliac occlusive disease; BMS = bare metal stent; ESC = European Society of Cardiology; TASC = Trans-Atlantic Inter-Society Consensus; ASCVD = atherosclerotic cardiovascular disease; ABI = ankle brachial index.

needed but currently lacking are also briefly summarised under [Section 8](#).

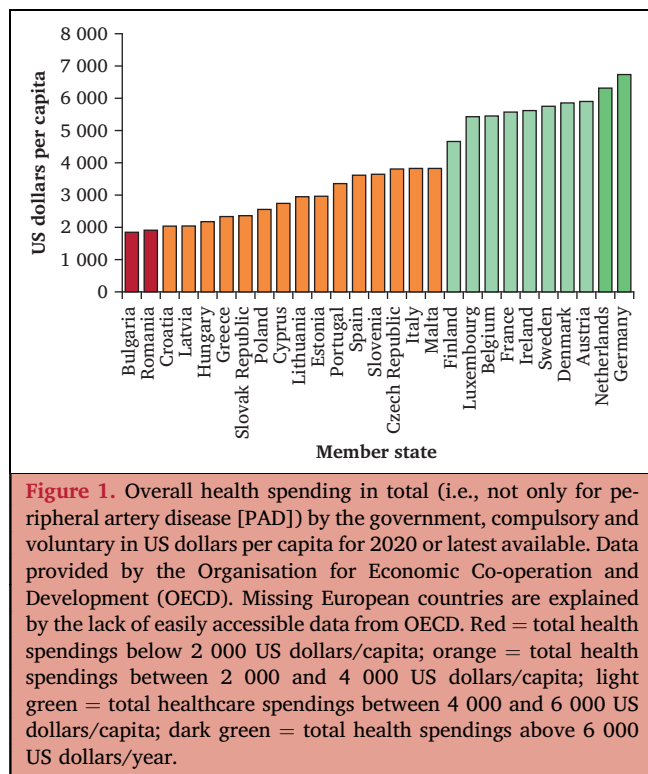
### 1.3. Benefits and harms

#### 1.3.1. Assessment of revascularisation outcomes and risks for procedure related complications

**1.3.1.1. Asymptomatic peripheral arterial disease.** Revascularisation procedures are not indicated in asymptomatic PAD. The exception to this is when the intervention aims to enhance the long term patency rate in a patient who remains clinically asymptomatic but has already undergone a

first revascularisation (the principal example being a patient who develops a high grade vein graft stenosis under ultrasound surveillance, see also [section 6.6.1](#)).

**1.3.1.2. Intermittent claudication.** The immediate and long term functional outcomes from a revascularisation procedure performed for IC depend on several important factors, which are usually identified during pre-operative evaluation. Such factors include the severity and extent of the target lesion(s), affected vessel segment(s), quality of inflow and outflow arteries, available procedural technical equipment and technology, adjunctive pharmacotherapies, adherence to best medical therapy and exercise therapy, and the pre-



operative functional status and comorbidity profile of the patient, including the presence or absence of other intercurrent diseases that also may impact negatively on ambulatory function.<sup>8,9</sup> Peri-procedural and post-operative treatment complications may also negatively impact on long term outcomes. Contemporary studies report relatively high re-admission rates (ranging from approximately 7% to 30%) following primary discharge after revascularisation for IC, also following endovascular interventions, mainly for symptom recurrence and complications related to the puncture site.<sup>10–12</sup> The risk of post-operative surgical site infections after open vascular surgical procedures in the groin is substantial,<sup>13,14</sup> and the risk of suffering such complications may be predicted in the pre-operative setting.<sup>15</sup>

All these aforementioned factors are very important to consider when deciding whether to offer revascularisation to patients with IC, as the surgical indication remains relative, and as alternative treatments (risk factor modification; pharmacotherapy; exercise) are also valid treatment options for many patients and should be implemented in a first step (and subsequently maintained) before offering an invasive procedure (please see section 6.1 for further details). In a large prospective single centre cohort study on the natural history of 1 107 IC patients (71 years mean age, 71% men) initially receiving medical management, the incidence of progression to CLTI was only 1.1% per five years, and the

major amputation rate was 0.2% per five years.<sup>16</sup> Limb prognosis following conservative treatment thus remains benign for the majority of IC patients. Subsequent re-interventions following both endovascular and open surgical revascularisation procedures for IC are common.<sup>17</sup> Observational studies also indicate that an early revascularisation procedure following an IC diagnosis places the patient at greater risk of subsequent re-interventions, the development of CLTI, and even limb loss, although the latter risk is very low in contemporary series of IC patients carefully selected for revascularisation.<sup>16,18–21</sup> Therefore, all revascularisation decisions in IC should be individualised, and involve the patient in a shared decision making process. Ideally, shared decision making implies that individuals are supported to make decisions that are right for them through a collaborative process where the clinician supports the patient to reach a decision about their treatment by bringing together the clinician's expertise on available treatment options, evidence, risks, and benefits with the patient's preferences, personal circumstances, goals, values, and beliefs.<sup>22</sup>

The expected procedural benefits on daily living activities and health related quality of life should be weighed against the potential procedure related risks and expected long term patency.<sup>23</sup> In general, revascularisation in IC should be undertaken in well informed, carefully selected, active patients with pronounced lifestyle limiting symptoms unresponsive to conservative therapies. Before considering any intervention, it is vital to ensure that the patient has followed all evidence based recommendations after comprehensive lifestyle advice. Such a stepwise care approach limits the numbers at risk of suffering complications or suboptimal patency rates after revascularisation procedures and should play a key role in comprehensive IC management algorithms. Although the degree of functional impairment correlates with both anatomic extent of disease and haemodynamic measures (i.e., ankle brachial index [ABI]),<sup>24–27</sup> such measures in isolation should not form the grounds for revascularisation decisions. The decision should instead mainly be based on the patient's perceived functional impairment or disability during everyday activities and on health related quality of life issues such as severe limitations to work and or participate in recreational and social activities. The patient's attitude towards necessary lifestyle changes, willingness to implement such changes and to participate in prescribed post-procedural follow up and monitoring should also be considered to optimise the long term treatment results of revascularisation. Finally, the anatomic extent of the affected vessel segment(s) should be brought into the decision, as overall treatment efficacy ranges from the favourable efficacy, safety and durability of aortoiliac interventions over, at best, reasonable primary

patency rates for contemporary femoropopliteal interventions, to substantially poorer results when isolated infrapopliteal lesions are treated for IC indications.<sup>28–32</sup>

Recommendation 1			
For patients with intermittent claudication, it is recommended that all revascularisation decisions are individualised and involve the patient in a shared decision making process that considers available non-invasive therapies, expected treatment benefit, procedure related risk, and long term patency.			
Class	Level	References	ToE
I	C	Golledge <i>et al.</i> (2018) <sup>18</sup> Kumakura <i>et al.</i> (2017) <sup>16</sup> Djerf <i>et al.</i> (2020) <sup>19</sup>	

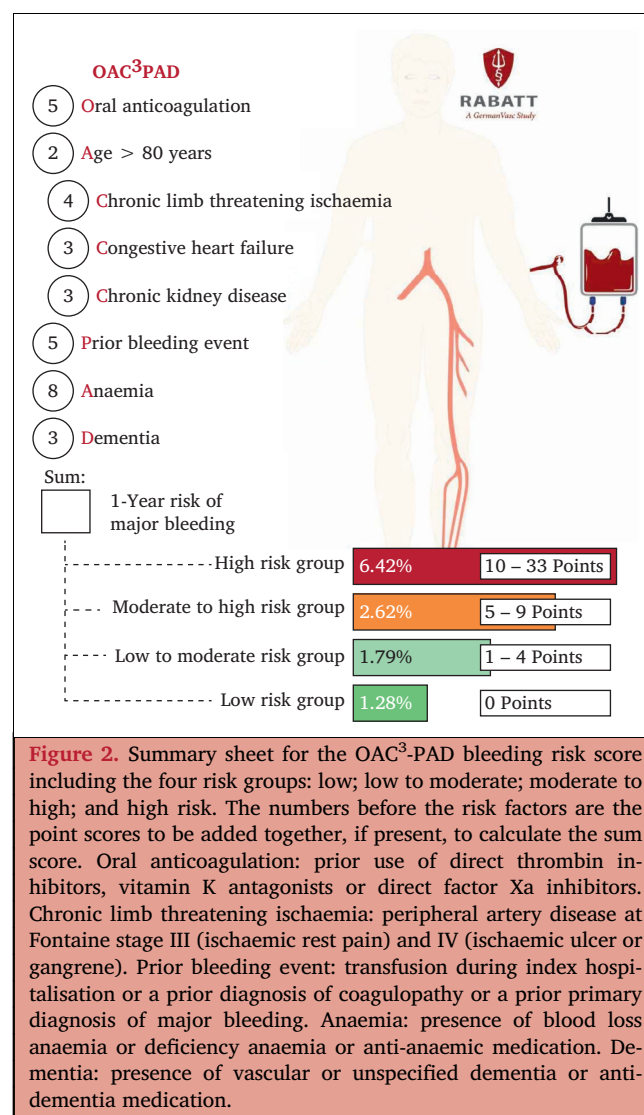
**1.3.2. Benefits and risks with medical therapies in peripheral arterial disease.** As for revascularisation procedures in lower limb PAD (section 1.3.1 above), a careful assessment of the risk–benefit balance of common medical therapies is important in lower limb PAD management algorithms. The purpose of this section is accordingly to briefly provide the reader with some useful information on some important aspects to consider when initiating or modifying such medical treatments in the specific context of lower limb PAD. More details on risk factor management and medical treatment of PAD are provided later in the guideline document (see Chapter 4).

Two main drug classes commonly indicated in PAD, and often instituted both in primary care and by vascular specialists, are antithrombotic and lipid lowering drugs. High intensity treatment with statins (with or without ezetimibe) may also impact positively on intermittent claudication distance, and perhaps also on maximum walking distance, in patients with IC.<sup>33–35</sup> Substantial evidence demonstrates that both these drug classes reduce subsequent major adverse cardiovascular event (MACE) and major limb event (MALE) rates in PAD patients; and antithrombotic drugs are also indispensable drugs that mitigate atherothrombotic complications and enhance patency during and after lower limb revascularisation procedures.<sup>35–37</sup>

As all antithrombotic therapies also increase the risk of bleeding, the potential harm caused by bleeding side effects must also be considered. With the pragmatic OAC<sup>3</sup>-PAD bleeding score that was recently developed on German health insurance claims data covering nationwide inpatient treatment for symptomatic PAD, the following major bleeding risk predictors were identified and included in the model: previous oral anticoagulation, age above 80 years, chronic limb threatening ischaemia, congestive heart failure, severe chronic kidney disease, prior bleeding event, anaemia, and dementia. The one year risk of major bleeding

events requiring hospital re-admission varied between 1.3% in the low risk group and 6.4% in high risk patients, while overall approximately 20% of patients undergoing intervention were included in the high risk group (Fig. 2) (online calculator available at <https://score.germanvasc.de>).<sup>38</sup> It must be stressed, however, that the score has not yet been fully externally validated (nor has any other risk score for this specific target population). While further and larger validation studies are clearly warranted, the first attempts at external validation studies demonstrated adequate model discrimination.<sup>39,40</sup>

Thus, the ischaemic risk and events prevented must be important enough for a patient to accept the associated bleeding risks with antithrombotic therapies. The ischaemic risk profile will differ across the different PAD stages which is why the initiation of antithrombotic therapies should be tailored for each individual patient



and be discussed as part of shared decision making. For example, current evidence does not support the use of antithrombotic drugs in asymptomatic PAD patients without other contemporary indications for such therapies, whereas certain high risk PAD patient phenotypes entail a very high absolute risk of suffering ischaemic MACE and or MALE complications and therefore clearly benefit from intense antithrombotic treatment(s). When initiating antithrombotic therapies, modifiable risk factors for bleeding under such therapies should be assessed and corrected to prevent unnecessary bleeding complications.<sup>41</sup>

### Recommendation 2

**For all patients with lower limb peripheral arterial disease, an evaluation of individual benefit and bleeding risk with suitable prediction scores is recommended as part of shared decision making before initiation of antithrombotic therapy or modification of an ongoing well tolerated antithrombotic treatment regimen to keep bleeding complications at a minimum.**

Class	Level	Reference
I	C	Consensus

In randomised trials of statin therapy, patients up to the age of 80 – 85 have participated. Subgroup analyses show comparable relative risk reduction in elderly patients and thus a higher absolute risk reduction.<sup>42</sup> Elderly people (i.e., > 80 years) with PAD should therefore be offered secondary preventive treatment with statins using the same indications (and contraindications) that apply to younger people. However, the increased risk of side effects in the elderly should also be considered, for example in polypharmacy with a risk of drug to drug interactions and drug accumulation, and in elderly patients with increased susceptibility to side effects due to impaired organ function.

Several studies also suggest that statin therapy may have a detrimental effect on haemoglobin A1c levels in patients with diabetes, and may promote earlier onset of type 2 diabetes mellitus, although this risk is commonly stated as acceptable given the large cardiovascular (CV) preventive effect of statin therapy.<sup>43,44</sup>

Reported side effects of statins include elevation of transaminases and statin associated muscle symptoms. Severe hepatic dysfunction is rare. In recent meta-analyses of randomised trials, no significant increase in myalgia was demonstrated,<sup>45–47</sup> whereas a higher frequency of statin associated muscle symptoms has been reported under statin treatment in observational studies.<sup>48</sup> In a large contemporary meta-analysis encompassing 176 randomised and non-randomised studies that included a total of more than four million patients, statin intolerance was low overall (9.1%, 95% CI 8.0 – 10%), and the prevalence of statin intolerance was substantially higher in non-randomised

studies (4.9% [95% CI 4.0–6.0%] in the RCTs vs. 17% [95% CI 14 – 19%] in the non-randomised studies).<sup>49</sup> This was further confirmed by a more recent meta-analysis of 19 RCTs, which concluded that statin therapy caused a small excess of muscle pain, most frequently mild (absolute excess rate was 11 [6 – 16] events per 1 000 person years).<sup>50</sup> This discrepancy may be due to a selection of healthier patients in RCTs but may also be explained by placebo effects in non-blinded studies as well as recall and other bias in observational studies.<sup>51</sup> In patients who had discontinued statin therapy because of side effects in the Self-Assessment Method for Statin side effects Or Nocebo (SAMSON) trial, 90% of the symptom burden elicited by a statin challenge was also elicited by placebo and half the patients were able to successfully restart therapy.<sup>52</sup> A recent population based cohort study in France also indicated that statin discontinuation was associated with a 33% increased risk of admission with a cardiovascular event in 75 year old primary prevention patients.<sup>53</sup> Muscle symptoms occur mainly during interaction with other drugs, in the elderly, at low body weight and in patients with impaired liver or kidney function. Such symptoms can often be managed by dose reduction or switching to another statin. For obvious or prolonged muscle symptoms, the rare but potentially life threatening side effect of myositis with rhabdomyolysis, resulting in approximately 0.15 deaths per 1 million prescriptions,<sup>54</sup> should be suspected and evaluated. Although scarcely studied in specific PAD contexts, newer lipid lowering drugs such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be reasonable alternatives in patients who are adherent to drug prescriptions and who prove intolerant to statins with or without ezetimibe, or who fail to reach an adequate low density lipoprotein (LDL) target.<sup>55</sup> For further information on treatment of dyslipidaemia in lower limb PAD please refer to [Chapter 4, section 4.1.2.2](#).

## 2. PERIPHERAL ARTERIAL DISEASE EPIDEMIOLOGY AND RISK FACTORS

### 2.1. Definition, causes, and clinical classification

Peripheral arterial disease leading to stenosis or occlusion of arteries supplying the lower limbs is caused by atherosclerosis in approximately 95% of cases. The remaining 5% is mainly caused by vasculitis, hereditary conditions, undiagnosed past embolism or local thrombosis, lower limb aneurysms, trauma, popliteal entrapment, or cystic adventitial disease; conditions not covered by these guidelines.<sup>56–58</sup> Lower extremity PAD can be defined as obstructive atherosclerotic disease of the arteries from the distal aorta to the foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular testing or medical imaging, resulting in disturbed or impaired circulation to one or both lower extremities. The diagnosis of lower limb PAD is commonly established by an ABI measurement that falls

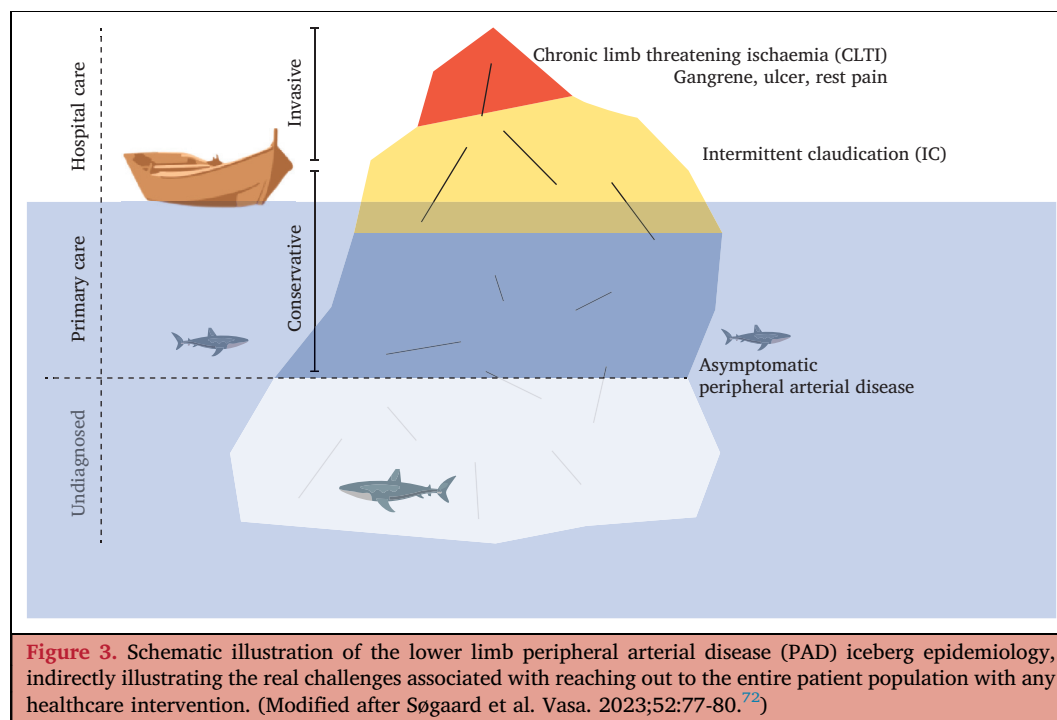
outside the normal range (0.91 – 1.39), which confirms the presence of lower limb stenosis or occlusion, and at the same time identifies subjects at high risk of future CV events.<sup>59–62</sup> Numerous PAD classification systems have been developed for different purposes, based on symptomatology, anatomic disease distribution, or a combination of clinical factors. A definition guided by the clinical presentation is most often used in treatment algorithms and guidelines (see section 3.1.6.6), where asymptomatic PAD and IC are discriminated by the absence (asymptomatic PAD) or presence (IC) of exercise induced lower limb symptoms deemed to be of ischaemic origin based on history, clinical presentation, and a thorough clinical vascular examination (see Chapter 3).

## 2.2. Epidemiology

**2.2.1. Prevalence and incidence of asymptomatic lower limb peripheral arterial disease.** Assessment and comparison of epidemiological data among asymptomatic PAD cohorts is challenging (Fig. 3). First, the PAD diagnosis entails many methodological issues as it depends on an accurate ABI measurement and calculation method.<sup>63</sup> Second, different epidemiological datasets are seldom comparable because of, for example, varying study design and heterogeneity in terms of age, study populations, gender distribution, and ethnicity. Third, few studies have clearly specified PAD stage and fully targeted the asymptomatic stage. However, the Global Peripheral Artery Disease Study estimated a prevalence of 237 million PAD cases worldwide in 2015, which is a relative increase of 17% compared with 2010.<sup>64</sup> The prevalence is booming in low and middle income

countries (22.6% relative increase, vs. 4.5% in high income countries), which may also be related to tobacco use epidemiology, the widespread use of screening, demographic changes, and increased access to healthcare provided for patients with cardiovascular disease.<sup>64–66</sup> The US PAD Awareness, Risk and Treatment Survival Program included approximately 7 000 patients aged 50 – 69 years with a history of cigarette smoking or diabetes in primary care. New asymptomatic PAD cases were identified in 45%.<sup>67</sup> In a general population, among 5 980 persons between the ages of 50 and 90 years, 18% had PAD as defined by an ABI < 0.9, and 62% were asymptomatic.<sup>68</sup> The PANDORA study enrolled 9 816 patients at non-high CV risk from Italy, Belgium, France, the Netherlands, Greece, and Switzerland. Among these subjects, the prevalence of asymptomatic PAD was 17.8% at a mean age of 64.3 years.<sup>69,70</sup> In the Edinburgh Artery Study (1 592 community dwelling men and women aged 55 – 74 who underwent an ABI measurement), 9% had an ABI < 0.90, consistent with PAD; however, only 15% of those had classical symptoms of IC and 84% of those reported no exertional leg symptoms.<sup>71</sup> In the PARTNERS study (6 979 men and women in primary care practices across the United States who were screened for PAD with the ABI), 29% had an ABI < 0.90 consistent with PAD. Of those who were newly diagnosed with PAD, 48% remained asymptomatic.<sup>67</sup>

The method for ABI measurement and calculation may also impact on the observed prevalence. In a cohort of volunteers from a general population, in the Arteriomobil Project, the prevalence of PAD varied from 8% to 16% depending on whether the ABI value was based on the



highest or lowest recorded ankle blood pressure.<sup>73</sup> An even larger variation was observed in the Multi-Ethnic Study of Atherosclerosis. Among 6 590 subjects aged 45 – 84 years and free of apparent clinical cardiovascular disease, the PAD prevalence was 4.0 times higher in women and 2.7 times higher in men when the lowest ankle pressure was used for the ABI measurement compared with the highest ankle pressure.<sup>74</sup>

Previous studies on PAD incidence have shown considerably varying incidence rates (3.8 to 23.0 per 1 000 person years).<sup>75,76</sup> In a prospective epidemiological trial on Ankle Brachial Index (getABI), the observed incidence varied from 25.0 to 41.2 per 1 000 person years depending on the method being used to define asymptomatic PAD.<sup>77</sup> In a trend analysis of longitudinally linked health insurance claims data from Germany, a slight decrease in the annual hospital incidence of new PAD diagnoses was observed while the annual prevalence and number of hospitalisations increased rapidly by approximately 25% during recent years.<sup>78</sup> Most recently, the epidemiological Hamburg City Health Study (HCHS) included a contemporary sample of 10 000 participants from the general population between 2016 and 2018. The prevalence of lower extremity PAD using an ABI definition at  $\leq 0.9$  was 24%, and increasing age, female sex, current smoking, dyslipidaemia, diabetes, coronary artery disease, and congestive heart failure were associated with PAD.<sup>79</sup>

These discrepant epidemiological observations on incidence and prevalence of PAD impact on public health, clinical practice, and scientific reports. This emphasises the importance of using a global standard PAD definition, including the measurement and calculation of ABI (see chapter 3.1.3.1).

**2.2.2. Prevalence and incidence of intermittent claudication.** The prevalence and incidence of symptomatic PAD among global populations has often been estimated using hospitalised cohorts with remarkably heterogeneous study design. While the ABI with commonly accepted thresholds can be used to validly identify PAD even among asymptomatic people, additional selection criteria (e.g., any self reported history of exercise induced intermittent claudication or imaging data) exist for symptomatic patients. Previous studies have used different questionnaires that were developed and recommended to identify IC under both clinical and research settings with certain methodological limitations interacting with prevalence and incidence estimation.<sup>80–82</sup> Due to the apparent evolution of definitions and methods over time, direct comparisons of historical and more recent studies seem challenging.

In an updated systematic review, approximately 237 million people aged 25 years and older were affected by PAD in 2015 while the estimated prevalence was 202 million in 2010. To improve the specificity and avoid invalid estimates, the authors decided to primarily select studies that used common ABI thresholds instead of self reported symptoms.<sup>64,65</sup> It has been shown in numerous studies that asymptomatic PAD is more prevalent than symptomatic PAD.

The Edinburgh Artery Study used a cross sectional survey of an age stratified sample of men and women aged 55 – 74 years. In total, 1 592 participants were interviewed between 1987 and 1988 using the WHO questionnaire on IC along with an ABI measurement. The prevalence of IC was 4.5% and equally common in both sexes.<sup>71</sup> The Nord-Trøndelag Health Survey (HUNT study), which invited all residents aged 20 years and older between 1995 and 1997 for screening, investigated the prevalence of IC in a sub-population of almost 20 000 individuals between 40 and 69 years. The age adjusted prevalence was 1.1% for men and 1.2% for women in this high income population.<sup>83</sup> In the multicentre German Epidemiological Trial on Ankle Brachial Index (getABI study), 6 880 primary care patients who were aged 65 years and older were enrolled by 344 general practitioners. IC as assessed by the WHO questionnaire was reported by 3.6% of men and 2.3% of women, while the sensitivity of the questionnaire was only 11% (99% specificity).<sup>84</sup> A more recent study included 5 080 subjects from an age standardised randomly selected population between 60 and 90 years in Sweden. Using a questionnaire and ABI measurement, the prevalence of IC was 7%.<sup>68</sup> In contrast, in a cross sectional survey based study from India, the prevalence of IC in a low income population was 0.7%, while the authors discussed that another study from a comparable region revealed a higher prevalence of IC when additionally using ABI measurement (3.2%).<sup>85</sup> There are many methodological limitations that are likely to have adversely affected prevalence estimations and ultimately led to heterogeneous conclusions.

### 2.3. Natural history of asymptomatic lower limb peripheral arterial disease and intermittent claudication

The pathophysiology of asymptomatic PAD mimics that of established symptomatic PAD, and thus the risk factors leading to its development are also likely to be similar. Indeed, it is considered that asymptomatic disease is merely an early stage in the continuum of this chronic complex disease, which in a relatively low proportion of cases may progress and later manifest with symptoms of IC and CLTI. Progression of the atherosclerotic lesions in asymptomatic PAD has been documented, with a variable progression to symptomatic PAD ranging from an estimated 5% progressing to symptoms over five years to 21% becoming symptomatic at one year.<sup>86–88</sup> There are also important regional differences in disease progress patterns between Western countries and other regions of the world such as China and India, which may in part be attributable to lower public awareness and poorer risk factor control in older ages in those areas.<sup>85,89</sup>

Transition rates from asymptomatic PAD to symptomatic PAD were further addressed in the Limburg PAOD Study (1988), where 9% of asymptomatic PAD subjects developed IC during the seven years of follow up.<sup>90,91</sup> Similar results were found in the Edinburgh Artery Study; 9.5% deteriorated within five years.<sup>92</sup> Mohler *et al.* prospectively followed a small sample of asymptomatic PAD patients over one year

with ABI, ultrasound, and the San Diego Claudication Questionnaire. Of the 44 included patients, 33 were eligible for follow up, and 21% developed IC within one year.<sup>88</sup>

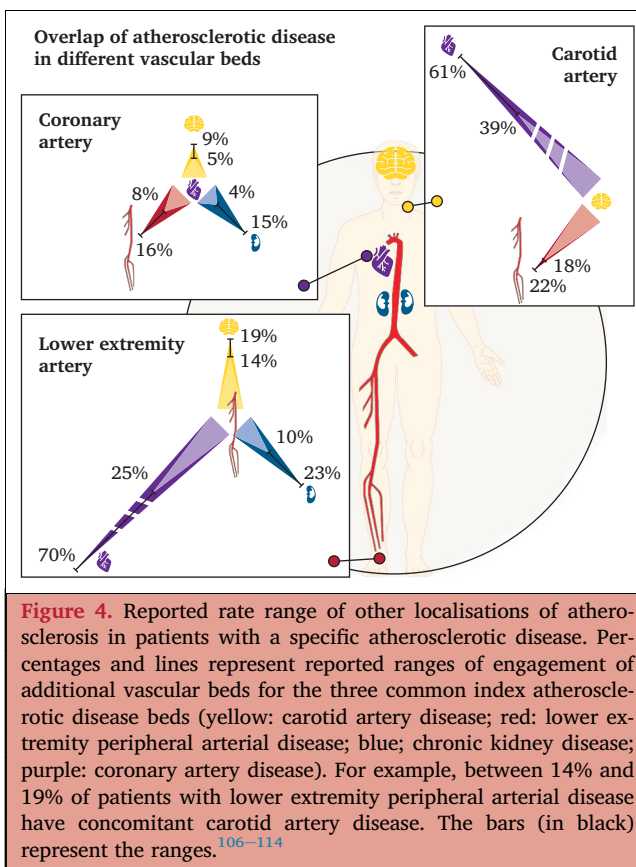
Beyond lower limb disease deterioration and functional decline, individuals with asymptomatic PAD are at heightened risk of CV events. The Ankle Brachial Index Collaboration investigated 16 population based cohorts in 2008 and revealed that the 10 year cardiovascular mortality in men with a low ankle brachial index ( $\leq 0.90$ ) was 18.7% (95% CI 13.3 – 24.1%), whereas it was 4.4% (95% CI 3.2 – 5.7%) in men with normal ankle brachial index (1.11 – 1.40), hazard ratio (HR) 4.2 (95% CI 3.5 – 5.4). Corresponding CV mortalities in women were 12.6% (95% CI 6.2 – 19.0%) and 4.1% (95% CI 2.2 – 6.1%), HR 3.5 (95% CI 2.4 – 5.1).<sup>93</sup> Thus, the long term CV outcomes for PAD patients remain poor. Mortality rates for asymptomatic PAD are similar to IC and have remained unchanged during the last three decades.<sup>94–96</sup>

Robust data on IC natural history are also limited. In a large but now somewhat outdated prospective natural history study that followed an IC patient cohort from 1983 to 1998 (with a mean follow up of 45 months and statistically valid follow up to 12 years), the average yearly ABI drop was 0.014 and the mean self reported walking distance was reduced by 8.4 metres per year. The cumulative 10 year risks of developing ischaemic rest pain and ischaemic ulcers were 30% and 23%, respectively, and concurrent diabetes and ABI reduction were independent predictors of the development of CLTI.<sup>97</sup> In a more recent prospective cohort study on the natural history of 1 107 IC patients initially receiving medical management, the incidence of progression to CLTI was only 1.1% per five years, and the major amputation rate was 0.2% per five years. Diabetes and haemodialysis were clear independent predictors of progression to CLTI in the multivariable analysis, whereas a history of cerebral infarction ( $p = .059$ ) and femoropopliteal revascularisation ( $p = .068$ ) also tended to increase the risk of progression to CLTI.<sup>16</sup>

Despite the fear of developing cardiac disease in the general population, in fact the mortality rate in patients with PAD is much higher. Various recent studies put this at between 13% and 50% for death at five years,<sup>94,98,99</sup> while the mortality rate for post myocardial infarction patients was 13% at six years.<sup>100</sup> While mortality from heart disease has fallen over the past two decades, this is not the case with PAD<sup>101</sup> for a number of reasons, including late presentation with higher atheroma burden, underdiagnosis, and undertreatment.<sup>94,101–104</sup>

#### 2.4. Peripheral arterial disease in the context of other cardiovascular diseases

Among 3.6 million individuals volunteering for systematic ultrasound screening for PAD, carotid artery stenosis, and abdominal aortic aneurysm, the proportion of subjects with two or more vascular beds affected by atherosclerosis increased with age, from 0.04% at 40 – 50 years to 3.6% at 81 – 90 years.<sup>105</sup> Figure 4 summarises the co-prevalence of coronary artery disease (CAD), carotid stenosis, and lower limb PAD when atherosclerotic disease is diagnosed in one territory.



**2.4.1. Coronary artery disease.** PAD overlaps with CAD (Fig. 4). It is often asymptomatic or masked by angina and or dyspnoea limiting mobility. PAD (ABI  $< 0.90$ ) is present in 8 – 16% of patients who have signs of CAD on coronary angiography.<sup>115–117</sup> Patients with PAD exhibit more extensive, calcified, and progressive coronary atherosclerosis.<sup>118</sup> The coexistence of PAD in CAD patients has been consistently associated with a worse outcome, although it remains unclear whether PAD is a marker or a cause of cardiac adverse events.<sup>119,120</sup> An individual patient meta-analysis of four trials examined the relationship between PAD and cardiovascular (CV) outcomes in subjects with left ventricular systolic dysfunction, heart failure, or both after myocardial infarction (MI).<sup>121</sup> PAD was an independent predictor of all individual and composite CV outcomes; the adjusted HR for all cause mortality was 1.25 (95% CI 1.15 – 1.37;  $p < .001$ ) and the HR for the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure was 1.24 (1.16 – 1.33;  $p < .001$ ). In registries focusing on acute coronary syndrome, in hospital death, acute heart failure, and recurrent ischaemia rates were substantially higher (up to five fold) in subjects with concurrent PAD. In a pooled analysis of 19 867 patients enrolled in RCTs on percutaneous coronary intervention (PCI), 8% had clinical PAD which was identified as an independent predictor of death at 30 days (HR 1.67), six months (HR 1.76), and one year (HR 1.46).<sup>117</sup> Concomitant PAD (clinical or subclinical) is also associated with a worse outcome in patients undergoing coronary revascularisation.<sup>122,123</sup>



Screening for PAD by means of ABI measurement might represent a non-invasive and inexpensive method for prognostic stratification of CAD patients. Despite these data, the AMERICA trial failed to demonstrate the benefit of a proactive strategy of polyvascular disease screening in patients.<sup>124</sup> However, the trial was small with some limitations and therefore does not entirely rule out a role for screening for asymptomatic PAD in CAD patients for prognostic stratification. Importantly, in patients with severe CAD, the presence of symptomatic or asymptomatic PAD is also associated with a high probability (almost 20%) of carotid stenosis.<sup>125</sup>

**2.4.2. Atrial fibrillation.** A significant increase in the risk of a stroke or thromboembolism in patients with concomitant atrial fibrillation (AF) and PAD has been observed when compared with patients with AF without PAD.<sup>126,127</sup> The largest isolated cohort of PAD patients ( $n = 7\,716$ ) was studied in the REACH registry, and in this analysis the combined endpoint of CV death, MI, and stroke was also higher in PAD subjects with AF compared with those without AF (27.1% vs. 21.4%,  $p = .010$ ).<sup>127</sup> In a nationwide cohort study by Olesen *et al.*, the concomitant presence of PAD increased the hazard of suffering stroke or thromboembolism (HR 1.93, 95% CI 1.70 – 2.19) in patients with AF.<sup>128</sup> Atherosclerotic vascular disease in the lower limbs is thus a predictor of a stroke, thromboembolism, and death in subjects with AF.

**2.4.3. Carotid artery disease.** Carotid artery stenosis is frequent in patients with PAD (Fig. 4),<sup>108,129</sup> but there is no evidence that the presence of carotid artery stenosis influences lower limb outcomes, or any evidence to support screening for PAD among patients with carotid artery stenosis.

**2.4.4. Renal artery disease.** Renal artery disease is frequently discovered incidentally during imaging for PAD. Opinions on whether atherosclerotic renal artery disease could be a marker of a worse CV prognosis in PAD patients are conflicting.<sup>107,130</sup> The only report looking at limb outcome found no prognostic alteration in the presence of concomitant renal artery disease. Moreover, the therapeutic value of renal artery stenting for atherosclerotic lesions is questionable.<sup>107,131,132</sup>

**2.4.5. Chronic kidney disease.** Mild to moderate chronic kidney disease confers an increased risk of incident PAD. In a collaborative meta-analysis of individual participant data for > 800 000 individuals, chronic kidney disease measures were independently associated with the incidence of PAD. Compared with an eGFR of 95 mL/min per 1.73m<sup>2</sup>, adjusted HRs for incident study specific PAD were 1.22 (95% CI 1.14 – 1.30) at an eGFR of 45 mL/min per 1.73m<sup>2</sup> and 2.06 (95% CI 1.70 – 2.48) at an eGFR of 15 mL/min per 1.73m<sup>2</sup>. Both eGFR and urine albumin to creatinine ratio improved PAD risk discrimination beyond traditional predictors. Clinical attention should thus be paid to the development of PAD symptoms and signs in people with any stage of chronic kidney disease, as establishing the PAD diagnosis in this high risk population could lead to improved medical management that may in turn impact on long term prognosis.<sup>133</sup>

### 3. DIAGNOSIS, CLASSIFICATION, AND SCREENING IN PERIPHERAL ARTERIAL DISEASE

#### 3.1. Diagnostic approach

##### 3.1.1. Clinical manifestations of peripheral arterial disease.

The clinical presentation of lower limb PAD varies widely. Most subjects will have asymptomatic disease without leg symptoms while the most common symptomatic presentation is exercise induced pain in the lower extremities relieved by rest (IC). However, exercise induced ischaemic leg pain may be masked by several other factors and conditions that can lead to underdiagnosis. Some examples are lack of physical activity, sedentary lifestyle, peripheral neuropathy, constraining comorbidity, or misinterpretation of atypical symptoms.<sup>82,134–136</sup> The diagnosis of PAD should focus on the past medical history including an accurate assessment of the patient's walking ability.<sup>81</sup> The classic leg symptom of PAD, IC, was originally described and characterised for the purposes of epidemiological study by Dr Geoffrey Rose, a London epidemiologist: exertional calf pain that does not begin at rest, does not resolve during walking activity, and resolves within 10 minutes of rest.<sup>81</sup> The extent of impairment of blood flow depends on flow velocity, degree and extent of stenosis or occlusion, number of occlusive lesions, and development of collaterals, and reflects the severity of IC.<sup>137,138</sup> Patients may also suffer more proximal pain, located in the thigh, hip, and or buttock areas, or (less commonly) foot pain. However, community based studies suggest that many patients do not present with such typical symptoms for the disease.<sup>67,139</sup> In one study of patients with an ABI < 0.9, 19% were asymptomatic, 49% had atypical symptoms, and 32% had typical IC symptoms.<sup>139</sup> Atypical symptoms included leg pain that was unrelated to walking, or present at rest but still not typical of ischaemic rest pain. Other atypical symptoms include weakness and numbness of the leg, paraesthesia, and feeling of cold, all more common in patients with diabetes. Important aspects of the medical history also include cardiovascular risk factors such as smoking, hypertension, dyslipidaemia, and diabetes.<sup>140,141</sup>

**3.1.1.1. Asymptomatic peripheral arterial disease.** Thus, many PAD patients may not demonstrate ischaemic exertional leg symptoms. Physically inactive patients with significant arterial lesions may not develop leg symptoms until there is a demand for increased blood flow to leg muscles. Patients with severe congestive heart failure, angina, chronic obstructive pulmonary disease, and musculoskeletal disease may not reach the walking distance threshold that provokes symptoms.<sup>142</sup> Altered pain perception, as observed in patients with diabetes and peripheral neuropathy, may also mask the symptoms of PAD. Additionally, some PAD patients limit their walking activity during daily life to avoid leg symptoms. Thus, patients who do not report any exertional leg symptoms may develop leg pain during an objective assessment, such as during a six minute walk test.<sup>143</sup> Another potential explanation for lack of symptoms in asymptomatic PAD is that some patients may decrease their walking speed to avoid exertional leg symptoms.<sup>144</sup>

People with asymptomatic PAD also have greater functional impairment and faster functional decline than people without PAD.<sup>145,146</sup> Although the aetiology of functional limitations has not been fully assessed, pathophysiological skeletal muscle and peripheral nerve changes, including reduced calf muscle mass, increased calf muscle fat content, and reduced lower extremity peripheral nerve function have been identified in PAD patients without exertional leg symptoms.<sup>143,144</sup>

**3.1.1.2. Screening for asymptomatic peripheral arterial disease.** The purpose of screening for PAD, either in the general population or focused on high risk populations, is mainly the early detection and secondary prevention of this complex chronic condition before any disease related symptoms or adverse events occur. Early health intervention and risk factor modification may slow the progression of atherosclerosis and functional decline. As PAD is also considered to be an important manifestation of systemic atherosclerosis, screening for PAD in asymptomatic individuals may allow for earlier CV risk factor interventions in individuals with manifest but undiagnosed atherosclerosis. Therefore, the cost effectiveness and efficacy of screening should be evaluated by weighing the estimated benefits (e.g., prevention of CV events) against possible harms (e.g., avoidable adverse events related to the complementary treatment of PAD).

In the last Cochrane review no RCTs were identified that met the inclusion criteria for providing direct evidence of the effectiveness of screening for PAD in asymptomatic and undiagnosed individuals in terms of reduction of all cause mortality, MACE, lower limb morbidity (incident IC, amputation, reduced walking distance), and improvement in health related quality of life.<sup>147</sup> As the recommendation of screening for PAD with ABI, or any other test, in asymptomatic individuals remains controversial, some investigators have considered pre-screening tests such as PREVALENT or REASON. PREVALENT is a clinical prediction model that includes an asymptomatic population older than 54 years with at least one risk factor such as smoking, hypertension, diabetes, or dyslipidaemia, but this model has not been validated.<sup>148</sup> REASON is a risk score (including BMI, CAD, dyslipidaemia, diabetes mellitus, arterial hypertension, and smoking), identifying candidates to screen for PAD using the ABI in a population which is 50 – 79 years old with a better predictive capacity than that of intersociety consensus criteria.<sup>149</sup>

In 2018, a systematic review of evidence from the US Preventive Services Task Force was undertaken on PAD screening with the ABI, the diagnostic accuracy of the test, and the benefits and harms of treatment of screening detected PAD.<sup>150</sup> The current evidence base for screening for PAD is limited, with no direct evidence examining the effectiveness of ABI screening alone. No population based randomised trials of ABI screening alone were identified. Three multicomponent screening trials, of which two in Denmark (the VIVA trial, NCT00662480 and the DANCAVAS trial, ISRCTN12157806) and one in Spain (The ILERVAS Project, NCT03228459), included PAD screening with ABI as part of a comprehensive vascular screening programme.

However, none of these trials tested the independent effectiveness of ABI screening in certain populations.

In the VIVA trial, undertaken between 2008 and 2011, 50 156 men aged 65 – 74 in Denmark were randomly allocated 1:1 to cardiovascular screening (ultrasound of the abdominal aorta, ABI measurements, and laboratory analysis of total cholesterol concentration) or to a non-screening group. After a median follow up of 4.4 (IQR 3.9, 4.8) years, they observed a reduced overall mortality risk from abdominal aortic aneurysm, PAD, and hypertension (HR 0.93, 95% CI 0.88 – 0.98), with a number needed to invite of 169, which had never been seen before in the population screening literature and could primarily be linked to the initiation of pharmacological risk reducing therapy.<sup>151</sup> In the same trial it was also concluded that vascular screening (ultrasound, ABI, and total cholesterol concentration) appeared to be cost effective and compared favourably with current screening programmes.<sup>152</sup> The cost of screening was estimated at €148 (95% CI 126 – 169), and the effectiveness at 0.022 (95% CI 0.006 – 0.038) life years and 0.069 (95% CI 0.054 – 0.083) QALYs, resulting in average costs of €6 872 per life year and €2 148 per QALY. The probability of cost effectiveness was 71% when all the sensitivity analyses were combined into one conservative scenario. The DANCAVAS trial randomly allocated > 46 000 men in a 1:2 ratio to either comprehensive cardiovascular screening or control. Screening included non-contrast electrocardiography gated computed tomography, ABI measurements, and a blood sample to detect diabetes mellitus and hypercholesterolaemia. The primary outcome was all cause mortality. After approximately five years of follow up, 2 106 men (12.6%) in the invited group and 3 915 men (13.1%) in the control group had died (HR 0.95; 95% CI 0.90 – 1.00;  $p = .060$ ).<sup>153</sup> It should be noted, however, that neither the VIVA trial nor the DANCAVAS focused the screening intervention on individuals with presumed increased risk of PAD (beyond the selected age span of invited patients). The ILERVAS Project has not yet provided any outcomes on the role of PAD screening.

Screening for PAD fits most of the WHO criteria.<sup>154</sup> On current evidence, and generally consistent with current guidelines, a potential target population could include anyone aged 70 years or older and those aged 45 – 69 with at least one risk factor for PAD.<sup>154</sup> A recent systematic review of PAD screening identified several major guidelines.<sup>155–163</sup> The guidelines were evaluated with the Appraisal of Guidelines and Evaluation in Europe (AGREE) tool and scores varied from 33% to 81%. The ABI was considered the primary screening tool in all guidelines.<sup>155</sup>

The Society for Vascular Surgery recommended against routine screening for lower extremity PAD in the absence of risk factors, history, or signs or symptoms of PAD.<sup>164</sup> The American Heart Association and American College of Cardiology Foundation recommended against PAD screening in adults who are not at increased risk and do not have a history or physical examination findings suggestive of PAD, but stated that such screening is reasonable in patients at increased risk of PAD (defined as those 65 years or older;

those aged 50 – 64 years with risk factors for atherosclerosis, including diabetes, history of smoking, hyperlipidaemia, hypertension, or family history of PAD; those younger than 50 years with diabetes and one other risk factor for atherosclerosis; or those with known atherosclerotic disease in another vascular bed).<sup>165,166</sup> Focused ABI screening in such high risk populations holds clear potential to be effective given the expected much higher PAD prevalence than in the general population.

Recommendation 3			
For clinically asymptomatic individuals without increased cardiovascular risk, screening for lower limb peripheral arterial disease with ankle brachial index measurements is not recommended due to the lack of direct evidence for screening in the general population.			
Class	Level	References	ToE
III	B	Guirguis-Blake <i>et al.</i> (2018) <sup>150</sup> Alahdab <i>et al.</i> (2015) <sup>167</sup> Andras <i>et al.</i> (2014) <sup>147</sup> Lindholt <i>et al.</i> (2022) <sup>153</sup>	

Recommendation 4			
For clinically asymptomatic individuals at increased risk of lower limb peripheral arterial disease*, focused screening for peripheral arterial disease with ankle brachial index measurements based on the lowest recorded ankle pressure may be considered, to support secondary prevention strategies.			
Class	Level	References	ToE
IIb	B	Lindholt <i>et al.</i> (2017) <sup>151</sup> Shah <i>et al.</i> (2017) <sup>154</sup> Matsushita <i>et al.</i> (2017) <sup>145</sup> Sartipy <i>et al.</i> (2018) <sup>94</sup> Lindholt <i>et al.</i> (2022) <sup>153</sup>	

\* Individuals 65 years or older; individuals aged 50 – 64 years with risk factors for atherosclerosis (diabetes, history of smoking, hyperlipidaemia, hypertension, chronic kidney disease, or family history of PAD); individuals younger than 50 years old with diabetes and one other risk factor for atherosclerosis; or those with known atherosclerotic disease in another vascular bed.

**3.1.1.3. Intermittent claudication.** Claudication most commonly occurs in the calves but may also occur in the buttocks, hips, thighs, or feet depending on the level of the arterial disease (Table 4). IC may be unilateral or bilateral. Patients experience exercise induced symptoms when the metabolic demands exceed oxygen supply and symptoms are accordingly relieved at rest when the blood supply again meets lower limb muscle oxygen requirements.<sup>168–171</sup>

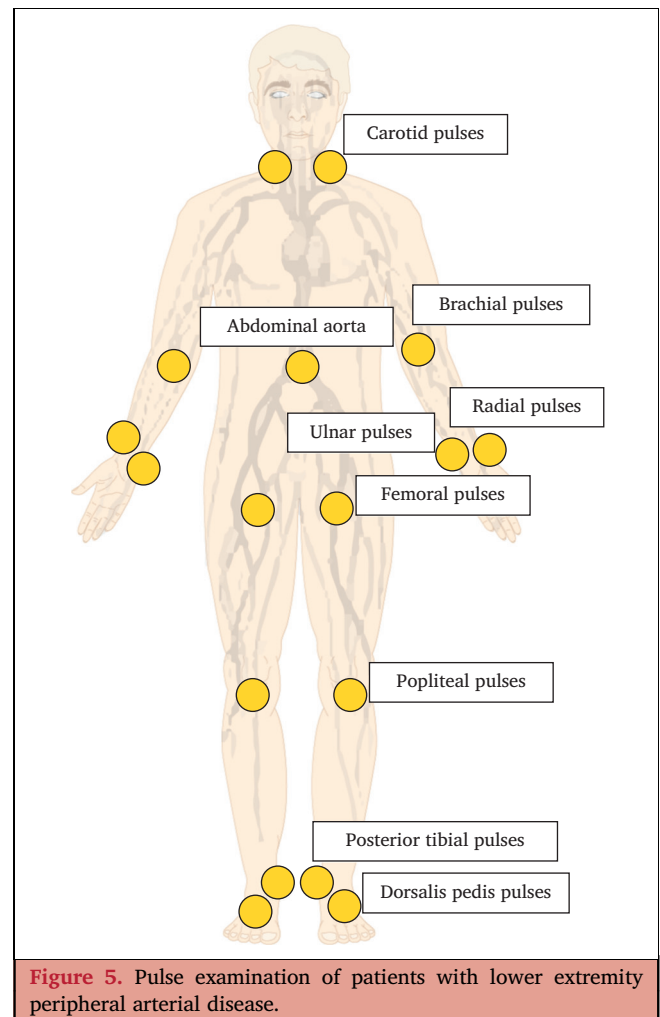
### 3.1.2. Vascular examination and differential diagnosis

**3.1.2.1. Pulse examination.** Every patient should be examined for the presence or absence of the femoral, popliteal, posterior tibial, and dorsalis pedis pulses bilaterally (Fig. 5) after the patient has been lying supine for a few minutes. Additionally, brachial pulses and the abdominal aorta should be also palpated. The femoral

**Table 4. Classical symptoms of intermittent claudication, modified from Rose.<sup>81</sup>**

<i>Exertional leg pain that:</i>
Does not begin at rest
Involves the calf, thigh and or buttock
Causes the patient to reduce their walking speed or stop walking
Resolves within 10 minutes of rest

artery is palpated just below the inguinal ligament, two finger breadths lateral to the symphysis pubis. The popliteal artery is palpated in the patient's popliteal area with the patient's knee slightly flexed and relaxed. The posterior tibial artery pulsation can be palpated below and behind the medial malleolus.<sup>172</sup> The location of the dorsalis pedis artery can be variable, but most commonly it is present halfway down the dorsum of the foot, just lateral to the extensor tendon of the first toe.<sup>173</sup> Any palpable pulse abnormality (absence or reduction) should raise a suspicion of PAD.<sup>174</sup> Pulses can also be affected by room temperature and the skill level of the examiner performing the examination in addition to being non-palpable due to congenital absence of the artery.<sup>173</sup> Palpation of foot pulses may also be particularly difficult in the presence of significant foot oedema.



**Figure 5. Pulse examination of patients with lower extremity peripheral arterial disease.**

**3.1.2.2. Adjunctive clinical signs.** Auscultation with a stethoscope (lower abdominal quadrants; groin) can identify arterial bruits that increase the likelihood of PAD (likelihood ratio 5.60; 95% CI 4.70 – 6.70).<sup>174–177</sup>

**3.1.2.3. The ankle brachial index.** The ABI is a commonly accepted reference standard for PAD diagnosis with high sensitivity and specificity and is further discussed in section 3.1.3.1.

**3.1.2.4. Claudication questionnaires to establish the peripheral arterial disease diagnosis.** A variety of questionnaires have been used to assist with establishing the PAD diagnosis in individuals with lower limb symptoms. Rose developed a claudication questionnaire<sup>81</sup> that was later adopted by the World Health Organisation (WHO) and is now known as the Rose or WHO/Rose Claudication Questionnaire. The Edinburgh Claudication Questionnaire was a modified version of the WHO/Rose Claudication Questionnaire.<sup>178</sup> The Edinburgh Claudication Questionnaire included a lower extremity diagram, which enabled individuals to indicate the location of the pain directly on the diagram.<sup>71</sup>

**3.1.2.5. Differential diagnosis.** There are several diseases that can produce lower limb pain and accordingly mimic PAD symptoms. Neurogenic claudication, also known as spinal claudication or pseudo-claudication, is common in patients with spinal stenosis.<sup>142,179</sup> Neurogenic claudication typically occurs with extension of the spine and is relieved with flexion of the spine and is associated with fatigue. The pain may also be relieved when sitting or lying supine. Chronic iliofemoral venous obstruction may also cause venous claudication with severe thigh pain and a sensation of tightness with vigorous exercise.<sup>180</sup> Osteoarthritis (of knees or hips) may cause lower extremity pain that occurs with exertion. However, the walking distance is variable from time to time and not as specific as claudication pain due to PAD. Neither spinal stenosis nor osteoarthritis pain are relieved as quickly with rest as vascular claudication. Other potential differential diagnoses are presented in Table 5.<sup>174,181</sup>

### 3.1.3. Diagnostic methods and medical imaging in peripheral arterial disease

**3.1.3.1. The ankle brachial index.** The ABI is a non-invasive diagnostic tool useful for diagnosis of PAD, for surveillance, for screening purposes in research studies, and may be used as a marker of the risk of atherosclerosis and of future CV events. The sensitivity and specificity for diagnosing PAD with ABI at rest is reported to be 69 – 89% and 69 – 99%, respectively,<sup>63,182,183</sup> with an acceptable intertester and intratester reliability on average of 10%.<sup>184</sup> The sensitivity and specificity increase if the pre-test likelihood is high. ABI measurements pre- and post-exercise may be considered to confirm the diagnosis in patients with suspected PAD. Compared with healthy subjects, ankle pressure will decrease more during exercise with a prolonged recovery time.<sup>63</sup> Further details are given in section 3.1.3.3. Arteries of the elderly, patients with diabetes or kidney disease may be severely calcified and less compressible leading to falsely high ABI values ( $\geq 1.4$ ).

Besides the aforementioned factors, lower limb oedema and wounds may lead to a poor sensitivity and therefore inconclusive results.<sup>185–191</sup>

An ABI  $\leq 0.9$  is a solid marker of atherosclerosis and CV risk, including in subjects without leg symptoms who face a two to three fold increased risk of all cause and CV death.<sup>95,192</sup> A similar association is shown for abnormally high ABI.<sup>193–195</sup> The individual predictive value of ABI for a CV event is limited but may be improved in combination with other risk scores, especially for women.<sup>93,196</sup>

Different cutoff values to diagnose PAD have been used, but an index  $\leq 0.9$  is the most common and consensual threshold and has been issued by available guidelines.<sup>6,56,165,179,197,198</sup> The mode of ABI calculation will greatly affect the estimation of PAD prevalence. When examining bilaterally, by using the lowest ankle pressure, the PAD prevalence will be higher and this will increase the sensitivity for identification of high risk patients but also lower the specificity and include cases with early disease.<sup>74,199–201</sup> More subjects at risk will be identified using the lower ankle blood pressure for ABI calculation and hence should be preferred for risk stratification.<sup>199,201–203</sup> Detailed recommendations for ABI measurement and interpretation are provided in Figure 6 and Table 6.

#### Recommendation 5

The ankle brachial index is recommended as the appropriate test to establish the diagnosis of lower limb peripheral arterial disease.

Class	Level	References	ToE
I	B	Aboyans <i>et al.</i> (2012) <sup>63</sup> Xu <i>et al.</i> (2013) <sup>60</sup> Donohue <i>et al.</i> (2020) <sup>204</sup> Weragoda <i>et al.</i> (2016) <sup>205</sup> Crawford <i>et al.</i> (2016) <sup>206</sup>	

#### Recommendation 6

It is recommended that an ankle brachial index cutoff value at  $\leq 0.9$  is used for lower limb peripheral arterial disease diagnosis, and that a value  $\geq 1.4$  be considered inconclusive.

Class	Level	References	ToE
I	C	Aboyans <i>et al.</i> (2012) <sup>63</sup> Weragoda <i>et al.</i> (2016) <sup>205</sup>	

#### Recommendation 7

When the ankle brachial index is used to estimate the severity of lower limb peripheral arterial disease in symptomatic patients or is being used during follow up after revascularisation, it is recommended to be calculated by dividing the highest systolic pressure at ankle level by the highest systolic arm pressure.

Class	Level	References	ToE
I	C	Niazi <i>et al.</i> (2006) <sup>199</sup> Schroder <i>et al.</i> (2006) <sup>200</sup> Klein <i>et al.</i> (2006) <sup>207</sup>	

**Table 5.** Potential differential diagnostic alternatives causing lower limb pain, that may either present with intermittent claudication symptoms or be misclassified as intermittent claudication.

Condition	Location	Characteristics	Effect of exercise	Effect of rest	Effect of position
Baker's cyst	Behind knee	Swelling behind knee and distally. When ruptured, tenderness and calf pain	Worsening of symptoms	None	None
Deep vein thrombosis and venous claudication caused by chronic venous obstruction	Entire lower limb	Ipsilateral oedema, tightness, worse in calf	Worsening of symptoms	Subsides slowly	Relief by elevation
Thromboangiitis obliterans – Buerger's disease	Often bilateral	Young age smokers, pain (most commonly) located in the foot	Worsening of symptoms	Relief with rest	Worse with elevation
Spinal cord stenosis	Often bilateral buttock and lower limbs	Pain, weakness, numbness	May mimic claudication	Variable relief and may take a long time to recover	Relief with lumbar spine flexion
Nerve root compression	Radiates down along the posterior aspect of the lower limb	Sharp pain	Induced mainly by standing and walking	Present at rest and on sitting	Improved by change in position
Hip arthritis	Ipsilateral lower limb – thigh	Pain and discomfort	Worse with exercise	Relief but it takes time	Less symptoms when not weight bearing
Foot or ankle arthritis	Ankle or foot	Pain and discomfort	Worse with exercise	Relief but it takes time	Fewer symptoms when not weight bearing or related to activity level
Chronic exertional compartment syndrome	Lower limb	Pain, swelling, disability	Worse with exercise	Pain even at rest, relief takes time	Worsening or improvement according to position
Popliteal artery entrapment syndrome	Lower limb	Cold feet after exercise Tingling or burning in calf Numbness in the calf area	Worse with exercise	Relief with rest	Flexion of foot results in worsening of symptoms
Cystic adventitial degeneration in the popliteal artery	Calf, always unilateral	Exercise induced pain and discomfort, most common in younger patients	Worse with exercise	Relief with rest	None
Lymphangitis or cellulitis	Entire lower limb, mostly in calf	Ipsilateral pitting oedema, worse in calf	Heaviness	None	None

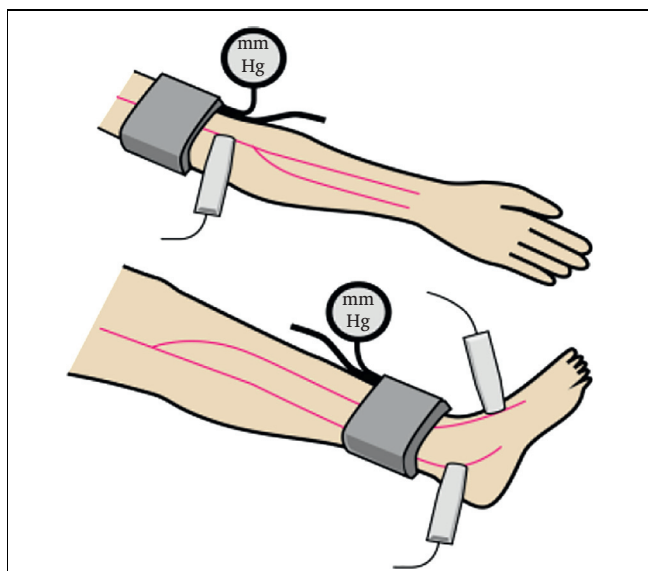
**Recommendation 8**

When the ankle brachial index is used as a cardiovascular risk marker, it is recommended that it is calculated by dividing the lowest recorded systolic pressure at ankle level by the highest systolic arm pressure due to the higher sensitivity to detect peripheral arterial disease.

Class	Level	References	ToE
I	B	Niazi <i>et al.</i> (2006) <sup>199</sup> Le Bivic <i>et al.</i> (2019) <sup>202</sup> O'Hare <i>et al.</i> (2006) <sup>203</sup> Espinola-Klein <i>et al.</i> (2008) <sup>201</sup> Pereira Fihlo <i>et al.</i> (2022) <sup>208</sup>	

**3.1.3.2. Toe pressures and toe-brachial index.** Assessment of the absolute toe pressure (TP) and the toe brachial index (TBI) is an additional measuring method that should be used to ascertain a PAD diagnosis in cases of suspected falsely elevated ABIs due to partly or completely incompressible arteries at ankle level. A special mini cuff connected to a manometer is placed around the great toe, and the systolic pressure is measured over the digital arteries by

either a handheld continuous wave Doppler or by a photoplethysmography or laser Doppler method. The investigation should be performed after a rest of 10 minutes.<sup>209</sup> The digital arteries are less often affected by incompressibility. Under normal circumstances the absolute systolic toe pressure is about 20 – 40 mmHg lower than the corresponding ankle pressure. The TBI is then calculated from the quotient of the systolic toe pressure and brachial pressures. An index of lower than 0.7 is considered to be abnormal.<sup>210</sup> Absolute pressures of lower than 30 mmHg are diagnostic of severe ischaemia.<sup>211,212</sup> The intra- and interobserver reproducibility is excellent for both TP and TBI (intraclass correlation coefficient 0.85 – 0.99).<sup>213</sup> A recent systematic review determined the pooled estimates of the capacity of the TBI to detect a stenosis of 50% or greater at a sensitivity of 81% (95% CI 70 – 94) and a specificity of 77% (95% CI 66 – 90), also recognising wide heterogeneity of the included studies and emphasising the known limitations of the method such as previous toe or forefoot amputation.<sup>191,214,215</sup> Thus, the main advantage may be the higher sensitivity for diagnosing PAD in challenging populations



**Figure 6.** Measurement of the ankle brachial index (ABI): The measurement is made in the supine position and by using a manual blood pressure cuff and a pen Doppler. The cuff is placed distally at ankle level. Flow signal is identified with a pen Doppler held over the posterior tibial and dorsalis pedis arteries, respectively. Once the flow signal has been identified, the cuff is inflated until the flow signal disappears. Thereafter, the cuff is slowly released until the flow signal returns. The blood pressure that coincides with the return of the flow signal is the systolic ankle pressure. Measurements are performed for both the posterior tibial and dorsalis pedis arteries and depending on the purpose of the examination, the lowest (screening for lower limb peripheral arterial disease in asymptomatic high cardiovascular risk populations) or the highest (to determine the severity of the peripheral arterial disease, for pre- and post-operative assessments in the context of lower limb revascularisation, and for longitudinal surveillance) recorded ankle pressure is used in the calculations. The systolic blood pressure in both arms is then measured, and the ABI is calculated by dividing the recorded ankle pressure by the highest recorded arm pressure.

(diabetes and chronic kidney disease patients) such as in patients with medial arterial calcification with inconclusive ABIs.<sup>189</sup> This is of particular importance as low TPs are also associated with higher rates of cardiovascular mortality<sup>216</sup> and these patients might accordingly remain unidentified if TP/TBIs are not performed in cases with inconclusive or uncertain ABI recordings. This was demonstrated by Laivuori *et al.* investigating 6 784 consecutive patients at different symptomatic PAD stages.<sup>216</sup>

#### Recommendation 9

For individuals with a clinical suspicion of lower limb peripheral arterial disease but with inconclusive ankle brachial index recordings due to partly or completely incompressible arteries at ankle level, the use of toe brachial index or absolute toe pressures should be considered as additional diagnostic tools to detect peripheral arterial disease.

Class	Level	References	ToE
Iia	B	Herraiz-Adillo <i>et al.</i> (2020) <sup>214</sup> Laivuori <i>et al.</i> (2021) <sup>216</sup>	

#### Recommendation 10

For individuals with a clinical suspicion of lower limb peripheral arterial disease despite an ankle brachial index within the normal range, the use of toe brachial index or absolute toe pressures should be considered, to confirm peripheral arterial disease.

Class	Level	Reference	ToE
Iia	B	Laivuori <i>et al.</i> (2021) <sup>216</sup>	

**3.1.3.3. Treadmill testing.** The treadmill test is an adjunctive method to assess claudication symptoms objectively. It can be used for establishing the PAD diagnosis, especially in patients where the ultimate cause of limb symptoms remains unclear, to determine the severity of IC symptomatology, and to follow up on PAD patients after treatment. For the initial assessment, an immediate post exercise ABI drop of at least 20% or an absolute pressure drop of at least 30 mmHg, using the highest ankle pressure, confirms PAD and can therefore detect clinically relevant stenoses.<sup>63,217</sup> Different protocols for treadmill testing have been used such as constant load walking protocols (e.g. 3.0 – 3.2 km/h and 10 – 12% gradient), as well as different graded load protocols (e.g. 3.2 km/h starting at 0% gradient, increasing every three minutes by 3.5%).<sup>218</sup> Additionally, different outcome parameters have been discussed, such as the initial claudication distance (distance covered until claudication symptoms commenced) and the maximum walking distance (distance covered until the patient needed to stop due to claudication symptoms). A meta-regression analysis including a total of 658 patients identified the absolute claudication distance during a graded treadmill protocol as the most reliable test.<sup>218–220</sup> If the graded protocol is not applicable, the constant load protocol can be used with good reliability. Limitations of the treadmill test include difficulties for certain patients to walk on a treadmill due to frailty, balance disorders, or walking limitations for reasons other than PAD.

#### Recommendation 11

For patients with suspected intermittent claudication and normal ankle brachial index at rest, a treadmill test with pre- and post-test measurements of the ankle brachial index\* may be considered, to establish the peripheral arterial disease diagnosis and to quantify severity.

Class	Level	Reference	ToE
Iib	C	Gardner <i>et al.</i> (1991) <sup>220</sup> Birkett <i>et al.</i> (2021) <sup>218</sup> Hoogveen <i>et al.</i> (2008) <sup>217</sup>	

\* A post exercise ABI drop of  $\geq 20\%$  or ankle pressure decrease  $> 30$  mmHg confirms the PAD diagnosis.

#### Recommendation 12

When evaluating patients with suspected or confirmed intermittent claudication on a treadmill, the maximum walking distance observed during a graded treadmill test may be considered the most reliable treadmill parameter.

Class	Level	References	ToE
Iib	C	Nicolai <i>et al.</i> (2009) <sup>219</sup> Gardner <i>et al.</i> (1991) <sup>220</sup>	

<b>Table 6. Overview of the measurement conditions, calculation, interpretation, and target populations for the ankle brachial index measurement</b>	
Measurement	An ABI measurement requires a continuous wave Doppler probe, 8 – 10MHz, ultrasound transmission gel and a blood pressure cuff with a width $\geq$ 40% of the leg circumference, 2 cm above the medial malleolus. The patient should rest for 5 – 10 minutes in the supine position prior to measurement. SBP is measured in each arm. If differences between arms is $\geq$ 15 mmHg, subclavian artery stenosis should be suspected. The ankle cuff should be placed just above the malleoli and the SBP of the posterior and the anterior tibial (dorsalis pedis) arteries of each foot is measured by a Doppler probe.
Calculation	The probe is placed in the area of the pulse at a 45° – 60° angle to the skin. The cuff should be inflated up to 20 mmHg above the level of flow signal disappearance. Inflation should not exceed 250 mmHg. The highest SBP of both arms should be used as denominator. The highest ankle SBP in each leg is used for ABI calculation if used as a diagnostic tool in symptomatic patients, and for surveillance. The lower of the ankle SBP of the left and right leg is recommended to be used as a prognostic marker of CV events and death.
Interpretation	An ABI $\leq$ 0.90 is the threshold for confirming the diagnosis of PAD. A post-exercise ABI drop of $\geq$ 20% or ankle pressure decrease $>$ 30 mmHg confirms the PAD diagnosis. ABI $\leq$ 0.90 or $\geq$ 1.40 is associated with increased risk of CV events and death. If ABI $\geq$ 1.40 with clinical suspicion of PAD, use toe brachial index or other non-invasive tests.
Target population for ABI measurement	Patients with suspected PAD. Pre- and post-revascularisation. Patients with other CV comorbidity. Subjects at high risk of CV events and death.
Who should measure the ABI?	ABI may be performed at vascular clinics, at healthcare centres, at nursing homes, or in home based care settings. The ABI may be performed by physicians, nurses, podiatrists, vascular technicians, or other allied health professionals. A basic knowledge of vascular anatomy, physiology, PAD and doppler device function is required. All health professionals who perform ABI should have didactic and practical training under supervision.

ABI = ankle brachial index; PAD = peripheral arterial disease; SBP = systolic blood pressure; CV = cardiovascular.

**3.1.3.4. Corridor based walk tests.** The corridor based walk tests encompass different walk tests such as the six minute walk test (6MWT) or the increment shuttle walk test. The more commonly used 6MWT assesses the maximum walking distance covered by the participant during a walking time of six minutes. Therefore, the participant walks back and forth along a 30 metre corridor without talking. The participant is allowed to rest when needed during the test.<sup>221</sup> The test, first developed within pulmonary medicine, can be adapted to IC patients where initial claudication distance (distance covered until claudication symptoms commenced) can also be measured during the test.

The increment shuttle walk test can be done with a space of 10 metres. The participant walks on a course around two cones (placed 10 metres apart) at a constant speed guided by audible tones. Each minute the speed is increased, and finally the maximum walking distance is measured.<sup>222</sup> Two discussed advantages of corridor based walk tests compared with treadmill tests is that the so called learning effect observed during repeated treadmill testing in placebo or control arms can be avoided and that corridor based tests may better reflect daily walking situations.<sup>223–225</sup> Importantly, the observed maximum walking distances of corridor based walking tests and treadmill walking tests are not interchangeable measures of walking endurance.<sup>223</sup> For

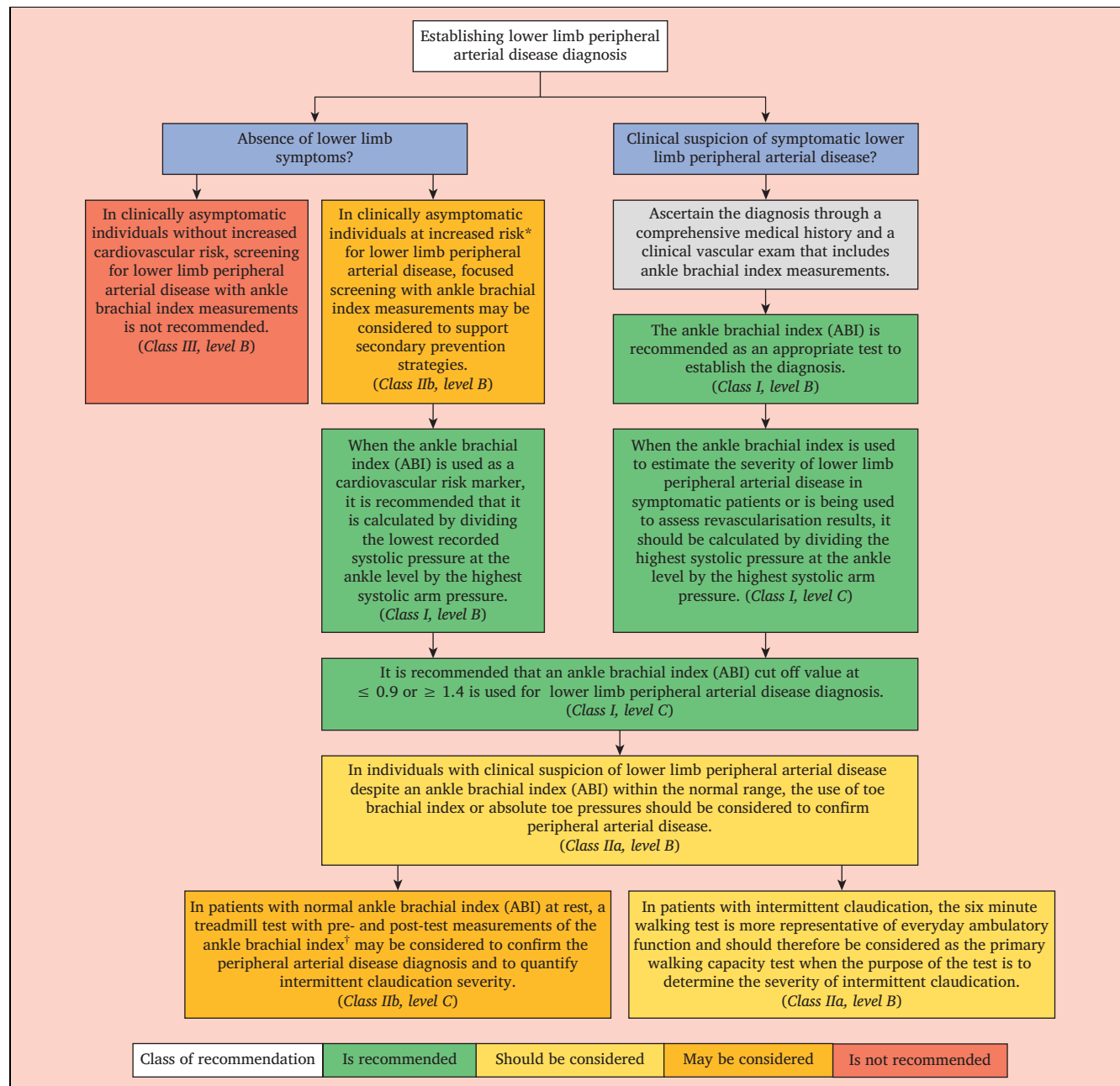
the 6MWT a very good test–retest reliability among IC patients was shown by Sandberg *et al.*<sup>226</sup> Figure 7 summarises the diagnostic process in asymptomatic PAD and IC.

#### Recommendation 13

**For patients with intermittent claudication, the six minute walking test should be considered as the primary walking capacity test to determine the severity of intermittent claudication, as it is more representative than treadmill testing of everyday ambulatory function.**

Class	Level	References	ToE
IIa	B	McDermott <i>et al.</i> (2008) <sup>224</sup> McDermott <i>et al.</i> (2014) <sup>221</sup> Nordanstig <i>et al.</i> (2014) <sup>227</sup> McDermott <i>et al.</i> (2020) <sup>223</sup>	

**3.1.3.5. Medical imaging.** For the diagnosis and conservative treatment of intermittent claudication, imaging is neither indicated nor needed, as the diagnosis can be fully established on clinical grounds from the medical history, a comprehensive medical examination, and non-invasive bedside tests (see 3.1.2, 3.1.3.1, 3.1.3.2 and 3.1.3.3). When planning a revascularisation procedure, medical imaging can, however, determine the presence, location as well as the extent of atherosclerotic lesions.



**Figure 7.** Flow chart describing the principal steps to establish the lower limb peripheral arterial disease (PAD) diagnosis. \*Individuals 65 years or older; individuals aged 50 to 64 years with risk factors for atherosclerosis (diabetes, history of smoking, dyslipidaemia, hypertension, chronic kidney disease or family history of PAD); individuals younger than 50 years old with diabetes and one other risk factor for atherosclerosis; or those with known atherosclerotic disease in another vascular bed. <sup>†</sup>A post-exercise ABI drop of  $\geq 20\%$  or ankle pressure decrease  $> 30$  mm Hg confirms PAD diagnosis.

**Recommendation 14**

**For diagnosis and conservative treatment of intermittent claudication, medical imaging is not indicated as the diagnosis can be fully established on clinical grounds from the medical history, a comprehensive medical examination and non-invasive bedside tests.**

Class	Level	Reference
III	C	Consensus

**3.1.3.5.1. Duplex ultrasound.** Duplex ultrasonography (DUS) is operator dependent and has a fair 88% (95% CI 80 – 98%) sensitivity and high 96% (95% CI 89 – 99%) specificity to

detect lower limb arterial lesions.<sup>228,229</sup> Hence, it is slightly less accurate than CTA and MRA (see sections 3.1.3.5.2 and 3.1.3.5.3). Below the knee, the diagnostic accuracy of duplex ultrasound decreases (four studies, sensitivity range 41 – 96% and specificity range 80 – 99%, respectively).<sup>228</sup> However, although not all lesions may be detected with duplex ultrasound, it is unlikely to misclassify a whole limb as normal and thus to inappropriately exclude patients from further investigations.<sup>228</sup> Therefore, duplex ultrasound may be used as a first modality after non-invasive bedside tests to evaluate the vascular tree for abnormalities.<sup>229</sup> Advantages of DUS are its non-invasive character, the absence of radiation,



and the relatively low costs compared with other diagnostic modalities. Drawbacks are the relatively large interobserver variability, and the reduced accuracy in obesity, patients with excessive bowel gas, and heavily calcified lesions.<sup>228</sup>

**3.1.3.5.2. Computed tomography angiography.** CT angiography is performed by a 16 - 128+ slice multidetector computed tomography scanner using thin slices (usually between 0.75 and 2 mm) and iodine based contrast medium. Overall sensitivity and specificity for detection of arterial lesions is well over 90% compared with DSA as reference standard.<sup>228,230–233</sup> Accuracy may vary slightly below and above the knee; however, these differences are neither clinically nor statistically significant.<sup>228,232</sup> Drawbacks are radiation exposure, misinterpretation of disease severity in the presence of heavily calcified lesions, and contrast induced acute kidney injury, especially in patients with chronic kidney disease. In patients with a glomerular filtration rate of less than 30 mL/min/1.73m<sup>2</sup> due to chronic or acute kidney disease, the latter may be reduced by non-pharmacological precautions such as minimisation of the contrast media dose. Whether saline or bicarbonate hydration may further aid in reduction of contrast induced acute kidney injury remains controversial and there is no proven protective effect of pharmacological adjuncts.<sup>234–236</sup>

**3.1.3.5.3. Magnetic resonance angiography.** Contrast enhanced multislice MR angiography with gadolinium has an overall sensitivity and specificity for detection of arterial lesions of well over 90% compared with DSA.<sup>228,230,237–239</sup> Accuracy may vary slightly below and above the knee; however, these differences are neither clinically nor statistically significant.<sup>228,238</sup> A separate crural artery imaging technique as well as a bolus chase technique by an expert radiographer both result in high diagnostic accuracy for crural artery anatomy,<sup>230</sup> although venous contamination may occur. Drawbacks are the absence of information on calcium burden, difficulty assessing the lumen within metal stents, higher costs compared with CTA, and contraindications for magnetic resonance imaging (MRI), including ferromagnetic implants and claustrophobia. Currently, most cardiac implant devices are compatible with MRI provided a number of

precautions are taken.<sup>240</sup> A rare complication described is gadolinium induced nephrogenic systemic fibrosis,<sup>241</sup> although this risk seems to be minimised by using a group II gadolinium based contrast (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol).<sup>242</sup>

Promising non-contrast techniques include time of flight, quiescent interval slice selective MRA, three dimensional fast spin echo, flow sensitive dephasing magnetisation preparation technique, and velocity selective MRA to reduce gadolinium use.<sup>243</sup>

**3.1.3.5.4. Digital subtraction angiography.** Digital subtraction angiography used to be the gold standard<sup>244–246</sup> but has been replaced by non-invasive CTA and MRA imaging methods. However, in cases of equivocal results from CTA and or MRA, (selective) DSA may still be used as an adjunct, although in most cases this will be combined with intervention in the same session. Drawbacks are the invasive nature, relatively high cost, radiation exposure, and use of contrast agents (Table 7). In patients with severe chronic kidney disease, DSA with carbon dioxide may be used as an alternative. A recent meta-analysis of 677 patients in eight studies revealed a modest decrease in acute kidney injury, defined as a minimum 25% rise in serum creatinine within 48 hours, for CO<sub>2</sub> compared with iodine contrast medium (4.3% vs. 11.1%, OR 0.465; 95% CI 0.218 – 0.992, *p* = .048). In patients with pre-existing chronic kidney disease, a comparable difference was observed, but this was not statistically significant (4.1% vs. 10.0%; OR 0.449; 95% CI 0.165 – 0.1221; *p* = .117). Moreover, more non-kidney adverse events were reported for CO<sub>2</sub> angiography, including limb pain and nausea or vomiting.<sup>247</sup>

#### Recommendation 15

**For patients with lower limb peripheral arterial disease in whom lower limb revascularisation is indicated and being considered, pre-procedural vascular imaging is recommended, to evaluate the location(s) and extent of arterial lesions.**

Class	Level	Reference
I	C	Consensus

**Table 7.** Sensitivity, specificity, and (dis)advantages of different imaging modalities to detect PAD, compared with digital subtraction angiography (= gold standard).

Imaging modality	Sensitivity	Specificity	Advantages	Disadvantages
Duplex US	> 85%	> 95%	Low cost, no radiation exposure, non-invasive	Interobserver variability, accuracy affected by patient characteristics, time consuming and lower accuracy below the knee
CTA	> 90%	> 90%	Imaging of whole vascular tree, relatively short imaging time, non-invasive	Radiation exposure, misinterpretation in heavily calcified lesions, contrast agent nephrotoxicity
MRA	> 90%	> 90%	Imaging of whole vascular tree, non-invasive, no radiation	Relatively expensive, contraindications include ferromagnetic implants, and claustrophobia, risk of gadolinium induced nephrogenic systemic fibrosis
DSA	–	–	Imaging of the entire vascular tree, option for immediate intervention	Relatively expensive, invasive, radiation exposure, nephrotoxicity of contrast agents

US = ultrasound; CTA = computed tomography angiography; MRA = magnetic resonance angiography; DSA = digital subtraction angiography.

Recommendation 16			
For patients with lower limb peripheral arterial disease in whom imaging is indicated, duplex ultrasound, magnetic resonance angiography, or computed tomography angiography are recommended as primary imaging modalities, at the discretion of the treating physician.			
Class	Level	References	ToE
I	B	Jens <i>et al.</i> (2013) <sup>230</sup> Menke <i>et al.</i> (2010) <sup>237</sup> Met <i>et al.</i> (2009) <sup>231</sup> Heijnenbrok-Kal <i>et al.</i> (2007) <sup>232</sup> Collins <i>et al.</i> (2007) <sup>228</sup> Sun <i>et al.</i> (2006) <sup>233</sup> Koelemay <i>et al.</i> (2001) <sup>238</sup> Nelemans <i>et al.</i> (2000) <sup>239</sup> Visser <i>et al.</i> (2000) <sup>229</sup> Verma <i>et al.</i> (2022) <sup>248</sup>	

### 3.1.3.5.5. Additional non-invasive diagnostic methods.

Additional non-invasive methods can be used in cases of inconclusive results from ABI and TBI measurements to confirm or reject the diagnosis of PAD. These methods use either segmental pressure characteristics, leading to a more detailed overview about the location of the arterial stenosis or occlusion, or they are able to assess skin perfusion, albeit some methods are especially related to revascularisation procedures (e.g., skin perfusion pressure, transcutaneous oxygen measurement (tcpO<sub>2</sub>, laser Doppler flowmetry, indocyanine green fluorescence angiography).<sup>249–254</sup> Skin perfusion assessments are advantageous mainly in CLTI patients and in wound healing disorders.<sup>255</sup> Most of these methods are influenced by different confounding factors and are, even in the CLTI diagnostic process, not routinely used and not well standardised as shown in a recent meta-analysis.<sup>256–259</sup> However, tcpO<sub>2</sub> measurement can also be used after exercise to detect buttock claudication.<sup>260</sup> Additionally, some studies have published thresholds for diagnosis of PAD in patients with diabetes (< 50 – 60 mmHg).<sup>261</sup> Promising methods such as multispectral optoacoustic tomography which directly addresses muscle perfusion and therefore effectively investigate the end organ in intermittent claudication transcutaneously, are currently under evaluation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04641091) Identifier: NCT04641091), as are different deep tissue perfusion MRI protocols.<sup>259,262</sup>

## 3.2. Classification systems

**3.2.1. General considerations.** Clinical PAD classification systems include classifications describing either the entire PAD spectrum or tools focusing on further sub-categorisation of a distinct PAD stage. Classifications are also either based on clinical symptoms and signs, on the severity and extent of vascular lesions as determined from medical imaging; or combinations thereof.<sup>59</sup> The traditional classification systems relate to the entire PAD spectrum and are widely used in everyday clinical practice. While there is currently no single and universally accepted classification system for PAD, physicians working with PAD patients are

still advised to be familiar with the different scoring systems. Despite important shortcomings, the Fontaine and Rutherford classifications are still used extensively in everyday practice, and the Trans-Atlantic Inter-Society Consensus (TASC II) classification system is used widely to guide clinical decisions of principal invasive treatment modalities (i.e., endovascular, or open surgery). The most important elements of the different classifications were also suggested to be recorded in prospective registries in a recent consensus recommendation by the VASCUNET and the International Consortium of Vascular Registries.<sup>263,264</sup> A brief overview of the most common classification systems is provided below, but evidence is currently insufficient to enable distinct recommendations on the use of the different available scoring systems.

**3.2.2. The Fontaine classification.** The oldest system is the Fontaine classification (1954), which entirely rests on clinical symptoms and is still widely used in common daily practice (Table 8).<sup>265</sup> This classification does not contain any objective measures besides the maximum walking distance in stage II, but it gives guidance in primary healthcare and may also guide decisions about conservative or invasive treatment.

**3.2.3. The Rutherford classification.** Rutherford published his suggestion for a PAD classification in 1986 and it was revised in 1997 (Table 8).<sup>266</sup> This system also takes patients' symptoms into consideration, but adds more objective characteristics as determined by non-invasive methods, such as Doppler measurements, ankle brachial index, treadmill test, reactive hyperaemia, and pulse volume recordings. The Rutherford classification is used extensively both in clinical settings and in research and facilitates the determination of suitable treatment pathways for PAD patients.

**3.2.4. The Trans-Atlantic Inter-Society Consensus (TASC II) classification.** The modified Trans-Atlantic Inter-Society Consensus Document (TASC II, 2007) aimed to give recommendations related to all types of lower extremity arterial disease including patients with PAD.<sup>179</sup> The proposed PAD disease classification from the TASCII authors has been principally cited and used as a tool in the decision making process on the choice of type of invasive treatment to offer PAD patients. This classification system was accordingly defined based on the patho-anatomical location and overall extent of the atherosclerotic lesions as determined on vascular imaging (lesion length, degree of stenosis, presence of occlusions). The arterial lesions were categorised into four categories: A, B, C, D, and the preferred choice of principal invasive treatment modality (i.e., endovascular, or open revascularisation) was also suggested to be linked to these categories. The original classification encompassed the aorto-iliac and the femoropopliteal segments, but the infrapopliteal segment was later included in an update of the classification in 2015 (Fig. 8–10).<sup>267</sup> The accuracy of the infrapopliteal classification has been questioned by a relatively poor interobserver agreement regarding the

**Table 8. The Fontaine and the revised Rutherford peripheral arterial disease classifications.**

Fontaine		Rutherford			
Class	Symptoms	Grade	Category	Symptoms	Objective criteria
Stage I	Asymptomatic	0	0	Asymptomatic	Normal treadmill or reactive hyperaemia test
Stage II	Claudication pain in limb IIA: Claudication at a distance $\geq$ 200 m IIB: Claudication at a distance < 200 m	I	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
			2	Moderate claudication	Between categories 1 and 3
			3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mmHg
Stage III	Rest pain, mostly in the feet	II	4	Ischaemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
Stage IV	Ulceration and or gangrene of the limb	III	5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischaemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
			6	Major tissue loss – extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

AP = ankle pressure; PVR = pulse volume recordings; TP = toe pressure.

choice of a single target vessel, a prerequisite for infra-popliteal TASC II grading.<sup>268</sup> The idea of using the TASC II classification to link a certain extent and severity of disease to a preferred treatment modality has been largely hampered by the rapid developments in endovascular techniques during recent years, but the classification still remains one of the most widely used patho-anatomical PAD classification systems to date.

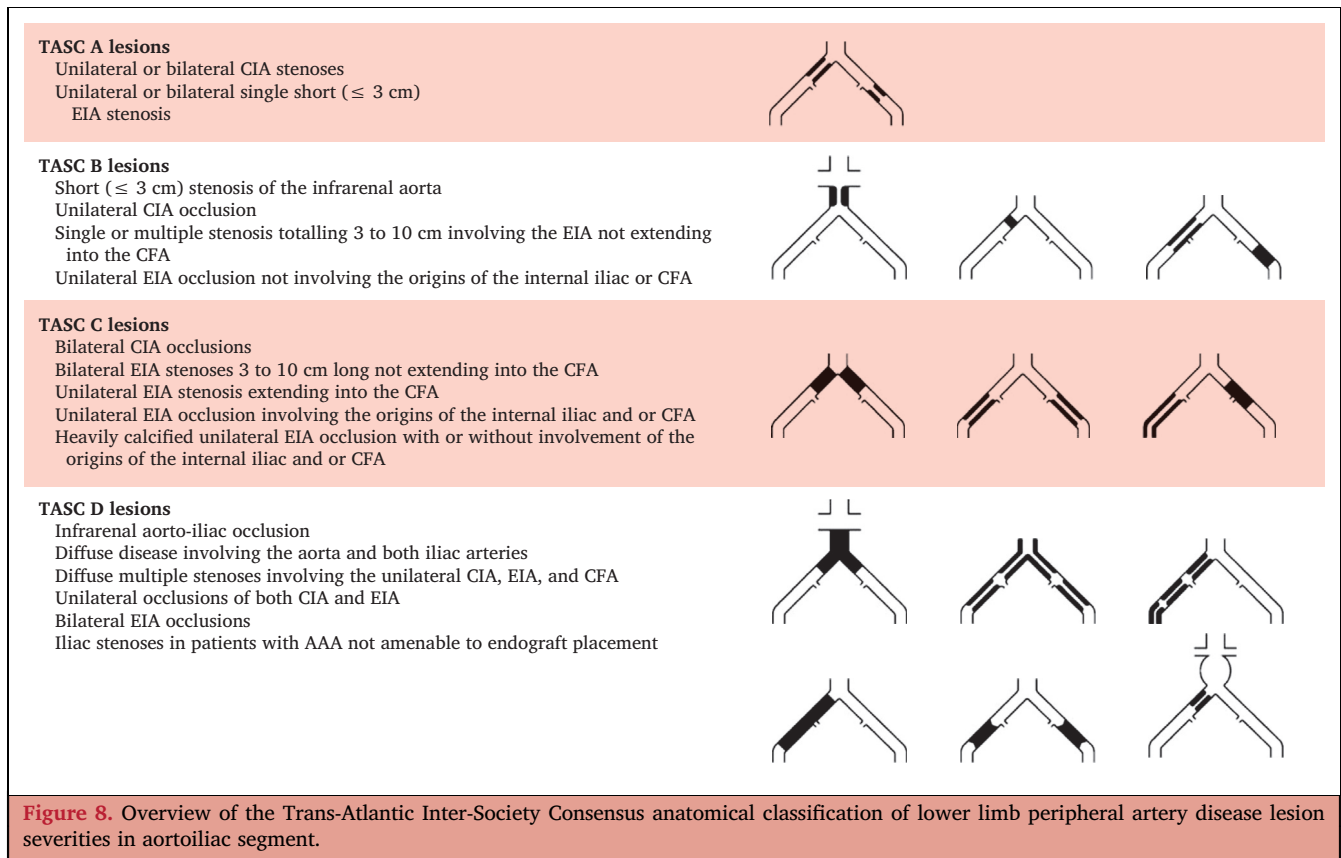
**3.2.5. Other peripheral arterial disease classification systems.** The Bollinger classification system focuses on the anatomical location and extent of lower limb chronic atherosclerotic stenoses and occlusions. This system is based on an additive score measured angiographically: the severity (degree of stenosis, occlusion) and the length of lesions are noted from the infrarenal aorta to the crural vessels bilaterally.<sup>269</sup>

The American Medical Association developed criteria for lower extremity impairment determination for the authorities based on a questionnaire of symptoms and physical examination findings. This classification includes symptomatic atherosclerotic patients and also venous diseases, and has not gained wide acceptance.<sup>270</sup>

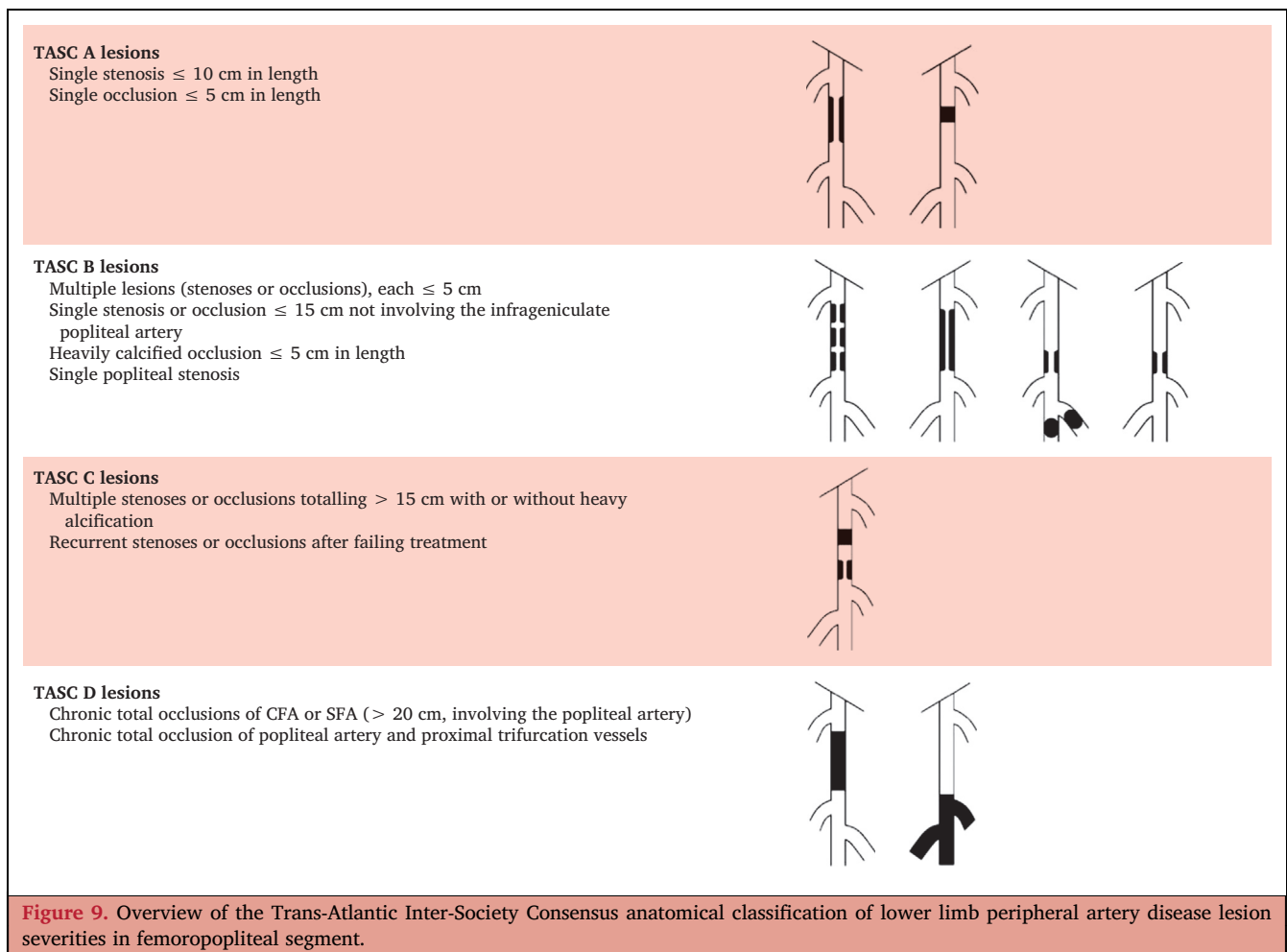
There are also other recent and important PAD classification systems, but these are relevant only for CLTI patients or populations with diabetes and diabetic foot syndrome and therefore are not discussed in these guidelines (e.g., angiosome concept, Wifi classification of the Society for Vascular Surgery, University of Texas classification and Global Anatomic Staging System [GLASS] as proposed by the Global Vascular Guidelines).<sup>271</sup>

### 3.3. Patient reported outcome measures to assess peripheral arterial disease severity

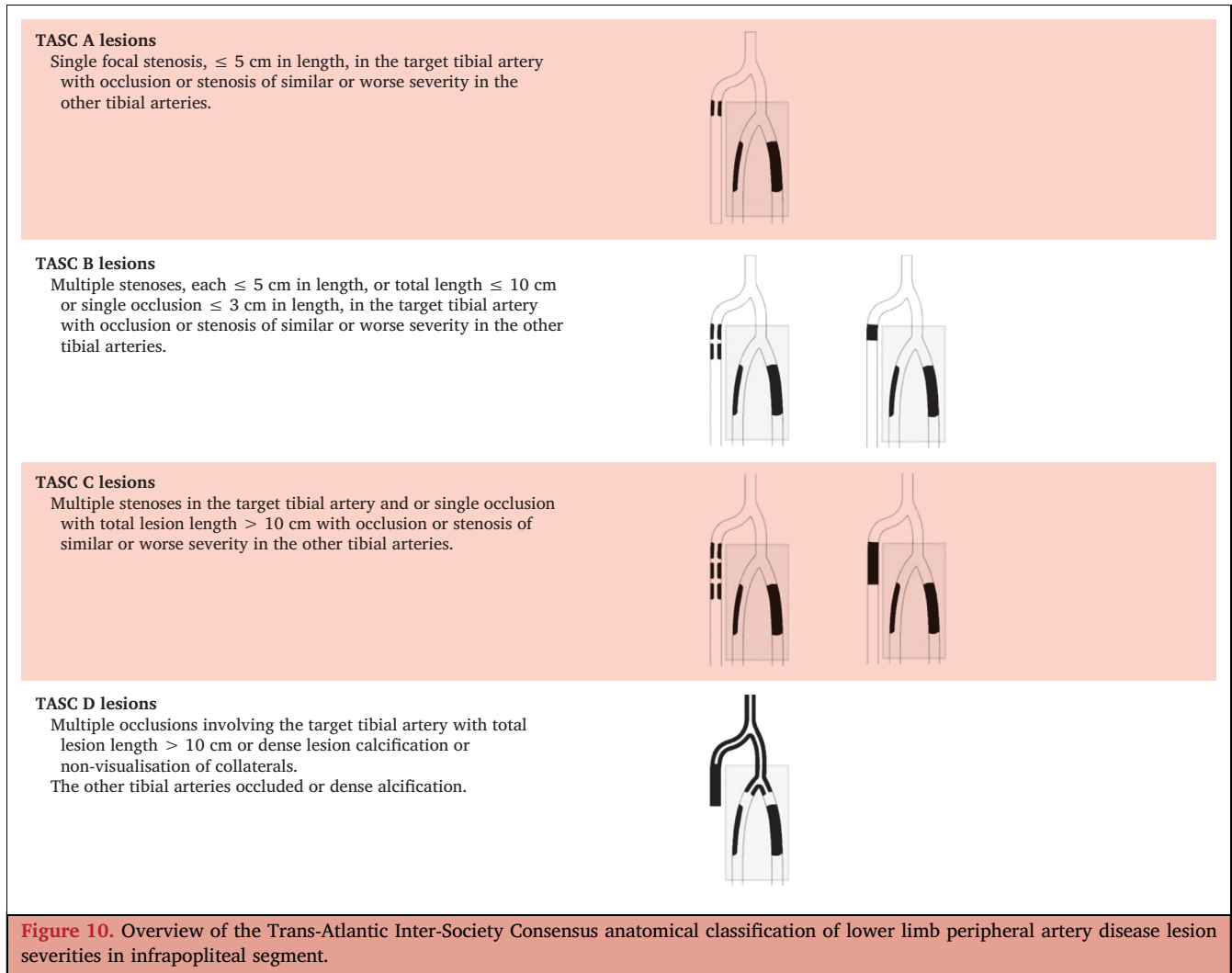
As previously described in sections 3.1 and 3.2, traditional clinical tools to determine PAD severity include objective walking capacity, clinical classification systems, different imaging modalities, and physiological measurements. Such outcomes have inherent limitations as they do not fully address the patient's own perception about everyday physical ability, pain and discomfort, or the social and emotional implications of IC on everyday life.<sup>272,273</sup> These important areas of IC management can be captured using patient reported outcome measures (PROMs). A PROM is any report of a patient's health condition that comes directly from the patient and is based on the patient's own perception of a disease, its treatment and outcomes, without interpretation by a clinician or anyone else.<sup>274</sup> PROMs are typically measured using paper based or digital surveys. PROM surveys also associate with important IC outcomes, including major adverse cardiovascular events, major adverse limb events, and lower extremity revascularisation.<sup>275</sup> In a comprehensive review of the literature followed by a modified Delphi consensus study with 60 international panel experts involving patient representatives as well as multiple medical specialties treating patients with IC, a total of 145 PROMs in eight different domains were identified. The consensus process, which was undertaken for the purpose of this guideline as previous evidence was deemed insufficient, led to the recommendation of the VasuQoL-6 survey and 12 optional items to be collected by trials and registries on IC treatment.<sup>4</sup>



**Figure 8.** Overview of the Trans-Atlantic Inter-Society Consensus anatomical classification of lower limb peripheral artery disease lesion severities in aortoiliac segment.



**Figure 9.** Overview of the Trans-Atlantic Inter-Society Consensus anatomical classification of lower limb peripheral artery disease lesion severities in femoropopliteal segment.



To provide useful information, it is essential that a HRQoL instrument satisfies certain development, psychometric, and scaling standards. For the purpose of IC assessment, PROMs can be divided practically into surveys that determine: (1) functional status and (2) HRQoL, where the latter can be further subdivided in generic and disease specific surveys.<sup>276</sup> While generic HRQoL instruments allow comparisons across diseases, disease specific instruments focus on the specific limitations experienced by IC patients, making them more sensitive to characterise the disease and capture health status changes in response to treatment. Commonly used validated functional status instruments include the Walking Impairment Questionnaire (WIQ) and the Walking Estimated Limitation Calculated by History (WELCH), whereas the Medical Outcomes Short Form 36 (SF-36) remains the most used generic HRQoL instrument.<sup>277,278</sup> There are also several validated PAD specific instruments with demonstrated PAD content validity including the Peripheral Artery Questionnaire (PAQ), the PAD Quality of Life Questionnaire (PADQOL), the Intermittent Claudication Questionnaire (ICQ), and the Vascular Quality of Life Questionnaire (VascuQoL; also

available as a short version, VascuQoL-6).<sup>277,279,280</sup> However, a fairly recent systematic review also pointed out that the validation process for many of the currently available PAD specific PROMs has been suboptimal, and such shortcomings should be taken into account when interpreting their results.<sup>278</sup> Widespread use of PROM questionnaires is also currently restricted by a relative lack of validated language translations for some of the available instruments. A relative abundance of items for some questionnaires also limits their usefulness in routine clinical scenarios.

#### Recommendation 17

**For patients with intermittent claudication, properly developed and tested patient reported outcome measures should be considered to characterise functional status and health related quality of life when considering indications for treatment, outcome evaluation, and for scientific purposes.**

Class	Level	References	ToE
IIa	C	Poku <i>et al.</i> (2016) <sup>277</sup> Mays <i>et al.</i> (2011) <sup>276</sup> Conijn <i>et al.</i> (2015) <sup>278</sup>	

Recommendation 18			
Trials and registries on the treatment of patients with intermittent claudication should consider using the Vascular Quality of Life six items survey (VascuQoL-6) to incorporate patient reported outcome measures in a comparable way.			
Class	Level	References	ToE
Iia	C	Nordanstig <i>et al.</i> (2014) <sup>227</sup> Kumlien <i>et al.</i> (2017) <sup>279</sup> Arndt <i>et al.</i> (2022) <sup>4</sup>	

### 3.4. The evolving role of biomarkers in peripheral arterial disease

Many studies have shown that patients with PAD present with higher levels of inflammatory biomarkers than individuals without PAD.<sup>281</sup> A direct association between inflammatory biomarkers and the development or progression of lower extremity atherosclerosis has not yet been established, however.<sup>281</sup> Increasing CRP levels have been associated with a higher risk of developing PAD<sup>282,283</sup> and greater ABI declines during follow up.<sup>283</sup> Elevated levels of inflammatory biomarkers are also associated with greater functional impairment and faster functional decline in people with PAD.<sup>284–293</sup>

Circulating matrix metalloproteinases (MMPs) have been increasingly recognised as biomarkers of atherosclerosis, degrading collagen, and allowing vascular smooth muscle cell migration within the vessel wall potentially leading to vessel occlusion and ischaemia. In a large community based study, patients with confirmed but previously undetected PAD presented higher MMP-2/MMP-9 ratios compared with non-PAD control subjects.<sup>294</sup> Elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity troponin T (hs-TnT) levels were also independently associated with incident symptomatic PAD.<sup>295,296</sup>

Recent evidence has also suggested that microribonucleic acids are involved in the onset and progression of CV diseases and thus might be emerging as promising non-invasive biomarkers for several CV disorders including PAD.<sup>297</sup>

Different markers of lipoprotein metabolism are also potentially useful biomarkers in PAD settings. In a pre-specified analysis from the ODYSSEY RCT ( $n = 18\,924$ ) that evaluated the PCSK-9 (proprotein convertase subtilisin/kexin type 9) inhibitor alirocumab vs. placebo in patients with recent acute coronary syndrome, the risk of subsequent PAD limb events in the placebo arm was closely related to lipoprotein(a) levels, and this risk was reduced by alirocumab.<sup>298</sup> Golledge *et al.* noted similar observations in a prospective observational study of 1 472 individuals with vascular disease.<sup>299,300</sup> In the CAVASIC study, Kheirkhah *et al.* reported higher PCSK-9 levels among male patients with intermittent claudication than controls without.<sup>300</sup> Finally, the levels of lipoprotein (a) (Lp[a]) have also been demonstrated to correlate with the angiographic severity of femoropopliteal lesions.<sup>301</sup>

Recently, Kremers *et al.* published a meta-analysis showing that some biomarkers (increased high sensitivity

C-reactive protein, fibrinogen, D dimer and NT-proBNP levels) may be associated with an increased relative risk of death and MACE in PAD patients.<sup>302</sup>

Still, there are insufficient data to conclude that inflammatory and or lipoprotein metabolism biomarkers are causally related to adverse outcomes in PAD and their role in the diagnosis and management of PAD remains unclear. However, non-invasive circulating biomarkers could be of value in this setting and several candidates have been evaluated as potentially useful for both PAD diagnosis and risk stratification in PAD.

Recommendation 19		
For patients with lower limb peripheral arterial disease, the use of laboratory biomarkers for clinical risk stratification purposes is not recommended due to insufficient scientific data to support such strategies.		
Class	Level	Reference
III	C	Consensus

## 4. PERIPHERAL ARTERIAL DISEASE RISK FACTOR MANAGEMENT

### 4.1.1. Lifestyle factors

**4.1.1.1. Tobacco smoking.** Tobacco use is the leading preventable cause of disease and death globally.<sup>303</sup> The smoking of tobacco is an important risk factor for development and progression of PAD and is associated with an increased need for revascularisation, increased risk of CLTI, and amputation.<sup>304</sup> In a longitudinal registry analysis of > 96 000 patients who were hospitalised for treatment of symptomatic PAD for the first time, approximately 7% of men and 4% of women developed incident lung cancer within 10 years of follow up. Together with an increased risk of bladder cancer, these results emphasised the multifactorial harm of tobacco in this population as both PAD and selected cancer groups have overlapping risk profiles with smoking contributing in a relevant manner.<sup>305</sup> Patients with PAD who manage to successfully stop smoking enjoy improved outcomes,<sup>306,307</sup> making smoking cessation a key target for vascular clinicians. A planned smoking cessation strategy for each PAD patient under risk is therefore crucial. Even verbal advice from physicians has been associated with improved cessation.<sup>308</sup> Many studies have confirmed the benefits of smoking cessation counselling, including a randomised study of PAD patients receiving either intensive counselling or minimal intervention which showed that patients in the intensive counselling group were more likely to achieve smoking abstinence at six months compared with the minimal intervention group (21.3% vs. 6.8%,  $p = .023$ ).<sup>309</sup> There is thus good evidence that smoking cessation is beneficial in PAD. The US Preventive Services Task Force (USPSTF) also determined with a high level of certainty that there is substantial benefit from behavioural interventions for smoking cessation. The USPSTF recommends that clinicians should ask all adults about tobacco

use, advise them to stop smoking, and should provide behavioural interventions and approved pharmacotherapy for smoking cessation.<sup>310</sup> However, it is likely there will be a need for more than counselling, as long term abstinence often requires pharmacological intervention as well as counselling. Such intervention includes nicotine replacement therapy, varenicline, or bupropion.<sup>311</sup> Meta-analyses, along with a large randomised controlled trial show that these medications are more effective than placebo in supporting smoking cessation over six months or more.<sup>312,313</sup> Importantly the agents appear safe for use in patients with cardiovascular disease.

There are many forms of nicotine replacement therapy each with their own advantages and disadvantages. These include nicotine patches (least intrusive but dose cannot be altered during the day), gum or lozenges (cannot eat for 15 minutes beforehand, difficult to use with dentures), inhaler (most popular as mimics cigarette smoking), and nasal spray (can irritate nasal mucosa). Selection can be discussed with the patient. Although not harmless, it is likely to be much less harmful than smoking tobacco. While newer modified risk products, such as electronic vaping cigarettes and heated tobacco products that avoid combustion (heat not burn cigarettes), are clearly linked to an overall increased cardiovascular risk,<sup>314</sup> the average risk with these products compared with traditional cigarette smoking seems less and these alternatives may therefore be used as interim alternatives to conventional cigarettes in risk modifying strategies ultimately aimed at complete nicotine abstinence.<sup>315–317</sup>

Bupropion is a dopamine and norepinephrine re-uptake inhibitor. When used alone or in addition to nicotine replacement, bupropion leads to higher rates of smoking cessation at 12 months compared with placebo or NRT alone.<sup>318</sup> Bupropion is approved for a 12 week course, but treatment for 12 months reduces the relapse rate.<sup>319</sup> Combination therapy with nicotine patches and bupropion is more effective than either therapy alone.<sup>320</sup> Bupropion has also been studied in combination with varenicline, showing substantially more smoking cessation in the first few months.<sup>321</sup>

Varenicline is a partial agonist of  $\alpha$ -4 and  $\beta$ -2 nicotinic acetylcholine receptor. It is the most effective smoking cessation aid. Randomised controlled trials have demonstrated that it is more effective than placebo, bupropion, and nicotine patches at improving three month smoking abstinence rates.<sup>322,323</sup> Importantly, varenicline does not increase the risk of neuropsychiatric side effects.

#### Recommendation 20

For all patients with suspected or confirmed lower limb peripheral arterial disease, it is recommended to ask about tobacco use and advise to stop smoking due to the risk of atherosclerotic disease progression, major cardiovascular events, and limb events from continued smoking.

Class	Level	Reference
I	C	Consensus

#### Recommendation 21

For all patients with lower limb peripheral arterial disease who smoke, it is recommended that both behavioural interventions and pharmacotherapy for smoking cessation are offered to provide the most effective means for successful smoking cessation.

Class	Level	References	ToE
I	A	Morgan <i>et al.</i> (1996) <sup>324</sup> Canga <i>et al.</i> (2000) <sup>325</sup> Weissfeld <i>et al.</i> (1991) <sup>326</sup> Bock <i>et al.</i> (2013) <sup>327</sup> Smith <i>et al.</i> (2013) <sup>328</sup> Carson-Chahhoud <i>et al.</i> (2020) <sup>329</sup>	

#### Recommendation 22

For patients with lower limb peripheral arterial disease who smoke, counselling as part of intensive smoking cessation intervention is recommended.

Class	Level	Reference	ToE
I	B	Henrikus <i>et al.</i> (2010) <sup>330</sup>	

#### Recommendation 23

For patients with lower limb peripheral arterial disease who smoke, varenicline, either alone or in combination with nicotine replacement therapy, is recommended as the first line pharmacological smoking cessation treatment due to its higher effectiveness compared with other pharmacological alternatives.

Class	Level	References	ToE
I	B	Barua <i>et al.</i> (2018) <sup>322</sup> Anthenelli <i>et al.</i> (2016) <sup>323</sup>	

Many long time smokers with PAD initiate a quit attempt but the long term effectiveness is not fully evaluated.<sup>330,331</sup> The ACC Expert Consensus on Tobacco Cessation Treatment recommends a follow up within two to four weeks as the risk of relapse is highest in the first week after making a quit attempt. Smoking status, adherence, response, and side effects from pharmacotherapy should be monitored. Further detailed timelines for follow up are not given.<sup>311</sup> The European guidelines on prevention summarise stop smoking into five As: ask, assess, advise, assist, and lastly, arrange a schedule of follow up visits.<sup>332</sup>

#### Recommendation 24

For patients with lower limb peripheral arterial disease who smoke, a follow up contact is recommended to monitor adherence, treatment response, and adverse events within two to four weeks after initiation of a smoking cessation attempt.

Class	Level	Reference
I	C	Consensus

**4.1.1.2. Screening for obesity, metabolic syndrome, and diabetes.** Reducing obesity, high cholesterol, hypertension, and diabetes with dietary change has an impact on cardiovascular disease and its risk factors.<sup>333–337</sup> Dietary changes may be performed by education, diet assessment, self monitoring, motivation, and encouragement.<sup>338–340</sup> It is recommended for overweight and obese people to aim for weight reduction. A desirable body mass index is 18.5 – 24.9 kg/m<sup>2</sup>. An increased CV risk is proven at BMI > 30.0 kg/m<sup>2</sup>.<sup>332</sup> Another study linked a low Mediterranean diet intake as measured by a self administered food frequency validated questionnaire with asymptomatic PAD, and the subjects were more obese.<sup>341</sup> In a three armed, multi-centre, randomised, primary prevention trial that assessed the long term effects of the Mediterranean diet on subsequent MACE risk ( $n = 7\,447$ ), two types of Mediterranean diets had important health benefits over a control diet. During a median time of 4.8 years, HRs were 0.70 (95% CI 0.53 – 0.91) for a Mediterranean diet with extra virgin olive oil and 0.70 (95% CI 0.53 – 0.94) for a Mediterranean diet supplemented with nuts, compared with the control group.<sup>342</sup>

Both metabolic syndrome and diabetes are linked to the occurrence of asymptomatic PAD<sup>67</sup> and diabetic control is important in the progression of atheroma in symptomatic PAD. Indeed diabetes and smoking are the two most strongly associated risk factors for PAD development.<sup>343</sup> It therefore makes sense both from the PAD and CV risk point of view to manage any detected diabetes optimally. (See 4.1.3.4 for more information about optimal management of the PAD patient with diabetes.)

#### Recommendation 25

For patients with lower limb peripheral arterial disease, screening for obesity, metabolic syndrome, and diabetes, with subsequent optimal management should be considered, to reduce the risk of lower limb disease progression with the added benefit of reducing overall cardiovascular risk.

Class	Level	Reference
Ila	C	Consensus

#### Recommendation 26

For patients with lower limb peripheral arterial disease, comprehensive screening for cardiovascular risk factors, with subsequent optimal management should be considered, to reduce the risk of lower limb disease progression with the added benefit of reducing overall cardiovascular risk.

Class	Level	Reference
Ila	C	Consensus

**4.1.2. Pharmacotherapy.** The optimal pharmacotherapy for patients suffering from PAD is an important pillar of comprehensive best medical therapy. The primary aims of pharmacotherapy in this target population are: (1) to decelerate or stop the progression of systemic

atherosclerosis; (2) to reduce the incidence of major ischaemic cardiovascular, cerebrovascular, and limb events; (3) to treat common concomitant diseases such as diabetes, chronic kidney disease, chronic obstructive airways disease, atrial fibrillation, or heart failure; and (d) to improve the quality of life by reducing walking pain and improve functional status.

With increasing age and multimorbidity, the number of medicines may rise to a critical level. Polypharmacy, commonly defined as five or more medications daily,<sup>344</sup> is known to be associated with reduced physical function and adverse outcomes in the elderly.<sup>345,346</sup> Therefore, a need based patient centred approach should always aim to avoid polypharmacy in patients with PAD if possible.

#### Recommendation 27

For patients with lower limb peripheral arterial disease, it is recommended that each new medical prescription should be accompanied by patient centred counselling and include appropriate recommendations to change modifiable risk factors, lifestyle, and health behaviour.

Class	Level	Reference
I	C	Consensus

**4.1.2.1. Antithrombotic therapy.** Antithrombotic therapy is indicated for all patients with symptomatic lower limb PAD. For specific advice on post-revascularisation antithrombotic treatment please refer to chapter 6.5; and for any other patient scenario please consult the comprehensive 2023 ESVS Clinical Practice Guidelines on Antithrombotic Therapy in Vascular Disease.<sup>37</sup>

**4.1.2.2. Lipid lowering agents.** Although there is ample evidence that patients with symptomatic PAD benefit from lipid lowering therapy with regard to major adverse cardiovascular events (MACE), major adverse limb events (MALE) and cost effectiveness,<sup>347</sup> there is no direct evidence for asymptomatic PAD patients from clinical trials stratified for this dedicated patient subgroup.<sup>348,349</sup> Elevated low density lipoprotein (LDL) cholesterol values are, however, an important risk factor for the development and progression of cardiovascular disease.<sup>350,351</sup> Recent guidelines for the management of dyslipidaemias lowered the target lipid goals in accordance with recent large scale trials of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors.<sup>352</sup> Different thresholds are recommended according to the individual cardiovascular risk profile and patients suffering from PAD were generally included in the very high risk group translating to a LDL target of  $\leq 1.4$  mmol/L (55 mg/dL).<sup>352,353</sup>

Newer statins such as atorvastatin and rosuvastatin showed a greater benefit in terms of reaching lipid targets than simvastatin and pravastatin, especially when using high intensity dosing (i.e.,  $\geq 40$  mg atorvastatin or  $\geq 20$  mg rosuvastatin).<sup>353,354</sup> The addition of ezetimibe to simvastatin also provided additional benefit in a trial with  $> 18\,000$  high risk patients treated for acute coronary syndrome



(thereof 5.5% with PAD), where the net clinical benefit (relative reduction of cardiovascular event rates by 6.4%) was consistent across different patient subgroups. However, no differences concerning cardiovascular mortality were observed between the groups.<sup>355,356</sup>

Several large trials have suggested that PCSK9 inhibitors (evolocumab, alirocumab) may further reduce the risk of cardiovascular events when given in addition to statins.<sup>357–359</sup> However, the evidence in relevant subpopulations outside ischaemic heart disease and acute coronary syndrome treatment remains limited. In a secondary study of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, a subcohort of 3 642 patients (13.2%) with peripheral arterial disease was analysed. In that secondary analysis, evolocumab notably reduced the primary efficacy endpoint of major cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation after 2.5 years by 21% (HR 0.79, 95% CI 0.66 – 0.94). Furthermore, a reduced risk of MALE by 42% was observed.<sup>359</sup> Besides the fact that these benefits were revealed from a pre-specified secondary subgroup analysis with implications for statistical power calculations, the included cohort showed some peculiarities in terms of the guideline directed lipid lowering therapy. Only 69% were on high intensity statin therapy while only 7% received ezetimibe. Interestingly, in line with the overall trial results, no differences in overall mortality were observed between the treatment arms. Along with the paucity of long term safety data and economic considerations in many countries, there remains no common consensus regarding this new drug class.

Hence, PCSK9 inhibitors should remain a third line option for PAD patients at very high risk of ischaemic events who did not reach their stipulated LDL target despite being treated with high dose statin and ezetimibe. More recently, small interfering RNA (siRNA) molecules have been developed as the next generation of drugs designed to antagonise PCSK9. Inclisiran is a siRNA specific for PCSK9 that prevents translation of PCSK9 messenger RNA, leading to decreased concentrations of the protein and lower concentrations of LDL cholesterol. Its definite role in the lipid lowering algorithm of patients with PAD is yet undetermined.

More recently, the role of lipoprotein (a), Lp(a), concentrations on the development and progression of PAD was highlighted. In an analysis of three independent populations, an association between Lp(a) concentrations and outcomes related to PAD was revealed, which emphasised its potential value as a target for pharmacotherapy in this target population.<sup>360</sup> For additional information on this potential new PAD biomarker, please refer to chapter 3.4.

#### Recommendation 28

**For all patients with symptomatic lower limb peripheral arterial disease, high intensity statin treatment is recommended, to reduce the subsequent risk of major cardiovascular events, limb events, and disease progression.**

Class	Level	References	ToE
I	A	Antoniou <i>et al.</i> (2015) <sup>361</sup> Heart Protection Study Collaborative Group (2007) <sup>362</sup> Aung <i>et al.</i> (2007) <sup>35</sup> Kumbhani <i>et al.</i> (2014) <sup>363</sup> Mohler <i>et al.</i> (2003) <sup>33</sup> Peters <i>et al.</i> (2020) <sup>364</sup> Ramos <i>et al.</i> (2016) <sup>365</sup> Vogel <i>et al.</i> (2013) <sup>366</sup> Mills <i>et al.</i> (2011) <sup>367</sup> Rodriguez <i>et al.</i> (2017) <sup>368</sup> De Martino <i>et al.</i> (2014) <sup>369</sup> Cholesterol Treatment Trialists Collaborators (2005) <sup>370</sup> Cholesterol Treatment Trialists Collaborators (2015) <sup>371</sup>	

#### Recommendation 29

**For all patients with asymptomatic lower limb peripheral arterial disease, high intensity statin treatment is recommended to reduce the subsequent risk of major cardiovascular events, limb events, and disease progression.**

Class	Level	Reference
I	C	Consensus

#### Recommendation 30

**For patients > 80 years with lower limb peripheral arterial disease, it is recommended to offer treatment with statins for the same indications that apply to younger people, but caution should be exercised in patients who are under polypharmacy and or with severely impaired liver or kidney function.\***

Class	Level	References	ToE
I	A	Ponce <i>et al.</i> (2019) <sup>42</sup> Leya <i>et al.</i> (2017) <sup>372</sup>	

\* Refer to [Chapter 1.3.1](#) for more information.

#### Recommendation 31

**For patients with lower limb peripheral arterial disease, it is recommended to monitor long term prescription rates and longitudinal adherence to statin therapy to improve treatment concordance.**

Class	Level	References	ToE
I	C	Kokkinidis <i>et al.</i> (2020) <sup>373</sup> Pastori <i>et al.</i> (2020) <sup>36</sup> Peters <i>et al.</i> (2020) <sup>364</sup> Sigvant <i>et al.</i> (2009) <sup>374</sup>	

**Recommendation 32**

For patients with lower limb peripheral arterial disease, it is recommended to reduce the low density lipoprotein cholesterol concentrations to < 1.4 mmol/L (< 55 mg/dL) and decrease it by ≥ 50% if baseline values are within 55 – 110 mg/dL.

Class	Level	References	ToE
I	B	Mach <i>et al.</i> (2020) <sup>352</sup> Cannon <i>et al.</i> (2015) <sup>356</sup> Cholesterol Treatment Trialists Collaborators (2015) <sup>371</sup> Sabatine <i>et al.</i> (2017) <sup>358</sup> Belch <i>et al.</i> (2021) <sup>375</sup>	

**Recommendation 33**

For patients with lower limb peripheral arterial disease who are unable to achieve appropriate lipid targets despite following lifestyle advice and adherence to a high intensity statin therapy with appropriate doses of atorvastatin or rosuvastatin, the addition of ezetimibe is recommended, to reach recommended low density lipoprotein cholesterol target levels.

Class	Level	Reference	ToE
I	C	Cannon <i>et al.</i> (2015) <sup>356</sup>	

**Recommendation 34**

For patients with lower limb peripheral arterial disease who may reach their lipid targets under high intensity statin therapy with or without ezetimibe, the primary use of proprotein convertase subtilisin-kexin type 9 inhibitors is not recommended as first line therapy.

Class	Level	Reference
III	C	Consensus

**4.1.2.3. Antihypertensive agents.** Hypertension is associated with the development and progression of atherosclerosis as well as with unfavourable long term outcomes.<sup>376–384</sup> In line with observations regarding lipid lowering drugs, international data suggest that the prescription rates for antihypertensive medication are considerably lower than recommended.<sup>385,386</sup>

In addition to lifestyle advice including decreased sedentary behaviour and nutritional habits which can reduce the cardiovascular risk and prevalence of hypertension,<sup>387–390</sup> pharmacotherapy should be initiated in accordance with multisocietal guidelines on the management of hypertension.<sup>391,392</sup>

The staged approach recommended by multisocietal guidelines ideally contains a single pill combination therapy of a dual low dose combination (e.g., angiotensin converting enzyme inhibitor or angiotensin receptor blocker plus dihydropyridine calcium channel blocker), followed by a dual full dose combination in a subsequent step. A further escalation can be considered by adding a thiazide like diuretic.<sup>392,393</sup> Some caution is recommended, however, when using fixed dose polypill combinations, as these may cause unwanted side effects when prescribed to reach the considerably lowered blood pressure treatment targets stipulated in the most contemporary guideline recommendations. As there is evidence for their efficacy and safety in patients suffering from PAD, beta blockers

may be added at any step when there is a specific indication (e.g., heart failure, angina, atrial fibrillation).<sup>394–396</sup>

**Recommendation 35**

For patients with lower limb peripheral arterial disease, it is recommended to reduce the blood pressure to ≤ 120 – 129/80 mmHg in patients < 70 years and to ≤ 130 – 139/80 mmHg in patients ≥ 70 years to reduce the risk of major adverse cardiovascular events.

Class	Level	References	ToE
I	A	Unger <i>et al.</i> (2020) <sup>392</sup> Visseren <i>et al.</i> (2021) <sup>397</sup> Williams <i>et al.</i> (2019) <sup>398</sup> Lewington <i>et al.</i> (2002) <sup>384</sup>	

**Recommendation 36**

For patients with lower limb peripheral arterial disease and hypertension, it is recommended that antihypertensive pharmacotherapy follows a stepwise approach.\*

Class	Level	References	ToE
I	A	Visseren <i>et al.</i> (2021) <sup>397</sup> Unger <i>et al.</i> (2020) <sup>392</sup> Yusuf <i>et al.</i> (2008) <sup>382</sup> Ostergren <i>et al.</i> (2004) <sup>378</sup> Heart Outcomes Prevention Evaluation Study Investigators (2000) <sup>381</sup>	

\* Including angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) plus dihydropyridine calcium channel blocker ideally as one pill low (step 1) or full dose combination (step 2). An escalation should be considered by adding a thiazide like diuretic in step 3.

**4.1.2.4. Antidiabetic agents.** While both lifestyle modification and antidiabetic drugs reduce the risk of developing type 2 diabetes in patients with pre-diabetes, it remains uncertain whether antidiabetic drugs as part of secondary prevention in patients with pre-diabetes and manifest macrovascular disease are beneficial.<sup>399</sup>

Consequent glycaemic control in patients with PAD and established type 2 diabetes is clearly important, however, to improve the long term prognosis. Recently published guidelines on the diagnosis and management of diabetes include comprehensive recommendations on lifestyle behaviour change and pharmacotherapy.<sup>400,401</sup> A total of 301 clinical trials were included in a network meta-analysis on the relative efficacy and safety of glucose lowering drugs, including metformin, glucagon like peptide 1 (GLP-1) receptor agonists, sodium glucose linked transporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase 4 (DPP-4), and others alone or in combination. The authors concluded that among adults with type 2 diabetes, there were no notable differences between the drug classes and the risk of cardiovascular or all cause mortality. However, metformin as monotherapy was associated with moderately lower HbA1c levels compared with any other drug classes, and all drugs were effective when added to metformin.<sup>402</sup>

**4.1.2.4.1. Glucagon like peptide 1 receptor agonists.** Besides the effects of other incretin based therapies, glucagon like peptide 1 (GLP-1) receptor agonists have demonstrated cardiovascular as well as renal benefits among patients with cardiovascular disease independent from lowering of HbA1c levels.<sup>403–405</sup> Hence, they are recommended for use in diabetic patients with cardiovascular diseases, chronic kidney disease, and heart failure.<sup>332,400,401</sup>

**4.1.2.4.2. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes, heart failure, and kidney failure.** In 2012, dapagliflozin was one of the first SGLT-2 inhibitors (also known as gliflozins) on the European market and canagliflozin became the first SGLT-2 inhibitor on the US market one year later. Since then, three different drug classes have become available for treatment of type 2 diabetes (2012) and heart failure with reduced ejection fraction (2020).<sup>406</sup> Based on the unprecedented phase-3 Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial, the EMA issued a positive opinion and ultimately also approved the use of dapagliflozin for the treatment of chronic kidney disease in August 2021.<sup>407</sup> Most recently, the 2022 update of the National Institute for Health and Care Excellence (NICE) guidelines on type 2 diabetes in adults included a recommendation to treat patients with diabetes and chronic kidney disease with SGLT2 inhibitors. SGLT2 inhibitors are available as single pill or as combination compounds with metformin to lower the blood glucose through blockage of SGLT-2 receptors in the kidneys, leading to reduced re-absorption of glucose from the urine to the bloodstream.

Several trials have reported important benefits, including lower rates of hospitalisation for heart failure in patients with type 2 diabetes.<sup>408</sup> In 2017, the publications of the CANagliflozin cardioVascular Assessment Study (CANVAS) programme involving 10 142 patients from 30 countries raised concerns about excess major and minor amputation rates in patients who were treated with canagliflozin vs. placebo.<sup>409</sup> Although CANVAS provided evidence that patients with diabetes and high cardiovascular risk who were treated with SGLT2 inhibitors had a notably lower risk of the composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, and renal impairment, the possible safety signal led to boxed warnings by European (February 2017) and US (May 2017) regulators. Interestingly, more recent clinical trials specifically focusing on empagliflozin via the EMPA-REG OUTCOME trial<sup>410</sup> and dapagliflozin via the DECLARE-TIMI 58 trial<sup>408</sup> did not confirm the presence of a higher amputation risk.

The beneficial effects on cardiovascular outcomes in patients with diabetes led to several discussions about the possible underlying mechanism which is probably glucose independent. To further determine the outcomes in patients with established heart failure, the phase 3 placebo controlled DAPA-HF trial randomly assigned 4 744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less to

receive either dapagliflozin or placebo.<sup>411</sup> The treatment with dapagliflozin resulted in a 26% reduction in the composite endpoint including hospitalisation for heart failure and cardiovascular death, regardless of the presence or absence of diabetes.<sup>411</sup> Similar effects were observed in subsequent trials such as EMPEROR.<sup>412</sup>

#### Recommendation 37

**For patients with lower limb peripheral arterial disease and diabetes, it is recommended to reduce the blood glucose to near normal haemoglobin A1c values  $\leq 7\%$  ( $\leq 53$  mmol/mol) to prevent vascular complications.**

Class	Level	References	ToE
I	A	Cosentino <i>et al.</i> (2020) <sup>400</sup> American Diabetes Association (2021) <sup>401</sup> UK Prospective Diabetes Study Group (1998) <sup>413</sup> Diabetes Control and Complications Trial Research Group (1993) <sup>414</sup> Holman <i>et al.</i> (2008) <sup>415,416</sup>	

#### Recommendation 38

**Patients with lower limb peripheral arterial disease and type 2 diabetes, both sodium glucose cotransporter 2 inhibitors and glucagon like peptide 1 receptor agonists are recommended as first line hypoglycaemic agents to reduce the risk of major cardiovascular and renal events.**

Class	Level	References	ToE
I	B	Cosentino <i>et al.</i> (2020) <sup>400</sup> American Diabetes Association (2021) <sup>401</sup> Visseren <i>et al.</i> (2021) <sup>397</sup>	

**4.1.2.5. Influenza vaccination.** There is a paucity of high level comparative effectiveness evidence concerning influenza vaccination in the elderly and or in patients with peripheral arterial disease.<sup>417</sup> In a retrospective observational study by Peters *et al.*,<sup>418</sup> the risk of inpatient hospital stay associated with influenza, acute respiratory distress syndrome, and acute respiratory disease was more than four times higher in patients with peripheral arterial disease than in the control sample. The authors concluded that the strikingly low influenza vaccination rates observed (37.2%), which clearly missed the European and national coverage goals, emphasised the importance of awareness campaigns.<sup>418</sup> Two randomised trials on acute coronary syndrome patients determined the impact of vaccination on long term outcomes. Gurfinkel *et al.*<sup>419</sup> enrolled 200 patients and revealed that the incidence of the primary endpoint cardiovascular death at one year was substantially lower among patients receiving vaccination.<sup>419</sup> Ciszewski *et al.*<sup>420</sup> found that in optimally treated coronary artery disease patients influenza vaccination improved the clinical course and reduced the frequency of coronary ischaemic events.<sup>420</sup>

Recommendation 39			
For patients with lower limb peripheral arterial disease, annual influenza vaccination is recommended, to reduce the risk of a severe influenza infection.			
Class	Level	References	ToE
I	C	Peters <i>et al.</i> (2021) <sup>418</sup> Ciszewski <i>et al.</i> (2008) <sup>420</sup> Gurfinkel <i>et al.</i> (2004) <sup>419</sup>	

**4.1.2.6. Vaccination against SARS-CoV-2.** In a recent registry study on patients hospitalised for SARS-CoV-2 between 1 March and 10 November 2020 ( $n = 3\,830$ , of which 693 had PAD), PAD was independently associated with an increased mortality rate (OR 1.45, 95% CI 1.11 – 1.88) and MACE (OR 1.48, 95% CI 1.16 – 1.87); after controlling for known risk factors.<sup>421</sup> Therefore, it is important to attach a high priority to vaccination against COVID-19 infection in all PAD patients.<sup>422</sup>

Recommendation 40			
For patients with lower limb peripheral arterial disease, full vaccination against COVID-19 disease is recommended due to the increased risk of hospitalisation with severe COVID-19 illness.			
Class	Level	Reference	ToE
I	C	Smolderen <i>et al.</i> (2022) <sup>421</sup>	

## 5. SPECIFIC MANAGEMENT ASPECTS IN ASYMPTOMATIC LOWER LIMB PERIPHERAL ARTERIAL DISEASE

### 5.1. General considerations

Trends in clinical medicine and CV research are moving towards improvements in risk stratification and preventive medicine.<sup>423</sup> Asymptomatic PAD confers a long subclinical phase easily detected by ABI measurements or femoral artery plaque burden assessment using duplex ultrasound.<sup>6,352</sup> Management of asymptomatic PAD is a challenge, however. It is an understudied, growing group with a high risk of fatal and non-fatal CV events and a similar all cause mortality rate today as that reported three decades ago.<sup>92,94,96,424,425</sup> There is a lack of consistency in practice. The underlying reasons may be explained by the absence of direct evidence for patient benefits of lifestyle interventions and medical prophylactic treatment from studies specifically addressing asymptomatic PAD. Furthermore, the wide range of CV risk among the heterogeneous asymptomatic PAD group causes conflicting results regarding potentially beneficial preventive measures and treatments.<sup>62,63,66,150,196,426</sup>

### 5.2. Physical activity

Although individuals with asymptomatic PAD report no exertional leg symptoms, they commonly have impaired lower extremity functioning.<sup>144,427,428</sup> One study has shown that individuals with asymptomatic PAD have notably poorer 6MWD, slower usual paced and fast paced walking speed, smaller calf muscle area, and poorer SF-36 physical

functioning score compared with patients with PAD and classic IC symptoms.<sup>144</sup> Also, compared with an age matched sedentary non-PAD cohort, asymptomatic individuals with PAD have a smaller calf muscle area, worse 6MWD, and poorer WIQ scores.<sup>144</sup> In another study, asymptomatic PAD was associated with a greater mean annual decline in 6MWD, compared with individuals without PAD.<sup>428</sup>

To date, adequately powered RCTs assessing the effects of exercise programmes in asymptomatic PAD are not available. In one pilot RCT, asymptomatic individuals with PAD ( $n = 32$ ) were randomised to supervised treadmill exercise three times a week for three months or to a control group.<sup>429</sup> There were no statistically significant differences between groups in terms of 6MWD, maximum treadmill walking distance, or WIQ walking impairment scores. However, the exercise group experienced statistically significant within group differences. These findings indicate that a supervised treadmill walking programme may improve physical functioning for individuals with PAD who do not have classical IC symptoms, but the results need to be confirmed in studies with larger sample sizes. Another small RCT randomised 38 sedentary volunteer participants with asymptomatic PAD to an interactive home based on-line sedentary reduction programme, including behavioural medicine strategies and an activity tracker or to active control (the active control group received six different on-line videos with PAD educational content, the same educational content was also offered to the investigational treatment arm), including bimonthly online videos with health recommendations related to PAD.<sup>430</sup> Statistically significant differences between groups were found for mean non-sleep sit or lie hours per day, total steps per day, sit to stand transitions per day and 6MWD, favouring the intervention group. In addition, the authors found that increased physical activity and reduced sedentary behaviour were associated with improvements in microvascular reactivity.

Several RCTs have included mixed populations of individuals with IC and asymptomatic PAD. A meta-analysis including nine RCTs has determined the effects of structured and supervised exercise programmes on individuals with PAD, with or without IC.<sup>431</sup> It was observed that supervised exercise improved the primary outcome measures of 6MWD, maximum and pain free walking distance, and haemodynamic variables. In a study by McDermott *et al.*,<sup>432</sup> individuals (81% with asymptomatic PAD) were randomised to supervised treadmill exercise, lower extremity resistance exercise, or to a control group for six months. For the primary outcome of 6MWD, the supervised treadmill exercise group increased their distance walked by 35.9 m (95% CI 15.3 – 56.5,  $p < .001$ ) compared with the control group. In addition, the treadmill group had greater increases in maximum treadmill walking time, brachial artery flow mediated dilation, the WIQ walking impairment distance score, and the SF-36 physical functioning score than the control group. The resistance exercise group had greater increase in maximum treadmill walking time, WIQ walking impairment scores for distance and stair climbing, and SF-36

physical functioning score compared with the control group. The magnitude of changes was similar between asymptomatic and symptomatic individuals. In another study, individuals (72% with asymptomatic PAD) were randomised to a home based, group mediated cognitive behavioural exercise intervention or to a control group.<sup>433</sup> At six months follow up, individuals in the intervention group improved their primary outcome of 6MWD compared with the control group (mean difference 53.5 m (95% CI 33.2 – 73.8,  $p < .001$ ). The intervention group also improved treadmill walking performance, WIQ distance and speed scores, and physical activity levels compared with the control group.

Even though the present studies are small with moderate to high risk of bias and mixed populations, preliminary results indicate that supervised exercise programmes may be beneficial for individuals with asymptomatic PAD to improve functional capacity and HRQoL. Future high quality RCTs are warranted, however, to confirm these findings and to further identify effective interventions for these individuals.

As there is evidence to suggest that the risk of cardiovascular disease increases in patients with diagnosed PAD,<sup>434</sup> striving to reach the general physical activity recommendations for cardiovascular disease prevention,<sup>435</sup> including at least 150 – 300 minutes a week of moderate intensity aerobic physical activity or 75 – 150 minutes a week of vigorous intensity aerobic activity, or an equivalent combination thereof, is of particular importance for individuals with asymptomatic PAD to reduce all cause mortality, cardiovascular mortality, and morbidity. In addition, guidelines recommend decreasing sedentary time to engage in at least light physical activity throughout the day to reduce all cause and cardiovascular mortality and morbidity.<sup>435</sup>

#### Recommendation 41

For all patients with lower limb peripheral arterial disease (including asymptomatic stages) it is recommended to strive for at least 150 – 300 minutes a week of moderate intensity or 75 – 150 minutes a week of vigorous intensity aerobic physical activity, to reduce all cause and cardiovascular mortality and cardiovascular morbidity.

Class	Level	References	ToE
I	A	Kraus <i>et al.</i> (2019) <sup>436</sup> Powell <i>et al.</i> (2018) <sup>437</sup>	

#### Recommendation 42

For individuals with asymptomatic lower limb peripheral artery disease, supervised exercise programmes or structured home based exercise programmes may be considered, to improve maximum walking distance, health related quality of life, physical activity levels, and self reported functional impairment.

Class	Level	References	ToE
Iib	C	McDermott <i>et al.</i> (2004) <sup>429</sup> Laslovich <i>et al.</i> (2020) <sup>430</sup> Farhad <i>et al.</i> (2019) <sup>431</sup> McDermott <i>et al.</i> (2009) <sup>432</sup> McDermott <i>et al.</i> (2013) <sup>433</sup>	

### 5.3. Pharmacotherapy

**5.3.1. Antithrombotic therapy.** In brief, the Prevention Of Progression of Arterial Disease And Diabetes (POPADAD) trial tested whether aspirin and antioxidant therapy, combined or alone, are more effective than placebo in reducing CV events in patients with diabetes mellitus and asymptomatic PAD. Some 1 276 adults aged 40 or more with type 1 or 2 diabetes and  $ABI \leq 0.99$  without CV disease were enrolled. There was no evidence of benefit from either aspirin or antioxidant treatment on the composite hierarchical primary endpoints of CV events and cardiovascular mortality.<sup>438</sup> In the Aspirin for Asymptomatic Atherosclerosis trial, 3 350 participants from a general population without clinical CV disease with a low ABI ( $\leq 0.95$ ) were enrolled. The administration of aspirin compared with placebo did not result in a significant reduction in vascular events.<sup>439</sup>

Another recently published umbrella review and meta-analysis reviewed 28 meta-analyses testing 33 clinical outcomes and 41 antiplatelet comparisons in 72 181 patients. In asymptomatic PAD patients taking antiplatelet monotherapy, the only positive secondary prevention outcome was for non-fatal stroke, where moderate quality evidence of a small absolute reduction was found (5 [0 – 8] events fewer per 1 000 patients;  $p = .055$ ), but there was a statistically significant increase in the risk of major bleeding.<sup>440</sup>

#### Recommendation 43

Patients with asymptomatic lower limb peripheral arterial disease without other contemporary indications for antithrombotic treatment should not be treated with aspirin as bleeding risk and side effects are likely to outweigh the benefit.

Class	Level	References	ToE
III	A	Belch <i>et al.</i> (2008) <sup>441</sup> Fowkes <i>et al.</i> (2010) <sup>439</sup> Ambler <i>et al.</i> (2020) <sup>440</sup>	

**5.3.2. Antihypertensive therapy.** A *post hoc* analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial assessed the prognostic importance of ABI measurement as a predictor of CV events and the effect of ramipril treatment on prognosis in patients with symptomatic PAD and in groups of patients with asymptomatic PAD evaluated by ABI, followed for a mean of 4.5 years. The HOPE study patients at high risk of CV events were randomised in a 2x2 factorial design to treatment with ramipril or placebo and vitamin E or placebo. A primary outcome event of myocardial infarction, stroke, or death from cardiovascular causes was seen in 13.1% of patients with normal  $ABI > 0.9$ , in 18.2% with  $ABI > 0.6 - 0.9$  and in 18.0% with  $ABI < 0.6$  ( $p < .001$ ), respectively. Ramipril reduced the risk of clinical outcomes in those with symptomatic PAD as well as in the patients with asymptomatic PAD. However, given that the event rates were higher in those with an  $ABI < 0.9$ , the absolute benefits are about twice as large in this group (50 per 1 000 events prevented) compared with those with an  $ABI > 0.9$  (24 per 1 000 events prevented). This suggests

that in patients with CAD and asymptomatic PAD, using the ABI is a simple method to further identify high risk patients who can benefit from preventive strategies.<sup>378</sup> See 4.1.2.3 for further details on antihypertensive treatment in lower limb PAD patients with hypertension.

**5.3.3. Lipid lowering therapy.** The Heart Protection Study randomly allocated 6 748 patients and 13 788 other high risk participants, regardless of cholesterol levels, to receive 40 mg simvastatin daily or placebo. A benefit of cholesterol lowering treatment was demonstrated with a 22% (95% CI 15 – 29) relative reduction in rate of major vascular events. However, asymptomatic PAD was not specifically included unless patients had manifestations in other vascular territories which is why the benefit for asymptomatic PAD remains unclear.<sup>362</sup> Recently published treatment guidelines suggested a femoral artery plaque burden, on arterial ultrasonography, as a risk modifier indicating a more aggressive lipid lowering therapy in individuals at low or moderate risk of atherosclerotic CV disease even without symptoms (336) (see section 4.1.2.2 and Recommendation 29). The 2017 ESC guidelines on the diagnosis and treatment of PAD (in collaboration with the European Society for Vascular Surgery [ESVS]) stated that patients with asymptomatic PAD are at high risk of CV events and concluded that these patients will benefit from most CV preventive strategies, especially strict control of risk factors. In addition, the document clarified that an ABI < 0.9 is associated with an increased CV event rate and that CV risk scores when combined with an ABI < 0.9 criterion upgraded one third and one fifth of low risk women and men, respectively.<sup>6</sup>

**5.3.4. Cost effectiveness of secondary prevention in asymptomatic lower limb peripheral arterial disease.** Ten years ago, a first estimation of long term costs and quality adjusted life years (QALYs) in asymptomatic PAD was performed by employing a decision analytic model for preventive medication based on earlier published data. Using ACE inhibition resulted in a hazard ratio (HR) of 0.67 (95% CI 0.55 – 0.79) whereas the corresponding HRs for statins and clopidogrel were 0.74 (95% CI 0.70 – 0.79) and 0.72 (95% CI 0.43 – 1.00), respectively. Aspirin had a statistically non-significant HR of 0.87 (95% CI 0.72 – 1.03). ACE inhibition was associated with the largest reduction in events leading to the highest gain in QALYs.<sup>442</sup> More recently, Itoga *et al.* re-evaluated the cost effectiveness of initiating medical therapy after a positive ABI screen in 65 year old patients using a Markov model.<sup>434</sup> They modelled progression to symptomatic PAD and CV events with and without ABI screening, evaluating differences in costs and QALYs. The model found an incremental cost of US \$338 and an incremental QALY of 0.00380 with one time ABI screening, resulting in an incremental cost effectiveness ratio (ICER) of \$88,758/QALY over a 35 year period. The long term effects of medication on asymptomatic PAD patients encompass one of the larger uncertainties in the predicted ICER, including the HR for CV related events. The lack of high quality data leads to an indeterminate conclusion on whether asymptomatic PAD screening with the ABI test in the general population is truly below the generally accepted thresholds for cost effectiveness

of secondary preventive medications.<sup>434</sup> See section 3.1.1.2 for further details on ABI screening.

#### Recommendation 44

**For patients with lower limb peripheral arterial disease, even if asymptomatic, it is recommended to consider an ankle brachial index  $\leq 0.9$  or  $\geq 1.4$  a risk enhancing factor for a cardiovascular event and for an increased all cause mortality.**

Class	Level	References	ToE
I	A	Fowkes <i>et al.</i> (2006) <sup>110</sup> Hajibandeh <i>et al.</i> (2017) <sup>95</sup> Heald <i>et al.</i> (2006) <sup>443</sup> Qu <i>et al.</i> (2015) <sup>444</sup> Pereira Filho <i>et al.</i> (2022) <sup>208</sup> Sigvant <i>et al.</i> (2016) <sup>87</sup>	

## 6. SPECIFIC MANAGEMENT ASPECTS IN INTERMITTENT CLAUDICATION

### 6.1. General approach and stepwise care approaches

Alongside pharmacological interventions, there are several potentially effective treatment options that target IC limb symptoms, i.e., exercise therapy, endovascular and surgical revascularisation. In general, exercise therapy is non-invasive and has a favourable safety profile whereas invasive treatment options commonly offer symptom relief, but durability may be limited. In line with previous guidelines, it is recommended that patients with PAD should be treated in a stepwise care fashion to improve the patient tailored benefit–harm ratio of the treatment approach.<sup>6,445</sup> A stepwise care approach means that the first line treatment strategy in IC should be based on risk factor management and best medical treatment alongside suitable exercise therapy interventions, whereas revascularisation procedures should be reserved for a potential secondary treatment step and should be undertaken only in suitable patients whose conditions do not meaningfully improve on conservative treatment. The aims of stepwise care approaches are to reduce the risk of complications associated with invasive treatment and to enhance overall cost effectiveness. Importantly, it is reasonable to consider such a stepwise management strategy both in patients with *de novo* IC symptoms and in patients who present with recurrent IC symptomatology after a failed revascularisation attempt.

In one RCT, 178 IC patients with femoropopliteal lesions were allocated to either SET or percutaneous transluminal angioplasty, or a combination of both. Costs of care, quality of life, QALY, and clinical outcome measures were obtained during one year of follow up. Although all treatment options were clinically effective, SET as first line of treatment was shown to be the most cost effective option compared with primary endovascular intervention or a combination of both in the UK healthcare system (cost per QALY €6 147 vs. €11 777 vs. €10 649).<sup>446</sup> The IRONIC trial randomised patients with IC and aorto-iliac or femoropopliteal lesions to either a primary revascularisation strategy and structured unsupervised exercise or structured unsupervised exercise alone. At one and two years, a

primary revascularisation strategy led to higher HRQoL and walking distances<sup>447,448</sup> whereas these observed differences were lost at the five year follow up.<sup>449</sup> The CLEVER trial allocated 111 PAD patients with moderate to severe claudication due to aorto-iliac stenosis to SET, endovascular treatment or best medical treatment. From the US societal perspective, the incremental cost effectiveness ratio for endovascular treatment vs. SET at five years was USD 122 600 per QALY.<sup>450</sup> Comparable results in favour of SET as a first line of therapy were observed by others, with varying costs per QALY.<sup>451–457</sup>

In the prematurely stopped SUPER study ( $n = 240$ , of a planned 400) that compared iliac artery stenting with SET, comparable results between the treatments were observed in terms of treadmill walking capacity and disease specific HRQoL at one year.<sup>458</sup> Recently, a *post hoc* cost effectiveness analysis of 206 IC patients from the same study indicated that endovascular revascularisation of lesions in the iliac segment was slightly more cost effective than SET, but the authors questioned the clinical relevance of this due to the small observed differences and relatively high costs associated with endovascular therapy as primary treatment.<sup>459</sup> A stepwise care approach has been studied to a greater extent in the Netherlands, where SET is organised in a community based setting.<sup>460</sup> It was hypothesised that higher adherence to a stepped care approach would result in lower rates of limb revascularisation. Using healthcare claims, 54 504 patients with PAD were included and compared by primary treatment. Over time, between 2013 and 2017, adherence to stepped care increased to 87%. Patients who underwent primary endovascular treatment had a higher risk of secondary interventions than those who received SET first (multivariable HR 1.44; 95% CI 1.37 – 1.51;  $p < .001$ ). Approximately 83% of patients in the primary SET group remained free of revascularisation for up to five years of follow up.<sup>461</sup>

Of note, a stepped care approach may be hampered by the availability of adequate SET programmes. For further details see 6.2.4. In addition, due to comorbid conditions, not all patients will be able to undergo SET (see 6.2.4).

## 6.2. Exercise therapy

**6.2.1. Mechanisms.** The pathophysiological mechanisms underlying the functional impairment in IC are multifaceted and incompletely understood. Current evidence suggests that both anatomical and functional vascular abnormalities, contributing to blood flow limitation during exercise, and structural and pathophysiological abnormalities in calf skeletal muscle are major contributors. Several mechanisms underlying the beneficial effects of exercise therapy have been suggested, including both local and systemic adaptations leading to an increased walking capacity. There is evidence that a standard supervised exercise programme leads to reduced levels of inflammatory markers, improved endothelium dependent vasodilation, increased capillary density of the gastrocnemius muscle, change in muscle fibre composition, and altered skeletal muscle metabolism through an increase in oxidative enzymes.<sup>464–466</sup>

**6.2.2. Different designs of exercise therapy.** The efficacy of exercise to improve maximum and pain free walking distance and HRQoL in patients with IC is supported by a large body of evidence from the past 30 years.<sup>467–473</sup> The modality that has been most studied in IC is SET, performed as treadmill based intermittent walking exercise to at least a moderate level of claudication pain followed by a short period of rest for a total duration of 30 – 60 minutes/session, three times a week for three to six months.<sup>464</sup>

More recently, there has been increasing interest in evaluating the effects of different exercise settings, typically comparing SET with usual medical care or unsupervised exercise programmes. In the meta-analyses by Parmenter *et al.*<sup>468</sup> and Fakhry *et al.*,<sup>474</sup> SET resulted in a mean improvement in maximum and pain free walking distance, compared with usual medical care. Vemulapalli *et al.*<sup>471</sup> demonstrated that compared with unsupervised exercise, various types of SET programmes were associated with an improvement in maximum and pain free walking distance at six and 12 months, but there was no difference in HRQoL or the walking impairment questionnaire. Moreover, it was confirmed in the meta-analysis by Gommans *et al.*<sup>472</sup> that SET was superior to no exercise (control group), walk advice, or unsupervised home based exercise programmes (HBET) in terms of maximum and pain free walking distance.<sup>472</sup> However, results from this study indicate that the efficacy of HBET may be equal to SET at six month follow up. Similarly, the most recent meta-analysis confirmed the results that SET is superior to HBET for improvement in maximum and pain free walking distance.<sup>475</sup> Overall, the risk–benefit ratio for SET in IC is favourable with extremely low cardiovascular complication rates.<sup>476</sup>

### Recommendation 45

**For patients with intermittent claudication, a stepwise approach is recommended, providing risk factor management, best medical treatment, and exercise therapy as a first step, and revascularisation as a second step in compliant patients with continued disabling limb symptoms.**

Class	Level	References	ToE
I	B	Fakhry <i>et al.</i> (2021) <sup>454</sup> Hageman <i>et al.</i> (2017) <sup>455</sup> Van den Houten <i>et al.</i> (2016) <sup>453</sup> Reynolds <i>et al.</i> (2014) <sup>450</sup> Fokkenrood <i>et al.</i> (2014) <sup>452</sup> Mazari <i>et al.</i> (2013) <sup>462</sup> Spronk <i>et al.</i> (2008) <sup>463</sup> Treesak <i>et al.</i> (2004) <sup>456</sup> De Vries <i>et al.</i> (2002) <sup>457</sup>	

Recommendation 46			
For patients with intermittent claudication, a supervised exercise programme is recommended as first line therapy to improve maximum and pain free walking distance, health related quality of life, and self reported functional impairment.			
Class	Level	References	ToE
I	A	Fokkenrood <i>et al.</i> (2013) <sup>477</sup> Hageman <i>et al.</i> (2018) <sup>470</sup> Parmenter <i>et al.</i> (2015) <sup>468</sup> Vemulapalli <i>et al.</i> (2015) <sup>471</sup> Gommans <i>et al.</i> (2014) <sup>478</sup> Fakhry <i>et al.</i> (2012) <sup>474</sup> Pymmer <i>et al.</i> (2021) <sup>475</sup>	

Although SET provides benefit for patients with IC, it remains underused.<sup>479–481</sup> Walking advice (WA) without any follow up or structured home based exercise therapy (HBET) with an observation component, e.g., exercise logbooks or accelerometers, to increase exercise motivation, are therefore considered interesting alternatives to SET.<sup>479</sup> Studies supporting effects of HBET are more recent than studies supporting SET and there are conflicting results on the efficacy. A Cochrane report showed that HBET was not superior to WA and was less effective than SET in improving maximum and pain free treadmill measured walking distance.<sup>470</sup> In addition, there were no clear differences in HRQoL parameters nor in self reported functional impairment between SET and HBET, but some improvements in HRQoL favouring SET over WA were found. Data showed no clear difference in HRQoL between the HBET and WA groups. On the contrary, a meta-analysis including a total of 11 RCTs showed that HBET improved maximum walking distance (assessed with treadmill tests and 6MWT) and pain free walking distance (assessed with treadmill tests) in the short term, compared with usual care.<sup>482</sup> The most recent meta-analysis concluded that HBET was inferior to SET.<sup>475</sup> In comparison between HBET and unsupervised exercise advice or controls, results were conflicting, but generally in favour of HBET. All HBET programmes included walking exercises between three and five sessions/week, typically for a total programme duration of 12 – 24 weeks. Motivational approaches in the included studies varied substantially, and findings suggest that the type of behaviour intervention was more important than the number of contacts with healthcare professionals. When evaluating effects of exercise therapy in patients with IC, it is important to consider the phenomenon, exercise on the outcome measure (i.e., the inappropriate use of treadmill walking both as part of the exercise intervention and as the trial endpoint, leading to potential imbalances between treatment arms, as one treatment arm in the study become substantially more familiar with treadmill testing) and to take note that the outcomes of walking distance obtained by treadmill tests and 6MWT cannot be used interchangeably.<sup>223</sup>

Recommendation 47			
For patients with intermittent claudication, a structured home based exercise programme with behaviour intervention strategies should be considered, to improve maximum and pain free walking distance, when supervised exercise therapy is not possible.			
Class	Level	References	ToE
Iia	A	Golledge <i>et al.</i> (2019) <sup>482</sup> Pymmer <i>et al.</i> (2021) <sup>475</sup>	

**6.2.3. Alternative exercise modalities.** As not all patients with IC are able to complete the commonly recommended treadmill or track walking programmes, alternative exercise modalities have been suggested. Being able to offer different exercise alternatives may potentially improve adherence, as this enables better alignment with patient preferences. A recently published Cochrane Report including 10 RCTs determined the effect of alternative exercise modes on walking distance compared with traditional walking exercise.<sup>483</sup> Alternative modes of exercise included arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, or combinations of exercise. All exercise programmes had to be supervised at least twice a week during at least six weeks to be included in the meta-analysis. Overall, there was no clear difference between groups regarding maximum and pain free walking distance. As only a few studies reported on HRQoL and functional impairment, meta-analysis was not possible except for the WIQ distance score showing little or no important difference between groups. The certainty of evidence was judged to be low, mainly due to risk of bias and low sample sizes. In addition, more studies are needed to make a meaningful subgroup comparison between each alternative exercise mode and walking exercise. These findings indicate that alternative modes of exercise should be considered when supervised walking exercise is not an option.

Protocols for exercise therapy in patients with IC have traditionally recommended intermittent walking to moderate or higher claudication pain levels.<sup>464</sup> As exercise related pain is considered one potential reason for poor exercise adherence,<sup>484</sup> effects of exercise interventions including no, or mild levels of claudication pain have been considered. A systematic review suggests that pain free SET may be as beneficial as moderate pain SET for improving walking performance in patients with IC.<sup>485</sup> Importantly, there were only two small RCTs identified, and these studies did not include a SET group exercising at maximum claudication pain. The most recently published meta-analysis concluded that there is strong evidence in support of structured high pain exercise, and some evidence in support of structured low pain exercise, to improve walking ability in patients with IC, with both performing better than unstructured exercise advice only.<sup>486</sup>

Regarding exercise intensity, a recently published meta-analysis showed a larger increase in maximum walking distance following walking exercise at vigorous intensity



compared with light to moderate intensity. In contrast, a larger increase in pain free walking distance was observed following light to moderate intensity exercise compared with vigorous intensity exercise.<sup>487</sup> In addition, results from a RCT showed that among patients with IC, low intensity HBET was less effective than high intensity HBET and was not notably different from non-exercised controls.<sup>488</sup> Therefore, adequately powered RCTs are needed to compare all three pain thresholds in different settings before firm conclusions can be made.

#### Recommendation 48

**For patients with intermittent claudication, alternative modes of supervised exercise programmes, including arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, and combinations of exercise should be considered, to improve maximum and pain free walking distance, when supervised walking exercise is not possible.**

Class	Level	Reference	ToE
Ia	A	Jansen <i>et al.</i> (2020) <sup>483</sup>	

#### 6.2.4. Implementation of supervised exercise programmes.

Even though the evidence supporting the efficacy of SET programmes is robust, only a small proportion of all diagnosed IC patients receive this safe, efficient, and structured treatment in most countries.<sup>479–481</sup> According to a recently published overview from 17 European countries, SET programmes only exist in 59% of countries and SET reimbursement is available in 41% of countries.<sup>489</sup> In another study, vascular surgeons in parts of Europe generally recognise SET to be beneficial for patients with IC, but less than one in three reported having access to SET programmes.<sup>481</sup> Where SET programmes are available, barriers to patients are commonly described, such as poor health literacy, comorbidities, lack of motivation, claudication pain, travel expenses, and distance to the hospital.<sup>479–481</sup> Patient adherence to SET programmes are reported to be generally low.<sup>490,491</sup> To increase referral and adherence to SET programmes, it is important to further understand the barriers and enablers to exercise for patients with IC. Although some may be similar across healthcare systems, others may be specific to each system. In the Netherlands, for example, a community based network for SET was implemented to solve the problems of transportation time and costs for patients, as well as the restricted capacity of hospital based SET.<sup>492</sup> The national integrated care network (Claudication-Net) in the Netherlands has resulted in improved SET referral rates, for example by increased accessibility to physiotherapists, increased awareness of referring physicians and by offering full reimbursement.<sup>493</sup> The American Heart Association (AHA) has published a practical guide for how to deliver SET programmes to patients with IC, which summarises requirements for referral and coverage of SET to increase availability of exercise.<sup>494</sup> In addition to the IC specific evaluations of functional capacity, it is suggested by both AHA and the European Society of Cardiology (ESC) to

perform a bicycle ergometry exercise stress test in patients with current or prior symptomatic cardiac disease for better evaluation of central limitations before starting a SET programme.<sup>494,495</sup> Helping patients transition to long term maintenance of unsupervised exercise once SET is completed is a requisite to maintain and further improve exercise outcomes.<sup>494</sup>

#### 6.2.5. The place for cardiovascular exercise rehabilitation in intermittent claudication.

A position paper from the ESC argues that PAD is a qualifying diagnosis to enter cardiac rehabilitation (CR) programmes in several European countries.<sup>495</sup> However, patients with PAD are currently referred to CR in only a minority of cases and often when associated with other cardiovascular conditions.<sup>496</sup> A recently published European position paper showed that 34% of the SET programmes are PAD dedicated, while 23% are part of a CR programme.<sup>489</sup>

The evidence for CR programmes in patients with PAD is, however, still limited due to lack of RCT studies. One recently published RCT has shown that a specialised cross sector CR programme for three months for patients with IC demonstrated substantial effects on maximum walking distance, physical activity, health related quality of life, and healthy diet, but not on pain free walking distance and smoking, compared with usual care including best medical treatment and walk advice.<sup>497</sup> Several cohort studies have shown that CR attendance is associated with a similar reduction in mortality<sup>498</sup> and physical fitness<sup>498–500</sup> for patients with and without PAD. Stauber *et al.*<sup>501</sup> reported that following a 12 week CR programme, patients with PAD showed improvements in anxiety levels, negative affect, and bodily pain. These results suggest that CR programmes may be beneficial for patients with PAD and could be an option for providing access to supervised exercise and enhanced medical care for these patients. Further high quality RCTs are needed to confirm these results.

#### Recommendation 49

**For patients with intermittent claudication, participation in an exercise based cardiac rehabilitation programme may be considered, to improve maximum walking distance and self reported functional impairment when supervised exercise therapy is not possible.**

Class	Level	Reference	ToE
Ib	B	Siercke <i>et al.</i> (2021) <sup>497</sup>	

#### 6.2.6. Exercise therapy as an adjunct to lower limb revascularisation procedures.

As recommended in chapter 1.3.1 (Recommendation 1), all IC revascularisation decisions should be individualised and involve the patient in a well informed and shared decision making process that considers expected treatment benefit, procedure related risk, and long term patency. For patients who are ultimately deemed suitable and subsequently undergo a

revascularisation procedure, evidence suggests that patient benefits as offered by the procedure could be enhanced by combining the invasive procedure with SET. The combination of revascularisation with a SET programme results in a more marked walking distance improvement and additional HRQoL benefits compared with both revascularisation and SET monotherapy.<sup>502–509</sup> The added benefit of SET in combination with revascularisation has been consistently shown after both open and endovascular IC treatment procedures.<sup>506</sup> Moreover, to offer such combination therapy reduces the number of secondary revascularisation procedures compared with revascularisation as a standalone treatment of limb symptoms.<sup>507</sup> This additive effect of SET when added to a revascularisation procedure has been demonstrated up to one year after a revascularisation procedure, whereas more sustainable effects of combination therapy over monotherapeutic strategies have not been confirmed.<sup>503,508,510,511</sup> While a recent network meta-analysis based on RCTs that investigated the efficacy of the currently available distinct treatment options for IC limb symptoms indicated that the combination of SET and revascularisation was the overall most effective method to improve maximum walking distance during moderate term follow up, none of the commonly available treatment methods (revascularisation, SET, HBET, cilostazol and different combinations) translated to sustained patient benefits after two years following treatment initiation, clearly indicating a need for more durable IC limb symptom treatment options.<sup>512</sup>

#### Recommendation 50

For patients with intermittent claudication who have undergone a revascularisation procedure, it is recommended to initiate or continue with supervised exercise therapy to increase walking capacity and health related quality of life and to decrease the need for secondary revascularisation procedures.

Class	Level	References	ToE
I	A	Saratzis <i>et al.</i> (2019) <sup>513</sup> Klaphake <i>et al.</i> (2018) <sup>503</sup> Meneses <i>et al.</i> (2017) <sup>504</sup> Aherne <i>et al.</i> (2015) <sup>506</sup> Fakhry <i>et al.</i> (2018) <sup>507</sup> Doshi <i>et al.</i> (2021) <sup>508</sup> Bø <i>et al.</i> (2013) <sup>514</sup> Fakhry <i>et al.</i> (2015) <sup>511</sup> Thanigaimani <i>et al.</i> (2021) <sup>512</sup> Kruidenier <i>et al.</i> (2011) <sup>515</sup>	

**6.2.7. Behavioural interventions to support exercise programmes in intermittent claudication.** Supervised exercise programmes have been demonstrated to improve walking distance in patients with intermittent claudication; however, there is relatively low uptake of these lifestyle modifications in clinical practice.

In a systematic review, Abaraogu found that most exercise programmes for patients with IC either did not incorporate structured patient education into the programme or

it was unclear how education was delivered. This review found that data from a small number of trials identified potential for physical activity improvement with structured education interventions.<sup>516</sup>

In a small non-randomised single arm pilot study of 30 IC patients, a low intensity psychological intervention using a motivational interviewing approach was used by a health psychologist to build patient self confidence and reduce patient resistance to behaviour change. The study demonstrated a borderline statistically significant change in step counts and a trend towards lower body weight from baseline.<sup>517</sup>

Cunningham *et al.* undertook a small randomised, parallel group trial (total  $n = 58$ ) of usual care or a brief psychological intervention (two sessions of one hour each) plus usual care. Motivational interviewing techniques were used in 28 patients. There was a statistically significant increase in daily steps at four months (measured by a pedometer) of 1 576 in the group having psychological intervention compared with the control group ( $p < .001$ ). This difference was sustained at one and two years. Fewer patients in the intervention group required subsequent angioplasty or bypass surgery.<sup>518,519</sup>

McDermott *et al.*<sup>433</sup> randomised 194 patients with PAD to a six month home based exercise programme including weekly, group mediated cognitive behavioural intervention or to a weekly health education session only. At six months, there was a notable improvement in six minute walk distance of 53.5 metres in favour of the home based exercise programme.

#### 6.3. Pharmacotherapy to improve walking capacity

Few studies have determined the impact of cilostazol, naftidrofuryl, pentoxifylline, and others on the maximum walking distance in IC patients, with heterogeneous results. Momsen *et al.*<sup>520</sup> identified 220 trials, of which only 43 fulfilled the quality criteria. In those trials, the observed improvements in maximum walking distance were only modest. The authors concluded that given the limited benefits, statins seemed to be the most efficient drug at that moment.<sup>520</sup> In another systematic review and meta-analysis on the efficacy of cilostazol, naftidrofuryl oxalate, and pentoxifylline for treatment of intermittent claudication, Stevens *et al.*<sup>521</sup> identified 26 randomised controlled trials, of which 11 trials provided relevant data. Naftidrofuryl oxalate was ranked first for both maximum and pain free walking distance followed by cilostazol and pentoxifylline. The authors concluded that both naftidrofuryl oxalate and cilostazol are effective treatments with minimal serious adverse events.<sup>521</sup> Bedenis *et al.*<sup>522</sup> and Brown *et al.*<sup>523</sup> identified 16 double blind randomised controlled trials including 3 972 participants comparing cilostazol with placebo, of which five studies also compared cilostazol with pentoxifylline. Cilostazol has been shown to improve maximum walking distance but was associated with higher odds of experiencing headache. The authors further concluded that very limited data indicated no difference between cilostazol and pentoxifylline for improving walking distance and data were too limited for any conclusions on other outcomes.<sup>522,523</sup> In an updated Cochrane review on the

effect of pentoxifylline for intermittent claudication by Salhiyyah *et al.*,<sup>524,525</sup> the authors reviewed 24 studies and concluded that, although generally well tolerated, high quality data are currently insufficient to confirm the benefits of pentoxifylline for intermittent claudication. When using cilostazol or naftidrofuryl oxalate, it is further recommended to stop treatment after three to six months of therapy if no improvement has been noted, as all trials showed that the treatment benefit appeared within this time window in patients who responded to the treatment.

Recommendation 51			
For patients with lifestyle limiting intermittent claudication who adhere to best medical treatment including exercise therapy, cilostazol or naftidrofuryl oxalate should be considered, to improve walking distance, but treatment should be stopped after three to six months of therapy if no improvement has been noted.			
Class	Level	References	ToE
Iia	A	Bedenis <i>et al.</i> (2014) <sup>522</sup> Stevens <i>et al.</i> (2012) <sup>521</sup> Salhiyyah <i>et al.</i> (2015) <sup>524</sup> Salhiyyah <i>et al.</i> (2012) <sup>525</sup> Dawson <i>et al.</i> (2000) <sup>526</sup>	

Prostanoids are a family of lipid mediators derived from the cyclo-oxygenases or prostaglandin synthases with various interactions with the renal and cardiovascular system, atherothrombosis, and platelet activity. To date, most studies have concentrated on patients who suffer from chronic limb threatening ischaemia, with heterogeneous results.<sup>525,527,528</sup> No sufficient evidence is available addressing an impact on walking impairment in patients with intermittent claudication (Fig. 11).

Recommendation 52			
For patients with intermittent claudication, prostanoids are not recommended to improve walking distance.			
Class	Level	References	ToE
III	B	Salhiyyah <i>et al.</i> (2012) <sup>525</sup> Robertson <i>et al.</i> (2013) <sup>528</sup>	

#### 6.4. Invasive management of intermittent claudication

##### 6.4.1. General considerations and patient selection.

Various considerations are important when planning the invasive management of patients with intermittent claudication. Essentially, the patient individual risk profile and expected benefit should be weighed up. Due to the paucity of validated and commonly accepted tools to determine any lifestyle limitation beyond walking distance impairment, stringent patient involvement appears mandatory. Furthermore, the likelihood of achieving pre-defined treatment goals should be estimated which necessitates the meticulous consideration of complex lesion characteristics as well as available technical expertise. While the provision of infrastructure may differ widely between healthcare systems, a reasonable number of severely ill patients require inpatient

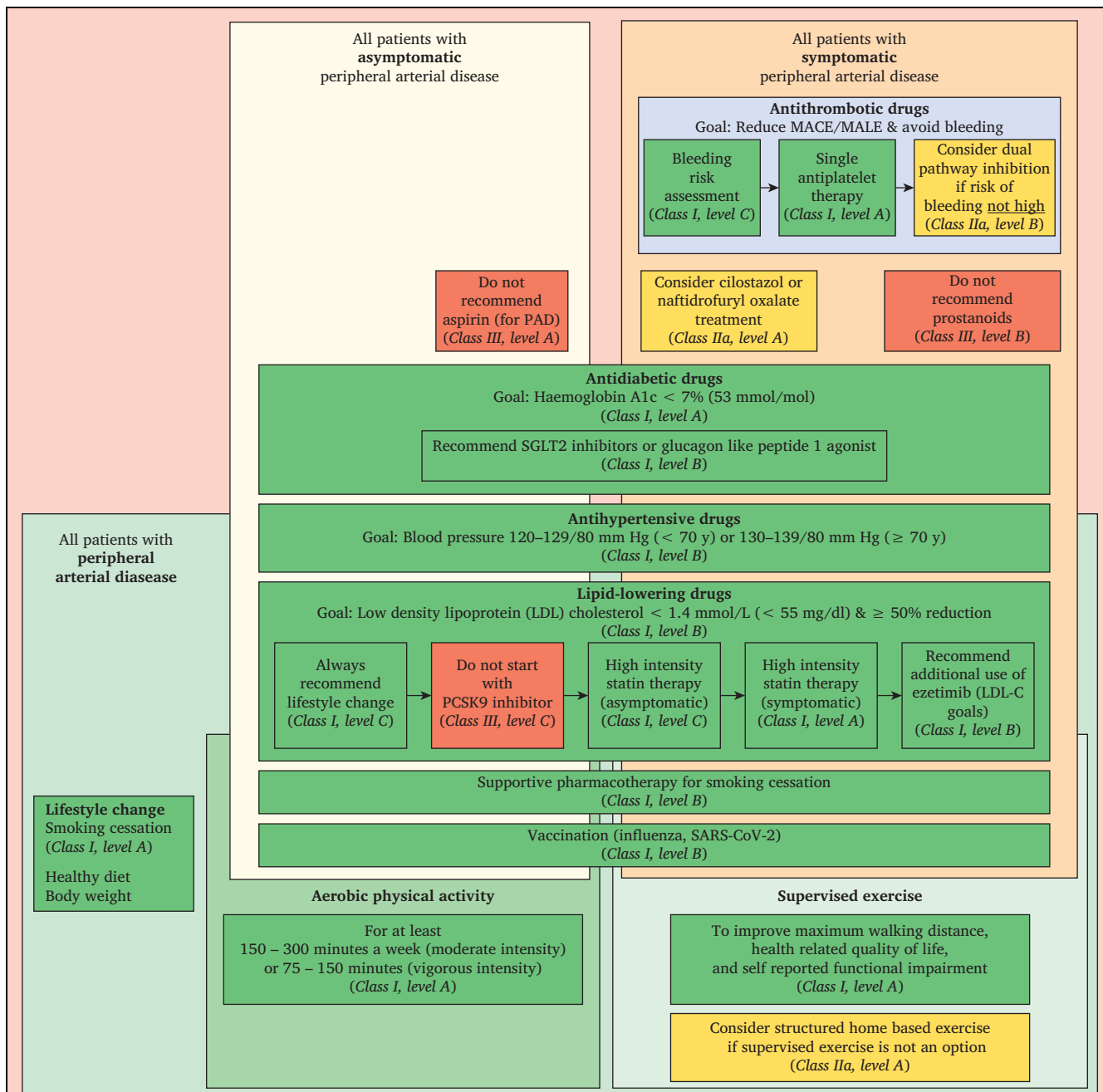
treatment whereas others can be treated under outpatient or daycare circumstances. These country specific aspects and reimbursement effects are beyond the scope of these guidelines. During recent years, the use of risk prediction models has gained increasing attention to guide both clinicians and patients through these challenges to find the best low risk approach to answer realistic expectations.

Figure 12 outlines the principal factors that need to be considered and carefully evaluated before considering an IC revascularisation procedure and refers to the different chapters in this guideline that provide more detail on these important steps in the management of IC.

##### 6.4.2. Anatomical segment considerations and choice of suitable invasive techniques.

Any invasive treatment for claudication should offer long term benefit at low risk of complications.<sup>529</sup> The revascularisation modality is an interdisciplinary decision making process and should be based on the anatomical location of disease (i.e., aorto-iliac segment, common and deep femoral artery, femoropopliteal or infra-popliteal segments or combinations) as well as the extent of arterial obstruction. The decision making process is complicated by a myriad of device technologies and surgical techniques available, the paucity of high quality randomised controlled trials (RCTs) with long term follow up, and inconsistent endpoints, as well as the heterogeneity among study participants. The guideline writing committee deemed that the previous systematic reviews and meta-analysis on this topic were inappropriate within the specific context of revascularisation for IC indications, which is why new systematic reviews and meta-analysis were performed by members of the GWC to support guideline development.<sup>5</sup> While the primary target population reported on in this guideline document are patients with IC, older randomised trials mainly included patients with CLTI or reported on a mixture of anatomical levels treated. In the more recent RCTs more specific patient cohorts have been evaluated (often with a majority of IC patients) and while lesion characteristics were rather precisely reported only a small percentage had CLTI. Clinical and methodological heterogeneity among studies is thus substantial with respect to patient comorbidities, lesion characteristics, endovascular device features, surgical techniques used, and endpoint definitions, thereby reducing the applicability of the results. The general quality of included studies is deemed low to moderate, echoing the small scale, industry sponsored, and open label nature of many past RCTs which often displayed substantial loss to follow up and were frequently underpowered for the assessment of long term, clinical endpoints, although the more recent trials in this field of research were of higher methodological quality. Accordingly, several limitations must be considered when applying the recommendations given below. As far as possible, the revascularisation chapter as below was based on IC specific evidence.

It is also advisable to be cautious about using new medical devices and techniques suggested for PAD treatment that have not been properly evaluated in clinical trials, and to restrict the use of such devices and technologies

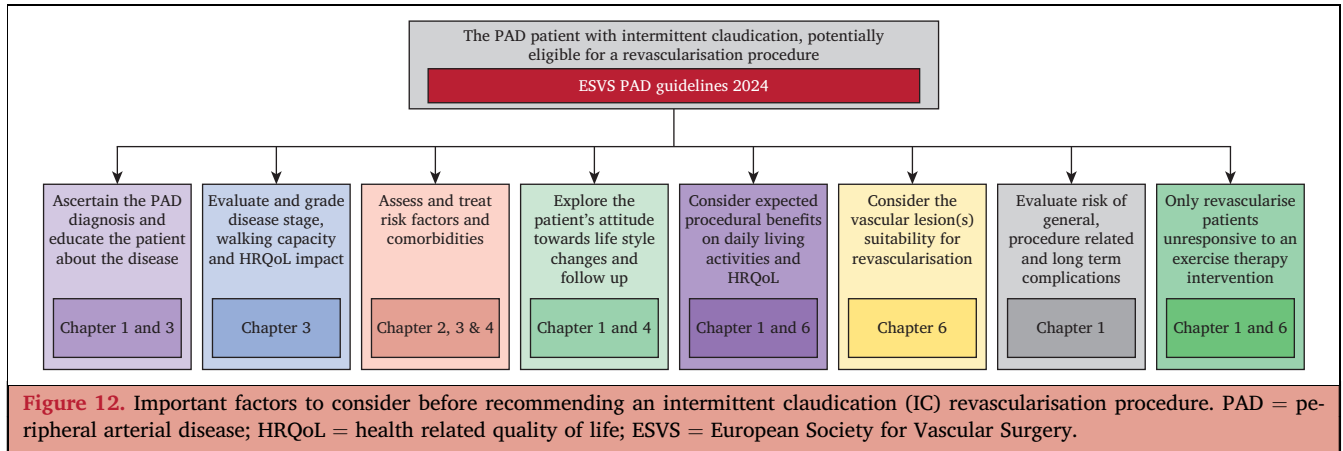


**Figure 11.** Schematic illustration of best medical treatment strategies in PAD patients. MALE = major adverse limb events; MACE = major adverse cardiovascular events; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGLT2 = sodium glucose co-transporter 2. Fields have been colour-coded to represent the Class of each recommendation (dark green = is recommended, yellow = should be considered, and red = is not recommended).

within the framework of studies approved by research ethics committees until adequately evaluated.

Recommendation 53		
It is recommended that new and emerging revascularisation concepts and techniques for intermittent claudication that have not yet been adequately evaluated in clinical trials and or have not yet received regulatory approval should only be used within the framework of studies approved by research ethics committees.		
Class	Level	Reference
I	C	Consensus

**6.4.2.1. Aorto-iliac segment.** Treatment of aorto-iliac occlusive disease frequently provides adequate symptom relief in patients with IC, even in the presence of distal arterial disease. Invasive interventions in this anatomical segment have largely shifted to endovascular techniques, including primary stenting or balloon angioplasty with selective stent placement. To date, only two randomised studies have directly compared primary stenting with balloon angioplasty with selective stenting in the iliac artery segment, the Dutch Iliac Stent Trial<sup>530</sup> and the STAG Trial.<sup>531</sup> A meta-analysis including both studies concluded that there is insufficient evidence to make general conclusions about



**Figure 12.** Important factors to consider before recommending an intermittent claudication (IC) revascularisation procedure. PAD = peripheral arterial disease; HRQoL = health related quality of life; ESVS = European Society for Vascular Surgery.

the effects of percutaneous transluminal angioplasty vs. primary stenting for stenotic and occlusive iliac artery lesions, but primary stenting in iliac artery occlusions reduces distal embolisation.<sup>532</sup>

Recommendation 54			
For patients with disabling intermittent claudication undergoing revascularisation, balloon angioplasty with selective bare metal stent placement should be considered as the primary approach for iliac artery stenoses due to similar effectiveness and safety compared with primary stenting.			
Class	Level	References	ToE
Ila	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Klein <i>et al.</i> (2006) <sup>530</sup> Goode <i>et al.</i> (2013) <sup>531</sup> Jongsma <i>et al.</i> (2020) <sup>532</sup>	

Recommendation 55			
For patients with disabling intermittent claudication undergoing revascularisation, primary bare metal stenting is recommended over primary balloon angioplasty for iliac artery occlusions due to the lower risk of distal embolisation.			
Class	Level	References	ToE
I	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Klein <i>et al.</i> (2006) <sup>530</sup> Goode <i>et al.</i> (2013) <sup>531</sup> Jongsma <i>et al.</i> (2020) <sup>532</sup>	

The potential benefits of specific primary stenting strategies were investigated in two randomised studies: the ICE and the COBEST trials.<sup>533,534</sup> The mechanical properties of self expanding bare metal stents (reduced radial force application, higher elasticity) may compare favourably with balloon expandable stents by preventing circumferential stress and preserving arterial distensibility. In the ICE trial, re-stenosis and target lesion revascularisation rates favoured the self expanding stent arm with no difference observed for safety endpoints.<sup>533</sup>

Recommendation 56			
For patients with disabling intermittent claudication undergoing revascularisation who need stent placement for iliac artery lesions, the application of self expanding bare metal stents rather than balloon expandable stents may be considered due to the lower risk of re-stenosis and target lesion revascularisation compared with balloon expandable stents.			
Class	Level	References	ToE
Iib	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Krankenber <i>et al.</i> (2017) <sup>533</sup>	

Covered stents have been postulated to improve long term patency rates for endovascular iliac artery revascularisation by ameliorating neointimal hyperplasia barrier formation. Theoretically, covered stents may offer safety benefits in long, heavily calcified iliac lesions which pose an increased risk of rupture. The COBEST trial compared covered and uncovered stents for aorto-iliac lesions. Covered and bare metal stents produced similar results for TASC B lesions, although, according to a subgroup analysis, covered stent placement resulted in higher patency rates for TASC C and D lesions.<sup>534</sup> In the more recent DISCOVER trial ( $n = 174$  limbs studied) that included a high proportion of IC patients and studied balloon expandable covered vs. balloon expandable uncovered stents in common iliac artery lesions of (mainly) moderate complexity, freedom from binary re-stenosis after two years of follow up was 84.7% (95% CI 76.7 – 92.7%) in the uncovered stent group and 89.1% (95% CI 82.4 – 95.8%) in the covered stent group ( $p = .40$ ). Freedom from occlusion was 95.0% (95% CI 90.3 – 95.7%) in the uncovered stent group and 96.4% (95% CI 92.5 – 100%) in the covered stent group ( $p = .66$ ). Target lesion revascularisation, technical success, complications, haemodynamic success, and clinical success were also comparable between groups and per protocol analysis did not affect outcomes.<sup>535</sup> Taken together, these trials lead to the conclusion that covered stents do not currently offer any treatment advantages over bare metal stents in less

complicated iliac (i.e., TASC IIA and B) lesions but may be beneficial in more complex (i.e., TASC II C and D) lesions.

Recommendation 57			
For patients with disabling intermittent claudication undergoing revascularisation who have Trans-Atlantic Inter-Society Consensus Document II C/D iliac lesions, covered stent placement may be considered over bare metal stents due to higher patency rates.			
Class	Level	References	ToE
IIB	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Mwipatayi <i>et al.</i> (2016) <sup>534</sup> Bekken <i>et al.</i> (2023) <sup>535</sup>	

For fit patients, with severe limiting intermittent claudication, open surgery with aortobifemoral bypass may be an option when occlusive lesions comprise iliac arteries as well as the aorta up to the renal arteries. When the vascular lesion also involves the femoral artery, a hybrid procedure combining common femoral artery endarterectomy and iliac stenting should be performed. However, there are no randomised studies comparing these various techniques. Reported series show observational findings and feasibility. Available meta-analyses are based on observational studies, often also including patients with chronic limb threatening ischaemia or a mixture of anatomical levels which have been treated. Regarding safety, there are increased mortality and morbidity rates for open surgery that need to be taken into consideration when recommending this in patients with intermittent claudication.

A meta-analysis evaluated the outcomes of open surgery, standard endovascular treatment, or covered endovascular reconstruction of the aortic bifurcation (CERAB) for extensive aorto-iliac occlusive disease with TASC II C/D lesions (66 studies, 9 319 patients).<sup>536</sup> Among the 66 studies included, four were RCTs, seven were multicentre studies and 55 were single centre studies. Among the 9 319 patients included in the meta-analysis, 3 204 had standard endovascular treatment, 240 had CERAB, and 5 875 had open surgery. The proportion of patients with intermittent claudication compared with patients with chronic limb threatening ischaemia was not specified in this meta-analysis. Thirty day morbidity (defined as any major adverse cardiovascular event requiring re-intervention) and mortality rates were in favour of endovascular techniques. Local complication rates were not reported. The thirty day mortality rate was 0.79% (95% CI 0.3 – 1.3%) for standard endovascular treatment, 0% for CERAB, and 3% (95% CI 2 – 3%) for open surgery. Thirty day morbidity was 9% (95% CI 6 – 12%) for standard endovascular treatment, 10% for CERAB (95% CI 1 – 26%), and 15% (95% CI 11 – 20%) for open surgery.

Primary patency at three years was higher with open surgery (93% for open surgery vs. 82% for CERAB and 78% for standard endovascular groups), whereas secondary patency was comparable in all groups (97% for open surgery, 93% for standard endovascular surgery, and 97% for CERAB). Five year primary patency was 71% for standard endovascular procedures and 88% for open surgery, five

year secondary patency was 89% and 95%, respectively. CERAB data were only available to three years.

Another meta-analysis evaluated the outcome of open surgery and endovascular and hybrid revascularisation for extensive aorto-iliac occlusive disease with TASC II C/D lesions (10 observational single centre studies, one case control study, 4 030 patients).<sup>537</sup> The indication for revascularisation was intermittent claudication in 60.5% of patients ( $n = 943$ ) for open surgery and 54.1% of patients ( $n = 1 253$ ) for endovascular and hybrid procedures. Local complication rates were not reported. Primary patency at a median follow up of 50 months was higher for open surgery (HR 0.51, 95% CI 0.36 – 0.73;  $p < .001$ ), although open surgery patients were younger and may have differed in other confounding variables. Primary patency was also better for endovascular revascularisation combined with common femoral artery endarterectomy than for endovascular revascularisation alone; HR for primary patency in favour of direct surgical revascularisation was 0.88 (95% CI 0.72 – 1.09) when compared with the subgroup for which the endovascular procedure was combined with common femoral endarterectomy, whereas it was 0.43 (95% CI 0.31 – 0.59) when compared with endovascular revascularisation alone.

Open surgery (bypass or endarterectomy) and endovascular procedures (guidewire and laser assisted recanalisation, percutaneous transluminal angioplasty, stenting using balloon expandable, self expanding, and or covered stents or a combination of these procedures) for TASC II C/D lesions were also analysed in a systematic review and meta-analysis (52 observational single centre studies, five RCTs, 5 358 patients).<sup>538</sup> The indication for revascularisation was intermittent claudication in 55% of patients ( $n = 2 053$ ) for open surgery and 76% of patients ( $n = 1 235$ ) for endovascular treatment. Mean length of hospital stay was 13 days for open surgery group vs. four days for endovascular treatment procedures ( $p < .001$ ). The open surgery group experienced more complications (18.0% vs. 13.4%,  $p < .001$ ) and higher 30 day mortality (2.6% vs. 0.7%,  $p < .001$ ). At one, three, and five years, pooled primary patency rates were higher for open surgery group vs. the endovascular cohort (94.8% vs. 86.0%, 86.0% vs. 80.0%, 82.7% vs. 71.4%, respectively,  $p < .001$ ), as well as secondary patency (95.7% vs. 90.0%, 91.5% vs. 86.5%, 91.0% vs. 82.5%,  $p < .001$ ).

A prospective randomised trial compared hybrid and open iliofemoral surgery for chronic occlusive arterial disease: 86% of the 202 included patients presented with IC (Rutherford 2 and 3). Hybrid procedures resulted in shorter length of hospital stay with reduced peri-operative morbidity, but similar midterm patency rates (secondary patency rates at 36 months were 79% in the hybrid group and 85% in the open surgical group).<sup>539</sup>

Accordingly, open surgery may be considered in low risk patients with IC with long life expectancy for TASC II C/D lesions comprising iliac arteries as well as the aorta up to the renal arteries, but endovascular and hybrid techniques are recommended as suitable alternatives to open surgery in high risk patients.

Recommendation 58			
For patients with disabling intermittent claudication undergoing revascularisation who are considered as low risk with long life expectancy, open surgery may be considered for Trans-Atlantic Inter-Society Consensus Document II C/D lesions that include the iliac arteries as well as the aorta up to the renal arteries, due to favourable primary and secondary patency rates compared with endovascular approaches.			
Class	Level	References	ToE
Iib	B	Salem <i>et al.</i> (2021) <sup>536</sup> Premaratne <i>et al.</i> (2020) <sup>537</sup> Indes <i>et al.</i> (2013) <sup>538</sup> Starodubtsev <i>et al.</i> (2022) <sup>539</sup>	

Femorofemoral crossover bypass may be an alternative for disabling claudication if endovascular repair and or direct open surgical repair is unsuitable, but the risk of local complications should be carefully evaluated. In a review of six studies (three observational studies, three RCTs) including 675 patients presenting with disabling claudication, peri-operative mortality of femorofemoral crossover bypasses was 0.2%, local complications (groin infection or false aneurysm) ranged from 0.4% to 13.4%, one year primary patency ranged from 71.6% to 96% and five year primary patency ranged from 49.4% to 72.0%.<sup>540</sup> In a randomised prospective multicentre trial, including 126 patients treated with femorofemoral crossover bypass for intermittent claudication, 7% of patients experienced infective complications within the first month, two year primary patency was 90%, two year freedom from symptoms was 76%, and no difference was noted between different graft materials (polytetrafluoroethylene vs. polyethylene terephthalate).<sup>541</sup>

Recommendation 59			
For patients with disabling intermittent claudication undergoing revascularisation who are not suitable for iliac endovascular, hybrid or surgical anatomical revascularisation, femorofemoral crossover bypass grafting may be considered, as an alternative for aorto-iliac occlusive lesions.			
Class	Level	References	ToE
Iib	B	Capoccia <i>et al.</i> (2010) <sup>540</sup> Eiberg <i>et al.</i> (2006) <sup>541</sup> Ricco <i>et al.</i> (2008) <sup>542</sup>	

**6.4.2.2. Common and deep femoral artery.** Isolated obstructive lesions of the common femoral artery can lead to substantial claudication, especially if the deep femoral artery is involved. Historically, disease involving the femoral artery bifurcation is treated with open surgery. There was resistance to treat such lesions using stents due to fear of stent fracture and compromise for future bypass surgery. With advances in endovascular techniques, stent design, and adjunctive technologies, endovascular treatment of common femoral artery steno-occlusive disease has emerged as an option.

A meta-analysis compared endovascular treatment with routine or selective stenting and common femoral endarterectomy for common femoral artery steno-occlusive disease (26 observational single centre studies, two RCTs;

2 684 patients).<sup>543</sup> The indication for revascularisation was claudication in 66.1% of patients ( $n = 191$ ) in the routine stenting group, 64.8% of patients ( $n = 419$ ) in the selective stenting group, and 53.7% of patients ( $n = 943$ ) in the common femoral endarterectomy group. The pooled mortality at 30 days was 0.8% (95% CI 0.1 – 2% for endovascular treatment with routine stenting, 1% (95% CI 0.4 – 2%) for endovascular treatment with selective stenting, and 1.3% (95% CI 0.6 – 2%) for common femoral endarterectomy. There was no statistically significant difference between the treatment strategies from a mortality perspective as the CIs of the three groups overlap. The pooled rate of local complications for endovascular treatment with routine stenting was 5% (95% CI 2 – 10%) while endovascular treatment with selective stenting had 7% local complication rates (95% CI 3.3 – 11.8%) and common femoral endarterectomy has a pooled local complication rate of 22% (95% CI 14 – 32%). The pooled proportion for primary patency at one year was 84% (95% CI 75 – 92%) for endovascular treatment with routine stenting, 78% (95% CI 69 – 85%) for endovascular treatment with selective stenting, and 93% (95% CI 90 – 96%) for common femoral endarterectomy. The complication and patency CIs of endovascular treatment and common femoral endarterectomy groups overlap, and a statistically significant difference was not observed between these two treatment strategies. On the other hand, common femoral endarterectomy showed a clear advantage over a selective stenting strategy in terms of primary patency at one year. At maximum follow up, primary patency did not differ between common femoral endarterectomy and endovascular treatment with routine stenting (88% and 83%, respectively).

Another meta-analysis focused on RCTs comparing midterm patency, re-intervention, and re-stenosis rates after endovascular or open management of common femoral artery steno-occlusive lesions (two RCTs, 197 patients).<sup>544</sup> The indication for revascularisation was claudication for 71.1% of patients ( $n = 68$ ) in the endovascular group and 79.9% of patients ( $n = 81$ ) in the open surgical group. Technical failure rates were similar for the endovascular group and the open surgical group (OR 1.55; 95% CI 0.11 – 14.45). While cumulative 30 day mortality did not differ statistically (OR 1.54; 95% CI 0.11 – 20.42), post-operative morbidity (defined as any procedure related complication, whether general, local, or vascular) was lower in the endovascular group (OR 0.059; 95% CI 0.01 – 0.26;  $p < .001$ ). Accordingly, endovascular treatment may be considered, especially in patients with increased risk during or following open surgery (hostile groin, redo surgery, obesity). There was no difference in the early re-intervention rate (OR 3.53; 95% CI 0.36 – 34.68). At one year no benefit of one technique over the other was noted in terms of primary patency (OR 0.49; 95% CI 0.29 – 3.06). Subgroup analysis showed that neither claudication nor associated lesions influence surgical patency results. In the endovascular cohort, subgroup analysis indicated that the re-stenosis rate was statistically significantly higher in complex lesions ( $p = .001$ )

while apparently unaffected by pre-operative symptoms. However, the latter seem to impact target lesion revascularisation, in that claudication is associated with lower target lesion revascularisation rate compared with CLTI.

According to the available literature, the peri-operative morbidity of interventions to the common and deep femoral arteries shows advantage for endovascular treatment. However, although comparable in the first year, common femoral endarterectomy offers a higher long term primary patency rate than endovascular surgery and studies focussing on an obstructive process involving the common femoral and deep femoral artery are missing for endovascular therapy. It might therefore be too early to propose strict recommendations regarding indications for endovascular surgery in disease involving common and deep femoral arteries. Uncertainty about long term outcomes persists and numerous limitations in the literature must be overcome. One of the prerequisites to compete with open surgery would be a better understanding of long term endovascular patency, which currently impedes broad acceptance of this technique in IC patients.

Recommendation 60			
For fit patients with disabling intermittent claudication at low risk of groin complications and with common femoral artery bifurcation stenosis or occlusion undergoing revascularisation, open surgery is recommended due to expected higher long term patency rates compared with endovascular approaches.			
Class	Level	References	ToE
I	C	Ballotta <i>et al.</i> (2010) <sup>545</sup> Kang <i>et al.</i> (2008) <sup>546</sup>	

Recommendation 61			
For patients with disabling intermittent claudication undergoing revascularisation, with common femoral artery stenosis or occlusion not extending down to the femoral bifurcation, endovascular treatment may be considered as an alternative to open surgery due to similar midterm patency rates compared with open surgery in non-complex common femoral artery lesions.			
Class	Level	References	ToE
IIb	B	Changal <i>et al.</i> (2019) <sup>543</sup> Boufi <i>et al.</i> (2021) <sup>544</sup>	

Recommendation 62			
For patients with disabling intermittent claudication and a hostile groin (e.g., prior ipsilateral common femoral endarterectomy, morbid obesity, or previous regional radiotherapy to the groin region) undergoing revascularisation, endovascular treatment of steno-occlusive disease of the femoral bifurcation may be considered over open surgery due to the lower risk of surgical wound complications.			
Class	Level	Reference	ToE
IIb	C	Consensus	

**6.4.2.3. Femoropopliteal segment.** **6.4.2.3.1. General considerations.** The long term value of revascularisation for intermittent claudication is not clear, and long term outcomes are rarely reported. In a prospective randomised single centre trial including 158 patients with lifestyle limiting intermittent claudication, a strategy of invasive treatment resulted in improved health related quality of life in the first two years, but this benefit was not maintained at five years.<sup>547</sup> The prospectively collected Swed-vasc registry evaluated the eight year outcome after invasive treatment of infra-inguinal lesions for intermittent claudication in 775 patients. Within the eight years of follow up, 261 patients underwent new vascular interventions, 239 interventions for intermittent claudication, and 226 interventions for chronic limb threatening ischaemia. The yearly incidence of new vascular intervention varied between 7% and 13%, but the need for new vascular interventions occurred more frequently during the first two years of follow up. During follow up, 40.1% of the patients died and the yearly need for hospitalisation in surviving subjects varied between 79% and 99%. The most common causes of hospitalisation were cerebrovascular and ischaemic heart diseases.<sup>548</sup>

A recent cross site blinded expert review evaluated the appropriateness of femoropopliteal ePTFE bypass in 325 patients with IC. In this study, 40% of lower extremity bypasses were deemed premature and therefore potentially avoidable, primarily because of a lack of appropriate medical and lifestyle management before surgery.<sup>549</sup>

Accordingly, the indication for invasive treatment of femoropopliteal lesions should be especially carefully weighed against concomitant comorbidities and the timing of this treatment optimised regarding the patient's possibilities of enjoying positive treatment effects on quality of life. Moreover, patients with intermittent claudication seem to be at an increased risk of acute limb ischaemia following invasive treatment within two years of follow up.<sup>550</sup>

Recommendation 63			
For patients with disabling intermittent claudication due to femoropopliteal steno-occlusive disease, a careful selection for revascularisation is recommended where the treatment indication is weighed against the degree of disability, results of non-invasive therapies, concomitant comorbidities, procedural risks, and expected procedural patency, due to remaining uncertainty about sustained clinical benefits and risks.			
Class	Level	References	ToE
I	C	Djerf <i>et al.</i> (2020) <sup>449</sup> Gunnarsson <i>et al.</i> (2020) <sup>548</sup> Howard <i>et al.</i> (2023) <sup>549</sup>	

**6.4.2.3.2. Endovascular interventions in the femoropopliteal segment.** Rapid progress in the endovascular field has led to the extension of its use even for complex lesions of the femoropopliteal segment. Endovascular intervention has now largely replaced open management as the first line



revascularisation strategy for femoropopliteal lesions shorter than 25 cm in view of high initial technical success and low peri-interventional morbidity. The device based treatment options for femoropopliteal lesions are numerous and include balloon angioplasty, primary or bailout stenting, covered stent placement, atherectomy devices, intravascular lithotripsy, and drug eluting technologies. Regardless of technique used, adequate vessel preparation is an important initial step in all revascularisation procedures, and this has gained more scientific interest during recent years. For instance, a randomised clinical trial ( $n = 306$ ) that foremost included IC patients with moderately to severely calcified femoropopliteal lesions recently demonstrated that the use of intravascular lithotripsy prior to drug coated balloon angioplasty or stenting was superior to conventional PTA ballooning in terms of immediate procedural endpoints, and the primary patency rates after one year seemed to favour the lithotripsy arm (80.5% vs. 68.0%,  $p = .017$ ).<sup>551,552</sup> However, it should be noted that acute PTA failure requiring provisional stenting at any time during the procedure was counted as a loss of primary patency.

The optimal approach for device based revascularisation of femoropopliteal lesions in intermittent claudication remains undefined despite the existence of numerous comparative studies. Most existing trials were conducted for regulatory purposes in highly selected, yet heterogeneous study populations, thereby limiting their translation to real world settings.

A recent meta-analysis evaluated the comparative efficacy and safety of endovascular devices used for the treatment of intermittent claudication due to *de novo* atherosclerotic lesions in the aorto-iliac, femoropopliteal, and infrapopliteal arteries. In the femoropopliteal territory, paclitaxel coated balloon angioplasty was associated with a higher likelihood of primary patency, a lower risk of target lesion revascularisation and similar risk estimates for all cause mortality across short, mid, and long term follow up, compared with uncoated balloon angioplasty.<sup>5</sup> Previous concerns about potential long term mortality increase associated with paclitaxel coated devices have also largely been refuted by data from a substantially larger randomised study, and several updated meta-analyses.<sup>553–555</sup> The use of paclitaxel coated balloon angioplasty is also supported by recent cost effectiveness analyses.<sup>556,557</sup>

#### Recommendation 64

**For patients with disabling intermittent claudication undergoing revascularisation who have Trans-Atlantic Inter-Society Consensus Document II A/B femoropopliteal lesions, the adjunctive use of paclitaxel coated balloon angioplasty should be considered after optimal balloon angioplasty without the need for stenting.**

Class	Level	Reference	ToE
<b>IIa</b>	<b>A</b>	Koeckerling <i>et al.</i> (2023) <sup>5</sup>	

Effect estimates for primary patency favoured a primary bare metal stenting approach over a selective bare metal stenting approach in the short and midterm (two years); however, patency point estimates were comparable in the long term (at five years). Similarly, primary bare metal stenting was associated with a lower risk of target lesion or vessel revascularisation in the midterm, but this benefit was not sustained in the long term. Risk estimates for all cause mortality remained similar between groups at all follow up times.<sup>5</sup> While short to midterm benefits may be desirable, in stent re-stenotic lesions are composed of fibrotic collagen matrix that poses considerable challenges to endovascular redo procedures with substantial failure and recurrence rates.<sup>558</sup> Accordingly, primary bare metal stenting is not recommended in femoropopliteal lesions responsible for intermittent claudication. This consensus decision is based on unfavourable secondary patency rates in patients with in stent re-stenosis.

#### Recommendation 65

**For patients with disabling intermittent claudication undergoing revascularisation, primary bare metal stenting is not recommended over balloon angioplasty with provisional stenting in femoropopliteal lesions due to the unfavourable secondary patency rates in patients with in stent re-stenosis.**

Class	Level	Reference
<b>III</b>	<b>C</b>	Consensus

Drug eluting stents can be both polymer free and polymer based. Polymer free drug eluting stents were first introduced within cardiology to reduce the risk of stent thrombosis associated with polymer based drug eluting stents. The comparison of safety and efficacy profiles between these two stent platforms remains unclear for lower limb PAD applications. No notable treatment effect on the likelihood of midterm patency and target lesion or vessel revascularisation was observed for the comparison between primary polymer free paclitaxel eluting stent and bare metal stent placement in the femoropopliteal segment.<sup>5</sup> Long term data were provided by the Zilver PTX trial, whereas the BATTLE trials provided midterm data.<sup>559,560</sup> The Zilver PTX trial compared primary DES placement with transluminal balloon angioplasty for the treatment of short femoropopliteal lesions. Patients with suboptimal PTA results underwent secondary randomisation to provisional DES or BMS placement. Five year primary patency and TLR rates favoured the intervention over the control group for both comparisons, overall DES vs. standard care (PTA with provisional BMS placement) and provisional DES vs. provisional BMS. All cause mortality was higher in the primary DES group, yet no deaths were deemed procedure or device related. In the BATTLE trial, no differences in primary patency and TLR rates were found between the DES and BMS groups after 24 month follow up. A trend towards higher all cause mortality was identified for the BMS group, while no major amputations were performed in either group.

More recently, the EMINENT trial, that mainly included patients with intermittent claudication and compared polymer based DES with BMS in femoropopliteal lesions, demonstrated superior 12 month primary patency rates for DES (83.2%) than for BMS (74.3%) ( $p < .010$ ). Longer follow up is warranted, however, to ultimately confirm the robustness of these findings.<sup>561</sup>

Two RCTs assessed the comparative efficacy and safety of polymer free paclitaxel eluting stent and paclitaxel coated balloon use in the femoropopliteal segment, finding no differences in primary patency and target lesion revascularisation between treatment arms.<sup>562,563</sup>

Recommendation 66			
For patients with disabling intermittent claudication undergoing revascularisation, selective drug eluting stent placement should be considered if femoropopliteal plain balloon angioplasty leads to suboptimal results i.e., residual stenosis or dissection.			
Class	Level	References	ToE
Iia	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Dake <i>et al.</i> (2016) <sup>559</sup> Gouëffic <i>et al.</i> (2020) <sup>560</sup> Bausback <i>et al.</i> (2019) <sup>562</sup> Liistro <i>et al.</i> (2019) <sup>563</sup> Gouëffic <i>et al.</i> (2022) <sup>561</sup>	

Calcification of femoropopliteal vessels presents a challenge to endovascular revascularisation techniques, frequently resulting in incomplete stent expansion, excessive residual stenosis, and ineffective drug delivery. Atherectomy offers the ability to debulk and modify atherosclerotic plaques with the goal of improving luminal gain, minimising barotrauma, and reducing adverse tissue remodelling without the need for bailout stent placement. To date, five randomised trials have investigated the comparison between atherectomy and PTA with selective bare metal stent placement for the revascularisation of femoropopliteal lesions, all of which failed to demonstrate superiority of atherectomy over conventional therapy with regards to both efficacy and safety endpoints.<sup>564–570</sup>

Recommendation 67			
For patients with disabling intermittent claudication undergoing revascularisation, routine use of atherectomy for the treatment of femoropopliteal lesions is not recommended due to the lack of superiority of atherectomy over conventional endovascular therapies in terms of efficacy and safety endpoints.			
Class	Level	References	ToE
III	A	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Vroegindewij <i>et al.</i> (1992) <sup>564</sup> Tielbeek <i>et al.</i> (1996) <sup>565</sup> Shammas <i>et al.</i> (2011) <sup>566</sup> Dattilo <i>et al.</i> (2014) <sup>567</sup> Ott <i>et al.</i> (2017) <sup>568</sup> Zeller <i>et al.</i> (2017) <sup>569</sup> Cai <i>et al.</i> (2020) <sup>570</sup>	

Polytetrafluoroethylene (ePTFE) self expandable covered stents were developed with the purpose of providing a barrier against the encroachment of hyperplastic intimal tissue and may thereby prevent diffuse in stent re-stenosis. Three RCTs have investigated the potential benefits of covered stent placement in the treatment of IC due to femoropopliteal artery disease.<sup>571–573</sup>

The earliest RCT compared the effectiveness of the Viabahn stent graft with PTA with selective BMS placement in 197 femoropopliteal lesions. At one year follow up, the covered stent group demonstrated superior primary patency and clinical success rates compared with controls, while no difference was observed in the incidence of major adverse events. The trial was terminated early because of the requirement for modifying the device itself and redefining originally specified endpoints.<sup>571</sup>

Two further RCTs, the VIBRANT and VIASTAR trials, evaluated the long term outcomes of Viabahn covered stent placement compared with BMS placement in patients with long complex femoropopliteal artery disease. At three year follow up, the VIBRANT trial found no difference in the primary endpoint with low primary patency rates observed in the covered stent and BMS arms (24.2% vs. 25.9%,  $p = .39$ ). The VIASTAR trial adopted a study design and study population like the VIBRANT trial but included an updated version of the Viabahn covered stent with a contoured proximal edge as well as a heparin bonded surface. Comparable primary patency rates between the covered stent and BMS groups were found after 12 months, but primary patency rates favoured the covered stent group after 24 month follow up. A subgroup analysis demonstrated higher patency rates at 12 and 24 months in favour of heparin bonded covered self expandable stents for lesions longer than to 20 cm.<sup>572</sup>

Recommendation 68			
For patients with disabling intermittent claudication undergoing revascularisation, covered stents may be considered an alternative to bare metal stents in the treatment of long (> 20 cm) femoropopliteal lesions due to favourable patency rates.			
Class	Level	References	ToE
Iib	B	Koeckerling <i>et al.</i> (2023) <sup>5</sup> Saxon <i>et al.</i> (2008) <sup>571</sup> Geraghty <i>et al.</i> (2013) <sup>572</sup> Lammer <i>et al.</i> (2015) <sup>573</sup>	

**6.4.2.3.3. Open surgical revascularisation in the femoropopliteal segment.** In terms of open vascular surgery in the femoropopliteal segment, three meta-analyses evaluated the outcome of above the knee femoropopliteal bypasses comparing autologous vein to prosthetic materials.<sup>574–576</sup> No clear difference in primary patency at three, six, or 12 months was identified, but a long term benefit for autologous vein was observed at 24 months (OR 0.59, 95% CI 0.37 – 0.94; 422 limbs, four studies,  $p = .030$ ). This was reflected in the continued primary patency benefit for autologous vein over prosthetic grafts by 60 months (OR 0.47, 95% CI

0.28 – 0.80, three studies, 269 limbs,  $p = .005$ ). There was no difference between Dacron and ePTFE grafts for primary patency, but Dacron may confer a slight secondary patency benefit over ePTFE in the long term (OR 1.67, 95% CI 0.96 – 2.90, two studies, 247 limbs). These findings were also supported by a study of 282 patients with IC where the primary patency rates were  $76.7 \pm 5.9\%$  at one year and  $59.3 \pm 7.3\%$  at five years for above knee venous bypass vs.  $69.5 \pm 5.3\%$  at one year and  $54.5 \pm 6.2\%$  at five years for above knee prosthetic bypass.<sup>577</sup> In the randomised ZilverPASS study that compared paclitaxel eluting stent (Zilver PTX) treatment with prosthetic bypass surgery in TASC II C and D femoropopliteal lesions, polymer free paclitaxel eluting stenting was non-inferior to prosthetic bypass surgery. However, the ZilverPASS study was limited by imbalanced treatment arms, including a higher proportion of CLTI patients and more severe risk factor profiles in the surgical bypass arm.<sup>578</sup> Overall, most of the studies on open surgery for femoropopliteal occlusive disease report on mixed cohorts including patients with intermittent claudication and CLTI, making it difficult to interpret the results.

Recommendation 69		
For patients with disabling intermittent claudication with long and heavily calcified femoropopliteal occlusions undergoing revascularisation, the revascularisation strategy should be individualised and include specific patient and lesion characteristics, centre and interventionist experience, device availability, and the presence or absence of a suitable venous conduit.		
Class	Level	Reference
Ila	C	Consensus

Recommendation 70			
For patients with disabling intermittent claudication undergoing femoropopliteal bypass, autologous vein grafts are recommended over prosthetic grafts due to the favourable long term patency rates.			
Class	Level	References	ToE
I	A	Ambler <i>et al.</i> (2018) <sup>574</sup> Vossen <i>et al.</i> (2022) <sup>575</sup> Kim <i>et al.</i> (2022) <sup>577</sup> Sharrock <i>et al.</i> (2019) <sup>576</sup>	

**6.4.2.4. Below the knee segment.** Whether patients with intermittent claudication benefit from below the knee intervention is controversial, and data supporting its utility are limited. Although below knee revascularisation by either open surgery or endovascular therapy is recommended for chronic limb threatening ischaemia, potential benefits following revascularisation for IC in the below knee segment are very uncertain, and treatment durability is questionable even when using the most contemporary medical devices and technologies available. It is therefore commonly agreed that best medical treatment should be the mainstay of treatment for patients with below knee

lesions responsible for claudication; and that routine endovascular treatment is not recommended for isolated below the knee disease.

Recommendation 71		
For patients with disabling intermittent claudication, endovascular treatment of isolated below the knee lesions is not recommended due to the risk of harm from tibial revascularisation.		
Class	Level	Reference
III	C	Consensus

The only available, randomised evidence for endovascular treatment of intermittent claudication due to crural lesions comes in the form of subgroup analyses from two small scale comparative trials. The BIOLUX P-II trial compared the performance of paclitaxel coated balloon angioplasty with uncoated balloon angioplasty in 72 patients with moderate length below knee lesions over a period of 12 months. In the small subset of patients with intermittent claudication (16 patients), major adverse event and target lesion revascularisation occurred at statistically similar rates in both treatment arms.<sup>579</sup>

The double blinded YUKON-BTK trial randomised 161 patients with short below knee lesions to receive either sirolimus eluting stents or bare metal stents. In the subgroup of patients with intermittent claudication (86 patients), one year primary patency rates favoured the sirolimus eluting stent group (85.3% vs. 55%,  $p = .006$ ), and additional benefits favouring the intervention group were observed for target vessel revascularisation rates (7.9% vs. 25%,  $p = .040$ ).<sup>580</sup> However, it is impossible to draw valid conclusions from such small samples as patients treated for intermittent claudication often represented only a small fraction of the entire patient sample.

Recommendation 72			
In the extreme scenario of highly selected patients with disabling intermittent claudication, where endovascular revascularisation of below the knee lesions is deemed necessary, balloon angioplasty with selective drug eluting stent placement may be considered.			
Class	Level	References	ToE
Iib	C	Zeller <i>et al.</i> (2015) <sup>579</sup> Rastan <i>et al.</i> (2012) <sup>580</sup>	

Recommendation 73			
In the extreme scenario of highly selected patients with disabling intermittent claudication who require stent placement for short below the knee lesions, the use of drug eluting stents rather than bare metal stents may be considered due to the favourable patency rates of drug eluting stents.			
Class	Level	Reference	ToE
Iib	C	Rastan <i>et al.</i> (2012) <sup>580</sup>	

There is also still no confirmatory evidence with respect to open surgical revascularisation for intermittent claudication caused by below the knee lesions with or without continuity to femoropopliteal lesions. The Vascular Quality Initiative (2003 – 2018) was queried for infra-inguinal bypasses performed for intermittent claudication and peri-operative and one year outcomes were compared between bypasses constructed to the popliteal and tibial arteries.<sup>581</sup> Of 5 347 infra-inguinal bypasses, 4 184 (78%) and 1 173 (22%) were popliteal and tibial bypasses, respectively. On multivariable analysis, tibial compared with popliteal bypass was independently associated with increased occlusion or death (HR 1.65; 95% CI 1.28 – 2.11), major ipsilateral amputation or death (HR 1.51; 95% CI 1.12 – 2.19), and ipsilateral re-intervention, amputation, or death (HR 1.51; 95% CI 1.28 – 1.79), with similar patient survival.

In a large national cohort, major adverse limb events (MALEs) and major adverse cardiovascular events (MACEs) at 30 days following revascularisation were studied within a population of patients with IC.<sup>29</sup> A total of 3 925 infra-inguinal revascularisation procedures were performed for claudication: 2 155 open procedures (55%) and 1 770 endovascular procedures (45%). There was no difference in 30 day MALEs between open and endovascular procedures (4.0% vs. 3.2%, respectively), but open procedures had higher 30 day MACEs (2.0% vs. 1.0%,  $p = .010$ ). On multivariable logistic regression, tibial revascularisation was a predictor of 30 day MALEs (OR 2.2;  $p < .001$ ).

#### Recommendation 74

**For patients with disabling intermittent claudication, open surgical treatment of isolated below knee lesions is not recommended for the majority of patients due to the risk of harm from tibial revascularisation.**

Class	Level	References	ToE
III	C	Levin <i>et al.</i> (2021) <sup>32</sup> Fashandi <i>et al.</i> (2018) <sup>29</sup>	

A single centre study evaluated the outcome of 49 distal venous bypasses performed in 43 patients with IC compared with distal venous bypasses performed in patients with chronic limb threatening ischaemia. Primary and secondary patency rates in patients with IC were 79% and 94% at one year, 71% and 90% at three years, 65% and 90% at five years, which were substantially higher than those of chronic limb threatening ischaemia patients. Graft failure occurred in 15 limbs (31%) requiring endovascular treatment in nine limbs, redo surgery in four limbs, and medical treatment in two limbs. The amputation free survival rate in patients with IC was 100% at one year, 93% at three years, and 90% at five years, which was substantially higher than in chronic limb threatening ischaemia patients.<sup>582</sup>

Accordingly, below knee open surgical management may be considered in patients with below the knee lesions suffering from disabling intermittent claudication if neither exhaustive and well conducted non-invasive treatment nor

endovascular treatment is suitable or effective. Crural artery bypass should only be considered for patients with the following conditions: (1) persistent lifestyle limiting claudication even after pharmacotherapy with well conducted supervised exercise therapy, (2) presence of a target artery with good runoff to the foot, (3) availability of a great saphenous vein as a single segment graft, (4) no severe comorbidity precluding the ability to undergo anaesthesia, (5) intense desire to walk, (6) in whom endovascular therapy is not possible, and (7) having undergone smoking cessation.

#### Recommendation 75

**In rare circumstances for patients with disabling intermittent claudication due to below knee lesions, bypass grafting with a venous graft may be considered if exhaustive non-invasive treatment and endovascular therapy is not an alternative option.**

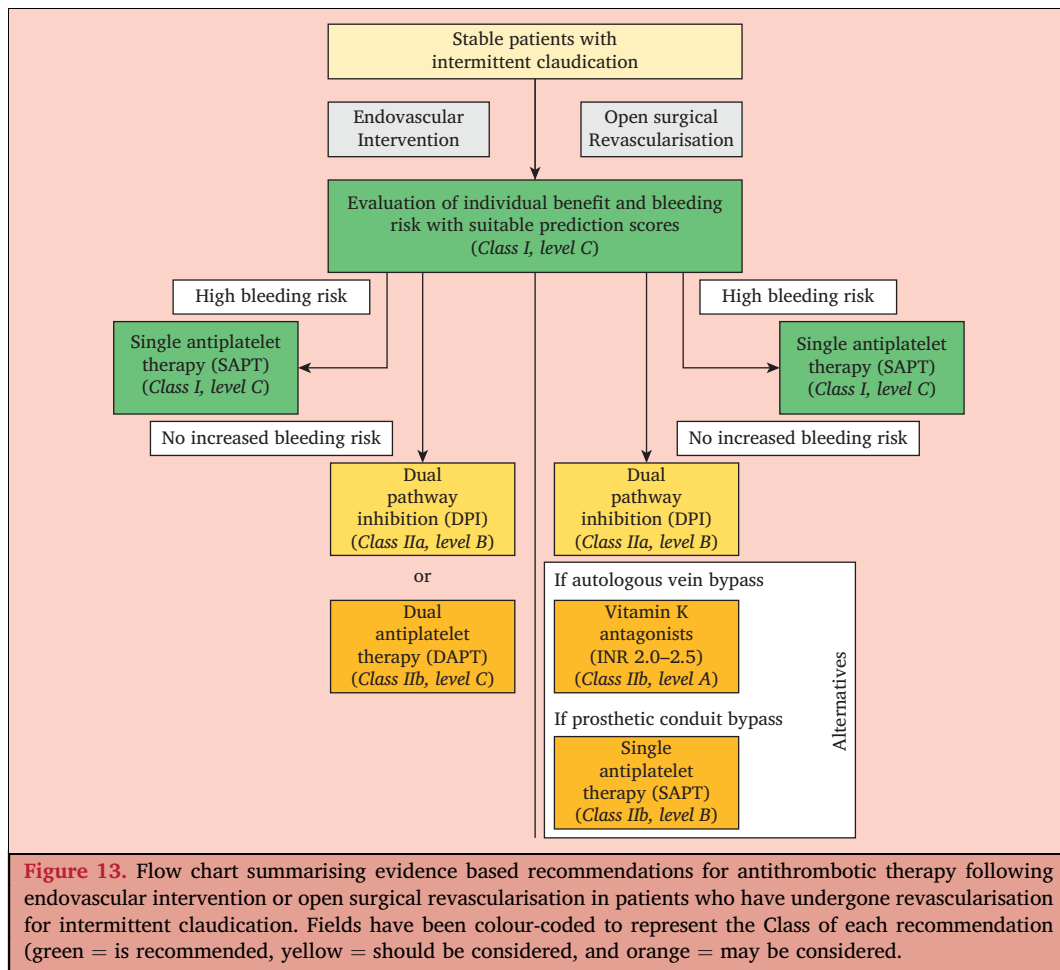
Class	Level	Reference	ToE
IIB	C	Kobayashi <i>et al.</i> (2021) <sup>582</sup>	

### 6.5. Antithrombotic treatment following invasive procedures

The European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases contain comprehensive recommendations on all important antithrombotic therapies for both asymptomatic PAD and IC patients.<sup>41</sup> For this section an updated literature search was done on this topic to account for potential new evidence that may have emerged following the publication of the antithrombotic guidelines and the goal of this chapter is to briefly summarise the most important clinical aspects of post-procedural antithrombotic therapy in PAD based on available evidence from RCTs and systematic reviews and meta-analysis of RCTs (Fig. 13). Regardless of intervention or not, all symptomatic PAD patients should be prescribed antithrombotic therapy unless contraindicated (see section 4.1.2.1). The overarching goal of post-procedural antithrombotic therapy enhancements is to optimise the efficacy of the procedure and to reduce the risk of systemic vascular complications, while minimising the inherent bleeding risk (see section 1.3.2). The following specific recommendations on antithrombotic therapy should be considered in the post-procedural setting following endovascular and open vascular interventions.

#### 6.5.1. Antithrombotic treatment after endovascular interventions

**6.5.1.1. Single and dual antiplatelet therapy.** Clinical trials comparing different endovascular devices have historically included post-procedural DAPT in their trial protocols despite a clear lack of PAD specific evidence for such regimens, which might have contributed to the common current practice of offering a treatment period with DAPT post-endovascular intervention.<sup>583</sup> In a systematic review and network meta-analysis undertaken on trials including both revascularised and non-revascularised PAD patients, a



reduction in major amputation rates was observed in patients treated with clopidogrel and aspirin compared with aspirin alone (HR 0.68, 95% CI 0.46 – 0.99) at the expense of a higher risk of severe bleeding observed with DAPT (HR 1.48, 95% CI 1.05 – 2.10).<sup>584</sup> In the recent meta-analysis by Ambler *et al.*, DAPT compared with single antiplatelet therapy following endovascular intervention conferred no clinical benefit but resulted in substantially more major bleeding events (37 more major bleeding events per 1 000 studied patients, 95% CI 8 – 102).<sup>440</sup> The only trial that exclusively included endovascular patients was the MIRROR trial, which was a small, placebo controlled trial of 80 patients that studied the efficacy of a six month course of DAPT compared with SAPT on biochemically measured platelet activation.<sup>585</sup> While not powered to study clinical endpoints, secondary endpoints included surrogate markers of clinical success. Six month secondary endpoint data demonstrated target lesion revascularisation rates of  $n = 2$  (5%) in the DAPT arm and  $n = 8$  (20%) in the placebo and aspirin arms. Following the termination of DAPT therapy after six months, these early benefits were not sustained at the 12 month analysis.<sup>586</sup> There are currently no dedicated RCTs showing the effect of prolonged DAPT in patients undergoing endovascular lower limb revascularisation and the optimal duration of DAPT therapy following endovascular interventions remains unclear. A recent subgroup analysis from the VOYAGER PAD trial indicated the relative

safety of combining DAPT up to six months with low dose rivaroxaban, but with a trend for more major bleeding events when clopidogrel use exceeded 30 days.<sup>587</sup> The additional use of clopidogrel did not enhance the observed clinical benefit for low dose rivaroxaban + aspirin vs. aspirin alone in the VOYAGER PAD trial.

#### Recommendation 76

**For patients with intermittent claudication not at high risk of bleeding who have undergone lower limb endovascular intervention, a minimum of one month to a maximum of six months of post-interventional dual antiplatelet therapy may be considered, to reduce the risk of secondary cardiovascular and major adverse limb events.**

Class	Level	Reference
<b>IIb</b>	<b>C</b>	Consensus

The effect of cilostazol following lower limb endovascular revascularisation was studied in a meta-analysis by Megaly *et al.*<sup>588</sup> Within the context of three heterogeneous RCTs and five observational studies, the addition of 200 mg cilostazol to standard antithrombotic regimens compared with standard antithrombotic regimens alone improved the primary patency (OR 2.28, 95% CI 1.77 – 2.94) while lowering the risk of target lesion revascularisation (OR 0.37, 95% CI 0.26 – 0.52) and major amputation (OR 0.15, 95% CI 0.040 – 0.62) after revascularisation in the femoropopliteal

segment (seven of the eight studies). Bleeding events were not reported consistently in the included studies and could not be analysed, resulting in a low possibility of providing treatment recommendations based on a comprehensive assessment of benefits and risks. In the randomised, double blind, placebo controlled safety study of cilostazol (CASTLE), no excess serious bleeding events were observed in patients on cilostazol regardless of concomitant treatment with SAPT, DAPT, or anticoagulation, while this study was underpowered to detect a small adverse impact of cilostazol on death.<sup>589</sup>

Single antiplatelet therapy has never been considered specifically as a treatment enhancement option following endovascular intervention (not considering the aspirin arm of the VOYAGER trial). Regardless of this, patients at higher risk of bleeding will still need an antiplatelet agent to reduce subsequent MALE risk following endovascular intervention. As the CAPRIE trial showed clopidogrel to be superior to aspirin in a chronic PAD cohort, it is reasonable to consider clopidogrel as the primary option when single antiplatelet therapy is indicated post endovascular therapy.<sup>106</sup>

#### Recommendation 77

For patients with intermittent claudication who have undergone endovascular intervention, single antiplatelet therapy is recommended to reduce major adverse limb events if the risk of bleeding is deemed high.

Class	Level	Reference
I	C	Consensus

**6.5.1.2. Dual pathway inhibition.** The combination of low dose rivaroxaban and aspirin in PAD patients undergoing lower limb revascularisation was examined in the VOYAGER PAD trial. VOYAGER randomised patients with PAD undergoing endovascular or open revascularisation to rivaroxaban 2.5 mg twice daily plus aspirin or matching placebo plus aspirin. The main finding was that treatment with the combination therapy reduced the primary composite efficacy outcome (acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, or death from cardiovascular causes) (HR 0.85, 95% CI 0.76 – 0.96) during a median follow up of 28 months.<sup>590</sup> Of the 6 564 patients randomised, 2 271 (35%) underwent surgical lower extremity revascularisation and 4 293 (65%) endovascular, and the majority were treated for claudication ( $n = 5 025$ , 77%). Compared with placebo, rivaroxaban reduced the primary endpoint consistently regardless of lower extremity revascularisation method ( $p$  interaction, 0.43).<sup>591</sup> In addition, the benefit of combining low dose rivaroxaban with aspirin following revascularisation was consistent across important subgroups including smokers, elderly patients, and patients with chronic kidney disease,<sup>592–594</sup> although it should be recognised that rivaroxaban has been poorly studied in patients with severe renal impairment (eGFR < 15 mL/min/1.73m<sup>2</sup>) and is therefore not recommended in such patients. Even in the range of 15–30 mL/min/1.73m<sup>2</sup>, rivaroxaban should be used with

some caution. The VOYAGER trial primarily studied the prevention of the first MACE or MALE event, but subsequent analysis has also demonstrated that combination therapy reduces both primary endpoint events (HR 0.86; 95% CI 0.75 – 0.98;  $p = .020$ ) and total vascular events (HR 0.86; 95% CI 0.79 – 0.95;  $p = .003$ ).<sup>595</sup> Moreover, combination therapy seems to protect revascularised PAD patients from subsequent venous thrombosis.<sup>596</sup> There was also a notable concomitant use of clopidogrel in VOYAGER, which overall was given to 51% of patients for up to six months after revascularisation, in addition to the studied treatments. Altogether, 91% of clopidogrel users in the trial underwent endovascular revascularisation. In a subgroup analysis clopidogrel did not benefit clinical endpoints when added to the primary treatment strategy, but a trend for more major bleeding events was observed when clopidogrel use exceeded 30 days.<sup>587</sup>

One additional small multicentre double blind RCT ( $n = 203$ ) compared edoxaban (60 mg daily) with clopidogrel (75 mg daily) on a background of aspirin.<sup>597</sup> After six months there was no difference in re-stenosis or re-occlusion rates (RR 0.89, 95% CI 0.59 – 1.34). There was no substantial difference in major bleeding rates between the groups.

#### Recommendation 78

For patients with intermittent claudication who have undergone an infra-inguinal endovascular intervention and have no increased bleeding risk\*, low dose aspirin (75 – 100 mg once daily) in combination with low dose rivaroxaban (2.5 mg twice daily) should be considered, to reduce the risk of secondary cardiovascular and major limb events.

Class	Level	Reference	ToE
Ia	B	Bonaca <i>et al.</i> (2020) <sup>590</sup>	

\* Medical history or active clinically noteworthy bleeding, lesions, or conditions within the last six months considered to be a major risk of major bleeding (including current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known oesophageal varices, vascular aneurysms of the large arteries, or major intraspinal or intracerebral vascular abnormalities), any known hepatic disease associated with coagulopathy or bleeding risk, major trauma, or accidents within 30 days, any medically documented history of intracranial haemorrhage, stroke or TIA, known active malignancy (excluding basal or squamous cell carcinoma) (VOYAGER criteria).

#### Recommendation 79

In the rare post-revascularisation scenario where triple antithrombotic therapy is deemed necessary on clinical grounds, patients with intermittent claudication not at high risk of bleeding who have undergone endovascular intervention and receive post-procedural treatment with aspirin (75 – 100 mg once daily) combined with low dose rivaroxaban (2.5 mg twice daily) should not have clopidogrel (75 mg) for longer than 30 days as the bleeding risk is likely to outweigh the benefit.

Class	Level	Reference	ToE
III	C	Hiatt <i>et al.</i> (2020) <sup>587</sup>	

### 6.5.2. Antithrombotic treatment after open vascular surgery.

When compared with the antithrombotic treatment after endovascular interventions, most RCTs in the field of open vascular surgery stem from the past century. In the Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study of 2 690 patients, oral anticoagulants demonstrated beneficial effects in terms of infra-inguinal venous bypass graft occlusion (HR 0.69, 95% CI 0.54 – 0.88), whereas low dose aspirin was beneficial in non-venous grafts (HR 1.26, 95% CI 1.03 – 1.55). Patients who were treated with oral anticoagulants (INR target range 3.0 – 4.5) had more bleeding episodes than those treated with aspirin.<sup>598</sup> In a secondary analysis of 1 326 patients who were allocated to oral anticoagulation with 2 287 patient years of follow up, the optimal intensity of oral anticoagulation with the lowest incidence of ischaemic and haemorrhagic events was estimated to be an INR between 3.0 and 4.0.<sup>599</sup> Johnson *et al.* evaluated benefits of long term administration of oral anticoagulant therapy with warfarin (INR 1.4 – 2.8) plus aspirin (325 mg) vs. aspirin alone in a trial including 831 patients who underwent bypass surgery for PAD. The intensified antithrombotic therapy was beneficial in terms of patency only in small (6 mm) prosthetic femoropopliteal bypasses, while the patency rate was unaffected in venous bypasses. The use of warfarin with aspirin increased the risk of major haemorrhagic events, and most of these events occurred when the INR was in the target range.<sup>600,601</sup> In the Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease (CASPAR) trial of 851 patients undergoing a below knee vascular bypass as treatment for PAD, no overall benefit of DAPT with aspirin plus clopidogrel vs. aspirin alone was proven, while a secondary subgroup analysis revealed that aspirin plus clopidogrel improved the primary endpoint for patients with prosthetic grafts (HR 0.65, 95% CI 0.45 – 0.95) but not for those with venous grafts.<sup>602</sup>

A Cochrane review has examined the effects of antiplatelet therapy for patients who underwent femoropopliteal or femorodistal bypass. This showed that antiplatelet therapy with aspirin or with aspirin plus dipyridamole had a beneficial effect on primary patency compared with placebo or no treatment after 12 months (OR 0.42, 95% CI 0.22 – 0.83). However, this effect was not evident when evaluating venous grafts alone (OR 0.76, 95% CI 0.26 – 2.25) but was strong for prosthetic grafts (OR 0.14, 95% CI 0.04 – 0.51). It must be emphasised that none of the included trials stratified by graft type before randomisation, and results should therefore be considered subgroup analyses. Furthermore, the authors highlighted that the small number of participants probably limited the conclusions concerning side effects, and that further high quality RCTs with adequate sample sizes are required to evaluate the efficacy of antiplatelet medications following bypass surgery.<sup>603</sup>

Most recently, the VOYAGER PAD trial also included patients undergoing endarterectomy or bypass grafting. A

subgroup analysis by treatment strategy showed that the positive primary efficacy composite outcome was driven by the surgical subgroup (HR 0.79, 95% CI 0.66 – 0.95). Moreover, the incidence of major bleeding was notably higher in the aspirin plus rivaroxaban group after endovascular treatment (HR 1.60, 95% CI 1.02 – 2.51) but not after surgical treatment (HR 1.02, 95% CI 0.47 – 2.19).<sup>591,604</sup> Results were not stratified by graft type at the moment of treatment assignment, but another subgroup analysis from VOYAGER PAD demonstrated a consistent effect favouring aspirin plus rivaroxaban regardless of bypass graft material.<sup>605</sup> A recent *post hoc* analysis of a CASPAR like population from the surgical revascularisation subgroup within the VOYAGER trial also evaluated a CASPAR like endpoint (a composite of acute limb ischaemia, unplanned index limb revascularisation, amputation, or CV death) and demonstrated that treatment with low dose rivaroxaban + low dose aspirin reduced the CASPAR like composite endpoint (that was neutral when comparing DAPT with SAPT in the original CASPAR study) at both one (HR 0.76, 95% CI 0.62 – 0.95,  $p = .013$ ) and three years (HR 0.84, 95% CI 0.71 – 1.00,  $p = .046$ ).<sup>606</sup>

#### Recommendation 80

**For patients with intermittent claudication who have undergone infra-inguinal endarterectomy or bypass surgery and have no increased bleeding risk\*, low dose aspirin in combination with low dose rivaroxaban should be considered, to reduce the risk of secondary cardiovascular and major limb events.**

Class	Level	References	ToE
IIa	B	Bonaca <i>et al.</i> (2020) <sup>604</sup> Debus <i>et al.</i> (2021) <sup>591</sup>	

\* Medical history or active clinically noteworthy bleeding, lesions or conditions within the last six months considered to be a major risk of major bleeding (including current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known oesophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities), any known hepatic disease associated with coagulopathy or bleeding risk, major trauma or accidents within 30 days, any medically documented history of intracranial haemorrhage, stroke or TIA, known active malignancy (excluding basal or squamous cell carcinoma) (VOYAGER criteria).

#### Recommendation 81

**In the rare post-revascularisation scenario where triple antithrombotic therapy is deemed necessary on clinical grounds, patients with intermittent claudication not at high risk of bleeding who have undergone lower limb surgical revascularisation and receive post-procedural treatment with aspirin (75 – 100 mg once daily) in combination with low dose rivaroxaban (2.5 mg twice daily) should not have clopidogrel (75 mg) for longer than 30 days as the bleeding risk is likely to outweigh the benefit.**

Class	Level	Reference	ToE
III	C	Hiatt <i>et al.</i> (2020) <sup>587</sup>	

Recommendation 82			
For patients with intermittent claudication who have undergone infra-inguinal bypass surgery with autologous vein and without increased bleeding risk, vitamin K antagonists with an international normalised ratio range at 2.0 – 2.5 may be considered to improve graft patency.			
Class	Level	References	ToE
I <b>b</b>	A	Geraghty <i>et al.</i> (2011) <sup>607</sup> Bedenis <i>et al.</i> (2015) <sup>603</sup> Monaco <i>et al.</i> (2012) <sup>608</sup> Tangelder <i>et al.</i> (2001) <sup>598</sup> van Hattum <i>et al.</i> (2009) <sup>609</sup> de Smit <i>et al.</i> (1992) <sup>610</sup>	

Recommendation 83			
For patients with intermittent claudication who have undergone infra-inguinal bypass surgery with a prosthetic conduit, single antiplatelet therapy may be considered, to improve graft patency.			
Class	Level	References	ToE
I <b>b</b>	B	Bedenis <i>et al.</i> (2015) <sup>603</sup> Geraghty <i>et al.</i> (2011) <sup>607</sup> Lassila <i>et al.</i> (1991) <sup>611</sup> Belch <i>et al.</i> (2010) <sup>602</sup> McCollum <i>et al.</i> (1991) <sup>612</sup> Clyne <i>et al.</i> (1987) <sup>613</sup>	

Recommendation 84			
For patients with intermittent claudication and increased bleeding risk who have undergone infra-inguinal bypass surgery using an autologous vein, single antiplatelet therapy may be considered, to improve graft patency.			
Class	Level	Reference	ToE
I <b>b</b>	C	Consensus	

## 6.6. Surveillance, outcomes, and quality indicators

### 6.6.1. General aspects on monitoring and follow up.

Patients with IC suffer from impaired quality of life and a high risk of subsequent CV events and death. Adherence to guideline recommended therapy, including smoking cessation, physical activity, and pharmacological therapy is associated with reduced MACE and MALE event rates.<sup>614–619</sup> This may justify close monitoring and long term follow up at specialised centres, but there is currently a lack of direct confirmatory evidence for such practice. Longitudinal follow up after revascularisation is advocated by all vascular societies, while guideline recommendations for non-revascularised patients are less clear.<sup>56,198,620–622</sup>

The primary rationale for patient follow up includes implementation and maintenance of optimal preventive care to reduce CV events and disease deterioration. An additional objective is to diagnose and treat revascularisation failure before patency loss. While procedure related events are most common early after revascularisation and

thereafter gradually decrease, CV event rates increase over time.

Clinical follow up should include comprehensive longitudinal assessment of any CV symptoms, including but not limited to, limb symptoms. Follow up for symptomatic relief in legs, improved functional status, and HRQoL may be evaluated by a PROM survey as discussed in [chapter 3.3](#) and further below in [chapter 6.6.2](#). It is also recommended to monitor adherence to prescribed drugs, dietary and physical activity habits, and to continuously address tobacco smoking status. Patients who continue to smoke should be offered support and be referred to smoking cessation programmes ([chapter 4.1.1.1](#)). Blood pressure ([chapter 4.1.2.3](#)), lipid levels ([chapter 4.1.2.2](#)), and if applicable, blood glucose levels ([chapter 4.1.2.4](#)) should be checked and treated to reach therapeutic target goals.

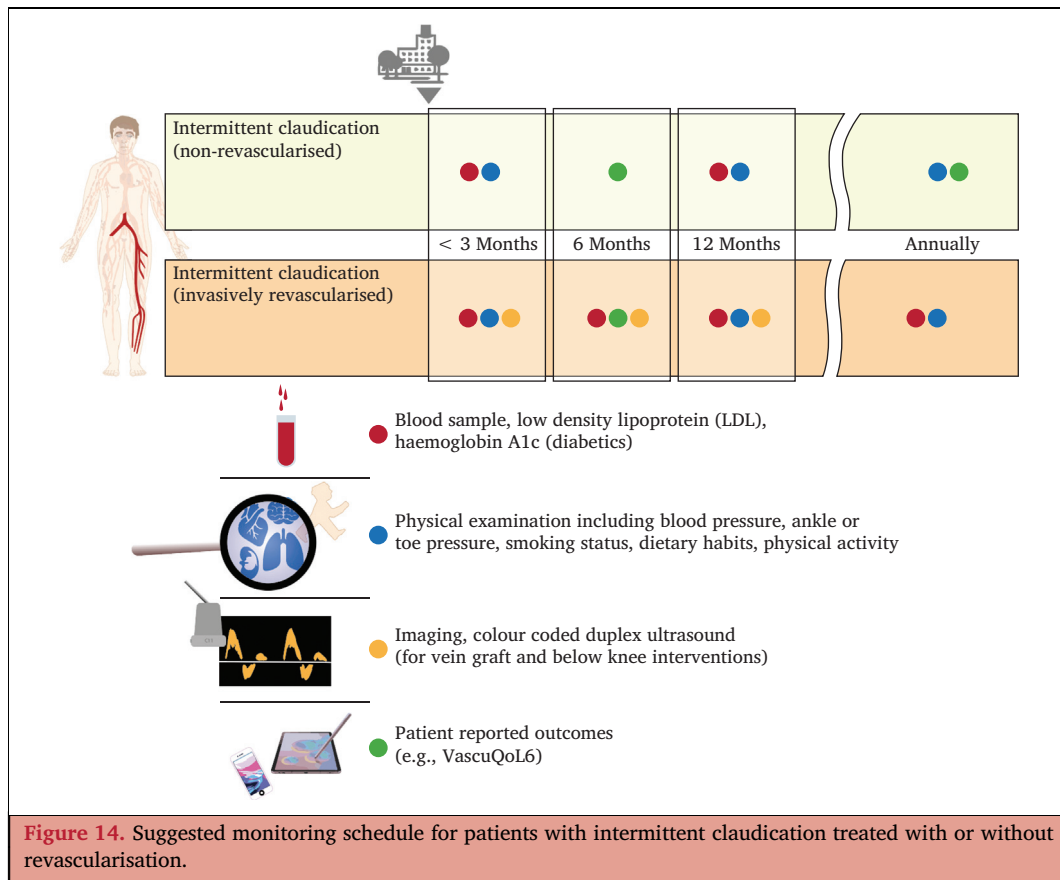
After infra-inguinal bypass with autogenous vein conduits, some 5 – 15% of graft failures occur within the first month and almost 80% within the first two years.<sup>623,624</sup> Most vein graft stenoses are clinically silent, asymptomatic, and difficult to detect by clinical examination or drop in ABI alone. However, such lesions are readily identifiable and can be graded in severity by duplex surveillance; hence duplex ultrasound surveillance is recommended to find a treatable graft stenosis.<sup>625–628</sup> Graft stenoses commonly develop at sites of unrepaired defects or at early appearing conduit abnormalities.<sup>629</sup> Although duplex surveillance following infra-inguinal bypass adds substantial cost, this added cost could be justified in the light of limb amputation costs avoided by such surveillance.<sup>630</sup>

Any benefits of post-procedure surveillance after endovascular intervention have not been established, and the potential impact of routine duplex guided re-intervention in patients after endovascular interventions is questionable.<sup>631–633</sup> A recently published review found a large variation in used modality, surveillance duration, and intensity.<sup>633</sup> Further research is needed to determine whether post endovascular intervention surveillance provides a clinically meaningful benefit in subjects with IC. [Figure 14](#) displays a suggested monitoring scheme for IC patients treated with or without revascularisation.

### 6.6.2. Patient reported outcomes and health related quality of life.

As described in [chapter 3.3](#), patient reported outcomes that cover health and functional status issues and or HRQoL may be used to characterise IC symptomatology and severity. Such questionnaires are also very useful to evaluate the results of different IC interventions as they typically capture important PAD areas such as pain and discomfort, everyday functional limitations, and social and emotional consequences of living with the disease. If properly developed, such surveys can highlight disease progression and problems that may arise because of prescribed treatments and interventions early





and constitute a practical way of integrating the patient's voice in the follow up, longitudinal monitoring, and overall management of IC.<sup>634,635</sup> Patient reported outcome questionnaires thus inform the more traditional outcomes and treatment targets in IC management (described in chapters 6.6.1 and 6.6.3) and should be combined with such objective endpoints. A prerequisite for the use of patient reported outcomes in the evaluation of treatment results following both invasive and non-invasive treatment procedures in IC is a high responsiveness to clinical change. While a combination of generic and disease specific HRQoL instruments may provide the most comprehensive overall picture of the HRQoL changes caused by a certain intervention (and therefore may be suggested for clinical trials), disease specific questionnaires are suitable choices in routine clinical practice scenarios as they focus on the specific limitations experienced by PAD patients, making them more sensitive for detecting clinically relevant health status changes in response to treatment.<sup>636</sup> The most commonly used patient reported outcomes in IC have already been described briefly in section 3.3. Among them, minimal important difference thresholds in response to IC treatment have been established for the Walking Impairment Questionnaire (WIQ), the Peripheral Artery Questionnaire (PAQ), and for the Vascular Quality of Life Questionnaire along with its short version (VascuQoL-25 and VascuQoL-6).<sup>98,637–640</sup> Such

thresholds greatly facilitate the clinical interpretation of these outcomes both in clinical trials and in routine clinical care settings.

#### Recommendation 85

**For all patients with lower limb peripheral arterial disease who have undergone lower limb revascularisation, disease specific health related quality of life instruments, preferably with established thresholds for minimally important clinical difference should be considered, to evaluate the treatment results.**

Class	Level	References	ToE
Ila	B	Cassar <i>et al.</i> (2003) <sup>641</sup> Guidon <i>et al.</i> (2010) <sup>636</sup> Donker <i>et al.</i> (2016) <sup>635</sup> Peri-Okonny <i>et al.</i> (2021) <sup>637</sup> Gardner <i>et al.</i> (2018) <sup>638</sup> Conijn <i>et al.</i> (2015) <sup>278</sup> Nordanstig <i>et al.</i> (2017) <sup>640</sup>	

**6.6.3. Remote and digital solutions to support peripheral arterial disease follow up.** Technology is a key driver of better health. Telemedicine and mobile health may strengthen care and can deliver care in people's home, also offering a tool for patients to manage their own health. Telephone counselling has been studied, for example, in the VIVA trial. Statin adherence was improved

among screened PAD patients by a single phone call at six month follow up but not over 60 month follow up.<sup>642</sup> Other examples are improved blood glucose levels and medication adherence by telemedicine follow up.<sup>643,644</sup> In a recent retrospective observational study ( $n = 457$ ) the 30 day re-admission rates after bypass surgery were lower in patients who received an early follow up telephone call after discharge.<sup>645</sup> The use of web based applications for promoting and maintaining a healthy lifestyle is increasing with promising results.<sup>646,647</sup> The striking gap between evidence based guideline recommendations and adherence to life and limb saving therapies for PAD patients may be bridged by new ways of patient centred counselling and education. In 2013, a review of smartphone apps relating to major vascular diseases documented the availability of 49 vascular themed apps.<sup>648</sup> In a cross sectional survey study among 13 institutions in Germany which aimed to determine the current user behaviour and acceptance of such digital technologies, almost half of the patients with PAD responded that they had not changed their lifestyle and health behaviour since the index diagnosis, and 33% did not know the reasons for all of their medication orders. Interestingly, 71% of the patients with IC and 64% with CLTI owned a smartphone, while only 43% used smartphone apps and 15% used mobile health applications.<sup>649</sup>

Digital health solutions offer the potential to provide an easily accessible, resource effective, and possibly a sustainable strategy that may help to promote necessary lifestyle changes and to reach CV treatment goals. Several clinical studies are ongoing for digital behaviour change interventions for patients with PAD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04947228) NCT04947228, NCT01134458, NCT03554564, NCT02472561, and NCT05029739), and the Society for Vascular Surgery already provide a digitally delivered SET intervention for patients with IC.

**6.6.4. Quality indicators in peripheral arterial disease treatment.** Various concepts to define healthcare quality exist in the literature. More than 50 years ago, Avedis Donabedian published an attempt to describe and evaluate methods to assess the quality of medical care including process, structure, and outcome quality.<sup>650</sup> Several institutions have adopted Donabedian's model ever since. The common denominator is the aim to reach desired healthcare outcomes and to improve the care delivered to patients. To date, practice guidelines do not contain suitable indicators of outcome quality or thresholds to define good versus bad quality as developed in accordance with commonly accepted methodology.

In a systematic review of clinical practice guidelines, consensus statements, systematic reviews, and meta-analyses reporting quality indicators in patients undergoing invasive open surgical and endovascular revascularisations

for symptomatic PAD, a total of 685 articles were identified.<sup>651</sup> From these sources, only three process quality indicators from two publications<sup>652,653</sup> matched the search criteria: one on pharmacological intervention, one on smoking cessation, and a third on surveillance of lower extremity vein bypass grafts.

The literature search revealed an additional 31 structure, process, and outcome quality indicators from societal databases and additional sources. Forwarding those results to a modified Delphi method among 40 invited experts, 12 indicators of outcome quality were recommended after two rounds with a high level of agreement for clinical relevance.<sup>654</sup>

- Major adverse cardiovascular events (MACE)
- Major adverse limb events (MALE)
- Myocardial infarction
- Stroke or transient ischaemic attack
- All cause death
- Major amputation above the ankle level
- Major re-intervention (bypass, bypass revision, thrombectomy, thrombolysis)
- Any open surgical or endovascular re-intervention
- Surgical wound infection
- Vascular access related major complication
- Change in maximum walking distance
- Change in the Rutherford classification category

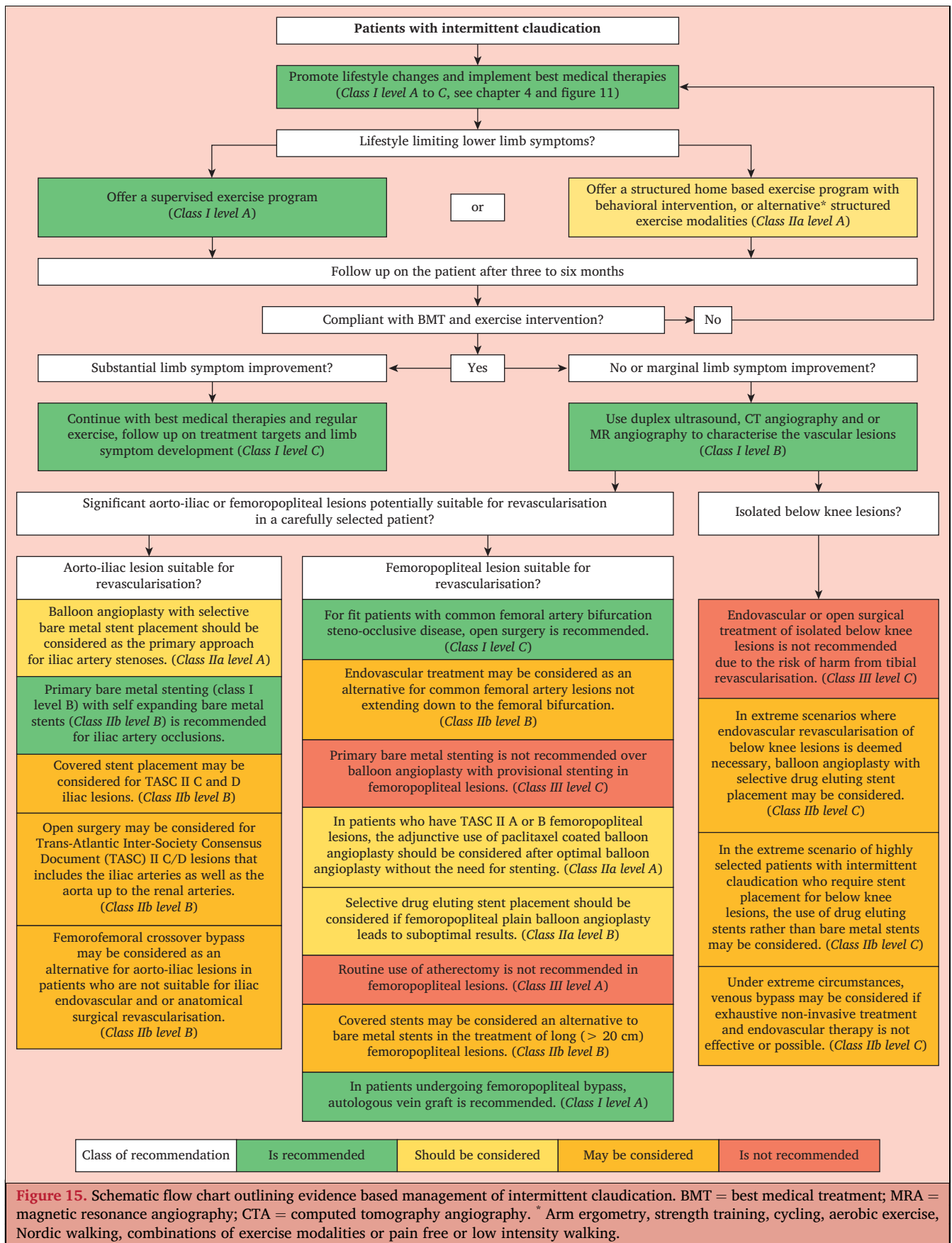
In addition to an improvement in long term cardiovascular and limb event free survival in all patients, patient reported outcome measures (PROM) are especially emphasised in the treatment of patients with lifestyle limiting claudication (see [chapters 3.3](#) and [6.6.2](#)). While the previously referred to Delphi consensus failed to reach consensus agreement in terms of PROMs mainly due to low practicability, another international Delphi consensus most recently generated consensual agreement to collect the VascuQoL-6 survey and 12 optional items in trials and registries on IC treatment (see [chapter 3.3](#)).

#### Recommendation 86

For patients with lower limb peripheral arterial disease, it is recommended that a continuous assessment of suitable indicators of quality of treatment (including survival, functional status, surgical complications and major adverse cardiovascular and limb events) is organised and maintained to improve the care delivered to those patients.

Class	Level	References	ToE
I	C	Bellmunt <i>et al.</i> (2014) <sup>652</sup> Olin <i>et al.</i> (2010) <sup>653</sup> Rieß <i>et al.</i> (2018) <sup>654</sup> Hischke <i>et al.</i> (2019) <sup>651</sup>	

6.7. Overall management strategy for patients with intermittent claudication



**Figure 15.** Schematic flow chart outlining evidence based management of intermittent claudication. BMT = best medical treatment; MRA = magnetic resonance angiography; CTA = computed tomography angiography. \* Arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, combinations of exercise modalities or pain free or low intensity walking.

## 7. ASPECTS ON SEX, SOCIO-ECONOMIC FACTORS, ETHNICITY, AND DIABETES

### 7.1. Sex aspects

Sex related aspects on PAD are not well identified, as women were underrepresented in previous studies. A systematic review reported that 27% of enrolled patients have been women, without major changes over time.<sup>655–657</sup> A higher enrolment of women in clinical trials is necessary to reach the appropriate statistical power in this group and map sex specific differences in PAD risk factors, presentation, and consequences.

Although most PAD subjects are asymptomatic,  $\approx 10\%$  in epidemiological cohorts will present with IC with an overall lower prevalence among women (range 1.0 – 12.7%).<sup>658–661</sup> One explanation is the more challenging diagnosis in women which may be related to higher rates of atypical leg symptoms, lower physical activity, and the later onset of PAD compared with men.<sup>135,143,659,662–665</sup> Exercise performance has been used to suggest that women decline faster in terms of functional ability once PAD is established. This difference, however, may merely be due to the smaller muscles in the calves of women. Singh *et al.* showed that after four years of follow up, women were more likely to be unable to walk for six minutes continuously than men, and the distance achieved in the six minute walk was less. Also, women were more likely to develop mobility disability and had faster declines in walking velocity. However, these apparent sex differences in functional decline were attenuated after additional adjustment for baseline calf muscle area, and so it may be attributable to smaller calf muscle area in women with PAD. Poorer leg strength is associated with increased mortality in men, but not women, with PAD.<sup>666</sup>

When compared with women, men have historically been more frequently selected for revascularisation.<sup>615,667,668</sup> Furthermore, women were more often treated by endovascular techniques at a more severe disease stage.<sup>667,669–671</sup> Sex related outcome after revascularisation for IC is scarce and available data remain conflicting. A meta-analysis, comprising three studies, showed similar all cause mortality between the sexes (HR 1.13, 95% CI 0.98 – 1.39).<sup>672</sup> Another meta-analysis including a mixed population of IC and CLTI identified women at increased risk of early death, CV events, amputation, and procedural complications, while the long term survival, graft patency, and limb salvage were similar between the sexes.<sup>673</sup> A large cohort ( $n = 119\ 620$  patients) from the American Vascular Quality Initiative showed that revascularised women were at higher risk than men of developing peri-procedural complications, including moderate or severe access site bleeding, above knee amputation, and in hospital death, despite adjustments for baseline and procedural characteristics.<sup>674</sup> A *post hoc* analysis from the EUCLID trial demonstrated that women had a lower risk of both MACE and all cause mortality, whereas the occurrence of limb events was comparable between sexes.<sup>675</sup>

Despite the increase of CV disease among postmenopausal women, hormone replacement therapy with

oestrogen and progestin has not been proven beneficial.<sup>676,677</sup> However, newer data suggest that the time point of starting hormone replacement therapy might influence effectiveness. When starting hormone replacement therapy within 10 years before the development of menopause, a subgroup analysis of the Women's Health Initiative data showed a non-significant trend (HR 0.76, 95% CI 0.50 – 1.16) in the direction of CVD protection.<sup>678</sup>

Diabetes and hyperlipidaemia are suggested to increase the risk of PAD four fold in women, as is tobacco use.<sup>656,679,680</sup> Smoking is more common among men; however, the overall use is decreasing, but at a slower pace among women.<sup>374,681–683</sup> McDermott *et al.* and Peters *et al.* found men to be more likely to be treated with intense cholesterol lowering drugs than women.<sup>684,685</sup> Likewise, female sex influences the therapeutic approach for diabetes resulting in delayed diagnosis among women, who also were less likely to achieve HbA1c target levels.<sup>686,687</sup>

#### Recommendation 87

It is recommended to pay attention to a balanced proportion of women and men in clinical studies, with a proportional representation of both sexes according to the sex specific frequency of the disorder or the intervention under study.

Class	Level	References	ToE
I	A	Jelani <i>et al.</i> (2018) <sup>656</sup> Mayor <i>et al.</i> (2021) <sup>688</sup> Hirsch <i>et al.</i> (2012) <sup>662</sup>	

#### Recommendation 88

In postmenopausal women, hormone replacement therapy with oestrogen or progestin is not recommended for prevention of cardiovascular disease due to the lack of proven cardiovascular benefits.

Class	Level	Reference	ToE
III	A	Rossouw <i>et al.</i> (2002) <sup>676</sup> Grady <i>et al.</i> (2002) <sup>677</sup>	

#### Recommendation 89

It is recommended to offer similar evidence based cardiovascular primary and secondary preventive strategies to men and women with peripheral arterial disease.

Class	Level	Reference	ToE
I	B	Jain <i>et al.</i> (2015) <sup>689</sup> Srivaratharajah <i>et al.</i> (2018) <sup>660</sup> Hirsch <i>et al.</i> (2012) <sup>662</sup> Peters <i>et al.</i> (2020) <sup>685</sup> Makowski <i>et al.</i> (2021) <sup>690</sup> Ramkumar <i>et al.</i> (2018) <sup>691</sup> Messiha <i>et al.</i> (2022) <sup>692</sup>	

### 7.2. Influence of geography and socio-economic status

PAD tends to affect individuals with lower socio-economic status to a greater extent as well as inhabitants of low income countries (LIC) compared with high income countries

(HIC) (52). The large prevalence increase between 2000 and 2010 was substantially more pronounced in LIC, where two thirds (72.9%, 173 million) of patients with PAD were located. Socio-economic factors may prevent access to healthcare and thus timely diagnosis of lower limb PAD, which in turn may lead to later clinical presentation at more severe disease stages.

Commonly used metrics for socio-economic status are income and education, whereas measures like total wealth, family and friend network, power and prestige are less well established. Pande *et al.* showed a two fold increased risk of PAD among patients with a low income compared with those with a high income.<sup>693</sup> Similar associations have been reported between PAD and low educational levels.<sup>694–696</sup> Subherwal *et al.* demonstrated disparities in the use of cardioprotective medications depending on both socio-economic status and the treatment facility, whereby patients with low socio-economic status less often received antiplatelet or statin therapy.<sup>697</sup> Jin *et al.* additionally identified time commitment, cost of therapy, and income as well as the social support as relevant factors that are influenced by the socio-economic status having impact on therapy adherence.<sup>698</sup> This highlights the need for health education and advocacy efforts in groups of lower socio-economic status.

### 7.3. Influence of ethnicity

The influence of ethnicity on the prevalence of PAD has been widely described.<sup>699</sup> Selvin *et al.* reported increased crude odds for PAD among individuals of African American ethnicity (OR 2.83, 95% CI 1.48 – 5.42).<sup>700</sup> After adjustment for relevant risk factors, the OR for PAD prevalence in the African American population was still 1.47 (95% CI 1.07 – 2.02), compared with a Caucasian population.<sup>701</sup> Inherent risk factors, unknown external risk factors, or different exposure periods and sensitivity to known risk factors may explain these differences. Additionally, several studies found lower rates of adherence to guideline recommended therapies, including drug prescription for individuals of African American ethnicity.<sup>702</sup> Whether this is related to lower socio-economic status, lower general access to health services, or a lack of physician awareness remain unknown.<sup>703</sup> The rate of insulin resistance is reportedly higher in individuals of African ethnicity, which might explain why African American individuals more often present with a more severe disease stage.<sup>704–706</sup> Simultaneously, patients of African American ethnicity carry the risk of worse outcomes after treatment including higher amputation and mortality rates in general, as well as a higher likelihood to be treated by primary amputation instead of revascularisation after admission for acute PAD.<sup>707–709</sup>

### 7.4. Peripheral arterial disease and concurrent diabetes

See chapters 4.1.1.2 and 4.1.2.4 for specific aspects regarding screening and treatment of diabetes. Diabetes triggers vascular inflammation, oxidative stress, and dyslipidaemia leading to endothelial dysfunction and atherothrombosis.<sup>710,711</sup> The risk of developing IC is reported to be two to four fold higher among subjects with diabetes, and it

debuts at a younger age with fewer other CV risk factors.<sup>712–715</sup> In addition, subjects with diabetes experience poorer lower extremity function.<sup>711,716</sup> Having diabetes has been shown to increase both mortality and amputation risk.<sup>717</sup> Among 21 197 IC patients, concomitant diabetes increased long term mortality (HR 1.3) and amputation rates by 2.3 times.<sup>712,713</sup> A longitudinal propensity score matched study demonstrated higher rates of MACE (HR 1.26, 95% CI 1.07 – 1.48,  $p < .010$ ) and major amputation (HR 2.31, 95% CI 1.24 – 4.32,  $p < .010$ ) in endovascularly treated patients with IC and diabetes.<sup>718</sup> The degree of hyperglycaemia is associated with an increased risk of PAD, which is why strict glycaemic control and aggressive management of CV risk factors remain important to reduce both MACE and MALE events.<sup>719–721</sup>

## 8. UNRESOLVED ISSUES AND FUTURE RESEARCH

### 8.1. Unresolved issues

As described in chapter 3.2, there are several lower limb PAD classifications available. With regard to an anatomical approach to create a classification system, the TASC II classification of lower limb PAD lesion severity was used for many years both in clinical practice and in different research settings.<sup>162,267</sup> In particular, the TASC II classification was used to describe lesion severity in several important clinical trials that support many of the revascularisation recommendations provided in this guideline. The TASC II classification has, however, also been criticised, primarily from a professional point of view, as it was also suggested as a tool to determine the best technical approach (i.e., open and or endovascular intervention) for lower limb revascularisation. This latter intention of the TASC II classification has largely been outdated by the recent rapid technical developments in the field of endovascular intervention, although this does not mean that the classification system cannot still be useful as a structured approach to define lesion severity. In 2019, the authors of the Global CLTI Guidelines suggested an entirely new anatomical classification system, the Global Limb Anatomic Staging System (GLASS), but this system was specifically designed for CLTI.<sup>1</sup> There are several reasons why this system cannot fully be used or implemented in IC, the first being that the GLASS system starts at proximal superficial femoral artery level (i.e., assumes that inflow disease is not present, or has already been fixed). Furthermore, the GLASS system is based on the notion that any revascularisation strategy should ultimately result in inline pulsatile flow to the foot, which is clearly not always necessary or indicated when performing revascularisation procedures for IC indications. It was discussed in the GWC whether to suggest a new patho-anatomical classification system solely for asymptomatic PAD and IC purposes, but the GWC refrained from doing so as it was thought that it would be more purposeful to develop a common system for all lower limb PAD disease stages. The development of a new patho-anatomical classification system that covers all PAD disease stages would be highly desirable but was not resolved during this guideline development.

Also, although it was possible to formulate rather precise recommendations on all the most important concurrent treatment options available for patients with lower limb PAD, there remains a relative lack of confirmatory lower limb PAD specific evidence for many important secondary prevention treatments, especially in asymptomatic PAD. Moreover, the continuous rapid developments with regard to revascularisation techniques used in symptomatic lower limb PAD have resulted in a relative paucity of high level evidence on important technical revascularisation details, including the optimal technical approach to vessel preparation, the optimal device driven approach to enhance long term patency rates, and more tailored revascularisation strategies based on a comprehensive assessment of both patient and lesion characteristics. Although full coverage of these important details was beyond the scope for this guideline, it may represent a topic for future ESVS guideline efforts. Finally, the entire field of lower limb revascularisation also suffers from a relative lack of confirmatory studies that were designed and initiated by physicians and academia without influence from the medical device industry.

## 8.2. Research recommendations

- Studies on objective assessment methods to characterise IC severity.
- Appropriate thresholds for lifestyle limitation in IC.
- Education interventions for lifestyle behaviour changes in IC.
- Health related quality of life assessment post-intervention in IC patients.
- Screening studied for PAD in general populations and in populations at high cardiovascular risk.
- Scientific assessment of sex based differences in diagnosis and treatment for IC.
- Associations between periodontitis and PAD.
- Studies to determine the best way of assessing frailty in PAD patients.
- Potential benefit (and harm) of SGLT2 inhibitors in PAD subgroups.
- Long term risks and benefits of e-cigarettes when used for smoking cessation.
- Clinical and cost effectiveness of DAPT vs. SAPT vs. DPI after endovascular revascularisation for IC.
- RCTs on newer antithrombotic agents in asymptomatic lower limb PAD patients.
- RCTs on statins in asymptomatic lower limb PAD patients.
- Appropriate thresholds for LDL-C in PAD subgroups (besides thresholds derived from PCSK9 trials).
- Benefits and harms of polypharmacy in very old people (> 85 years) with PAD.
- Healthcare behaviour interventions and lifestyle changes using mobile apps and wearables in PAD patients.
- Which patients should be treated invasively as inpatients, outpatient or day cases?
- High level comparative effectiveness and cost effectiveness evidence on open surgical vs. endovascular revascularisation in patients with IC.
- Long term patency of endovascular revascularisation vs. open surgery in the common femoral artery in IC patients.
- Confirmatory studies on the benefits and harms of atherectomy and lithotripsy in IC populations.
- Comparative studies on the efficacy and safety of different bare metal stents (i.e., balloon expandable vs. self expanding stents) in the common iliac and in external iliac artery positions, including in the kissing stent position.
- The value of duplex surveillance following endovascular intervention in IC patients.
- Cost effectiveness studies of different PAD treatments.
- Studies comparing polymer based DES with DCB in the femoropopliteal segment.
- Studies about the best treatment strategy in IC caused by long femoropopliteal lesions.

**8.2.1. Registries on peripheral arterial disease.** Various registries exist which collect data on the treatment of patients with PAD. Numerous national and regional registries are involved in the VASCUNET committee of the European Society for Vascular Surgery (ESVS) and the International Consortium of Vascular Registries, which is a coordinated registry network organised by the Medical Device Epidemiology Network (MDEpiNet).<sup>722</sup>

In a previous VASCUNET report on international variations in infra-inguinal peripheral bypass surgery, data submitted by registries in nine countries emphasised wide variations in everyday clinical practice.<sup>723</sup> Another recent data comparison of amputation practice in 12 countries confirmed the possible impact of external factors on treatment patterns.<sup>724</sup> These registry based analyses also emphasised that heterogeneous study design and variable definitions probably impacted on the comparison of international data in this target population. To further harmonise registry based research, two modified Delphi studies were conducted to find consensus agreement on core data variables and additional information to be collected by registries on acute and chronic peripheral arterial disease.<sup>263,264</sup> These and other PAD registry efforts are likely to be important to maintain a high standard of PAD care across countries, and to provide benchmarks that may guide quality improvement initiatives aiming to reduce differences and disparities in the overall management of PAD around the world.

## 9. PLAIN LANGUAGE SUMMARY AND INFORMATION FOR PATIENTS

### 9.1. The circulatory system, arteries, capillaries, and veins

All cells in the human body depend on a stable and continuous supply of oxygen and nutrients to survive and function properly. The cells also need to get rid of waste products and other substances that are formed during cell metabolism. Oxygen and nutrients are carried enclosed in the blood in a tubular circulation system around the body and in this way reach all the body's cells. The circulatory system is also important for distributing and re-distributing the right amount of blood to the organs and tissues that

currently have the greatest need. For example, a strong increase in blood flow to the legs occurs when the large muscle groups in the thigh and calf are activated when walking or running.

The blood is pumped around in the tube system by the heart. The heart consists of two parallel pumping mechanisms, where the right half of the heart pumps out low oxygen blood into the pulmonary circulation (small circuit), whereby the blood is oxygenated via the lungs and then returns to the left half of the heart. The left half of the heart then pumps out the oxygen rich blood to all the body's other organs and tissues (large circuit). The oxygen rich blood from the left heart ventricle is pumped out into the largest body artery, the aorta. The aorta then branches into successively smaller and smaller arteries which eventually merge into the network of thin walled very small blood vessels (capillaries) where the oxygen and nutrient exchange to and from the cells takes place. The blood that has given off oxygen and nutrients in the capillaries is then collected in progressively larger thin walled blood vessels (veins) that lead the low oxygen blood back to the heart for its return to the lungs via the small circuit.

Lower limb peripheral artery disease (PAD) affects the pelvic and leg arteries that carry oxygen rich blood down to the legs.

### **9.2. What is lower limb peripheral arterial disease and how common is it?**

By far the most common cause of lower limb PAD is atherosclerosis. Atherosclerosis is a chronic inflammatory disease in the arteries which gives rise to deposits of fat and calcium in the arterial walls. The arteries thus become stiffer and narrower. The full reasons why humans develop atherosclerosis are not known but the major risk factors leading to the disease are well characterised. As the atherosclerosis in the arteries of some people progresses, segmental obstructions to the normal arterial blood flow may arise, because the blood carrying channel in the arteries becomes progressively narrower. It is these obstructions that cause the symptoms in the legs that can appear in lower limb PAD. Lower limb PAD is a common disease in the population and is estimated to affect approximately 237 million people around the world. Thus, the disease is approximately as common as more well known common chronic health problems such as hip and knee osteoarthritis or chronic obstructive pulmonary disease (COPD), despite this it is considerably less well known among the public. The incidence of lower limb PAD has increased substantially during the last decades and its incidence is increasing in all regions of the world.

### **9.3. Who is affected by the disease?**

The incidence of lower limb PAD increases with age and the disease is very rare before the age of 50. The disease is seen about equally often in men and women. The main underlying causes of lower limb PAD are smoking, diabetes, high

blood pressure, and elevated blood fat (cholesterol) levels. This knowledge is important because it means that the disease and its major severe manifestations can potentially be prevented or at least mitigated with lifestyle changes and different medical treatments. If the disease can be identified early, it is accordingly possible to modify the disease course and to improve the individual patient's prognosis. Hereditary factors are also important for the development of atherosclerosis.

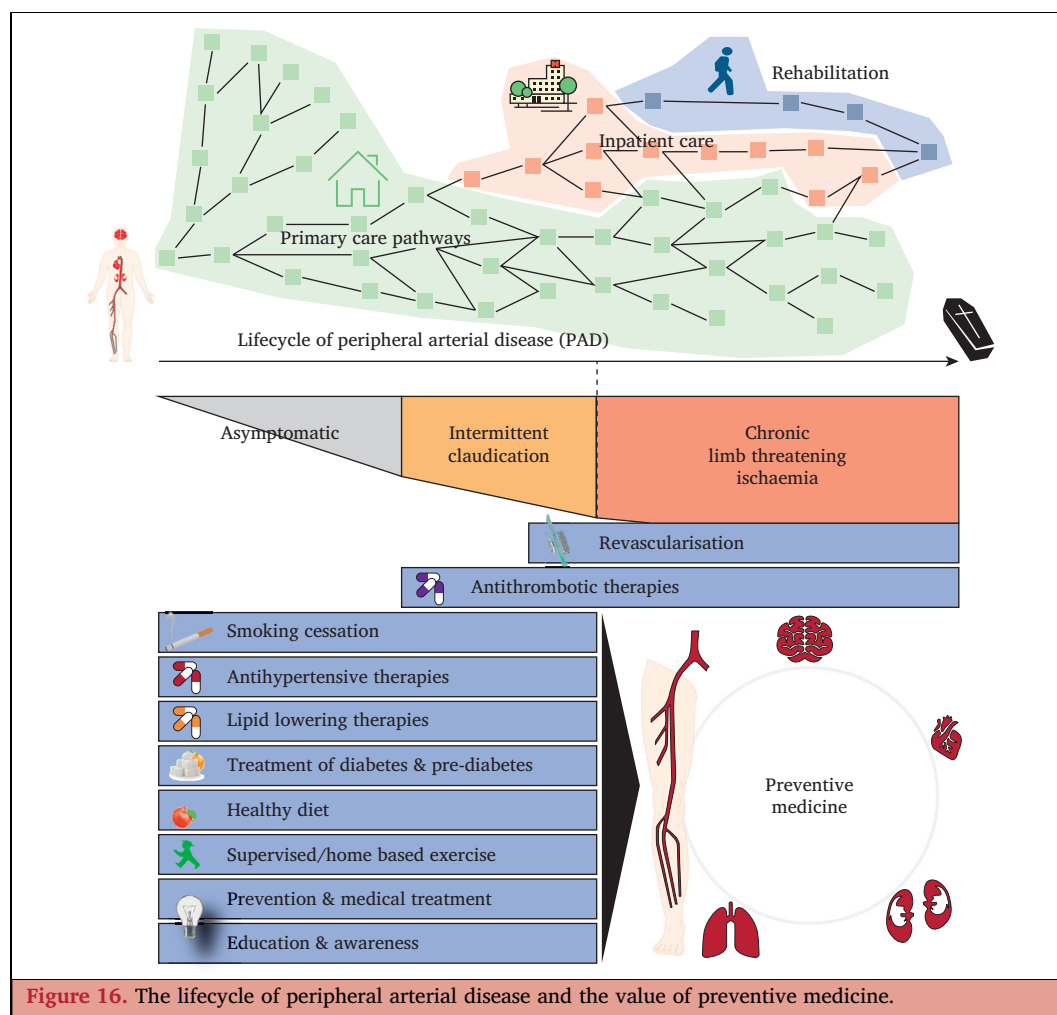
### **9.4. Lower limb peripheral arterial disease as a warning signal to you as a patient**

Lower limb PAD can be a dangerous disease. This is mainly as the root cause – atherosclerosis – can affect the entire arterial system. This means that a patient with lower limb PAD runs an increased risk of suffering serious cardiovascular complications in the arterial system elsewhere such as heart attack or stroke. Therefore, preventive measures to minimise this risk are very important in patients with lower limb PAD. Factors that can reduce the individual risk of serious complications are smoking cessation, lifestyle changes such as better diet, more exercise, optimised treatment of elevated blood pressure, diabetes, and elevated cholesterol levels along with various protective drug treatments (Fig. 16).

### **9.5. The different symptoms and stages of lower limb peripheral arterial disease**

Being able to walk is one of the most important daily activities in human life. As above, the atherosclerosis process in lower limb PAD leads to the development of narrowing in the pelvic and leg arteries, which prevents the normal transport of oxygen and nutrient containing blood to the bones, muscles, skin, and other tissue. The disease can be established and detectable in the leg arteries without a patient having symptoms in the legs or seeking contact with the healthcare system, which is usually referred to as asymptomatic lower limb PAD. However, it is not uncommon for such patients to instead have more atypical symptoms from the legs such as reduced or altered sensation, a feeling of numbness, and sometimes calf cramps. It is also known from research that already in its asymptomatic and early symptomatic stages the disease entails a markedly increased risk of suffering serious cardiovascular events. So, if you are a patient with diabetes, high blood pressure, or if you smoke and you develop leg symptoms such as numbness or cramping, a check up with your primary care physician is required.

A common and typical symptom of lower limb PAD is exertion related pain in the leg(s) associated with walking, which is caused by the accumulation of lactic acid and waste products in the muscles because the working muscles are not provided with enough oxygen rich blood to be able to maintain a normal energy metabolism in the muscle tissue during muscle work. In medical terminology, this symptom is called intermittent claudication. Thus, patients with intermittent claudication have pain in the leg(s) only



**Figure 16.** The lifecycle of peripheral arterial disease and the value of preventive medicine.

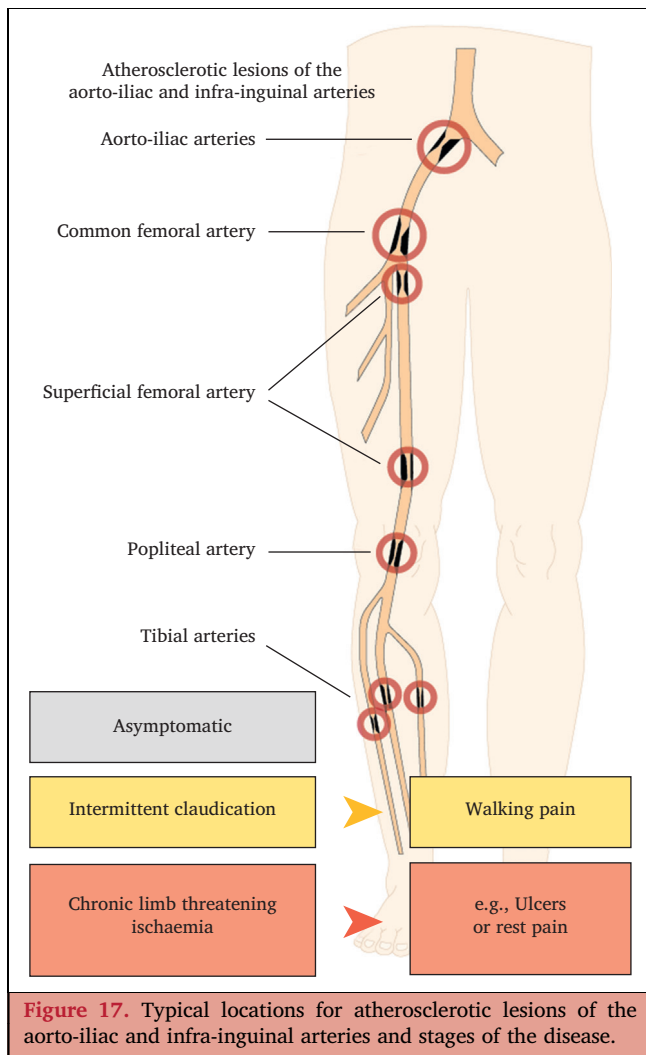
when walking, and if they continue to walk, the symptoms eventually become so severe that they must stop (Fig. 17). After a short period of resting, the symptoms subside, usually within a couple of minutes, after which the patient can continue to walk again until the symptoms develop again. The pain is most commonly located in the calf, but can also be experienced in the thigh, hip, and buttocks. The location of the pain is related to which lower limb arterial segment is most substantially narrowed. Depending on the frequency of the recurring pain and often accompanied by a reduced ability to walk, in combination with social consequences, the health related quality of life is often negatively affected by the disease. However, the pain that occurs is not dangerous or harmful, it is merely a symptom of the disease, and for patients with intermittent claudication it is very important to exercise and stay physically active as far as possible.

In its most severe form, patients with lower limb PAD develop such severely reduced circulation that it becomes insufficient even to maintain a normal energy metabolism at rest. This serious (but quite rare) form of PAD leads to the patient having continuous severe lower limb pain that often requires strong pain relieving medications. Moreover, spontaneous appearance of ulcers (i.e., wounds) or

gangrene (i.e., darkening due to tissue death) on the foot can occur. Using medical nomenclature, this is termed chronic limb threatening ischaemia, which without circulation improving vascular interventions means a high risk of limb amputation. A high proportion of individuals with chronic limb threatening ischaemia have diabetes. Nevertheless, good diabetes control can aid in the prevention of such serious events but when they do occur, ulcers and tissue necrosis occur most often in the forefoot and toes and are commonly accompanied by pain that is usually worst at night.

In some patients, a more sudden decrease in lower limb circulation occurs. This can be because a clot has formed in the leg that completely blocks the arterial blood flow. Such acute limb ischaemia is a serious condition that, if left untreated, can endanger the survival of both the limb and the affected individual. It is not uncommon for patients affected by this to have a previous medical history where milder symptoms of lower limb PAD have occurred. Rapid contact with the nearest emergency department at a hospital with vascular surgery expertise is called for in most of such cases, for clot dissolving endovascular treatment or vascular surgical intervention, which is very effective in treating the blockage.





### 9.6. How is lower limb peripheral arterial disease diagnosed?

The diagnosis is made based on the patient history combined with a thorough lower limb vascular examination. The disease can be established without you as a patient experiencing classic and clear symptoms. In these cases, the diagnosis is made solely with the guidance of the vascular examination. Lower limb PAD is characterised by weakened or absent pulses in the legs. A blood pressure measurement at the ankle level with a handheld ultrasound device is carried out. By comparing the blood pressure at the ankle level with the corresponding blood pressure in the arm, one can easily get a relatively clear idea of how serious the circulatory impairment in the leg is. This so called ankle brachial index (ABI) measurement should be available in all healthcare centres and is a good way to identify the disease as early as possible in patients at risk in primary care.

Despite careful examination, it can sometimes be difficult to distinguish lower limb PAD from hip and knee osteoarthritis, other diseases of muscles and joints in the leg, as well as from compression of the spinal cord or nerve roots to the legs due to pathological changes in the spine.

If a patient is eligible for vascular surgical intervention, the location, extent, and nature of the lower limb PAD must be mapped in more detail. This is done to determine the best way to carry out a lower limb revascularisation procedure, and can be done by vascular ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

### 9.7. How is lower limb peripheral arterial disease treated?

Evidence based preventive general treatments that can reduce the risk of serious cardiovascular complications in lower limb PAD are lifestyle changes (smoking cessation in smokers, weight reduction in obese people, and increased physical activity) as well as careful treatment of elevated blood pressure and diabetes where applicable. Important medical treatments include pharmaceutical agents that reduce the risk of clot formation and lower the blood cholesterol levels. All drug treatments must be monitored, and it must be checked that cholesterol levels, blood pressure, and blood sugar reach recommended levels, and that you as a patient do not experience troublesome or serious side effects from the treatment.

The treatment recommended for the lower limb symptoms largely depends on the severity of the lower limb PAD. In the case of intermittent claudication, there is strong evidence that physical exercise (especially walking) increases walking distance, which is why walking exercise is recommended for all such patients. Increased physical activity can also probably reduce the risk of heart attack and stroke in patients with lower limb PAD. The training involves walking until the pain in the leg is noticeable, after which the patient stops and rest until the pain subsides and then repeats. If the training is carried out regularly (at least three times per week, preferably more often than this), the pain free walking distance can be improved. Exercise can be recommended outdoors, preferably in the form of brisk walking, or on treadmills that are available at most gyms. Other forms of exercise also have beneficial effects on both walking distance and general cardiovascular risk and can be recommended as a supplement to walking exercise. So called supervised exercise therapy, where the training is carried out with the support of a physiotherapist, is more efficient than exercising without supervision. Some patients who do not respond satisfactorily to the above treatment may be considered for specific drug treatment (cilostazol), which in some cases can improve walking ability and health related quality of life. This drug may cause some side effects and is not suitable for everyone.

Some patients with lower limb PAD and symptoms of intermittent claudication will not improve to a sufficient extent despite the aforementioned treatments. In well selected cases, therefore, more invasive vascular treatment may also be considered. Today, such treatment is mainly carried out with minimally invasive, so called endovascular treatment (usually balloon dilation, with or without a stent). The risks of complications from such treatments are low and the treatment usually leads to improved walking ability and health related quality of life. More limited open

vascular surgical interventions may also be considered in particularly disabling cases. However, it is relatively common for the symptoms to return, despite an endovascular or surgical procedure, whereby the invasive treatment may have to be repeated.

In the relatively rare event of progression to chronic limb threatening ischaemia and in acute limb ischaemia there is a risk of amputation, which is why all these patients must be urgently evaluated by a vascular surgeon, and usually these patients undergo endovascular or open vascular surgery to save and preserve the limb.

#### APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2023.08.067>.

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