DEUTSCHE GESELLSCHAFT FÜR GEFÄSSCHIRURGIE UND GEFÄSSMEDIZIN e.V.
Gesellschaft für operative, endovaskuläre und präventive Gefäßmedizin

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Stellungnahme der DGG e.V. zum Entwurf eines Gesetzes zur Stärkung der Herzgesundheit (Gesundes-Herz-Gesetz – GHG)

Sehr geehrter Herr Minister Lauterbach,

mit großem Interesse haben wir die Vorstellung des Entwurfes eines Gesetzes zur Stärkung der Herzgesundheit (GHG) durch Ihr Ministerium und die anschließende mediale Debatte zu diesem Vorhaben verfolgt.

Die kontinuierlich steigenden Gesundheitsausgaben in Deutschland stehen aktuell besonders im Fokus des öffentlichen Interesses. Im internationalen Vergleich erscheinen diese besonders hohen finanziellen Aufwendungen allerdings nicht von einer Verbesserung der einschlägigen **Morbiditäts- und Mortalitätsstatistiken**, z.B. der Weltgesundheitsbehörde (WHO), begleitet zu werden. Dort steht Deutschland weiterhin auf den hinteren Plätzen.

In der Todesursachenstatistik des Bundes stellen **Herz-Kreislauf-Erkrankungen** bereits seit Jahren die häufigsten Ursachen dar, wobei Diagnosen zu Krankheiten des Herzens (z.B. Herzinfarkt) vor Hirninfarkten (Schlaganfall) und Komplikationen des Bluthochdrucks stehen. Generell gilt die Erfassung von Todesursachen allerdings systemimmanent als unvollständig und daher verzerrt. Es gilt dennoch als allgemein akzeptiert, dass die **systemische Gefäßverkalkung (Atherosklerose)** die gemeinsame Hauptursache der meisten chronischen Herz-Kreislauf-Erkrankungen mit tödlichem Ausgang darstellt. Die Bedeutung der Atherosklerose wurde auch in aktuellen bevölkerungsbezogenen Screening-Studien bestätigt, in denen bereits etwa jeder vierte Einwohner in Deutschland eine krankhafte Verkalkung der Halsgefäße oder der Becken-Bein-Gefäße mit Nachweis einer **peripheren arteriellen Verschlusskrankheit (PAVK)** aufwies.[1]

[1] Behrendt CA, Thomalla G, Rimmele DL, et al. Editor's Choice - Prevalence of Peripheral Arterial Disease, Abdominal Aortic Aneurysm, and Risk Factors in the Hamburg City Health Study: A Cross Sectional Analysis. Eur J Vasc Endovasc Surg. 2023 Apr;65(4):590-598. doi: 10.1016/j.ejvs.2023.01.002.

Obwohl die Todesursachenstatistik die Bezeichnung des Gesetzes und seine deutliche Fokussierung auf das „Herz“ als eines unter mehreren betroffenen Organsystemen durchaus erklärt, erscheint dieser Ansatz die Komplexität des Themas unangemessen zu reduzieren. Neben der epidemiologisch einfach messbaren **Gesamtmortalität** und der robusten **Erfassung von Herzkrankheiten** in administrativen und klinischen Registern existieren weitere atherosklerotische **Volkskrankheiten** und **patientenbezogene Endpunkte**, die präventive Ansätze und eine öffentliche Debatte erforderlich machen. Es gibt demnach mehrere Studien, die nahelegen, dass im haus- und fachärztlichen Versorgungssektor die Bedeutung der peripheren Durchblutungsstörungen der Beine als weniger wichtig eingeschätzt werden, was auch zu der aktuellen exklusiv auf das „Herz“ beschränkten medialen Diskussion passt. Wir würden daher empfehlen, von einem „**Gesunde-Gefäße-Gesetz (GGG)**“ zu sprechen, da diese Bezeichnung alle zentralen und peripheren Gefäße im menschlichen Körper komplementär einschließt und damit die Bedeutung für zahlreiche Behandlungsfelder besser herausstellt.

Mit etwa 237 Millionen Betroffenen weltweit – mehr als 40 Millionen davon in Europa – und einer zunehmenden Anzahl an **Menschen mit Diabetes und durchblutungsbedingten Wunden** gilt beispielsweise die PAVK als **komplexe chronische Volkskrankheit** mit einer besonders eingeschränkten gesundheitsbezogenen Lebensqualität, mit Multimorbidität und frühzeitiger Sterblichkeit.[2] Die mit ihrer Entstehung und ihrem Voranschreiten assoziierten Risikofaktoren entsprechen grundsätzlich den anderen Herz-Kreislauf-Erkrankungen, wobei Rauchen, Fettstoffwechselstörungen, Diabetes, Übergewicht, Bluthochdruck und „ungesundem Lebensstil“ die größte Bedeutung beigemessen wird.

In späteren Krankheitsstadien kommt es nach einer jahrelangen asymptomatischen Progression zu belastungsabhängigen Schmerzen in den Beinen (Claudicatio intermittens) mit eingeschränkter Mobilität und Lebensqualität sowie zu Wundheilungsstörungen und Amputationen der Beine. In einer **longitudinalen Auswertung von Krankenkassendaten der BARMER**, im Rahmen einer vom Innovationsfond des G-BA geförderten Studie,[3] konnte vor wenigen Jahren eindrücklich nachgewiesen werden, dass bei 9–48% bzw. 25–88% der Betroffenen, je nach Stadium und Risikoprofil, **innerhalb von fünf Jahren eine Amputation oder ein Todesfall** registriert wurde.[4] Das

[2] Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019 Aug;7(8):e1020-e1030. doi: 10.1016/S2214-109X(19)30255-4.

[3] https://innovationsfonds.g-ba.de/beschluesse/idomeneo-studie-ist-die-versorgungsrealitaet-in-der-gefaessmedizin-leitlinien-und-versorgungsgerecht.123; zugegriffen am 29.06.2024

[4] Kreutzburg T, Peters F, Kuchenbecker J, et al. Editor's Choice - The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease. Eur J Vasc Endovasc Surg. 2021 Feb;61(2):248-256. doi: 10.1016/j.ejvs.2020.11.013.

Krankheitsbild ist häufig Teil einer polyvaskulären Erkrankung verschiedener Gefäßregionen, wobei Menschen mit einer PAVK als besonders unterversorgt und anfällig für Herz-Kreislauf-Komplikationen gelten. Das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) und das Bundesministerium für Gesundheit haben die Bedeutung dieser Volkskrankheit daher auch mit einer **unabhängigen Gesundheitsinformation** des Bundes vor wenigen Monaten unterstrichen.[5]

Die DGG empfiehlt ausdrücklich, die PAVK und geeignete Screening-Maßnahmen in den Gesetzentwurf einzubeziehen –dies nach ausführlicher auch interdisziplinärer Diskussion mit unseren Kolleg:innen der Deutschen Gesellschaft für Angiologie (DGA) und der Deutschen Röntgengesellschaft (DRG) und vor dem Hintergrund aller vorgenannten Erwägungen zur Bedeutung dieser atherosklerotischen Kreislauferkrankung und angesichts des oft langjährigen asymptomatischen Verlaufs mit zahlreichen evidenzbasierten Ansatzpunkten für präventive Maßnahmen.

In einer vor wenigen Monaten veröffentlichten Praxisleitlinie zur Behandlung der asymptomatischen PAVK und der Claudicatio intermittens der European Society for Vascular Surgery (ESVS) wurde eine **evidenzbasierte Klasse-II-Empfehlung zum Screening in Risikopopulationen** herausgegeben, die auch in der in Überarbeitung befindlichen S3-Leitlinie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) eingefügt wurde. Demnach ist die Durchführung einer technisch einfachen und ambulant kostengünstig verfügbaren Messung der Dopplerverschlussdrücke mit Bildung des sogenannten Knöchel-Arm-Index (Ankle-Brachial-Index, ABI) zu erwägen, wobei international konsentierte einheitliche Grenzwerte zur Diagnose einer PAVK existieren.[6]

Bei der Feststellung eines erniedrigten Knöchel-Arm-Index geht es aber nicht nur um das **Screening einer peripheren Gefäßkrankheit** und die frühere Anbindung einer unterversorgten Bevölkerungsgruppe an präventivmedizinische Programme. Auch Menschen mit einer koronaren Herzkrankheit (KHK) können profitieren, da das gleichzeitige Vorliegen einer PAVK das Risiko für frühzeitigen Tod und Komplikationen gegenüber der isolierten Herzkrankheit deutlich erhöht. Die Messung des ABI ist insgesamt ein **international etablierter Parameter** mit hoher Sensitivität und Spezifität, um das Vorliegen einer signifikanten Atherosklerose zu sichern.

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[5] https://gesund.bund.de/periphere-arterielle-verschlusskrankheit-pavk; zugegriffen am 29.06.2024

[6] Nordanstig J, Behrendt CA, Baumgartner I,; ESVS Guidelines Committee; Antoniou GA, Björck M, Gonçalves FB, Coscas R, Dias NV, Van Herzeele I, Lepidi S, Mees BME, Resch TA, Ricco JB, Trimarchi S, Twine CP, Tulamo R, Wanhainen A; Document Reviewers; Boyle JR, Brodmann M, Dardik A, Dick F, Goëffic Y, Holden A, Kakkos SK, Kolh P, McDermott MM. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. Eur J Vasc Endovasc Surg. 2024 Jan;67(1):9-96. doi: 10.1016/j.ejvs.2023.08.067.

Die durch das Screening identifizierten Menschen mit einer PAVK profitieren dabei von einer frühen und konsequenten Optimierung der Risikofaktoren, z.B. durch Einschluss in Rauchentwöhnungsprogramme und Gefäßsportgruppen sowie Gesundheitsaufklärungsangebote zur Verbesserung des langfristigen Verlaufs.

Hochachtungsvoll,

Berlin, den 28. Juni 2024

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Medizinisch-wissenschaftlicher Direktor des DIGG

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Editor's Choice – Prevalence of Peripheral Arterial Disease, Abdominal Aortic Aneurysm, and Risk Factors in the Hamburg City Health Study: A Cross Sectional Analysis

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WHAT THIS PAPER ADDS

Cohort studies to determine the prevalence of cardiovascular disease among general populations remain scarce. However, the need for current figures is emphasised by changes in prevention and treatment patterns that may have influenced the situation in contemporary populations. In this cohort of 10 000 randomly enrolled subjects representative of the city of Hamburg, almost 45% suffered from any peripheral arterial disease, 30% had carotid artery disease, 24% had lower extremity peripheral arterial disease, and only 1.3% of males and 0.2% of females had an abdominal aortic aneurysm. These prevalences and associated risk factors give an insight into the situation in Germany today.

Objective: There is a paucity of current figures on the prevalence of carotid and lower extremity peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA) as well as the associated cardiovascular risk factors to support considerations on screening programmes.

Methods: In the population based Hamburg City Health Study, participants between 45 and 74 years were randomly recruited. In the current cross sectional analysis of the first 10 000 participants enrolled between February 2016 and November 2018, the prevalence of carotid artery disease (intima—media thickness $\geq$ 1 mm), lower extremity PAD (ankle brachial index $\leq$ 0.9), and AAA (aortic diameter $\geq$ 30 mm) was determined. Multivariable logistic regression models were applied to determine the association between vascular diseases and risk factors. To account for missing values, multiple imputation was performed.

Results: A total of 10 000 participants were analysed (51.1% females, median age 63 years, median body mass index 26.1 kg/m^2). In medians, the intima media thickness was 0.74 mm (interquartile range [IQR] 0.65 — 0.84), the ankle brachial index 1.04 (IQR 0.95 — 1.13), and the aortic diameter 17.8 mm (IQR 16.1 — 19.6). Concerning risk factors, 64% self reported any smoking, 39% hypertension, 5% coronary artery disease, 3% congestive heart failure, 5% atrial fibrillation, and 3% history of stroke or myocardial infarction, respectively. In males, the prevalence of carotid artery disease, lower extremity PAD, and AAA were 35.3%, 22.7%, and 1.3%, respectively, and in females, 23.4%, 24.8%, and 0.2%, respectively. Higher age and current smoking were likewise associated with higher prevalence while the impact of variables varied widely.

Conclusion: In this large population based cohort study of 10 000 subjects from Hamburg, Germany, a strikingly high prevalence of PAD was revealed. Almost 45% suffered from any index disease, while AAA was only diagnosed in 1.3% of males and 0.2% of females. The high prevalence of atherosclerotic disease and associated cardiovascular risk factors underline that it is essential to increase awareness and fuel efforts for secondary prevention.

Keywords: Peripheral arterial disease, Carotid arterial disease, Abdominal aortic aneurysm, Prevalence, Epidemiology, Screening
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INTRODUCTION

Long term consequences of systematic atherosclerotic disease pose a particularly high burden on affected people due to considerably elevated risks for adverse cardiovascular and limb events as well as death.

While several authors have concluded from observational studies that the prevalence of lower extremity and carotid peripheral arterial disease (PAD) as well as abdominal aortic aneurysm (AAA) increase over time, population based data from high quality epidemiological studies remain sparse. Due to significant changes in preventive medicine and best medical treatment of systemic atherosclerosis, the actual incidence of such diseases may even have dropped.[1] Furthermore, the rapid widespread of opportunistic screening as well as invasive treatment and secular changes in associated risk factors, and demographic changes may also have influenced the distribution of certain vascular diseases in contemporary populations.

In the field of AAA treatment, four high quality screening studies were conducted in Australia, United Kingdom, and Denmark in the 1990s. They revealed a prevalence of 4 — 8% among elderly men,[2–5] whereas more recent data from national screening programmes have reported far lower estimates of less than 2%.[6–9] This phenomenon was frequently referred to as the rise and fall of AAA.[10] After years of discussions, an ultrasound screening programme to detect AAA was only implemented in Germany in 2017, although the importance of the disease burden still remains unknown beyond estimates derived from hospitalised cohorts.[11,12]

In a recent systematic review of 118 articles on the prevalence of lower extremity PAD, approximately 237 million people were affected worldwide in 2015.[13] This corresponded to an increase by 35 million (+17%) when compared with 2010.[14] The authors also reported that regional and national estimates varied widely. Thereby, the Western Pacific Region had the most cases, whereas the Eastern Mediterranean Region had the least.[13] Interestingly, available practice guidelines have not yet implemented evidence based recommendations on population screening.[15,16] Considering carotid artery disease, several population based studies revealed a prevalence between 2% and 4.1% for asymptomatic carotid stenosis.[17–19] However, there is a lack of large systematic screening studies involving healthy populations and subclinical atherosclerotic lesions of the carotid arteries.[20] Hence, the actual burden of carotid artery disease remains fairly vague.

In summary, the paucity of up to date epidemiological data, the unknown prevalence of subclinical atherosclerotic lesions, and the fact that variations exist both over time and between regions emphasise the need for population based cohort studies.

Hence, this study aimed to determine the prevalence and associated risk factors of carotid artery disease, lower extremity PAD, and AAA using deep phenotyping in subjects living in the metropolitan area of Hamburg, Germany, from a large population based cohort study.

MATERIALS AND METHODS

This was a cross sectional study to determine the prevalence and associated risk factors of chronic vascular diseases including carotid artery disease, lower extremity PAD, and AAA. The STROBE statement was followed for reporting the current study.[21]

Study population

The Hamburg City Health Study (HCHS) is an ongoing, prospective, long term, population based cohort study and an innovative research platform to obtain substantial knowledge and deep phenotyping about major chronic diseases.[22]

The enrolled participants were selected from a statistical sample provided by the local residents' registration office. Participants between 45 and 74 years of age from the general population of Hamburg, Germany, were included between February 2016 and November 2018 in an extensive baseline assessment including approximately 10 000 variables during a seven hour examination at one dedicated study centre.[22] Currently, Hamburg is the second largest city in Germany with approximately 1.84 million inhabitants who were registered by the Federal Bureau of Statistics (Hamburg, Germany). The present study included quality assured data from the first 10 000 participants. More details on the specifics of this study have been reported previously.[22–25]

The ethics committee of the Medical Association of Hamburg approved the study protocol (PV5131), and the study was registered at ClinicalTrials.gov (NCT03934957). The study was carried out following the Helsinki Declaration of the World Medical Association and according to the principles of good clinical and good scientific practice. This manuscript was prepared according to the STROBE guidelines.[21]

Vascular phenotyping

Trained technicians performed the ultrasound examination following a standard protocol, and a regular quality assurance of research data was conducted via statistical measures (e.g., validation of outliers, interobserver reliability) as well as random and risk based controls by specialised physicians.

Carotid artery disease was evaluated by ultrasound using a Siemens SC2000 with a 7.5 MHz linear array transducer. Carotid intima to media thickness (CIMT) was measured three times in the B mode in a longitudinal view of the left and right common carotid artery $>$ 1 cm proximal to the carotid bulb, and mean values were calculated. Carotid artery disease was diagnosed if the CIMT was $\geq$ 1 mm or if the presence of atherosclerotic plaques was recorded. Plaques were defined as a circumscribed focal thickening of the intima-media $>$ 1.5 mm and measured in the common and proximal internal carotid artery. At the study centre, the lowest ankle brachial index (ABI) was measured after five minutes of rest in supine position in both legs and the cut off value for a diagnosis of PAD was $\leq$ 0.9.[26] Due to time restrictions, a complete examination was available in approximately 50% of unselected subjects. AAA was evaluated by ultrasound using a Siemens SC2000 with a 1.5 — 6 MHz convex array transducer. The anteroposterior diameter of the infrarenal aorta was measured during systole using the outer to outer method at the widest segment after

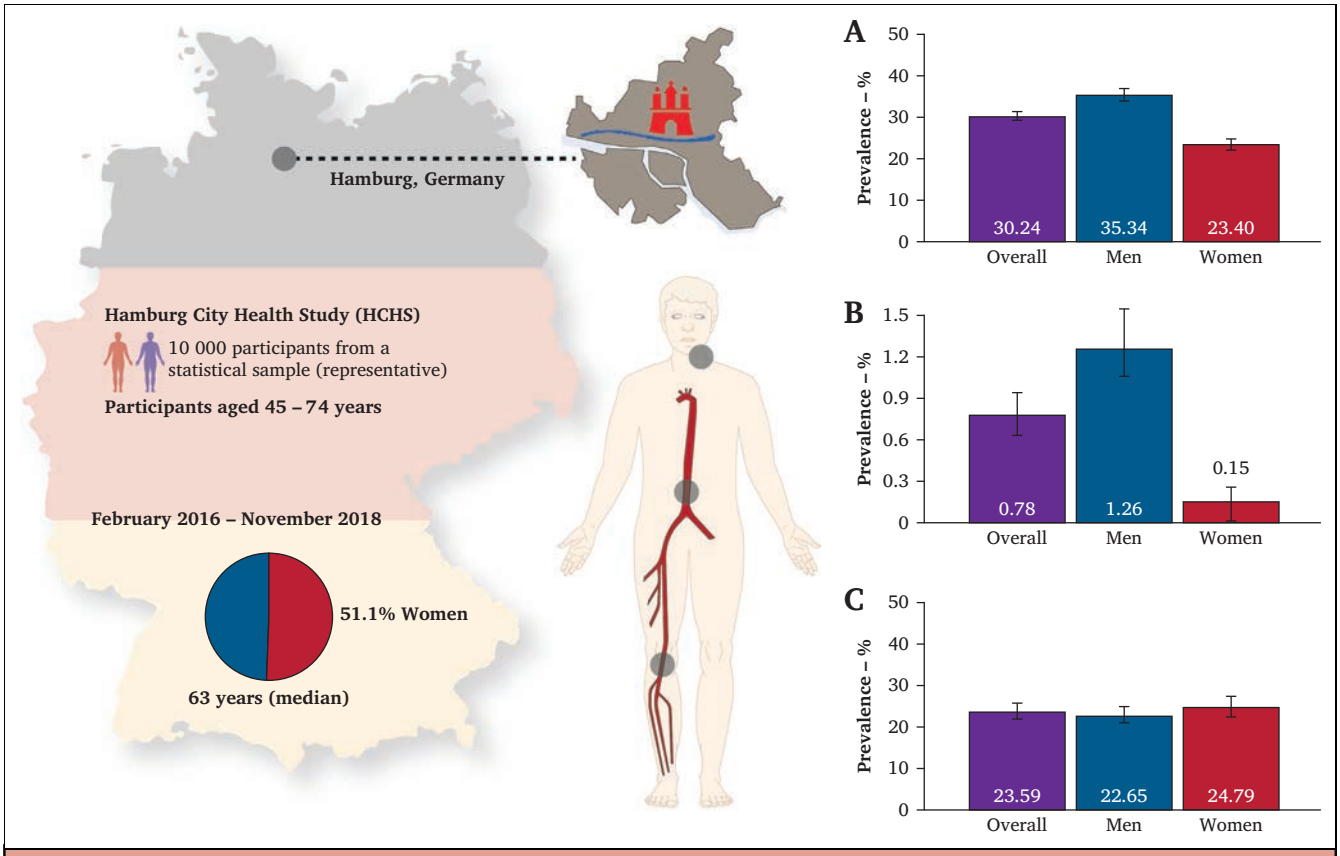

Figure 1. Prevalence of (A) carotid artery disease, (B) abdominal aortic aneurysm, and (C) lower extremity peripheral arterial disease in the first 10 000 participants enrolled in the Hamburg City Health Study (HCHS) between February 2016 and November 2018.

segmental evaluation. AAA was diagnosed if the diameter was $\geq$ 30 mm.[27]

Study variables

For the current study, the following study variables were used: dichotomised sex (male, female), age at inclusion in the study in years, aortic diameter in millimetres, intima to media thickness in millimetres for both common carotid arteries, presence of carotid plaques for both carotid arteries, lowest ABI for both legs, anamnestic information about the occurrence of clinical symptoms of lower extremity PAD (dichotomised self reported intermittent claudication, ischaemic rest pain, wound healing disorders), arterial hypertension, coronary artery disease, congestive heart failure, history of myocardial infarction, history of stroke, atrial fibrillation, history of cancer, alcohol abuse (more than two drinks per day), smoking status (active, never, current), never performing any sports activity, adherence to Mediterranean Diet (MEDAS score) grouped according to the quantiles of the distribution ($<$5 points, 5 points, 6 $-$ 7 points, $\geq$ 8 points), body mass index (kg/m^2), waist circumference (cm), self reported information and medical history about hypertension, systolic blood pressure at rest (mmHg), diastolic blood pressure at rest (mmHg), total cholesterol (mg/dL), low density lipoprotein (LDL, mg/dL), glomerular filtration rate (mL/min/m^2) was used involving the serum creatinine in mg/dL and a standardised body surface of 1.73 m^2.[28] Dyslipidaemia was defined as total cholesterol above 175 mg/dL and LDL above 100 mg/dL if diabetes or cardiovascular conditions were present, and as total cholesterol above 190 mg/dL and LDL above 115 mg/dL otherwise.

Target variables were the three vascular index diseases and the composite of them (any index disease). Finally, any index disease was defined as presence of either carotid artery disease, lower extremity PAD, or AAA.

Statistical analysis

Descriptive patient characteristics were expressed as median and interquartile range (IQR) for continuous variables and numbers and proportions for categorical variables, if not stated otherwise. Before computing the target variables, missing values were imputed for the dataset containing all study variables based on multivariable imputation by chained equations separately for five copies of the data with 10 iterations. The variables included in the models were chosen by discussion among experts and after reviewing the bivariable baseline characteristics. Subsequently, both the prevalence of each vascular disease group and the association of risk factors for each index disease group (using multivariable logistic regression models) were computed separately for each copy of the data. All estimates were averaged and standard errors adjusted using Rubin's rules.[29,30] The prevalence of each index disease group was computed for the full cohort and stratified by sex and single year of age.

Table 1. Baseline characteristics of the full Hamburg City Health Study (HCHS) cohort including 10 000 participants stratified by assessment of ankle brachial index (ABI)

	Missing	Full cohort (n = 10 000)	ABI not assessed (n = 4 753)	ABI assessed (n = 5 247)
Demographics				
Female sex	None	5 108 (51.1)	2 517 (53.0)	2 591 (49.4)
Age — y	None	63 (55, 70)	63 (55, 70)	62 (55, 69)
Vascular characteristics				
Intima to media thickness, right — mm	370 (3.7)	0.74 (0.65, 0.84)	0.74 (0.64, 0.84)	0.74 (0.66, 0.84)
Intima to media thickness, left — mm	408 (4.1)	0.75 (0.66, 0.86)	0.75 (0.65, 0.86)	0.76 (0.67, 0.86)
Presence of carotid plaques, right	475 (4.8)	2 164 (21.6)	982 (20.7)	1 182 (22.5)
Presence of carotid plaques, left	502 (5.0)	1 922 (19.2)	868 (18.3)	1 054 (20.1)
ABI, right	4 887 (48.9)	1.04 (0.95, 1.13)	Not applicable	1.04 (0.95, 1.13)
ABI, left	4 861 (48.6)	1.03 (0.95, 1.12)	Not applicable	1.03 (0.95, 1.12)
Self reported symptomatic lower extremity peripheral arterial disease	850 (8.5)	323 (3.2)	161 (3.4)	162 (3.1)
Aortic diameter — mm	430 (4.3)	17.80 (16.11, 19.64)	17.56 (15.89, 19.49)	17.97 (16.32, 19.75)
Comorbidities				
Hypertension	122 (1.2)	3 846 (38.5)	1 915 (40.3)	1 931 (36.8)
Coronary artery disease	149 (1.5)	498 (5.0)	246 (5.2)	252 (4.8)
Congestive heart failure	142 (1.4)	285 (2.9)	155 (3.3)	130 (2.5)
History of myocardial infarction	64 (0.6)	304 (3.0)	151 (3.2)	153 (2.9)
History of stroke	69 (0.7)	313 (3.1)	156 (3.3)	157 (3.0)
Atrial fibrillation	105 (1.0)	521 (5.2)	245 (5.2)	276 (5.3)
History of cancer	756 (7.6)	1 592 (15.9)	807 (17.0)	785 (15.0)
Lifestyle				
Alcohol abuse — >2 drinks per day	2 326 (23.3)	1 311 (13.1)	648 (13.6)	663 (12.6)
Smoking	51 (0.5)			
Never		3565 (35.6)	1 718 (36.1)	1 847 (35.2)
Previous		4406 (44.1)	2 042 (43.0)	2 364 (45.1)
Current		1978 (19.8)	955 (20.1)	1 023 (19.5)
Never performing any sports activity	778 (7.8)	2592 (25.9)	1 231 (25.9)	1 361 (25.9)
Adherence to MEDAS score	980 (0.98)	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)
Laboratory values and body measurements				
Body mass index — kg/m^2	555 (0.6)	26.12 (23.53, 29.20)	26.44 (23.72, 29.55)	25.82 (23.40, 28.90)
Waist circumference — cm	400 (0.4)	95.00 (85.80, 103.93)	95.20 (86.00, 104.27)	94.30 (85.60, 103.40)
Systolic blood pressure — mmHg	407 (0.4)	137.00 (125.00, 150.50)	138.50 (126.50, 152.00)	135.50 (124.00, 149.00)
Diastolic blood pressure — mmHg	406 (0.4)	81.50 (75.50, 88.00)	81.50 (75.00, 88.00)	81.50 (75.50, 88.00)
Total cholesterol — mg/dL	311 (0.3)	208.00 (181.00, 236.00)	210.00 (182.00, 239.00)	206.00 (180.00, 234.00)
Low density lipoprotein — md/dL	402 (0.4)	120.00 (95.00, 145.00)	120.00 (96.00, 147.00)	120.00 (95.00, 143.00)
Glomerular filtration rate — mL/min/1.73 m^2	952 (0.9)	89.10 (81.20, 96.00)	88.40 (80.20, 95.30)	89.70 (82.12, 96.57)

Data are presented as n (%) or median (interquartile range). ABI = ankle brachial index; MEDAS = Mediterranean Diet Adherence Score.

All analyses were performed with software R version 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Ten thousand participants were enrolled in the current study (51.1% females, 63 years in median) (Fig. 1). Thereof, 95.9% (n = 9 592) had valid carotid ultrasound, 95.7% (n = 9 570) valid abdominal ultrasound, and 52.5% (n = 5 247) had a valid ABI measurement (Table 1).

The right median CIMT was 0.74 mm (IQR 0.65 — 0.84), the left median CIMT was 0.75 mm (IQR 0.66 — 0.86), and 21.6% of patients had carotid plaques on the right side and 19.2% on the left. According to the study definition, the prevalence of carotid artery disease was 30.2% (95% confidence interval [CI] 29.3 — 31.2) in the total cohort (35.3% in females, 23.4% in males) (Table 2). Higher age (odd ratio (OR) 2.53 per 10 years, 95% CI 2.23 — 2.88), female sex (OR 0.70, 95% CI 0.63-0.77), previous smoking (OR 1.32, 95% CI 1.17 — 1.48) and current smoking (OR 2.32, 95% CI 1.99 — 2.70), hypertension (OR 1.64, 95% CI 1.44 — 1.88), both coronary artery disease (OR 1.45, 95% CI 1.21 — 1.73) or history of myocardial infarction (OR 1.45, 95% CI 1.19 — 1.78), diabetes (OR 1.34, 95% CI 1.15 — 1.55), and history of stroke (OR 1.34, 95% CI 1.13 — 1.60) were significantly associated with carotid artery disease (Table 3). Over age, the prevalence increased from 4.6% (95% CI 1.6 — 7.5) in males and 6.9% (95% CI 2.9 — 10.9) in females at 46 years to 58.1% (95% CI 50.5 — 65.7) and 53.0% (95% CI 41.6 — 64.5) at 75 years, respectively (Supplementary Figure S2).

In a direct comparison between the total cohort and participants with and without ABI measurement, the baseline characteristics were broadly comparable (Table 1).

Table 2. Prevalence of peripheral arterial diseases (in %) in the Hamburg City Health Study. Estimates were extracted from five imputed datasets with 10 iterations each and combined using Rubin's rules

	Total (n = 10 000)	Males (n = 4 892)	Females (n = 5 108)
Carotid artery disease	30.24 (29.31–31.18)	35.34 (34.08–36.6)	23.4 (22.08–24.72)
Lower extremity peripheral arterial disease	23.59 (21.92–25.27)	22.65 (20.94–24.36)	24.79 (22.45–27.12)
Abdominal aortic aneurysm	0.78 (0.61–0.96)	1.26 (0.97–1.55)	0.15 (0.03–0.26)
Any index disease (composite)	44.74 (43.41–46.07)	47.84 (46.1–49.59)	40.57 (38.52–42.63)

Data are presented in percentage (95% confidence interval).

The median ABI on the right was 1.04 (IQR 0.95 — 1.13) and on the left 1.03 (IQR 0.96 —1.12), and 3.2% of subjects reported they had symptomatic lower extremity PAD. According to both information sources, the prevalence of lower extremity PAD was 23.6% in the total cohort (24.8% in females, 22.7% in males) (Table 2). Thereby, higher age (OR 1.34 per 10 years, 95% CI 1.17 — 1.53), diabetes (OR 1.65, 95% CI 1.23 — 2.21), dyslipidaemia (OR 1.59, 95% CI 1.40 — 1.80), congestive heart failure (OR 1.52, 95% CI 1.24 — 1.85), coronary artery disease (OR 1.47, 95% CI 1.10 — 1.48), current smoking (OR 1.46, 95% CI 1.23 — 1.75), and female sex (OR 1.26, 95% CI 1.05 — 1.51) were significantly associated with lower extremity PAD (Table 3). Over age, the prevalence increased from 9.1% (95% CI 0.0 — 24.6) in males and 17.2% (95% CI 0.0 — 35.6) in females at 46 years to 34.7% (95% CI 26.1 — 43.3) and 34.7% (95% CI 23.4 — 45.9) at 75 years, respectively (Supplementary Figure S1). Among subjects with diagnosed lower extremity PAD according to an ABI $\leq$ 0.9, 18.4% of males and 12.2% of females reported any history of intermittent claudication (Supplementary Table S5).

The median aortic diameter of the participants was 17.8 mm (IQR 16.1 — 19.6). The prevalence of AAA was 0.8% in the total cohort (0.2% in females, 1.3% in males) (Table 2). Higher age (OR 2.66 per 10 years, 95% CI 1.58 — 4.50), current smoking (OR 3.17, 95% CI 1.62 — 6.21), history of myocardial infarction (OR 2.75, 95% CI 1.40 — 5.41), and high adherence to the Mediterranean diet score (+8 points *vs.* < 5 points, OR 2.23, 95% CI 1.14 — 4.36) were associated with AAA (Table 3).

The prevalence of any index disease (composite endpoint) was 47.8% in males and 40.6% in females (Table 2). Risk factors associated with the composite endpoint were higher age (OR 2.01 per 10 years, 95% CI 1.77 — 2.29), current smoking (OR 1.97, 95% CI 1.69 — 2.29), coronary artery disease (OR 1.62, 95% CI 1.30 — 2.02), diabetes (OR 1.59, 95% CI 1.28 — 1.98), history of myocardial infarction (OR 1.57, 95% CI 1.20 — 2.05), hypertension (OR 1.44, 95% CI 1.25 — 1.66), history of stroke (OR 1.38, 95% CI 1.13 — 1.67), congestive heart failure (OR 1.31, 95% CI 1.05 — 1.64), dyslipidaemia (OR 1.29, 95% CI 1.16 — 1.44), and previous smoking (OR 1.18, 95% CI 1.04 — 1.33) (Table 3).

DISCUSSION

The current large population based cohort study revealed both carotid artery disease and lower extremity PAD, as common manifestations of systemic atherosclerosis, were strikingly frequent in a contemporary Western European

Table 3. Association between established cardiovascular risk factors and peripheral arterial diseases in the Hamburg City Health Study. Estimates were extracted from five imputed datasets with ten iterations each and combined using Rubin's rules

	Carotid artery disease	Lower extremity peripheral arterial disease	Abdominal aortic aneurysm	Any index disease — composite
Age (per 10 years)	2.53 (2.23–2.88)*	1.34 (1.17–1.53)*	2.66 (1.58–4.50)*	2.01 (1.77–2.29)*
Female sex	0.70 (0.63–0.77)	1.26 (1.05–1.51)*	0.19 (0.10–0.36)	0.90 (0.79–1.02)
Smoking — ref. never				
Previous	1.32 (1.17–1.48)*	1.07 (0.94–1.23)	1.07 (0.58–1.96)	1.18 (1.04–1.33)*
Current	2.32 (1.99–2.7)*	1.46 (1.23–1.75)*	3.17 (1.62–6.21)*	1.97 (1.69–2.29)*
Alcohol abuse — >2 drinks/day	1.16 (1.00–1.34)	1.01 (0.84–1.23)	1.36 (0.65–2.82)	1.11 (0.94–1.31)
Waist circumference — per cm	1.00 (0.87–1.16)	1.01 (0.87–1.16)	1.03 (0.62–1.74)	1.00 (0.87–1.16)
Hypertension	1.64 (1.44–1.88)*	1.17 (1.00–1.37)	1.06 (0.60–1.87)	1.44 (1.25–1.66)*
Dyslipidaemia	1.00 (0.89–1.11)	1.59 (1.40–1.80)*	0.99 (0.56–1.74)	1.29 (1.16–1.44)*
Diabetes	1.34 (1.15–1.55)*	1.65 (1.23–2.21)*	0.8 (0.41–1.56)	1.59 (1.28–1.98)*
Coronary artery disease	1.45 (1.21–1.73)*	1.47 (1.10–1.98)*	1.62 (0.79–3.33)	1.62 (1.30–2.02)*
Congestive heart failure	1.04 (0.84–1.27)	1.52 (1.24–1.85)*	0.64 (0.26–1.55)	1.31 (1.05–1.64)*
History of myocardial infarction	1.45 (1.19–1.78)*	1.31 (0.93–1.84)	2.75 (1.40–5.41)*	1.57 (1.20–2.05)*
History of stroke	1.34 (1.13–1.60)*	1.25 (0.98–1.58)	1.11 (0.55–2.23)	1.38 (1.13–1.67)*
Adherence to MEDAS — vs. <5 points				
5 points	1.06 (0.94–1.20)	0.92 (0.78–1.08)	1.65 (0.84–3.24)	1.01 (0.91–1.12)
6–7 points	0.99 (0.88–1.13)	0.96 (0.81–1.14)	1.30 (0.70–2.42)	0.99 (0.87–1.12)
8+ points	1.03 (0.88–1.20)	0.96 (0.78–1.20)	2.23 (1.14–4.36)*	1.04 (0.87–1.24)

Data are presented as HR (95% CI). CI = confidence interval; MEDAS = Mediterranean Diet Adherence Score.
* Statistically significant risk factors.

population aged between 45 and 74 years. Thereby, almost 45% suffered from any index disease while only 1.3% of males and 0.2% of females had an AAA confirming recent results from population based screening programmes in Sweden.[8]

Interestingly, the risk factors associated with these three major chronic vascular diseases differed substantially. While higher age and current smoking had a major impact on all subgroups, congestive heart failure and female sex were associated with lower extremity PAD only. Furthermore, while dyslipidaemia was significantly associated with lower extremity PAD, no relationship between this established cardiovascular risk factor and carotid artery disease or AAA was observed.

The knowledge about prevalence and risk factors is not only important for the planning of screening studies. In a rapidly changing health care system with a global pandemic causing havoc and economic crises, it seems meaningful to get a valid overview of the situation. Thereby, the risk profile of the subjects included in the current study covered almost all predictors that have been associated with severe illness after SARS-CoV-2 infection and COVID-19 disease by the World Health Organisation.

A duplex ultrasound of the carotid arteries was conducted in all participants. This commonly established screening tool was recommended by several guidelines to detect even subclinical arterial disease for cardiovascular risk assessment.[15,31] Previous studies have determined the prevalence of carotid artery stenosis, plaques, or averaged values of intima to media thickness while the current study included increased intima to media thickness in combination with plaques to identify carotid atherosclerosis as a cardiovascular risk factor in general. Though intima to media thickness and plaques may differ in characteristics of development and consequent vascular events, they share cardiovascular risk factors, impact on organ function and underlying gene loci.[24,32,33] Their differential predictive value of cardiovascular events is supposed to contribute to each other if used paired.[34] Thus the combination used in this study is pragmatic and beneficial for risk stratification in primary preventive care. The presence of increased CIMT and plaques overlaps to a certain degree but due to differences in origin not in total and their combination leads to a higher and more complete prevalence of carotid atherosclerosis and its associated risk profile.

In a recent systematic review and meta-analysis on the global prevalence of carotid atherosclerosis among subjects aged 30 — 79 years, this difference was well illustrated. While a relevant stenosis was found in 1.8% of males and 1.2% of females, an increased CIMT was more prevalent (32% *vs*. 23%). Thereby, the number of people with increased CIMT increased by more than 57% between 2000 and 2020 which further emphasises the need for recent studies.[19] With 35% and 23%, the current findings confirmed previous evidence what also encouraged the robustness of the ultrasound examination and analyses.

Atherosclerosis and associated vascular diseases contribute to a significant economic and social burden and are the leading cause of death globally.[13,19,35—37] When compared with common heart disease, people with peripheral arterial and aortic disease are known to suffer from devastating outcomes what may be explained particularly by the impact of unhealthy lifestyle habits.[38,39] In a recent prospective cohort study including inpatients having invasive treatment of symptomatic lower extremity PAD, more than 44% reported current smoking at baseline.[40] In another multicentre survey study, 47% of the patients stated that they had not changed their lifestyle and health behaviour since the index diagnosis (four years in median) and 33% did not know the reasons for their medical prescriptions.[40,41]

There are probably more interesting collinearities between lifestyle habits and vascular disease. Two previous prospective cohort studies revealed that Mediterranean Diet was associated with reduced risk of AAA in smokers.[42] Against that background, the Coronary Risk of Atherosclerosis (CORA) study revealed that high intake of meat was significantly associated with an increase in coronary risk particularly in smoking women.[43] Paradoxically, the current study revealed an opposite association with more than twice the odds of having an AAA if adherence to Mediterranean diet was high. This may be explained by an overall better adherence to healthy lifestyle and dietary recommendations in people who get this diagnosis. However, it needs to be highlighted that recommendations on lifestyle change and nutrition are still lacking in practice guidelines and there is evidence for neglect of this topic in the patient centred communication.[15,27,44—46]

Previous studies have applied heterogeneous inclusion criteria and varying methods for the detection of lower extremity PAD.[26] The German Epidemiological Trial on Ankle Brachial Index (getABI) included 6 880 patients $\geq$ 65 years who were treated by general practitioners or specialists in the outpatient sector in October 2001. A pathological ABI was observed in 21% of the total cohort.[47,48] In contrast, the Heinz Nixdorf Recall cohort study included 4 814 participants aged 45 — 75 years between 2000 and 2003 in the metropolitan Ruhr area in Germany in which the prevalence of a pathological ABI was only 6.4% among male and 5.1% among female subjects.[49] The European PANDORA study enrolled 9 816 subjects without heightened cardiovascular risk between 2007 and 2008. In total, 18% of the 64 year old subjects (54% males) had undiagnosed lower extremity PAD, while the prevalence was lowest in Belgium (7%) and highest in Italy (23%).[50] Although the current study was mainly confirmative, it appears obvious that screening studies are prone to selection bias and affected by numerous methodological considerations. Against that background, the considerably low rate of self reported symptoms of lower extremity PAD (3%) appears striking and probably contributes to the complex relationship between disease awareness and adherence to best medical therapies. Even among subjects with diagnosed lower extremity PAD, only 18% of males and 12% of females reported any history of intermittent claudication which can be interpreted as lack of disease awareness to some degree.

The aspect of different screening methods was also frequently discussed in terms of AAA detection. Previous screening studies have applied different inclusion criteria

which makes it challenging to compare the estimates between countries. For instance, it is important to differentiate whether subjects at a certain age (e.g., 65 years) or above an age limit (e.g., $\geq$ 65 years) were screened. Moreover, there is increasing evidence that the prevalence of AAA has dropped significantly. Although large screening studies have recently shown that only 1.7% of males had an AAA in Sweden,[8] German ultrasound screening to detect AAA in the elderly male population was primarily based on historical screening studies that were conducted in the 1990s and revealed a prevalence between 4% and 8%.[2–5] Given the current estimates, the number needed to screen may be three times as high than it was 20 years ago.

The current study has several strengths but also limitations. First, although regular training and quality assurance of the examination were applied, the limited time contributed to the fact that approximately 50% of the subjects did not undergo an ABI measurement. This is an observation that has been made in epidemiological cohort studies before. In the light of experience of previous trials, it appears unlikely that sicker people participated in this study while the healthier declined, and the comparison of baseline characteristics between both strata (Table 1) was heartening. To account for uncertainty introduced by incomplete ABI measurement a probabilistic approach and multiple imputation was applied. Second, the current study followed a cross sectional design and included the first 10 000 subjects enrolled during recent years, while longitudinal outcomes will be available in the future. Hence, associations could only be derived between the vascular diseases of interest and the most relevant cardiovascular risk factors. Unfortunately, the current study could only enrol inhabitants from Hamburg, Germany, while this epidemiological study was designed to generate results that are representative of the German population. Future studies will address information on the genetic background and socioeconomic factors. Last, regression models applied to non-randomised cohorts can only be adjusted for observed confounding, while non-observed factors may introduce residual confounding.

The interesting findings of the current study may help to support the ongoing discussions concerning screening programmes to detect AAA or other chronic vascular diseases. For the first time, the low prevalence of AAA in Germany emphasises that more males need to be screened to avoid one aneurysm related death, while the even lower prevalence in females does not suggest that screening of females should be advised. Until tnow, these figures were not available for Germany and no structured data collection was implemented along with the screening programme. On the other hand, the high prevalence of carotid and lower extremity atherosclerosis suggest that efforts to improve preventive medicine in this vulnerable population should be intensified.

Conclusions

In this large population based cohort study of 10 000 healthy subjects from Hamburg, Germany, a strikingly high prevalence of peripheral arterial disease was revealed. Almost 45% suffered from any index disease, while AAA was only diagnosed in 1.3% of males and 0.2% of females. The high prevalence of atherosclerotic disease and associated cardiovascular risk factors underline that it is essential to increase awareness and fuel efforts for secondary prevention.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.01.002.

REFERENCES

1 Kreutzburg T, Peters F, Riess HC, Hischke S, Marschall U, Kriston L, et al. Editor's Choice – Comorbidity patterns among patients with peripheral arterial occlusive disease in Germany: a trend analysis of health insurance claims data. *Eur J Vasc Endovasc Surg* 2020;**59**:59–66.

2 Lindholt JS, Juul S, Fasting H, Henneberg EW. Cost-effectiveness analysis of screening for abdominal aortic aneurysms based on five year results from a randomised hospital based mass screening trial. *Eur J Vasc Endovasc Surg* 2006;**32**:9–15.

3 Ashton HA, Gao L, Kim LG, Druce PS, Thompson SG, Scott RA. Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms. *Br J Surg* 2007;**94**:696–701.

4 Norman PE, Jamrozik K, Lawrence-Brown MM, Le MT, Spencer CA, Tuohy RJ, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *BMJ* 2004;**329**:1259.

5 Thompson SG, Ashton HA, Gao L, Buxton MJ, Scott RA, Multicentre Aneurysm Screening Study G. Final follow-up of the Multicentre

Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. *Br J Surg* 2012;**99**:1649–56.
6 Anjum A, Powell JT. Is the incidence of abdominal aortic aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and Scotland. *Eur J Vasc Endovasc Surg* 2012;**43**:161–6.
7 Li X, Zhao G, Zhang J, Duan Z, Xin S. Prevalence and trends of the abdominal aortic aneurysms epidemic in general population–a meta-analysis. *PLoS One* 2013;**8**:e81260.
8 Svensjo S, Mani K, Bjorck M, Lundkvist J, Wanhainen A. Screening for abdominal aortic aneurysm in 65-year-old men remains cost-effective with contemporary epidemiology and management. *Eur J Vasc Endovasc Surg* 2014;**47**:357–65.
9 Earnshaw JJ. Doubts and dilemmas over abdominal aortic aneurysm. *Br J Surg* 2011;**98**:607–8.
10 Lederle FA. The rise and fall of abdominal aortic aneurysm. *Circulation* 2011;**124**:1097–9.
11 Reutersberg B, Salvermoser M, Haller B, Schäffer C, Knipfer E, Laugwitz K-L, et al. Screening cardiovascular patients for aortic aneurysms (SCAN) – high prevalence of abdominal aortic aneurysms in coronary heart disease patients requiring intervention. *Vasa* 2020;**49**:375–81.
12 Flessenkämper I, Kendzia A, Stalke J. Multizentrisches Screening eines arteriell vorerkrankten Patientenkollektivs in Hinblick auf die Prävalenz infrarenaler Aortenaneurysmen. *Gefässchirurgie* 2009;**14**:376–83.
13 Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health* 2019;**7**:e1020–30.
14 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329–40.
15 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice – 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
16 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**69**:e71–126.
17 de Weerd M, Greving JP, de Jong AW, Buskens E, Bots ML. Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. *Stroke* 2009;**40**:1105–13.
18 de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups. *Stroke* 2014;**45**:2366–71.
19 Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health* 2020;**8**:e721–9.
20 Naylor AR, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2023 clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. *Eur J Vasc Endovasc Surg* 2023;**65**:7–111.
21 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9.
22 Jagodzinski A, Johansen C, Koch-Gromus U, Aarabi G, Adam G, Anders S, et al. Rationale and Design of the Hamburg City Health Study. *Eur J Epidemiol* 2020;**35**:169–81.
23 Petersen EL, Goßling A, Adam G, Aepfelbacher M, Behrendt C-A, Cavus E, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: the Hamburg City Health Study COVID programme. *Eur Heart J* 2022;**43**:1124–37.
24 Rimmele DL, Borof K, Wenzel J-P, Jensen M, Behrendt C-A, Waldeyer C, et al. Differential association of flow velocities in the carotid artery with plaques, intima media thickness and cardiac function. *Atherosclerosis Plus* 2021;**43**:18–23.
25 Jacobi N, Walther C, Borof K, Heydecke G, Seedorf U, Lamprecht R, et al. The Association of Periodontitis and Peripheral Arterial Occlusive Disease in a Prospective Population-Based Cross-Sectional Cohort Study. *J Clin Med* 2021;**10**:2048.
26 Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:2890–909.
27 Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. *Eur J Vasc Endovasc Surg* 2019;**57**:8–93.
28 Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, et al. KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;**99**:S1–87.
29 Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Chichester: John Wiley & Sons; 2004.
30 Van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011;**45**:1–67.
31 Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015;**241**:507–32.
32 Rimmele DL, Borof K, Jensen M, Behrendt CA, Cheng B, Debus ES, et al. Association Between Carotid Atherosclerosis and Atrial Fibrillation, Cardiac, and Renal Function. *Eur J Vasc Endovasc Surg* 2022;**63**:641–7.
33 Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP, et al. GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nat Commun* 2018;**9**:5141.
34 Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2013;**2**:e000087.
35 Wei L, Bu X, Wang X, Liu J, Ma A, Wang T. Global Burden of Aortic Aneurysm and Attributable Risk Factors from 1990 to 2017. *Glob Heart* 2021;**16**:35.
36 Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol* 2014;**34**:2363–71.
37 Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**:1211–59.
38 Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories. *J Cardiovasc Risk* 1994;**1**:333–9.
39 Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. *J Am Heart Assoc* 2018;**7**:e009724.
40 Kotov A, Peters F, Debus ES, Zeller T, Heider P, Stavroulakis K, et al. The prospective GermanVasc cohort study. *Vasa* 2021.
41 Alushi K, Hinterseher I, Peters F, Rother U, Bischoff MS, Mylonas S, et al. Distribution of mobile health applications amongst patients with symptomatic peripheral arterial disease in Germany: a cross-sectional survey study. *J Clinic Med* 2022;**11**:498.
42 Kaluza J, Stackelberg O, Harris HR, Akesson A, Björck M, Wolk A. Mediterranean diet is associated with reduced risk of abdominal

aortic aneurysm in smokers: results of two prospective cohort studies. *Eur J Vasc Endovasc Surg* 2021;**62**:284–93.
43 Zyriax BC, Vettorazzi E, Hamuda A, Windler E. Interaction of smoking and dietary habits modifying the risk of coronary heart disease in women: results from a case-control study. *Eur J Clin Nutr* 2018;**72**:1673–81.
44 Wolbert L, Kreutzburg T, Zyriax BC, Adegbola A, Westenhöfer J, Jagemann B, et al. A cross-sectional survey study on the nutrition patterns of patients with peripheral artery disease. *Vasa* 2022;**51**:239–46.
45 Wan D, Li V, Banfield L, Azab S, de Souza RJ, Anand SS. Diet and Nutrition in Peripheral Artery Disease: A Systematic Review. *Can J Cardiol* 2022;**38**:672–80.
46 Adegbola A, Behrendt C-A, Zyriax B-C, Windler E, Kreutzburg T. The impact of nutrition on the development and progression of peripheral artery disease: a systematic review. *Clinical Nutrition* 2022;**41**:49–70. doi: 10.1016/j.clnu.2021.11.005.
47 Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis* 2004;**172**:95–105.
48 Meves SH, Diehm C, Berger K, Pittrow D, Trampisch HJ, Burghaus I, et al. Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the getABI study. *Cerebrovasc Dis* 2010;**29**:546–54.
49 Kroger K, Dragano N, Stang A, Moebus S, Mohlenkamp S, Mann K, et al. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vasc Med* 2009;**14**:289–96.
50 Cimminiello C, Kownator S, Wautrecht J-C, Carvounis CP, Kranendonk SE, Kindler B, et al. The PANDORA study: peripheral arterial disease in patients with non-high cardiovascular risk. *Intern Emerg Med* 2011;**6**:509–19.

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COUP D'OEIL

Extrinsic Dorsalis Pedis Artery Compression Due to Diabetic Arthropathy in a Non-Healing Foot Ulcer

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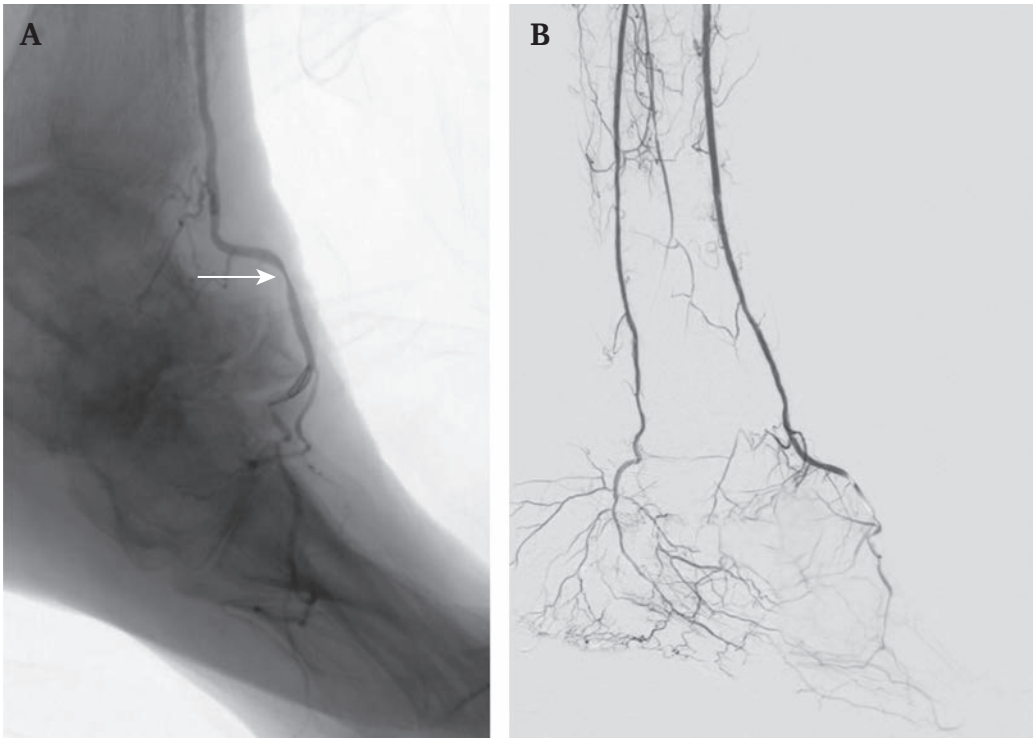

A 75 year old woman with a long history of diabetes consulted with a non-healing ulcer on her fifth toe. She had a palpable pedal pulse and an ankle brachial index with biphasic signals. An important deformity of the foot secondary to Charcot arthropathy stood out. (A) An arteriogram showed discrete disease of the distal trunks, highlighting at the level of the dorsalis pedis artery, a focal stenosis (arrow) with an external compressive appearance secondary to dorsal displacement of the tarsal bones, which could not be repaired. The posterior artery was recanalised (B) and the ulcer healed.

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Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis

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Summary

Background Peripheral artery disease is a major cardiovascular disease that affected 202 million people worldwide in 2010. In the past decade, new epidemiological data on peripheral artery disease have emerged, enabling us to provide updated estimates of the prevalence and risk factors for peripheral artery disease globally and regionally and, for the first time, nationally.

Methods For this systematic review and analysis, we did a comprehensive literature search for studies reporting on the prevalence of peripheral artery disease in the general population that were published between Jan 1, 2011, and April 30, 2019, in PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, the Allied and Complementary Medicine Database, and ProQuest Dissertations and Theses Global. We also included the Global Peripheral Artery Disease Study of 2013 and the China Peripheral Artery Disease Study as sources. Peripheral artery disease had to be defined as an ankle–brachial index lower than or equal to 0·90. With a purpose-built data collection form, data on study characteristics, sample characteristics, prevalence, and risk factors were abstracted from all the included studies identified from the sources. Age-specific and sex-specific prevalence of peripheral artery disease was estimated in both high-income countries (HICs) and low-income and middle-income countries (LMICs). We also did random-effects meta-analyses to pool the odds ratios of 30 risk factors for peripheral artery disease in HICs and LMICs. UN population data were used to generate the number of people affected by the disease in 2015. Finally, we derived the regional and national numbers of people with peripheral artery disease on the basis of a risk factor-based model.

Findings We included 118 articles for systematic review and analysis. The prevalence of peripheral artery disease increased consistently with age. At younger ages, prevalence was slightly higher in LMICs than HICs (4·32%, 95% CI 3·01–6·29, *vs* 3·54%, 1·17–10·24, at 40–44 years), but the increase with age was greater in HICs than LMICs, leading to a higher prevalence in HICs than LMICs at older ages (21·24%, 15·22–28·90, *vs* 12·04%, 8·67–16·60, at 80–84 years). In HICs, prevalence was slightly higher in women than in men up to age 75 years (eg, 7·81%, 3·97–14·77, *vs* 6·60%, 3·74–11·38, at 55–59 years), whereas in LMICs little difference was found between women and men (eg, 6·40%, 5·06–8·05, *vs* 6·37%, 4·74–8·49, at 55–59 years). Overall, the global prevalence of peripheral artery disease in people aged 25 years and older was 5·56%, 3·79–8·55, and the prevalence estimate was higher in HICs than that in LMICs (7·37%, 4·35–13·66, *vs* 5·09%, 3·64–7·24). Smoking, diabetes, hypertension, and hypercholesterolaemia were major risk factors for peripheral artery disease. Globally, a total of 236·62 million people aged 25 years and older were living with peripheral artery disease in 2015, among whom 72·91% were in LMICs. The Western Pacific Region had the most peripheral artery disease cases (74·08 million), whereas the Eastern Mediterranean Region had the least (14·67 million). More than two thirds of the global peripheral artery disease cases were concentrated in 15 individual countries in 2015.

Interpretation Peripheral artery disease continues to become an increasingly serious public health problem, especially in LMICs. With the demographic trend towards ageing and projected rise in important risk factors, a larger burden of peripheral artery disease is to be expected in the foreseeable future.

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Introduction

Peripheral artery disease is characterised by debilitating atherosclerotic occlusion of arteries in the lower extremities and is a major cardiovascular disease.[1,2] Peripheral artery disease can be asymptomatic or accompanied by symptoms, such as intermittent claudication, atypical leg pain, critical limb ischaemia, and occasionally acute limb ischaemia.[3–5] Regardless of the presence of symptoms, peripheral artery disease is linked to significantly increased risk of cardiovascular morbidity and mortality, representing a considerable public health concern.[6–9] Peripheral artery disease is the

Research in context

Evidence before this study

Peripheral artery disease, defined as an ankle–brachial index lower than or equal to 0·90, is a major cardiovascular disease worldwide. We searched PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, AMED, and ProQuest Dissertations and Theses Global to identify studies published from Jan 1, 2011, onwards that reported the prevalence of peripheral artery disease in the general population. Search terms were a combination of peripheral-artery-disease and epidemiological search terms. No language or geographic restrictions were applied. We did the search on April 30, 2019, and identified 14 719 records, of which 51 were included. Reference lists of the included studies were checked to identify studies of interest. Additional eligible studies came from our previous systematic reviews. Finally, 118 individual articles were included in this study. We previously estimated that in 2010, 202 million people had peripheral artery disease, among whom almost 70% were in low-income and middle-income countries (LMICs). However, those estimates were based on only 34 individual articles, and no national estimates have been reported.

Added value of this study

Based on an expanded dataset (118 articles from 33 individual countries), we provided updated estimates of peripheral artery disease prevalence at global and regional levels. We estimated that 236·62 million (5·56%) people aged 25 years and older had peripheral artery disease in 2015, among whom 73% were in LMICs. For the first time, we generated the national prevalence data of peripheral artery disease and found that 15 individual countries (Bangladesh, Brazil, China, France, Germany, India, Indonesia, Italy, Japan, Mexico, Pakistan, Russia, Spain, the UK, and the USA) contained more than two thirds of the global peripheral artery disease cases in 2015.

Implications of all the available evidence

This study is expected to prompt further epidemiological studies on peripheral artery disease, especially in LMICs. On the basis of our results, many governments will need to develop effective and appropriate strategies for preventing and treating peripheral artery disease, especially in countries where peripheral artery disease is a considerable public health concern.

third most common clinical manifestation of atherosclerosis after coronary artery disease and stroke.[10] Despite its implications and comorbidities, peripheral artery disease still receives relatively less research or public attention compared with the other two diseases.[10–13]

Peripheral artery disease is age related, with its prevalence increasing significantly with advancing age.[3,4,14] Given the increases in population ageing, an upward trend of peripheral artery disease prevalence is to be expected. Accurate and up-to-date epidemiological information is imperative for guiding public health policy making and updating burden of disease estimates. In 2013, the Global Peripheral Artery Disease Study[10] established the global and regional prevalence of peripheral artery disease in the general population for the first time. According to its estimates, peripheral artery disease, as defined by an ankle–brachial index (ABI; the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm) of 0·90 or less, affected approximately 202 million people worldwide in 2010, among whom almost 70% were residing in low-income and middle-income countries (LMICs).[10] The Global Peripheral Artery Disease Study of 2013[10] highlighted that priority needs to be given to adequate prevention, diagnosis, and control of peripheral artery disease. Thereafter, a growing body of epidemiological studies on peripheral artery disease has become available, enabling a more accurate and contemporary estimation of peripheral artery disease prevalence based on more data points.[4,15,16] Furthermore, the inclusion of more data in the assessment of risk factors for peripheral artery disease would lead to a better understanding of the disease causes and a more effective preventive strategy.[1,7]

In our study, we did an updated systematic review of population-based studies reporting peripheral artery disease prevalence in the general population. We sought to assess the prevalence of peripheral artery disease at global, regional, and national levels. The specific aims of this study were to estimate the age-specific and sex-specific prevalence of peripheral artery disease in high-income countries (HICs) and LMICs, to investigate major risk factors for peripheral artery disease in HICs and LMICs, and to establish the number of people with peripheral artery disease worldwide, in different geographical and income regions and in different countries and territories in 2015.

Methods

We did an updated systematic review and analysis in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting.[17] The review protocol was not registered in any database.

Study approach

Similar to the Global Peripheral Artery Disease Study of 2013,[10] our study approach can be classified into seven stages: identification of studies that reported peripheral artery disease prevalence in the general population using multiple sources; extraction of data on peripheral artery disease prevalence and risk factors for peripheral artery disease; modelling age-specific and sex-specific prevalence of peripheral artery disease in HICs and LMICs on the basis of the extracted prevalence data; estimation of the number of people with peripheral artery disease in HICs and LMICs in 2015 by multiplying

the age-specific and sex-specific prevalence estimates according to the corresponding demographic data derived from the UN Population Division (UNPD);[18] assessment of the associations of major risk factors with peripheral artery disease in HICs and LMICs on the basis of the extracted data on risk factors; distribution of the number of people with peripheral artery disease into different world regions using a risk factor-based model; and generation of the number of people living with peripheral artery disease in 201 countries and territories by the aforementioned risk factor-based model. The study approach is detailed in the appendix (pp 3–8).

Data sources

The articles included in the present study were collected from four types of sources. First, for the updated systematic review, we did a literature search in PubMed, MEDLINE, Embase, the Global Health database, CINAHL, the Global Health Library, the Allied and Complementary Medicine Database, and ProQuest Dissertations and Theses Global for articles and grey literature published between Jan 1, 2011, and April 30, 2019. The search strategy was a combination of terms related to peripheral artery disease and epidemiology. No language or geographical restrictions were applied. The specific search strategies for each bibliographic database and the detailed search terms for each database are presented in the appendix (pp 9–10). We did not make attempts to contact authors for further information. All non-English documents were translated into English by use of Google Translate before reviewing.

Only population-based studies that quantified prevalence estimates of peripheral artery disease in the general population were included. Studies that were hospital based or done in a sample with special characteristics (eg, patients with diabetes and people with a high risk of cardiovascular diseases) were excluded because they would not be representative of the general population. To capture the most accurate estimation of peripheral artery disease prevalence, peripheral artery disease had to be established by the presence of a lower ABI value rather than on the basis of typical symptoms or self-reporting; therefore, studies were only eligible for inclusion when defining peripheral artery disease as having an ABI of less than 0·90 or of 0·90 or less. Several publications from the same study were carefully compared and those with the largest sample size or contributing the most comprehensive results were included for further analysis. For the purpose of evaluating risk factors for peripheral artery disease, odds ratios (ORs) in the included studies had to be based on a multivariable analysis.

The second source was the Global Peripheral Artery Disease Study of 2013;[10] all the 34 included articles in the study were retained.

The third source was the China Peripheral Artery Disease Study;[19] we incorporated all the 37 included articles in the study.

Lastly, we did an additional search in which we identified studies of interest by screening the reference lists of included studies and related systematic reviews.

Data extraction

With a purpose-built data collection form, data on study characteristics, sample characteristics, prevalence, and risk factors were abstracted from all the included studies identified from the aforementioned four sources. When available, stratified prevalence data by age group and sex were extracted within the same study. For studies that were done in more than one geographical location (eg, prevalence estimates of peripheral artery disease in different countries reported in a single study), we extracted the data for each location separately (if available). In case of censoring age groups (eg, people older than 80 years), we imputed the missing age band

See Online for appendix

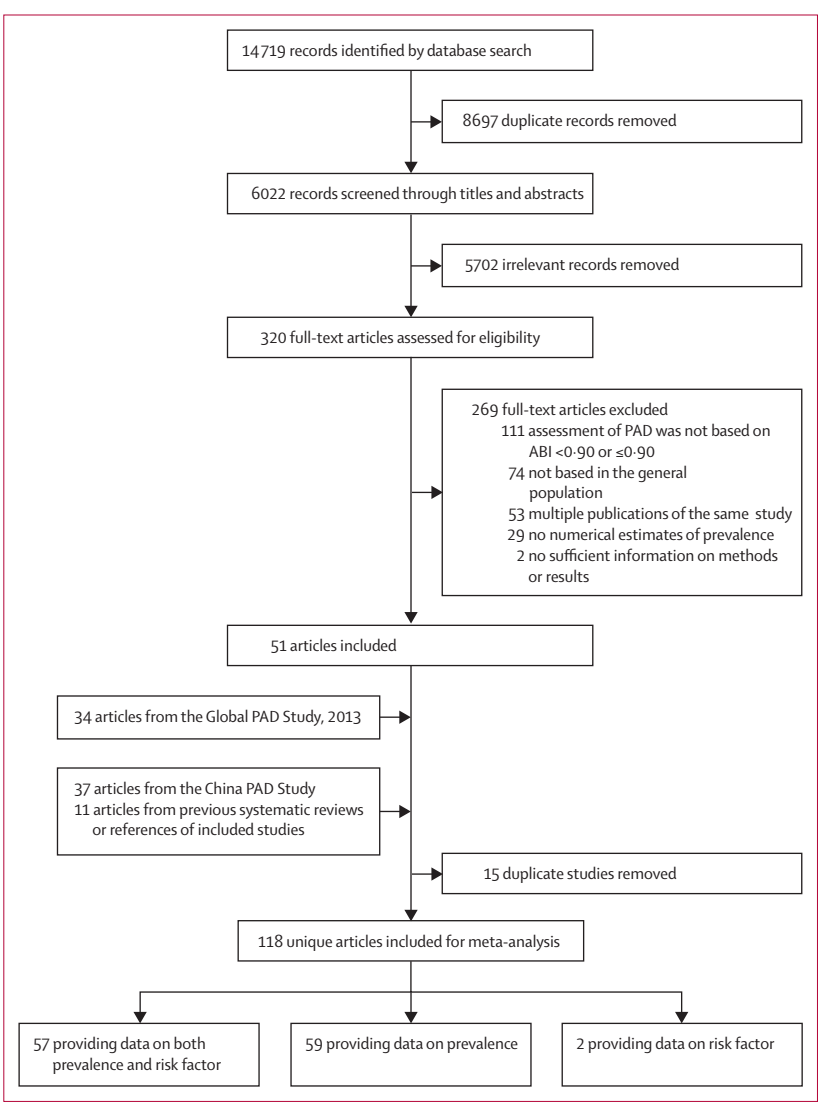

Figure 1: **Study selection**
ABI=ankle–brachial index. PAD=peripheral artery disease.

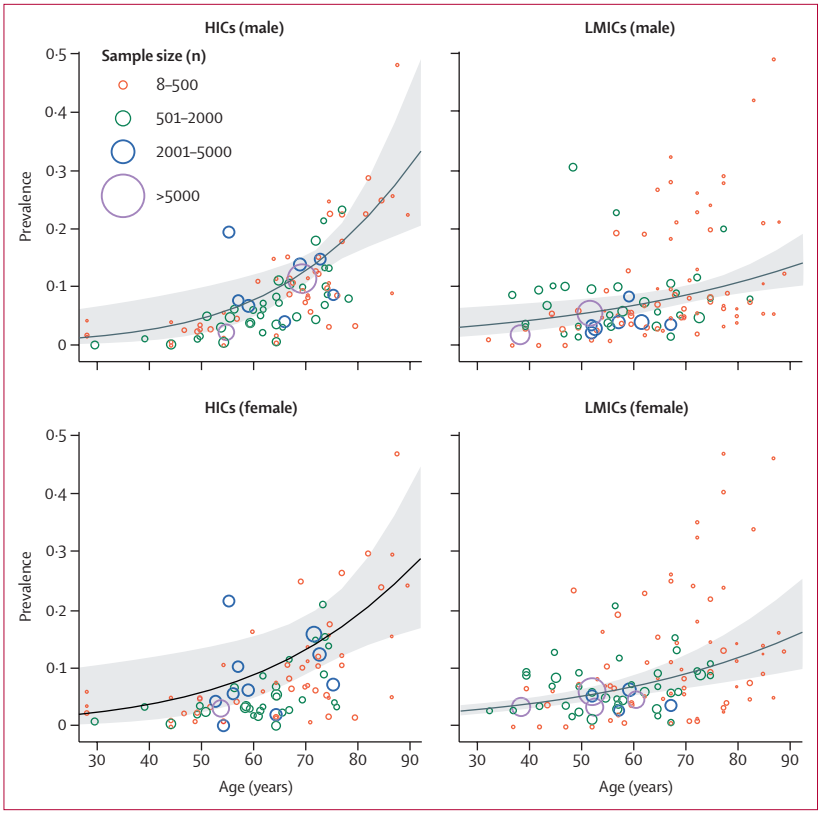

Figure 2: **Prevalence of peripheral artery disease in high-income countries and low-income and middle-income countries, by age and sex group**
The size of the bubble is proportional to the number of individuals in the sample. In LMICs, the regression lines for men and women in younger (<35 years) and older (>85 years) age groups are based on few data points or projections only. HICs=high-income countries. LMICs=low-income and middle-income countries.

by taking the same width as reported in other age groups in the same study. To enable the inclusion of zero prevalent cases as reported in some specific subgroups, a value of 0·0005 was adopted to replace zero cells. The systematic review was done by PS, DR, and FJIF and data extraction by PS and DR independently, and all discrepancies in study selection and data extraction were resolved by consensus.

Modelling age-specific and sex-specific prevalence of peripheral artery disease

To best describe and fit the hierarchical data structure (ie, several data points from the same study), a multilevel mixed-effects logistic regression was modelled to establish the relation between age and peripheral artery disease prevalence.[10,20,21] This modelling was done for men and women in HICs and LMICs. Among all the included studies from HICs, many studies were done in the USA. A similar phenomenon was found for China among studies from LMICs. Therefore, we controlled the effect of studies from the same study country by adding the study country identification number as the random effect.[21] Age was fitted as a fixed effect given that it was the covariate of interest (appendix, pp 5–6).

Estimation of the global number of peripheral artery disease cases in 2015

The number of people with peripheral artery disease in HICs (the HIC envelope) and LMICs (the LMIC envelope) were generated by multiplying the age-specific and sex-specific prevalence of peripheral artery disease derived by corresponding population data obtained from the UNPD.[18] This estimation was done for the year 2015 and in people older than 25 years, by every 5-year age group. The global number of peripheral artery disease cases was then calculated by adding the cases in HICs and LMICs together.

Meta-analysis of risk factors for peripheral artery disease

Because of the intrinsic heterogeneity between epidemiological studies, we chose a random-effects (DerSimonian Laird method) meta-analysis a priori to explore the effects of major risk factors for peripheral artery disease.[22] As a rule, we analysed only risk factors that shared similar definitions and had been investigated in at least three individual studies on the basis of a multivariable analysis. When available, the effects of suspected risk factors in HICs and LMICs were separately evaluated to assess whether a difference existed in the role of risk factors in these two contexts. The detailed process of meta-analysis is provided in the appendix (pp 6–7).

Estimation of the regional number of peripheral artery disease cases in 2015

To address both the features of geography (as designated by WHO) and income (as designated by the World Bank), we classified the world into ten different regions (the so-called WHO–World Bank regions across this study). The global number of people with peripheral artery disease in 2015 was distributed into different regions using a risk factor-based model. This model was initially proposed by the Child Health Epidemiology Reference Group and has been widely adopted in global burden of disease studies.[10,19,23] In brief, the HIC envelope and LMIC envelope were split by taking into account the regional prevalence of major risk factors and their meta-ORs. In line with the Global Peripheral Artery Disease Study of 2013, four major risk factors, including current smoking, hypertension, diabetes, and hypercholesterolaemia were selected for the risk factor-based model. The prevalence of current smoking (in 2015) was obtained from the WHO report on the global tobacco epidemic,[24,25] and those of hypertension (in 2015), diabetes (in 2014), and hypercholesterolaemia (in 2008) from the WHO Global Health Observatory data repository (appendix, pp 7–8).[26,27]

Estimation of the national number of peripheral artery disease cases in 2015

Using the same risk factor-based model approach as in the regional estimation of affected people, we estimated

the number of peripheral artery disease cases in 201 countries and territories in 2015. All analyses were done with STATA version 14.0 and R version 3.3.0.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the updated literature search, we identified a total of 14719 records from bibliographic databases. After removal of duplicates and an initial screening of titles and abstracts, 320 articles were assessed in full text, of which 51 met the inclusion criteria. We additionally included 34 articles from the Global Peripheral Artery Disease Study of 2013, 37 from the China Peripheral Artery Disease Study, and 11 from previous systematic reviews and reference screening. Finally, 118 individual articles covering 33 countries were included, among which 57 articles provided information on both peripheral artery disease prevalence and risk factors for peripheral artery disease, 59 contributed data only on peripheral artery disease prevalence, and two explored only the potential risk factors for peripheral artery disease. The study selection process is summarised in figure 1 and a full list of the included studies is shown in the appendix (pp 12–18).

Among the 118 articles included for analysis, 61 were from HICs (Australia, China, Denmark, Germany, Greece, Italy, Japan, the Netherlands, Poland, Saudi Arabia, Singapore, South Korea, Spain, Sweden, the UK, and the USA) and 57 from LMICs (Central African Republic, Ethiopia, Republic of Congo, Senegal, South Africa, Tanzania, Brazil, Colombia, Ecuador, Grenada, Mexico, India, Sri Lanka, Thailand, Turkey, China, and Benin). The geographical locations and detailed characteristics of every included article are shown in the appendix (pp 19–40).

The relationship between age and peripheral artery disease prevalence was constructed on the basis of a substantial number of data points (410 in total). The age ranges covered by informative data points were not consistent in HICs and LMICs, but the majority of estimates were between age 40 years to 80 years (figure 2). We also provide the age-specific and sex-specific prevalence of peripheral artery disease in HICs and LMICs (figure 2, table 1). Generally, the prevalence of peripheral artery disease increased with increasing age. This increasing trend was similar between sexes, but more pronounced in HICs than in LMICs. In HICs, the prevalence of peripheral artery disease was lower in men than in women up until age 75 years, at which point it became greater than in women. However, in LMICs, little differences were found between women and men. After being adjusted by the demographic profile in 2015, the prevalence of peripheral artery disease in people aged 25 years and older

	Prevalence of peripheral artery disease in men			Prevalence of peripheral artery disease in women			Overall prevalence of peripheral artery disease		
	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide
25–29 years	1·30 (0·26–6·24)	3·10 (1·47–6·41)	2·85 (1·31–6·38)	2·16 (0·43–10·17)	2·72 (1·98–3·73)	2·65 (1·77–4·59)	1·72 (0·34–8·13)	2·91 (1·72–5·10)	2·75 (1·54–5·51)
30–34 years	1·72 (0·41–6·90)	3·50 (1·80–6·70)	3·22 (1·58–6·73)	2·69 (0·63–10·78)	3·15 (2·38–4·14)	3·08 (2·12–5·15)	2·19 (0·52–8·78)	3·32 (2·09–5·44)	3·15 (1·85–5·95)
35–39 years	2·26 (0·64–7·63)	3·95 (2·20–7·00)	3·66 (1·93–7·11)	3·34 (0·92–11·43)	3·63 (2·84–4·63)	3·58 (2·52–5·77)	2·79 (0·78–9·47)	3·79 (2·52–5·83)	3·62 (2·22–6·45)
40–44 years	2·97 (1·00–8·43)	4·46 (2·68–7·33)	4·19 (2·37–7·53)	4·15 (1·34–12·13)	4·19 (3·35–5·22)	4·18 (3·00–6·45)	3·54 (1·17–10·24)	4·32 (3·01–6·29)	4·18 (2·68–6·99)
45–49 years	3·88 (1·56–9·32)	5·02 (3·25–7·68)	4·80 (2·93–7·99)	5·13 (1·94–12·90)	4·83 (3·91–5·96)	4·89 (3·54–7·26)	4·50 (1·75–11·08)	4·93 (3·58–6·82)	4·85 (3·23–7·63)
50–54 years	5·07 (2·43–10·29)	5·66 (3·94–8·06)	5·53 (3·62–8·54)	6·34 (2·79–13·77)	5·56 (4·48–6·89)	5·73 (4·12–8·33)	5·70 (2·61–12·02)	5·61 (4·21–7·47)	5·63 (3·87–8·44)
55–59 years	6·60 (3·74–11·38)	6·37 (4·74–8·49)	6·42 (4·51–9·17)	7·81 (3·97–14·77)	6·40 (5·06–8·05)	6·73 (4·81–9·62)	7·21 (3·86–13·09)	6·38 (4·91–8·27)	6·57 (4·66–9·39)
60–64 years	8·55 (5·70–12·62)	7·16 (5·66–9·01)	7·49 (5·67–9·88)	9·58 (5·56–15·99)	7·35 (5·66–9·49)	7·89 (5·64–11·07)	9·08 (5·63–14·35)	7·26 (5·66–9·25)	7·70 (5·66–10·49)
65–69 years	11·00 (8·50–14·11)	8·04 (6·66–9·67)	8·91 (7·20–10·97)	11·70 (7·58–17·61)	8·43 (6·28–11·23)	9·39 (6·66–13·10)	11·36 (8·02–15·94)	8·24 (6·46–10·48)	9·16 (6·92–12·08)
70–74 years	14·04 (12·01–16·36)	9·02 (7·63–10·62)	10·58 (8·99–12·41)	14·21 (9·90–20·00)	9·65 (6·93–13·29)	11·09 (7·87–15·41)	14·14 (10·87–18·32)	9·36 (7·26–12·05)	10·85 (8·39–14·01)
75–79 years	17·77 (14·93–21·01)	10·10 (8·47–12·01)	12·68 (10·64–15·04)	17·17 (12·15–23·69)	11·03 (7·61–15·72)	13·11 (9·15–18·43)	17·43 (13·37–22·51)	10·62 (7·99–14·08)	12·92 (9·81–16·93)
80–84 years	22·22 (16·94–28·58)	11·30 (9·14–13·90)	15·52 (12·16–19·57)	20·59 (14·06–29·12)	12·58 (8·34–18·54)	15·81 (10·65–22·81)	21·24 (15·22–28·90)	12·04 (8·67–16·60)	15·69 (11·27–21·48)
85–89 years	27·42 (18·75–38·22)	12·62 (9·71–16·25)	19·29 (13·78–26·14)	24·48 (15·61–36·24)	14·31 (9·11–21·76)	19·28 (12·29–28·84)	25·52 (16·71–36·93)	13·66 (9·34–19·63)	19·28 (12·84–27·84)
≥90 years	34·48 (20·90–51·05)	14·38 (10·33–19·68)	24·61 (15·71–35·65)	30·06 (17·24–46·91)	16·73 (10·14–26·33)	24·65 (14·36–38·55)	31·25 (18·23–48·03)	15·93 (10·21–24·05)	24·64 (14·77–37·68)
Total (>25 years)	6·50 (4·14–11·42)	5·07 (3·38–7·78)	5·36 (3·54–8·51)	8·21 (4·55–15·82)	5·12 (3·90–6·70)	5·75 (4·03–8·58)	7·37 (4·35–13·66)	5·09 (3·64–7·24)	5·56 (3·79–8·55)

Data are % (95% CI). Prevalence estimates in age groups 25–29 years, 30–34 years, 85–89 years, and ≥90 years are estimated predictions, in which original data points are relatively few. The overall prevalence in people older than 25 years was adjusted by the demographic structure in 2015. HICs=high-income countries. LMICs=low-income and middle-income countries.

Table 1: **Estimated prevalence of peripheral artery disease in high-income countries and in low-income and middle-income countries, by age and sex group**

	Men with peripheral artery disease in 2015 (millions)			Women with peripheral artery disease in 2015 (millions)			Overall number of people with peripheral artery disease in 2015 (millions)		
	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide	HICs	LMICs	Worldwide
25–29 years	0·56 (0·11–2·67)	8·37 (3·98–17·29)	8·93 (4·09–19·97)	0·86 (0·17–4·05)	7·07 (5·14–9·70)	7·93 (5·31–13·75)	1·42 (0·28–6·73)	15·44 (9·12–26·99)	16·86 (9·40–33·72)
30–34 years	0·76 (0·18–3·04)	8·29 (4·26–15·86)	9·05 (4·45–18·90)	1·11 (0·26–4·44)	7·27 (5·50–9·58)	8·38 (5·76–14·02)	1·86 (0·44–7·48)	15·56 (9·77–25·44)	17·43 (10·21–32·92)
35–39 years	0·99 (0·28–3·35)	8·28 (4·61–14·68)	9·28 (4·89–18·04)	1·39 (0·38–4·74)	7·47 (5·84–9·53)	8·86 (6·22–14·27)	2·38 (0·66–8·10)	15·75 (10·45–24·21)	18·13 (11·11–32·31)
40–44 years	1·32 (0·45–3·77)	8·97 (5·39–14·75)	10·30 (5·84–18·52)	1·76 (0·57–5·16)	8·28 (6·63–10·32)	10·05 (7·20–15·48)	3·09 (1·02–8·93)	17·25 (12·02–25·08)	20·34 (13·04–34·00)
45–49 years	1·71 (0·69–4·10)	9·30 (6·02–14·22)	11·01 (6·71–18·32)	2·18 (0·82–5·48)	8·90 (7·20–10·99)	11·08 (8·02–16·46)	3·89 (1·51–9·57)	18·20 (13·22–25·20)	22·09 (14·73–34·78)
50–54 years	2·19 (1·05–4·43)	8·97 (6·25–12·78)	11·15 (7·29–17·22)	2·68 (1·18–5·83)	8·86 (7·13–10·97)	11·54 (8·31–16·80)	4·87 (2·23–10·26)	17·83 (13·38–23·75)	22·70 (15·60–34·02)
55–59 years	2·60 (1·48–4·49)	8·20 (6·11–10·94)	10·80 (7·59–15·43)	3·12 (1·59–5·91)	8·44 (6·68–10·63)	11·57 (8·27–16·54)	5·72 (3·06–10·39)	16·65 (12·79–21·57)	22·37 (15·86–31·96)
60–64 years	2·96 (1·97–4·36)	7·80 (6·17–9·81)	10·75 (8·14–14·18)	3·50 (2·03–5·84)	8·38 (6·46–10·82)	11·88 (8·49–16·66)	6·46 (4·01–10·21)	16·18 (12·63–20·63)	22·63 (16·63–30·84)
65–69 years	3·33 (2·58–4·28)	5·87 (4·87–7·07)	9·21 (7·44–11·34)	3·88 (2·52–5·85)	6·74 (5·02–8·97)	10·62 (7·54–14·82)	7·22 (5·10–10·12)	12·61 (9·89–16·04)	19·83 (14·98–26·16)
70–74 years	3·13 (2·67–3·64)	4·45 (3·77–5·25)	7·58 (6·44–8·89)	3·69 (2·57–5·19)	5·43 (3·90–7·48)	9·13 (6·47–12·68)	6·82 (5·24–8·84)	9·89 (7·67–12·73)	16·70 (12·91–21·56)
75–79 years	3·05 (2·57–3·61)	3·42 (2·87–4·07)	6·47 (5·43–7·68)	3·76 (2·66–5·18)	4·70 (3·24–6·70)	8·46 (5·90–11·88)	6·81 (5·22–8·79)	8·12 (6·11–10·77)	14·93 (11·33–19·56)
80–84 years	2·54 (1·94–3·27)	2·05 (1·66–2·52)	4·59 (3·60–5·79)	3·51 (2·40–4·97)	3·17 (2·10–4·67)	6·68 (4·50–9·64)	6·05 (4·34–8·24)	5·22 (3·76–7·19)	11·27 (8·09–15·43)
85–89 years	1·71 (1·17–2·38)	0·96 (0·74–1·23)	2·66 (1·90–3·61)	2·81 (1·79–4·16)	1·72 (1·09–2·61)	4·53 (2·88–6·77)	4·52 (2·96–6·54)	2·68 (1·83–3·85)	7·19 (4·79–10·38)
≥90 years	0·89 (0·54–1·32)	0·36 (0·26–0·49)	1·25 (0·80–1·81)	2·10 (1·20–3·28)	0·80 (0·48–1·26)	2·90 (1·69–4·53)	2·99 (1·74–4·59)	1·16 (0·74–1·75)	4·15 (2·48–6·34)
Total (>25 years)	27·73 (17·67–48·71)	85·30 (56·94–130·98)	113·03 (74·61–179·68)	36·36 (20·15–70·08)	87·23 (66·43–114·22)	123·59 (86·58–184·30)	64·09 (37·81–118·78)	172·53 (123·37–245·20)	236·62 (161·19–363·98)

Data are n (95% CI). HICs=high-income countries. LMICs=low-income and middle-income countries.

Table 2: **Estimated number of people with peripheral artery disease in high-income countries and in low-income and middle-income countries in 2015, by age and sex group**

was 5·56% (95% CI 3·79–8·55) worldwide, and the prevalence estimate was higher in HICs than LMICs (7·37%, 4·35–13·66 *vs* 5·09%, 3·64–7·24), although the prevalence was higher in LMICs than in HICs in younger men (<55 years) and women (<45 years; figure 2, table 1).

A total of 236·62 million (95% CI 161·19–363·98) people aged 25 years and older were living with peripheral artery disease worldwide in 2015, among whom 72·91% were in LMICs (table 2). The age groups that contributed the largest share of cases were aged 65–69 years in HICs and aged 45–49 years in LMICs, implying a relatively younger demographic structure in LMICs than in HICs. Worldwide, 52·23% of people with peripheral artery disease were women.

After clustering all reported risk factors for peripheral artery disease by their definitions, we found that 30 individual factors were investigated in at least three studies and therefore included in the meta-analysis. Those 30 factors were further grouped into 13 broad categories according to their causal pathways. Apart from age, other risk factors for peripheral artery disease in both HICs and LMICs included smoking (former, current, and having ever smoked), hypertension, diabetes, and a history of concomitant cardiovascular diseases (table 3). We estimated the number of people with peripheral artery disease in each WHO–World Bank region by taking into account the different exposures to four major risk factors for peripheral artery disease (current smoking, hypertension, diabetes, and hypercholesterolaemia) based on a risk factor-based model (figure 3; appendix, pp 71–73). In 2015, the Western Pacific region (WPR) had the largest share of global peripheral artery disease cases (74·08 million, 95% CI 51·84–109·30), whereas the Eastern Mediterranean Region (EMR) had the least (14·67 million, 10·04–22·48). The prevalence of peripheral artery disease was highest in the European Region (7·99%, 5·10–13·41) and lowest in the African Region (4·06%, 2·90–5·91). The age group that contributed the most peripheral artery disease cases was that aged 55–64 years in the Region of the Americas, 65–74 years in the European Region, and 45–54 years in the South-East Asia Region and WPR (figure 3). In the African Region and EMR, however, the most peripheral artery disease cases were noted in people

aged 25–34 years. We estimated the national prevalence of peripheral artery disease and the number of affected people for 201 countries and territories (appendix, pp 80–84). The 15 countries with the highest number of people with peripheral artery disease accounted for 160·90 million, or more than two thirds (68%) of the estimated 236·62 million global peripheral artery disease cases. China, India, and the USA had the largest numbers of cases (figure 3).

Discussion

This systematic review and modelling analysis, based on a total of 118 articles covering 33 individual countries, provides the most up-to-date and comprehensive overview of the prevalence and number of people with peripheral artery disease at global, regional, and national levels. In 2015, the global prevalence of peripheral artery disease in individuals aged 25 years and older was 5·56% (95% CI 3·79–8·55), equivalent to 236·62 million (161·19–363·98) people with peripheral artery disease worldwide. Advanced age, smoking, hypertension, diabetes, and concomitant cardiovascular diseases were confirmed to be associated with a higher risk of peripheral artery disease in both HICs and LMICs. Substantial variations were highlighted in the distribution of peripheral artery disease cases across regions, where LMICs contributed almost 73% of the global cases. Among all the WHO regions, the share of peripheral artery disease cases was the largest in WPR (74·08 million, 95% CI 51·84–109·30), whereas the smallest was in EMR (14·67 million, 10·04–22·48) in 2015. More than two thirds of the global peripheral artery disease cases were concentrated in 15 individual countries.

The search strategies in this study were designed to obtain as much population-based data on peripheral artery disease prevalence as possible, while ensuring the quality and comparability of the results. During the selection process, we limited the inclusion of studies to those that confirmed the presence of peripheral artery disease with an ABI value of less than 0·90 or 0·90 or less. This is of both clinical and public health importance, because even patients with asymptomatic peripheral artery disease have an elevated risk of cardiovascular morbidity and mortality.[6,11] As such, the estimation of peripheral artery disease prevalence and cases presented in our study serves to inform stakeholders of the magnitude of this public health problem. The 236·62 million peripheral artery disease cases in 2015 as revealed in this study represent a relative increase of 17·10% from 202·06 million in 2010. However, this increase did not occur evenly in HICs and LMICs, where the increasing prevalence were higher in LMICs than in HICs across those 5 years (22·56% *vs* 4·48%). This disparity of increasing prevalence rates between HICs and LMICs has been observed in the Global Peripheral Artery Disease Study of 2013, and collectively resulted in an increased proportion of LMICs cases among all the

	Number of studies	Sample size	OR (95% CI)	HICs *vs* LMICs
Risk factor 1: age (per 10-year increase)				
Worldwide	26	117 428	1·55 (1·38–1·75)	..
HICs	17	32 609	1·65 (1·37–1·97)	Ref
LMICs	9	84 819	1·28 (1·17–1·41)	0·86 (0·62–1·19)
Risk factor 2: male sex				
Worldwide	29	119 743	0·74 (0·61–0·91)	..
HICs	12	16 897	0·94 (0·67–1·32)	Ref
LMICs	17	102 846	0·65 (0·51–0·83)	0·69 (0·43–1·11)
Risk factor 3: smoking				
Former smoker				
Worldwide	17	70 222	1·70 (1·39–2·09)	..
HICs	11	31 009	1·94 (1·62–2·32)	Ref
LMICs	6	39 213	1·36 (1·01–1·83)	0·68 (0·48–0·99)
Current smoker				
Worldwide	28	136 424	2·82 (2·00–3·98)	..
HICs	16	53 559	3·43 (2·58–4·58)	Ref
LMICs	12	82 865	2·15 (1·55–2·97)	0·62 (0·40–0·95)
Former smoker				
Worldwide	15	35 742	1·88 (1·39–2·54)	..
HICs	7	18 275	1·95 (1·33–2·85)	Ref
LMICs	8	17 467	1·83 (1·18–2·83)	0·92 (0·47–1·82)
Per ten pack–year increase of smoking in HICs	3	6440	1·33 (1·24–1·44)	..
Risk factor 4: current alcohol drinker				
Worldwide	7	37 857	0·84 (0·67–1·05)	..
HICs	1	2831	0·53 (0·31–0·90)	Ref
LMICs	6	35 026	0·89 (0·72–1·11)	1·69 (0·64–4·48)
Risk factor 5: hypertension				
Hypertension				
Worldwide	34	127 522	1·67 (1·50–1·86)	..
HICs	17	49 018	1·59 (1·46–1·74)	Ref
LMICs	17	78 504	1·76 (1·42–2·19)	1·05 (0·79–1·41)
SBP (per 10 mm Hg increase)				
Worldwide	9	28 709	1·15 (0·95–1·39)	..
HICs	4	8513	1·31 (1·20–1·42)	Ref
LMICs	5	20 196	1·07 (0·78–1·48)	0·85 (0·54–1·33)
DBP (per 10 mm Hg increase)				
Worldwide	3	10 917	1·19 (0·68–2·10)	..
HICs	1	1036	0·78 (0·61–0·99)	Ref
LMICs	2	9881	1·52 (0·79–2·95)	1·96 (0–2252·01)
Risk factor 6: diabetes				
Worldwide	40	167 096	1·89 (1·68–2·13)	..
HICs	19	48 873	1·98 (1·77–2·22)	Ref
LMICs	21	118 223	1·82 (1·49–2·23)	0·87 (0·64–1·18)
Risk factor 7: dyslipidaemia				
Dyslipidaemia				
Worldwide	7	68 645	1·51 (1·02–2·24)	..
HICs	1	1502	2·57 (0·95–6·97)	Ref
LMICs	6	67 143	1·44 (0·95–2·17)	0·56 (0·09–3·41)

(Table 3 continues on next page)

	Number of studies	Sample size	OR (95% CI)	HICs *vs* LMICs
(Continued from previous page)				
Hypercholesterolaemia				
Worldwide	16	63 225	1·34 (1·17–1·53)	..
HICs	10	32 221	1·43 (1·18–1·74)	Ref
LMICs	6	31 004	1·20 (0·88–1·63)	0·85 (0·59–1·24)
Low HDL				
Worldwide	8	37 342	1·67 (1·19–2·36)	..
HICs	3	16 119	1·84 (0·98–3·44)	Ref
LMICs	5	21 223	1·60 (1·01–2·56)	0·88 (0·32–2·43)
High LDL				
Worldwide	5	33 235	1·78 (1·41–2·25)	..
HICs	2	15 173	1·56 (0·79–3·10)	Ref
LMICs	3	18 062	1·93 (1·57–2·38)	1·34 (0·54–3·35)
High triglycerides				
Worldwide	8	34 409	1·41 (1·16–1·72)	..
HICs	4	23 429	1·48 (1·17–1·87)	Ref
LMICs	4	10 980	1·31 (0·89–1·91)	0·89 (0·50–1·57)
Risk factor 8: cardiovascular diseases				
Cardiovascular diseases				
Worldwide	11	39 837	2·31 (1·89–2·83)	..
HICs	7	19 036	2·41 (1·98–2·92)	Ref
LMICs	4	20 801	2·45 (1·40–4·29)	0·85 (0·53–1·35)
Coronary heart disease				
Worldwide	13	77 239	1·72 (1·48–1·99)	..
HICs	9	13 675	2·18 (1·65–2·86)	Ref
LMICs	4	63 564	1·56 (1·31–1·86)	0·72 (0·50–1·03)
Stroke				
Worldwide	6	28 790	2·35 (1·74–3·16)	..
HICs	4	6650	2·78 (1·48–5·22)	Ref
LMICs	2	22 140	2·23 (1·59–3·14)	0·80 (0·29–2·22)
Risk factor 9: obesity				
Overweight (BMI 25–30 kg/m^2)				
Worldwide	6	20 099	0·96 (0·82–1·13)	..
HICs	2	4731	0·92 (0·61–1·37)	Ref
LMICs	4	15 368	0·96 (0·80–1·17)	1·03 (0·59–1·79)
Obesity (BMI ≥30 kg/m^2)				
Worldwide	9	36 474	1·55 (1·23–1·96)	..
HICs	2	4731	1·07 (0·64–1·79)	Ref
LMICs	7	31 743	1·76 (1·42–2·18)	1·53 (0·93–2·51)
BMI (per 1 kg/m^2 increase)				
Worldwide	13	24 475	0·92 (0·87–0·97)	..
HICs	8	10 600	0·92 (0·86–0·99)	Ref
LMICs	5	13 875	0·92 (0·84–1·00)	1·00 (0·88–1·14)
Waist circumference (per 1 cm increase)				
Worldwide	3	24 101	1·03 (1·00–1·06)	..
HICs	1	1502	1·07 (1·03–1·12)	Ref
LMICs	2	22 599	1·01 (1·00–1·03)	0·95 (0·68–1·32)
Risk factor 10: renal impairment				
HICs only	5	9661	1·79 (1·03–3·12)	..

(Table 3 continues on next page)

peripheral artery disease cases worldwide in 2015 compared with 2010 (73% *vs* 69%).[10] The age-specific and sex-specific prevalence of peripheral artery disease in the Global Peripheral Artery Disease Study of 2013 and in this present study differed slightly. Given that our age-specific and sex-specific prevalence modelling and risk-factor assessment were based on more informative data points than in the previous study, the precision of our estimation has been improved.

Several limitations of our study should also be acknowledged. First, although we collected more than 347 (90%) of 410 data points for constructing the age-specific and sex-specific prevalence in HICs and LMICs from 2005 onwards, the accuracy of our models in reflecting the situation in 2015 is still questionable because the time trends of peripheral artery disease prevalence and its influencing factors were not fully understood. Second, the estimation of regional and national peripheral artery disease cases is likely to be biased given that it was driven by the demographic structure (age and sex) in every region and a risk factor-based model that only included four major risk factors (current smoking, hypertension, diabetes, and hypercholesterolaemia) for peripheral artery disease, and other explanatory variables were not accounted for. Moreover, the regional distribution of peripheral artery disease prevalence might also be a result of the different mean ABIs across ethnic groups.[28,29] Although this ethnic variation deserves further exploration, we could not do such an analysis because of the absence of relevant data from included studies. Third, because of the scarcity of the data, the regional and national prevalence of hypercholesterolaemia adopted in our risk factor-based model was based on a WHO estimation for the year 2008. Although the relative magnitudes of hypercholesterolaemia prevalence across regions and countries have probably not changed substantially within a decade, this data source still represented a considerable time lag, which needs to be improved in further study.

We found that the prevalence of peripheral artery disease was relatively higher in LMICs than in HICs in young people, but became lower from the age of 50 years, which might be related to a relatively lower life expectancy in LMICs than in HICs.[18] In line with previous epidemiological evidence from the Global Peripheral Artery Disease Study of 2013, the prevalence of peripheral artery disease was age related in both sexes and across regions.[10,19]

The positive relation between increasing age and the development of peripheral artery disease was also supported in our separate meta-analysis of risk factors for peripheral artery disease. In our risk factor estimation, women in LMICs were at a statistically higher risk of peripheral artery disease than men in LMICs, which was concordant with the results in the Global Peripheral Artery Disease Study of 2013.[10] Given that the prevalence of three major risk factors,

comprising current smoking, hypertension, and diabetes, were all higher in men in LMICs than in women in LMICs, this paradoxical female preponderance of peripheral artery disease might be inherent to the disease mechanism or a combined effect of other potential risk factors in LMICs settings, such as obesity and socioeconomic inequality.[26,27,30–32] A striking new finding in the present study is that the prevalence of peripheral artery disease in HICs did not statistically differ between men and women, as revealed by our meta-analysis of sex as a risk factor for peripheral artery disease in HICs settings. In the research field of peripheral artery disease, this epidemiological phenomenon has already attracted attention and experts have made calls for more attention on peripheral artery disease in women.[33–36]

Another key feature of our study is that the effects of 30 individual risk factors were investigated by meta-analysis. We only included studies that reported ORs based on a multivariable analysis to avoid suspected bias inherent to univariable analysis. On the basis of a substantial amount of existing data on risk factors for peripheral artery disease, our study showed an improved assessment of potential risk factors for peripheral artery disease, which has noteworthy clinical implications. In agreement with the Global Peripheral Artery Disease Study of 2013[10] and common clinical knowledge, smoking was again shown to be a strong risk factor for peripheral artery disease, irrespective of the status of smoking (current, former, or having ever smoked).[2,3,10] The benefits of smoking cessation in reducing the risk of peripheral artery disease have also been supported in our results, given that a lower OR was observed for former smoking than for current smoking. Another two risk factors for peripheral artery disease that have already been shown in the Global Peripheral Artery Disease Study of 2013[10] were diabetes and hypertension, implying the importance of proper control of blood sugar and blood pressure.[1–3] In the Global Peripheral Artery Disease Study of 2013,[10] a positive association between hypercholesterolaemia and peripheral artery disease was found in both HICs and LMICs settings, which, however, was not observed in LMICs in the present study. A possible reason for this result might be the relative lower total cholesterol concentrations in people living in LMICs than in those living in HICs, which might result in insufficient power for the synthesised estimation of hypercholesterolaemia as a risk factor in LMICs.[10,37] With an increasing trend of mean total cholesterol in both men and women in LMICs, the cumulative effect of elevated total cholesterol might be witnessed in the future and needs further confirmation with new data coming in.[37] Importantly, this finding does not indicate that lipid control is not necessary for peripheral artery disease management in LMICs given that the benefits of lipid-lowering treatment have long been established.[2,3]

	Number of studies	Sample size	OR (95% CI)	HICs *vs* LMICs
(Continued from previous page)				
eGFR (ten–unit increase)				
Worldwide	3	3001	0·90 (0·84–0·96)	..
HICs	2	1509	0·90 (0·84–0·96)	Ref
LMICs	1	1492	0·90 (0·78–1·04)	1·00 (0·35–2·87)
Risk factor 11: pulse pressure (per 1 mm Hg increase)				
Worldwide	5	5647	1·02 (0·98–1·06)	..
HICs	4	4601	1·03 (1·02–1·05)	Ref
LMICs	1	1046	0·96 (0·95–0·98)	0·93 (0·91–0·96)
Risk factor 12: inflammation				
HS–CRP 1·0–3·0 mg/L				
Worldwide	3	5536	1·89 (1·31–2·72)	..
HICs	2	4893	1·80 (1·17–2·76)	Ref
LMICs	1	643	2·16 (1·08–4·33)	1·20 (0·01–239·26)
HS–CRP >3·0 mg/L				
Worldwide	4	23 914	2·16 (1·48–3·14)	..
HICs	3	23 271	2·20 (1·44–3·36)	Ref
LMICs	1	643	2·01 (0·91–4·44)	0·91 (0·13–6·57)
HS–CRP (per mg/L increase) in HICs	5	6103	1·00 (0·94–1·06)	..
Risk factor 13: hyperfibrinogenaemia in HICs	3	15 957	1·83 (1·43–2·35)	..

Hyperfibrinogenaemia referred to an elevated concentration of fibrinogen (>400 mg/dL or ≥338 mg/dL).
The definitions of some risk factors varied slightly across studies. ORs for binary variable risk factors indicated risk of peripheral artery disease compared with those without the risk factor, except for former smokers (*vs* those who have never smoked), current smokers (*vs* those who have never smoked), current alcohol drinkers (*vs* those who have never drunk), individuals who were overweight (*vs* those with BMI <25 kg/m^2), individuals who were obese (*vs* BMI <25 kg/m^2), and those with HS-CRP of 1·0–3·0 mg/L (*vs* HS-CRP <1·0 mg/L) and HS-CRP higher than 3·0 mg/L (*vs* HS-CRP <1·0 mg/L). OR=odds ratio. HICs=high-income countries. LMICs=low-income and middle-income countries. SBP=systolic blood pressure. DBP=diastolic blood pressure. BMI=body-mass index. eGFR=estimated glomerular filtration rate. HS-CRP=high-sensitivity C-reactive protein.

Table 3: **Synthesised effect size of 13 groups of risk factors for peripheral artery disease that were investigated in at least three studies using multivariable analysis**

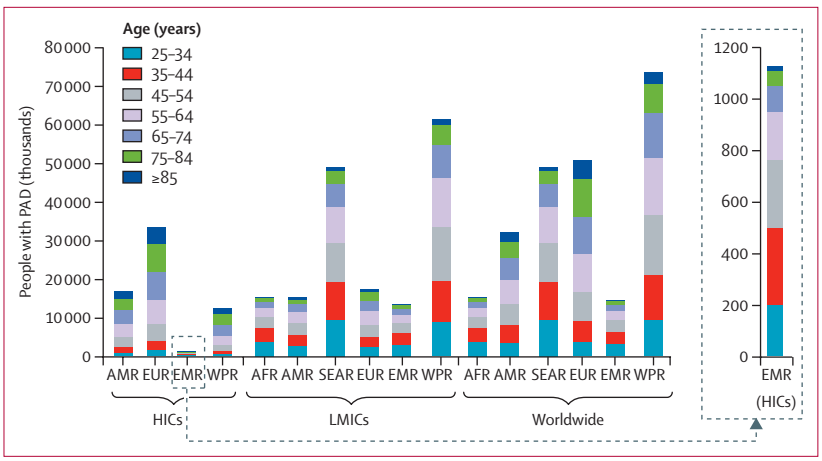

Figure 3: **Regional number of people with PAD and contributing age groups in 2015**
People with peripheral artery disease were restricted to those older than 25 years given the study context. AFR=African Region. AMR=Region of the Americas. EMR=Eastern Mediterranean Region. EUR=European Region. HICs=high-income countries. LMICs=Low-income and middle-income countries. PAD=peripheral artery disease. SEAR=South-East Asia Region. WPR=Western Pacific Region.

In this study, WPR was revealed to be the region with the largest share of peripheral artery disease cases, whereas EMR had the least. The regional disparity, as previously described in our methods section, was largely a combined result of uneven demographic structure and exposure to major risk factors. Our regional estimation of peripheral artery disease cases for different age groups implied a relatively younger age structure in affected LMICs compared with HICs. With the global ageing process continuing in the next several decades, a considerable increasing trend in the prevalence of peripheral artery disease and number of affected cases is likely to be seen, especially in LMICs. Also, the major risk factors for peripheral artery disease, especially smoking and diabetes, are projected globally to increase substantially over at least the next 10 years.[38,39] The large and increasing burden of peripheral artery disease (number of cases) in LMICs highlights that peripheral artery disease should not remain a neglected health issue in LMICs and more efforts to improve prevention, early diagnosis, and treatment of peripheral artery disease should be strengthened, as should awareness of the disease among health-care providers and the general public. In LMICs with scarce health resources, governments need to set priorities for the management of peripheral artery disease, with particular attention given to secondary prevention of acute cardiovascular events.[40] Especially, more attention should be paid to people with a high risk of peripheral artery disease, such as older women in LMICs settings, people who have a smoking habit, and those with hypertension, diabetes, or other cardiovascular diseases.

In conclusion, this study reveals that peripheral artery disease is continuing to be a major public health challenge worldwide. The majority of people with peripheral artery disease are in LMICs. Smoking, hypertension, and diabetes are positively associated with peripheral artery disease in both HICs and LMICs. With a demographic trend towards ageing and global increases in smoking and diabetes in the foreseeable future, an even larger number of peripheral artery disease cases is to be expected, especially in LMICs. More epidemiological studies and greater priority given to peripheral artery disease is required.

Contributors

IR, PS, and FGRF planned the study and IR and PS designed the methods. PS, DR, and FJIF contributed to the literature review and PS and DR extracted the data. PS, YZ, and IR did the statistical analyses. PS prepared the first draft with important contributions from KR and FGRF. All authors interpreted the results, commented on drafts of the Article, and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

All data generated or analysed in this study are included in the appendix.

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References

1 Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association For Vascular Surgery/Society For Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006; **113:** e463–654.

2 Ouriel K. Peripheral arterial disease. *Lancet* 2001; **358:** 1257–64.

3 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; **45:** S5–67.

4 Fowkes FGR, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017; **14:** 156.

5 McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA* 2004; **292:** 453–61.

6 Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. *Circulation* 2006; **114:** 688–99.

7 Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. *Mayo Clin Proc* 2010; **85:** 678–92.

8 Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation* 2017; **135:** e146.

9 Sampson UK, Fowkes FGR, McDermott MM, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Glob Heart* 2014; **9:** 145–58.

10 Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; **382:** 1329–40.

11 Novo S. Classification, epidemiology, risk factors, and natural history of peripheral arterial disease. *Diabetes Obes Metab* 2002; **4:** S1–S6.

12 Hirsch AT, Murphy TP, Lovell MB, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation* 2007; **116:** 2086–94.

13 Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; **286:** 1317–24.

14 Criqui MH. Peripheral arterial disease epidemiological aspects. *Vasc Med* 2001; **6:** 3–7.

15 Johnston LE, Stewart BT, Yangni-Angate H, et al. Peripheral arterial disease in sub-Saharan Africa: a review. *JAMA Surg* 2016; **151:** 564–72.

16 Sebastianski M, Makowsky MJ, Dorgan M, Tsuyuki RT. Paradoxically lower prevalence of peripheral arterial disease in South Asians: a systematic review and meta-analysis. *Heart* 2013; **100:** 100–05.

17 Stevens GA, Alkema L, Black RE, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *PLoS Med* 2016; **13:** e1002056.

18 UN, Department of Economic and Social Affairs, Population Division. World Population Prospects, the 2017 revision. 2017. https://esa.un.org/unpd/wpp/ (accessed Dec 8, 2017).

19 Song P, Rudan D, Wang M, Chang X, Rudan I. National and subnational estimation of the burden of peripheral artery disease (PAD) in China: a systematic review and meta-analysis. *J Glob Health* 2019; **9:** 010601.

20 Fanelli D, Costas R, Ioannidis JP. Meta-assessment of bias in science. *Proc Natl Acad Sci* 2017; **114:** 3714–19.

21 Hox JJ, Moerbeek M, Van de Schoot R. Multilevel analysis. Techniques and applications, 3rd edn. Routledge: Abingdon, 2017.

22 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: Cochrane Training, 2011.

23 Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bull World Health Organ* 2004; **82:** 895–903.

24 WHO. WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. Geneva: World Health Organization, 2017.

25 WHO. WHO report on the global tobacco epidemic 2015: raising taxes on tobacco. Geneva: World Health Organization, 2015.

26 WHO. Global Health Observatory data repository. http://apps.who.int/gho/data/node.home (accessed June 12, 2018).

27 Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2016 (GBD 2016) data resources. http://ghdx.healthdata.org/gbd-2016 (accessed June 12, 2018).

28 Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med* 2007; **32:** 328–33.

29 McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2005; **162:** 33–41.

30 Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults. *Circ Cardiovasc Qual Outcomes* 2014; **7:** 532–39.

31 Kröger K, Dragano N, Stang A, et al. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vasc Med* 2009; **14:** 289–96.

32 Huang Y, Xu M, Xie L, et al. Obesity and peripheral arterial disease: a Mendelian randomization analysis. *Atherosclerosis* 2016; **247:** 218–24.

33 Hirsch AT, Allison MA, Gomes AS, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation* 2012; **125:** 1449–72.

34 Teodorescu VJ, Vavra AK, Kibbe MR. Peripheral arterial disease in women. *J Vasc Surg* 2013; **57:** 18S–26S.

35 Srivaratharajah K, Abramson BL. Women and peripheral arterial disease: a review of sex differences in epidemiology, clinical manifestations, and outcomes. *Can J Cardiol* 2018; **34:** 356–61.

36 Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health* 2009; **5:** 669–83.

37 Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. *Lancet* 2011; **377:** 578–86.

38 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014; **103:** 137–49.

39 Méndez D, Alshanqeety O, Warner KE. The potential impact of smoking control policies on future global smoking trends. *Tob Control* 2012; **22:** 46–51.

40 Fowkes FG, Forster RB, Levin CE, et al. Prioritization of treatments for lower extremity peripheral artery disease in low- and middle-income countries. *Int Angiol* 2017; **36:** 203–15.

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Editor's Choice – The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease

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WHAT THIS PAPER ADDS

The first prediction score has been developed using machine learning techniques for long term outcomes in patients with a symptomatic peripheral arterial occlusive disease. The model exhibited high accuracy and adequate discrimination. The five year risk of amputation or death varied between 9% and 48% in patients with intermittent claudication, and between 25% and 88% in patients with chronic limb threatening ischaemia. In the routine clinical setting, the pragmatic score presented can help identify patients in need of intensified medical care and support decision making on invasive revascularisation opportunities.

Objective: Patients with peripheral arterial occlusive disease (PAOD) face an increased risk of both lower limb amputation and death. To date, it has been challenging to predict the long term outcomes for PAOD. The aim was to develop a risk score to predict worse five year amputation free survival (AFS).

Methods: In this retrospective analysis of claims data, symptomatic PAOD patients were split into training and validation sets. Variables in the model were patient age and sex, Elixhauser comorbidities, and the 190 most common secondary diagnoses. Penalised Cox regression (least absolute shrinkage and selection operator [LASSO]) with tenfold cross validation for variable selection was performed and patients were categorised into five risk groups using the ten most important variables. All analyses were stratified by intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI).

Results: In total, 87 293 patients with PAOD (female 45.3%, mean age 71.4 $\pm$ 11.1 years) were included in the analysis. The most important variable predicting worse five year AFS was patient age >80 years. The GermanVasc score exhibited good predictive accuracy both for IC (c statistic = 0.70, 95% confidence interval [CI] 0.69–0.71) and CLTI (c statistic = 0.69, 95% CI 0.68–0.70) with adequate calibration due largely to alignment of observed and expected risk. Depending on the cumulative point score, the five year risk of amputation or death ranged from 9% (low risk) to 48% (high risk) for IC, and from 25% to 88% for CLTI.

Conclusion: The GermanVasc score predicts worse five year AFS stratified for inpatients suffering from IC and CLTI, with good predictive accuracy. By separating low from high risk patients, the GermanVasc score may support patient centred consent.

Keywords: Chronic limb threatening ischaemia, Elastic net, Elixhauser comorbidity groups, Intermittent claudication, LASSO, Peripheral arterial occlusive disease

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INTRODUCTION

Patient centred health care should respect patients' individual needs without incurring delays. High quality medical evidence develops through research over decades, primarily by performing randomised clinical trials. Yet, in peripheral vascular medicine, trial data are frequently not available and therefore many guidelines are limited to consensus recommendations with a low level of evidence.[1–3]

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For patients with peripheral arterial occlusive disease (PAOD), quality of life is seriously impaired by the risk of amputation and death.[1] Knowledge about the individual probability of long term outcomes after hospitalisation for PAOD is sparse, therefore, it can be challenging to make the best choice from a wide range of possible invasive and best medical treatments.

Routinely collected data from registries or health insurance claims can help to quantify the risks for specific long term outcomes. With the FINNVASC registry study, a linear sum score for post-operative mortality and/or major lower limb amputation was developed. However, this score was developed for short term outcomes only.[4,5] Recruiting multicentre registry trials such as SWEDEPAD (Swedish Drug-elution Trial in Peripheral Arterial Disease),[6] BASIL-3 (BAlloon versus Stenting in severe Ischaemia of the Leg-3),[7] BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia),[8] and the GermanVasc registry trial[9] are currently collecting primary research data, including a follow up beyond 30 days. While those clinical registries usually need a certain time to collect enough data for valid prediction models, health insurance claims provide a large sample size suitable to use for data driven methods and predictive modelling. Although machine learning approaches have been used frequently in stroke and cardiac risk prediction, its use remains extremely rare in patients with PAOD.[10,11]

This study aimed to develop an easy to use score to estimate the five year probability of amputation free survival (AFS) of patients with PAOD, based on routinely collected health insurance claims data in Germany.

MATERIALS AND METHODS

Data source

Health insurance claims data from Germany's second largest insurance fund, BARMER, cover approximately nine million German citizens (10.8% of Germany's population). The German Modification of the World Health Organization's International Classification of Diseases 10th Revision (ICD-10-GM), Operations and Procedures Codes, and the German version of the international Anatomical Therapeutic Chemical classification for pharmacological treatment codes were used.

Study population

Adult patients aged 40 years and above treated in legally endorsed German hospitals and presenting with a primary diagnosis of symptomatic PAOD (stages II to IV, according to the Fontaine classification) from 1 January 2008 to 31 December 2016 were included. To identify an incident diagnosis of PAOD, a three year lookback was used (i.e., a disease free interval of three years). Patients with prior major amputation or death within 30 days after discharge were excluded (see Fig. 1).

Variables

Variables included age, sex (male *vs.* female), smoking, 30 different Elixhauser comorbidity groups (three year lookback),[12,13] year of discharge, history of prior myocardial infarction (MI) or prior stroke, atrial fibrillation (AF), dialysis, gangrene, discharge to rehabilitation or nursing home or

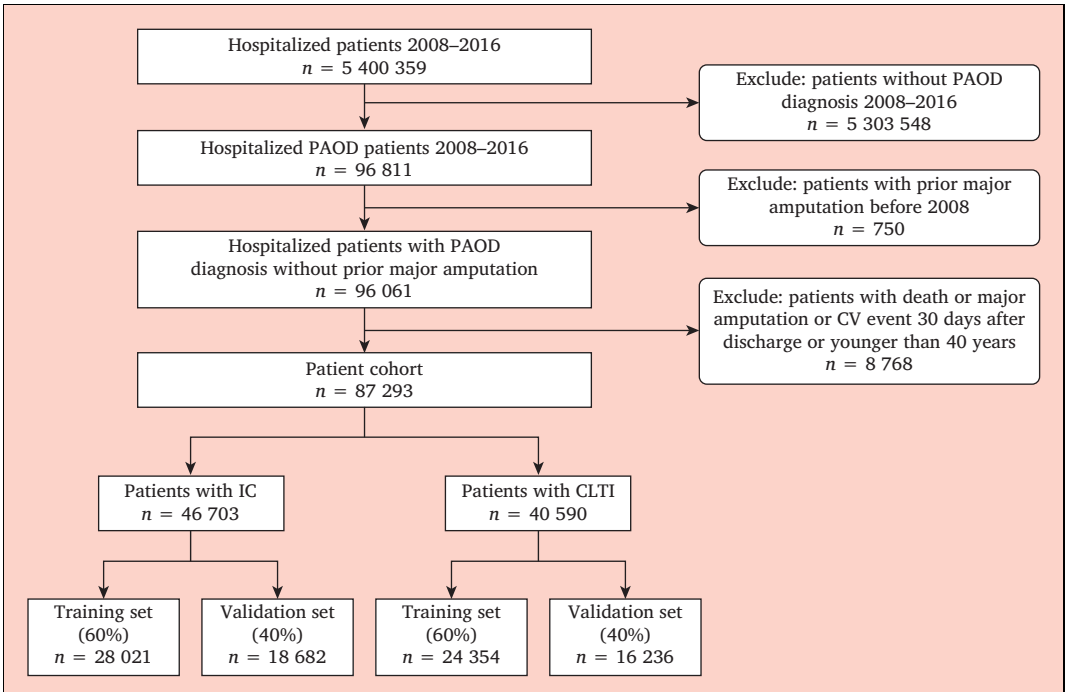

Figure 1. Flowchart for training and validation dataset of hospitalised patients with peripheral arterial occlusive disease (PAOD) stratified into intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI) groups. CV = cardiovascular event, including myocardial infarction or stroke.

hospice (three year lookback), and the 190 most common inpatient secondary diagnoses on admission. The patients were grouped according to age, to account for non-linear effects: 40—60 years; 61—70 years; 71—80 years; and ≥80 years. Missing data (0.5%) were deleted in a listwise manner (complete case analysis). All codes for the included variables are listed in Appendix S1 (see Supplementary Material).

Outcome

The primary outcome was death or major amputation above ankle level, measured as the composite endpoint of five year AFS after the index hospitalisation. Secondary outcomes were cardiovascular events, including MI or stroke after discharge.

Statistical analysis

To account for right censoring, a time to event framework using Cox proportional hazard models was used. The survival for five different risk groups from low to high risk was illustrated with Kaplan—Meier curves. The steps are outlined below. The implemented R code is given in the Appendix Table A5 (Supplementary Material), to encourage other research groups to use this risk score for better comparability.

Step 1: stratification. All analyses were stratified by Fontaine stages (according to the corresponding ICD-10 code) during the index stay: stage II for intermittent claudication (IC) *vs.* stage III/IV for chronic limb threatening ischaemia (CLTI).

Step 2: training and validation data set. The original dataset was separated into a training set (60%) and a validation set (40%). The predictive models and point score were developed in the training set, and model performance was assessed in the validation set.

Step 3: variable selection. Using the least absolute shrinkage and selection operator (LASSO) method, a parsimonious Cox survival model was estimated using a penalty term λ shrinking coefficients of irrelevant variables to zero (lambda).[14] The optimal λ was selected by tenfold cross validation. Using the non-zero variables only, the Cox survival model was re-estimated without a penalty term.

Step 4: top 10. To identify predictors contributing most to the generalisation power of the model from the previous step, variables were ranked based on the Breiman permutation method within the validation set.[15] The ten variables with c statistics (general term for area under the curve for a Cox regression; range 0—1) and highest Breiman importance were selected for use in the GermanVasc score.

Step 5: GermanVasc score. A final Cox model was fitted to the training set using only the 10 selected variables from step 4. The beta coefficients of this model were transformed to points (integer values), which, in sum, represent the GermanVasc score for individual risk prediction. The beta values were multiplied by ten and rounded to integers, following Austin *et al.*[16] This resulted in a pragmatic sum point score of the ten most important variables for usage in clinical routine care.

Step 6: model performance (discrimination). The discrimination of the variables was assessed in the validation set using the concordance statistics of c, a rank correlation coefficient accounting for censoring in the data. Further out of sample statistics were calculated for a subgroup of the validation set excluding high volume hospitals (>1000 interventions during the study period), a subgroup of the validation set excluding patients with an index stay after 2012, and cardiovascular event free survival as an outcome.

Step 7: model performance (calibration). Calibration of the prediction model was assessed by comparing the observed risk with the expected risk for each GermanVasc point value. The observed risk was measured by the Kaplan—Meier survival function fitted to the validation set and the expected risk by the Kaplan—Meier survival function fitted to the training set.

Step 8: risk groups. To categorise patients in five different risk groups, quantiles of the GermanVasc score points ($x_{0.2}$, $x_{0.4}$, $x_{0.6}$, and $x_{0.8}$) were used to find equal sized risk groups with low risk ($\leq x_{0.2}$) to high risk ($>x_{0.8}$). Risks for each group were estimated and plotted using Kaplan—Meier functions and hazard ratios (HRs) for each group using Cox regression models.

Step 9: summary sheet. To facilitate the application of the GermanVasc score, a summary sheet was created. Therein, points for each variable are displayed along with the risk associated with summarised points for each of the five risk groups. A tutorial and examples are provided in Fig. 2.

Sensitivity analyses

An elastic net approach was used as a sensitivity analysis (option alpha). The elastic net approach is known to perform better in feature selection if variables are highly correlated and more variables are used.[17] The results of these analyses are given in the Appendix (Supplementary Material).

Software

Data processing was performed with SAS version 9.04 (SAS Institute, Cary, NC, USA). Descriptive analyses, Cox models, LASSO, elastic net, model diagnostics, and illustrations were performed with R version 3.3 (*survival* and *glmnet* packages; R Foundation for Statistical Computing, Vienna, Austria). Visualisation was performed with Adobe Illustrator version 24.1.2 (Adobe, San Jose, CA, USA).

Reporting guidelines

Results were reported using the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[18]

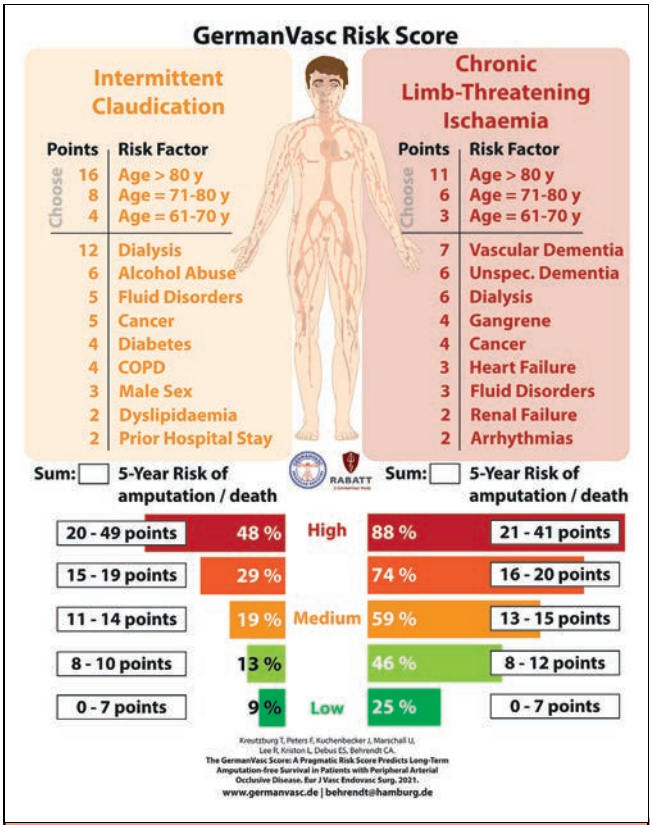

Figure 2. Summary sheet for the GermanVasc risk score stratified for intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI), including the five risk groups: low; low–moderate; moderate (medium); moderate–high; and high risk. The numbers before the risk factors are the point scores to be summarised for the presence of this risk factor. COPD = chronic obstructive pulmonary disease.

RESULTS

Baseline characteristics

In total, 87 293 patients with an incident symptomatic PAOD diagnosis between 2008 and 2016 (~10 000 per year; see Fig. 1) were included. Of these, 46 703 were diagnosed with IC (43% female) and 40 590 with CLTI (48% female). Patients with IC differed substantially from those with CLTI (Table 1). Patients with IC were younger (mean age 69 *vs.* 75 years); had fewer comorbidities such as congestive heart failure (14% *vs.* 33%), cardiac dysrhythmias (16% *vs.* 34%), or renal failure (19% *vs.* 37%); and were prescribed fewer medications (median 8 *vs.* 11). Within five years of index discharge, 19% of the patients with IC died and 1% had a major amputation, so that the composite endpoint was about 20%. For patients with CLTI, 50% died and 9% had a major amputation; the composite endpoint was 52%. The characteristics of the corresponding training and validation sets were largely similar (Table 1).

GermanVasc score

For the subgroup of patients with IC, the GermanVasc score exhibited good discrimination (model top 10 variables, c = 0.70, 95% confidence interval [CI] 0.69–0.71). The summarised point score ranged from 0 to 49. Patients with IC with lower point scores represented younger and healthier patients, and higher point scores older or sicker patients (Fig. A1a; see Supplementary Material). For the high risk group, the hazard ratio (HR) was 7.48 (95% CI 6.63–8.45), compared with the low risk group. The Kaplan–Meier survival curve (event rate for five year amputation or death in the low risk group was 8.7% and for the high risk group 47.6%) is given in Fig. 3(A). The 10 most important predictors of worse AFS were older age, male sex, cancer, absence of dyslipidaemia, alcohol abuse, chronic pulmonary disease, prior hospital stay, diabetes, dialysis, and fluid and electrolyte disorders (Tables 2 and 3). The point score also achieved good discrimination for the subgroups excluding high volume hospitals (c = 0.69, 95% CI 0.67–0.71 [Table A3; see Supplementary Material]) and excluding patients with an index stay after 2012 (c = 0.71, 95% CI 0.70–0.72) and for cardiovascular event free survival as the outcome (c = 0.63, 95% CI 0.62–0.64).

Likewise, for the subgroup of patients with CLTI, the GermanVasc score exhibited good discrimination (model top 10 variables, c = 0.69, 95% CI 0.68–0.70). The point score ranged from 0 to 41 (Tables 4 and 5), the distribution of the symmetric point score distribution is illustrated in Fig. A1b (Supplementary Material). For the high risk group, the HR was 7.83 (95% CI 7.24–8.48). The Kaplan–Meier survival curve (low risk event rate 25.2%; high risk five year rate of amputation or death 88.2%) is given in Fig. 3(B). The 10 most important predictors of worse AFS were older age, gangrene, unspecified dementia, dialysis, congestive heart failure, vascular dementia, cancer, fluid and electrolyte disorders, renal failure, and cardiac dysrhythmias (Tables 4 and 5). The point score also achieved good discrimination for the subgroups excluding high volume hospitals (c = 0.71, 95% CI 0.69–0.73 [Table A3; Supplementary Material]) and excluding patients with an index stay after 2012 (c = 0.70, 95% CI 0.69–0.71) and for cardiovascular event free survival as the outcome (c = 0.61, 95% CI 0.60–0.62).

Calibration

In the validation set, observed and expected risk showed a high degree of agreement for both IC and CLTI patients, except for high point score values, where only a few cases occurred. This is not only true for the full data, but also subgroups excluding high volume hospitals and excluding patients with index stay after 2012 (Fig. A2 – A4; Supplementary Material).

Sensitivity analysis

Elastic net. All analyses for five year AFS were performed with elastic net, which provided similar results for the top ten variables but with a slightly different ranking by Breiman's permutation method and the same range for the risk groups (from low risk to high risk). For the high risk IC group the HR was 7.18 (95% CI 6.35–8.11; c = 0.70 [95% CI 0.69–

Table 1. Patient characteristics of the training and validation dataset for patients with intermittent claudication (IC) and chronic limb-threatening ischaemia (CLTI)

	Total (n = 87 293)	IC training (n = 28 021)	IC validation (n = 18 682)	CLTI training (n = 24 354)	CLTI validation (n = 16 236)
Age − y	71.4 ± 11.1	68.8 ± 10.1	69.0 ± 10.2	74.5 ± 11.3	74.4 ± 11.3
Female sex	39 545 (45.3)	12 046 (43.0)	8 050 (43.1)	11 684 (48.0)	7 765 (47.8)
Elixhauser groups (3 *y*)					
Congestive heart failure	20 399 (23.4)	4 081 (14.6)	2 698 (14.4)	8 200 (33.7)	5 420 (33.4)
Cardiac dysrhythmias	21 351 (24.5)	4 530 (16.2)	3 081 (16.5)	8 205 (33.7)	5 535 (34.1)
Hypertension	68 384 (78.3)	21 437 (76.5)	14 316 (76.6)	19 587 (80.4)	13 044 (80.3)
Diabetes, complicated	24 004 (27.5)	4 116 (14.7)	2 792 (14.9)	10 268 (42.2)	6 828 (42.1)
Renal failure	23 728 (27.2)	5 045 (18.0)	3 533 (18.9)	9 074 (37.3)	6 076 (37.4)
COPD	12 634 (14.5)	3 655 (13.0)	2 507 (13.4)	3 915 (16.1)	2 557 (15.7)
Obesity	11 656 (13.4)	3 237 (11.6)	2 073 (11.1)	3 813 (15.7)	2 533 (15.6)
Smoking	15 330 (17.6)	5 919 (21.1)	3 880 (20.8)	3 385 (13.9)	2 146 (13.2)
Prior myocardial infarction	7 465 (8.6)	2 218 (7.9)	1 499 (8.0)	2 274 (9.3)	1 474 (9.1)
Prior stroke	7 307 (8.4)	1 545 (5.5)	1 031 (5.5)	2 846 (11.7)	1 885 (11.6)
Atrial fibrillation	12 801 (14.7)	2 379 (8.5)	1 580 (8.5)	5 303 (21.8)	3 539 (21.8)
Nursing care, discharge reason	2 076 (2.4)	119 (0.4)	86 (0.5)	1 141 (4.7)	730 (4.5)
Rehabilitation, discharge reason	5 367 (6.1)	1 147 (4.1)	761 (4.1)	2 109 (8.7)	1 350 (8.3)
Dialysis	1 812 (2.1)	180 (0.6)	122 (0.7)	880 (3.6)	630 (3.9)
Diagnosis (index stay)					
Dyslipidaemia, E78	28 580 (32.7)	10 812 (38.6)	7 111 (38.1)	6 399 (26.3)	4 258 (26.2)
Dementia, F03	1 711 (2.0)	107 (0.4)	73 (0.4)	918 (3.8)	613 (3.8)
Polypharmacy	9 (5–13)	8 (5–11)	8 (5–12)	11 (7–16)	11 (7–16)
Follow up time − d	1 503 (839–1825)	1 825 (1134–1825)	1 804 (1127–1825)	1 131 (481–1825)	1 144 (475–1825)
Antithrombotics	40 437 (46.3)	11 760 (42.0)	8 018 (42.9)	12 353 (50.7)	8 306 (51.2)
Lipid lowering drugs	39 431 (45.2)	14 271 (50.9)	9 546 (51.1)	9 280 (38.1)	6 334 (39.0)
Antihypertensive	72 602 (83.2)	22 557 (80.5)	15 041 (80.5)	20 971 (86.1)	14 033 (86.4)
Event rate within five years					
Composite endpoint: all cause death or major amputation	30 635 (35.1)	5 514 (19.7)	3 728 (20.0)	12 852 (52.8)	8 541 (52.6)
All cause death	29 129 (33.4)	5 323 (19.0)	3 592 (19.2)	12 118 (49.8)	8 096 (49.9)
Major amputation	4 256 (4.9)	401 (1.4)	255 (1.4)	2 169 (8.9)	1 431 (8.8)
Myocardial infarction	10 180 (11.7)	3 073 (11.0)	2 142 (11.5)	3007 (12.3)	1958 (12.1)
Stroke	11 874 (13.6)	3 541 (12.6)	2 295 (12.3)	3 596 (14.8)	2 442 (15.0)

Data are presented as n (%), mean ± standard deviation, or median (interquartile range). COPD = chronic obstructive pulmonary disorder.

0.71]), and for patients in the high risk CLTI group the HR was 7.83 (95% CI 7.24–8.48; c = 0.69 [95% CI 0.68–0.70]). The results are given in full in Tables A1 and A2 (Supplementary Material).

Summary sheet

All relevant information is provided in the summary sheet (Fig. A5; see Supplementary Material).

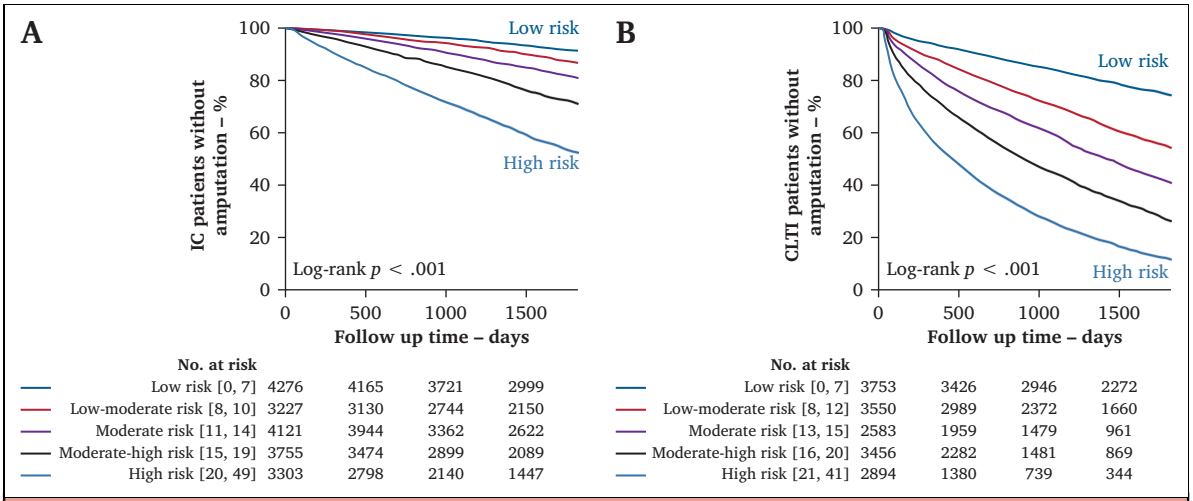

Figure 3. Cumulative Kaplan–Meier estimate of five year amputation free survival for GermanVasc score with the top 10 variables stratified for (A) intermittent claudication (IC) and (B) chronic limb threatening ischaemia (CLTI) for five risk groups: low; low–moderate; moderate; moderate–high; and high risk.

Table 2. Cox regression model prediction for five year amputation free survival for intermittent claudication in 46 703 patients: least absolute shrinkage and selection operator method with hazard ratios (HR) and 95% confidence intervals (CIs); the top 10 variables; and points for risk score based on highest Breiman importance

Variable	HR (95% CI)	Importance (Breiman)*	GermanVasc score
Age − y			
>80 (ref. 40–60)	4.80 (4.35–5.30)	1 168	16
71–80 (ref. 40–60)	2.21 (2.02–2.43)	552	8
61–70 (ref. 40–60)	1.50 (1.36–1.66)	144	4
Male sex	1.33 (1.26–1.41)	73	3
Cancer	1.62 (1.48–1.77)	69	5
Absence of dyslipidaemia (E78)	1.21 (1.14–1.27)	44	2
Alcohol abuse	1.75 (1.56–1.97)	33	6
Chronic obstructive pulmonary disease	1.56 (1.46–1.67)	31	4
Prior hospital stay	1.25 (1.18–1.32)	27	2
Diabetes	1.46 (1.38–1.55)	26	4
Dialysis	3.31 (2.74–3.98)	17	12
Fluid and electrolyte disorders	1.61 (1.51–1.71)	16	5

* Breiman importance multiplied by 10 000.

Table 3. Cox regression model prediction for five year amputation free survival for intermittent claudication in 46 703 patients: hazard ratios (HR) and 95% confidence intervals (CIs) and five year risk of amputation or death in five groups ranked from "low risk" to "high risk"

5 y risk of amputation or death*	HR (95% CI)	Amputation or death after 5 y − %	Range 0–49
Low risk	Reference	8.7	0–7
Low–moderate	1.54 (1.32–1.79)	13.0	8–10
Moderate	2.37 (2.07–2.70)	19.1	11–14
Moderate–high	3.82 (3.37–4.34)	28.9	15–19
High risk	7.48 (6.63–8.45)	47.6	20–49

* c = 0.70 (95% CI 0.69–0.71).

DISCUSSION

In this large scale health insurance claims data analysis, two pragmatic point scores were developed exhibiting high predictive accuracy and adequate discrimination between risk groups to predict worse five year AFS in patients with IC and CLTI. The scores were based on a data driven machine learning approach on longitudinal data. Owing to the advantages of the study sample, as compared with other data sources, there was only a small amount of missing data and no losses to follow up.[19]

Previous risk scores have been developed to predict outcomes in comparable target populations such as FINNVASC (3 925 patients with CLTI, 1991–1999, 30 day follow up),[4,5] the PREVENT-III risk score (1 166 patients with CLTI, 2003–2007, one year follow up),[20] the ERICVA simplified score (672 patients with CLTI, 2005–2010, one year follow up),[21] the

Table 4. Cox regression model prediction for five year amputation free survival for chronic limb threatening ischaemia in 40 590 patients: least absolute shrinkage and selection operator method with hazard ratios (HR) and 95% confidence intervals (CIs), the top 10 variables, and points for the risk score based on highest Breiman importance

Top 10 variables	HR (95% CI)	Importance (Breiman)*	GermanVasc score
Age − y			
>80 (ref. 40–60)	2.94 (2.72–3.17)	1 339	11
71–80 (ref. 40–60)	1.84 (1.70–1.99)	341	6
61–70 (ref. 40–60)	1.39 (1.28–1.51)	76	3
Gangrene	1.55 (1.48–1.62)	148	4
Unspecified dementia (F03)	1.87 (1.74–2.01)	46	6
Dialysis	1.74 (1.61–1.88)	41	6
Congestive heart failure	1.37 (1.32–1.43)	38	3
Vascular dementia (F01)	2.02 (1.84–2.21)	31	7
Cancer	1.47 (1.39–1.57)	31	4
Fluid and electrolyte disorders	1.34 (1.29–1.39)	29	3
Renal failure	1.26 (1.21–1.31)	20	2
Cardiac dysrhythmias	1.23 (1.18–1.28)	17	2

* Breiman importance multiplied by 10 000.

Table 5. Cox regression model prediction for five year amputation free survival for chronic limb threatening ischaemia in 40 590 patients: hazard ratios (HR) and 95% confidence intervals (CIs) and five year risk of amputation or death in five groups ranked from "low risk" to "high risk"

5 y risk of amputation or death*	HR (95% CI)	Amputation or death after 5 y − %	Range 0–41
Low risk	Reference	25.2	0–7
Low–moderate	2.06 (1.89–2.24)	45.5	8–12
Moderate	3.06 (2.81–3.33)	59.1	13–15
Moderate–high	4.61 (4.26–4.99)	73.7	16–20
High risk	7.83 (7.24–8.48)	88.2	21–41

*c = 0.69 (95% CI 0.68–0.70).

COPART (COhorte de Patients ARTériopathes) risk score (184 patients with IC, 2002–2004, five year follow up),[22] Arruda-Olsen *et al.* (1 676 patients with PAOD, 1998–2011, five year follow up),[23] or the SMART (Second Manifestations of Arterial Disease) risk score (5 788 patients with PAOD, 1996–2010, five year follow up).[24] and van Walraven *et al.*[25] who developed a comorbidity score using a large administrative database from Canada to predict in hospital mortality (345 795 patients, 1996–2008, in hospital follow up). Ambler *et al.*[26] used logistic regression methods to highlight the impact of frailty on outcomes (413 vascular surgery patients, one year follow up). On closer consideration, these previous risk scores were partially limited by several methodological issues. They either represented only a small subset of the entire target population (e.g., patients with CLTI or IC) with 184 to 5 788 patients or predicted short and mid term outcomes only, although most events occur in the longer term. The largest prediction model included a rather non-specific inpatient population, while the risk scores were most likely context specific. Furthermore, the variable selection was frequently subject to an investigator bias and therefore not objectifiable for external evaluation. For instance, the FINNVASC and PREVENT-III scores both relied on only four variables. The current study confirmed previous findings while adding an objectifiable variable selection using data driven approaches on a large disease specific sample.

A suitable risk score predicting long term outcomes may support the choice of optimal treatment and informed consent.[27] As an example, the American College of Cardiology and American Heart Association guidelines recommend initiation of statin treatment if the risk of stroke or MI exceeds 7.5%.[28] Those risk adjusted recommendations certainly demand an evidence based risk stratification. Another central advantage of the GermanVasc risk score may be a likely better comparability of studies using administrative data. With the increasing importance of real world data in health services research, harmonisation of methods appears crucial. By using the GermanVasc score, a single metric variable can be used to adjust multivariable models for major composite endpoints.

Interestingly, age was by far the most relevant predictor of long term outcomes for both IC and CLTI patients in the current study, while some prior studies deemed age to be less relevant for outcomes in PAOD.[4] Rather, the current study results are in line with the extensive literature on biomarkers predicting mortality, where even complex models rarely perform better than age alone.[29]

Besides age, only three comorbidities (dialysis, fluid and electrolyte disorders, and cancer) were equally included both in the IC and CLTI models. The notable differences between the models for IC and CLTI underscore the need for stratified risk estimation in fundamentally different groups. In line with this, guidelines separate PAOD patients with IC and CLTI,[1,2] and most risk scores had been developed for patients with CLTI only, for example, the PREVENT-III score.[20] Recent findings on interventions, treatment patterns, and outcomes also confirmed a stratified approach by disease severity.[30,31]

This is the era of large datasets and rapid development of "big data" methods in medicine, especially in clinical predictions. However, most of the cardiovascular disease prediction models lack external validation.[32] Differences between the included target populations, the contextual validity, and marked varieties between healthcare systems must be considered. A risk score validated for a heterogeneous cohort in a certain country needs to be validated before applying to another cohort in a different country.[33] To date, the available risk scores have not been validated for the German population, and there are reports that even among European populations outcomes in vascular medicine are significantly different.[34] Besides validation, the clinical relevance of the research question should be more focused than big datasets and be easy to achieve statistical significance.[35]

Limitations

Firstly, for most of the study variables, only inpatient data were used. There was a possibility that a small population were undergoing invasive revascularisation at outpatient facilities. Unlike the USA system, the German reimbursement system thus far motivates physicians to perform revascularisations as inpatients. The coding of health care in outpatient facilities differs from that in hospitals. Hence, very few publications are available to shed light on this aspect. Secondly, there is an ongoing discussion about the advantages and limitations of health insurance claims data. Some variables require a composite of codes to approximate to the relevant risk factor (e.g., smoking). No information about certain clinical parameters, for example, ankle brachial index, body mass index, cholesterol, or further laboratory tests, is available in routinely collected administrative data. Encouragingly, owing to regular external cross validation and harsh penalties for the submission of false claims, major comorbidities and endpoints

are known to be of high internal validity. This is especially true for observations that must be reported to different institutions and authorities such as major surgery, blood transfusion, or mortality. Lastly, as with many other models, the current score lacks independent external validation. Differences between the included target populations, the contextual validity, and marked variations between healthcare systems must be considered. Prospectively collected registry data, clinical parameters, and patient reported outcomes can be used to complement and extend the risk score. External validation of the GermanVasc score will be performed according to appropriate model approaches with a hierarchical structure (clustered data) and subgroup comparisons presented elsewhere.

Future directions

The GermanVasc score will be continuously updated with new claims data and registry data collected in the future. The most recent version and an online calculator are available at https://riskscore.germanvasc.de.

The GermanVasc score developed in the current analysis may help patients and their physicians to predict individual five year AFS to support patient centred consent and treatment decision making. Patients at high risk may benefit significantly from being directed to an intensified treatment in line with demand.

Conclusion

The GermanVasc score predicts worse five year AFS stratified for inpatients suffering from IC and CLTI with good predictive accuracy. By separating low from high risk patients, the GermanVasc score may support patient centred consent.

CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.11.013.

REFERENCES

1 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019;**58**:S1–109.
2 Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
3 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* 2017;**69**:e71–126.
4 Biancari F, Salenius JP, Heikkinen M, Luther M, Ylönen K, Lepäntalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. *World J Surg* 2007;**31**:217–25.
5 Arvela E, Söderström M, Korhonen M, Halmesmäki K, Albäck A, Lepäntalo M, et al. Finnvasc score and modified Prevent III score predict long-term outcome after infrainguinal surgical and endovascular revascularization for critical limb ischemia. *J Vasc Surg* 2010;**52**:1218–25.
6 Nordanstig J, Falkenberg M. The Swedish drug-elution trials in peripheral arterial disease (swedepad) – an update halfway through the overall inclusion phase. *Eur J Vasc Endovasc Surg* 2019;**58**:e367–8.
7 Hunt BD, Popplewell MA, Davies H, Meecham L, Jarrett H, Bate G, et al. BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a randomised controlled trial. *Trials* 2017;**18**:224.
8 Menard MT, Farber A, Assmann SF, Choudhry NK, Conte MS, Creager MA, et al. Design and rationale of the best endovascular versus best surgical Therapy for patients with critical limb ischemia (BEST-CLI) trial. *J Am Heart Assoc* 2016;**5**:e003219.
9 Debus ES, Kriston L, Schwaneberg T, Hischke S, Riess HC, Harter M, et al. Rationale and methods of the IDOMENEO health outcomes of the peripheral arterial disease revascularisation study in the GermanVasc registry. *Vasa* 2018;**47**:499–505.
10 Chen-Ying H, Wei-Chen C, Po-Tsun L, Ching-Heng L, Chi-Chun L. Comparing deep neural network and other machine learning algorithms for stroke prediction in a large-scale population-based electronic medical claims database. *Annu Int Conf IEEE Eng Med Biol Soc* 2017;**2017**:3110–3.
11 Weng SF, Reps J, Kai J, Garibaldi JM, Qureshi N. Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PLoS One* 2017;**12**:e0174944.
12 Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;**36**:8–27.
13 Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;**43**:1130–9.
14 Tibshirani R. Regression shrinkage and selection via the Lasso. *J R Stat Soc Ser B (Methodological)* 1996;**58**:267–88.
15 Breiman L. Random forests. *Machine Learn* 2001;**45**:5–32.
16 Austin PC, Lee DS, D'Agostino RB, Fine JP. Developing points-based risk-scoring systems in the presence of competing risks. *Stat Med* 2016;**35**:4056–72.
17 Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat Soc* 2005;**67**:301–20.
18 Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;**162**. W1–73.
19 Ohlmeier C, Langner I, Hillebrand K, Schmedt N, Mikolajczyk R, Riedel O, et al. Mortality in the German Pharmacoepidemiological Research Database (GePaRD) compared to national data in Germany: results from a validation study. *BMC Public Health* 2015;**15**:570.
20 Schanzer A, Goodney PP, Li Y, Eslami M, Cronenwett J, Messina L, et al. Validation of the PIII CLI risk score for the prediction of amputation-free survival in patients undergoing infrainguinal autogenous vein bypass for critical limb ischemia. *J Vasc Surg* 2009;**50**:769–75.
21 Brizuela Sanz JA, González Fajardo JA, Taylor JH, Río Solá L, Muñoz Moreno MF, Vaquero Puerta C. Design of a new risk score in critical limb ischaemia: the ERICVA model. *Eur J Vasc Endovasc Surg* 2016;**51**:90–9.
22 Hackl G, Jud P, Avian A, Gary T, Deutschmann H, Seinost G, et al. COPART risk score, endothelial dysfunction, and arterial

hypertension are independent risk factors for mortality in claudicants. *Eur J Vasc Endovasc Surg* 2016;**52**:211–7.
23 Arruda-Olson AM, Afzal N, Priya Mallipeddi V, Said A, Moussa Pacha H, Moon S, et al. Leveraging the electronic health record to create an automated real-time prognostic tool for peripheral arterial disease. *J Am Heart Assoc* 2018;**7**:e009680.
24 Dorresteijn JA, Visseren FL, Wassink AM, Gondrie MJ, Steyerberg EW, Ridker PM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart* 2013;**99**:866–72.
25 van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009;**47**:626–33.
26 Ambler GK, Brooks DE, Al Zuhir N, Ali A, Gohel MS, Hayes PD, et al. Effect of frailty on short- and mid-term outcomes in vascular surgical patients. *Br J Surg* 2015;**102**:638–45.
27 Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;**290**:2581–7.
28 Goff Jr DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American heart association task force on practice guidelines. *Circulation* 2014;**129**:S49–73.
29 Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *J Gerontol A Biol Sci Med Sci* 2013;**68**:667–74.
30 Secemsky EA, Kundi H, Weinberg I, Jaff MR, Krawisz A, Parikh SA, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol* 2019;**4**:332–40.
31 Peters F, Kreutzburg T, Rieß HC, Heidemann F, Marschall U, L'Hoest H, et al. Optimal pharmacological treatment of symptomatic peripheral arterial occlusive disease and evidence of female patient disadvantage: an analysis of health insurance claims data. *Eur J Vasc Endovasc Surg* 2020;**60**:P421–9.
32 Damen JAAG, Hooft L, Schuit E, Debray TPA, Collins GS, Tzoulaki I, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ* 2016;**353**:i2416.
33 Kriston L. Machine learning's feet of clay. *J Eval Clin Pract* 2020;**26**:373–5.
34 Beck AW, Sedrakyan A, Mao J, Venermo M, Faizer R, Debus S, et al. Variations in abdominal aortic aneurysm care: a report from the International Consortium of Vascular Registries. *Circulation* 2016;**134**:1948–58.
35 Steyerberg EW, Harrell Jr FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016;**69**:245–7.

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COUP D'OEIL

Phlebosclerotic Colitis

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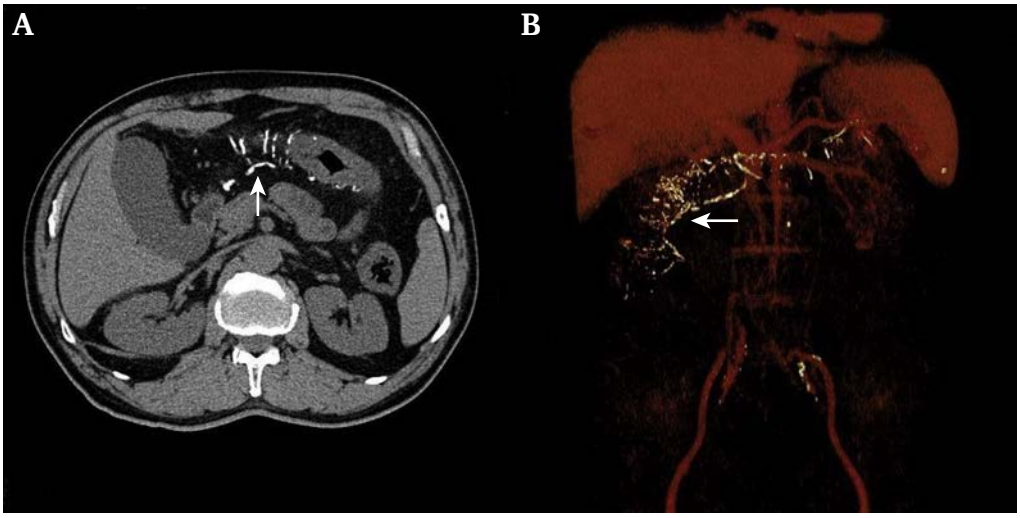

Phlebosclerotic colitis (PC) is a rare condition which impairs colonic venous return due to sclerosis and fibrosis of mesenteric veins, mostly observed in Asians. It may result in chronic ischemia, intestinal obstruction, and even perforation. A 64 year old male came complaining of abdominal pain and diarrhoea. He denied long term use of Chinese herbs. Physical examination showed diffuse tenderness without marked rebound tenderness. He underwent computed tomography angiography which revealed typical findings of PC: wall thickening and linear venous calcification of the ascending and transverse colon (A, B; arrows) Conservative treatment was initiated using alprostadil and low molecular weight heparin and his symptoms relieved remarkably.

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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☆

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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

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

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.[1] 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

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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).[2] 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.[3]

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). 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

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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.[4] 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.[5] 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.[6] 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.[7] 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

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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).	*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. (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)	*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. (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 section 3.1.1.2).
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)	*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. (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 section 3.1.1.2).
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)	*Recommendation 5:* 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 section 3.1.3.1)
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)	*Recommendation 5:* 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 section 3.1.3.1)

Continued

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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)	*Recommendation 5:* 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 section 3.1.3.1)
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)	*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. (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)	*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 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 *et al. Circulation* 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).	*Recommendation 22:* For patients with lower limb peripheral arterial disease who smoke, councelling as part of intensive smoking cessation intervention is recommended. (I, B) *Recommendation 23:* For patients with lower limb periperal 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 chapter 4.1.1.1)
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.	*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 $\geq$ 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.

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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.	*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. (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)	*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. (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	Recommendation 5.5 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)	*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. (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 chapter 6.4).
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	Recommendation 5.6 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)	*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. (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 chapter 6.4).

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)	*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. (III, C)	We have also considered the meta-analysis of Koeckerling *et al.*, demonstrating lack of long term target lesion revascularisation benefits from primary stenting compared with balloon angioplasty (see chapter 6.4).
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)	*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. (IIa, B)	We have considered the recent meta-analysis of Koeckerling *et al.* 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 chapter 6.4).
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication	2015	Recommendation 5.18 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)	*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. (IIa, B)	We have considered the recent meta-analysis of Koeckerling *et al.* 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 chapter 6.4).

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 subtilsin-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-

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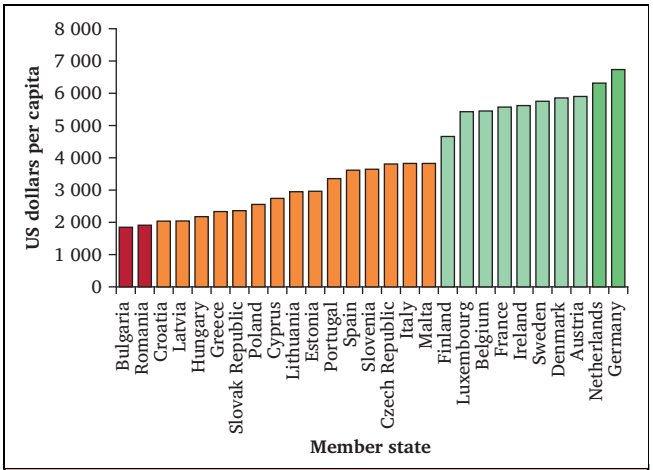

Figure 1. Overall health spending in total (i.e., not only for peripheral artery disease [PAD]) by the government, compulsory and voluntary in US dollars per capita for 2020 or latest available. Data provided by the Organisation for Economic Co-operation and Development (OECD). Missing European countries are explained by the lack of easily accessible data from OECD. Red = total health spendings below 2 000 US dollars/capita; orange = total health spendings between 2 000 and 4 000 US dollars/capita; light green = total healthcare spendings between 4 000 and 6 000 US dollars/capita; dark green = total health spendings above 6 000 US dollars/year.

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.[8,9] 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.[10–12] The risk of post-operative surgical site infections after open vascular surgical procedures in the groin is substantial;[13,14] and the risk of suffering such complications may be predicted in the pre-operative setting.[15]

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.[16] 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.[17] 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.[16,18–21] 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.[22]

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.[23] 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]),[24–27] 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 aorto-iliac interventions over, at best, reasonable primary

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patency rates for contemporary femoropopliteal interventions, to substantially poorer results when isolated infrapopliteal lesions are treated for IC indications.[28–32]

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 *et al.* (2018)[18] Kumakura *et al.* (2017)[16] Djerf *et al.* (2020)[19]	

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.[33–35] 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.[35–37]

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^3-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).[38] 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.[39,40]

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

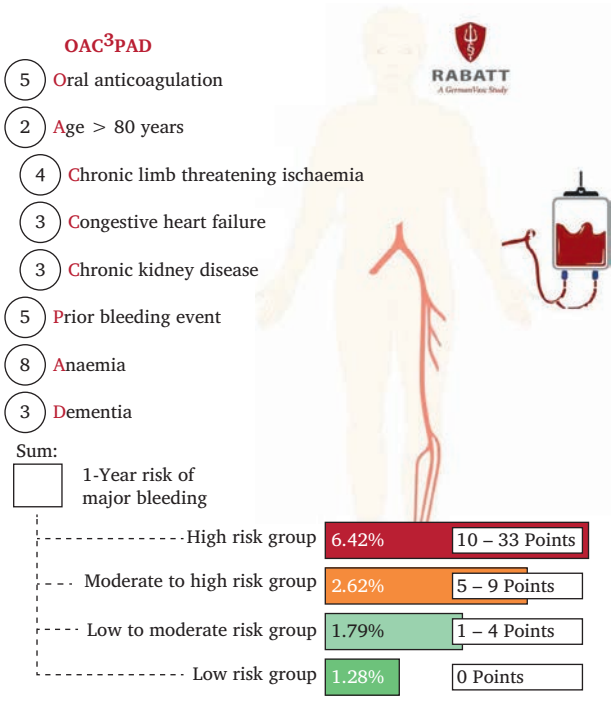

Figure 2. Summary sheet for the OAC^3-PAD bleeding risk score including the four risk groups: low; low to moderate; moderate to high; and high risk. The numbers before the risk factors are the point scores to be added together, if present, to calculate the sum score. Oral anticoagulation: prior use of direct thrombin inhibitors, vitamin K antagonists or direct factor Xa inhibitors. Chronic limb threatening ischaemia: peripheral artery disease at Fontaine stage III (ischaemic rest pain) and IV (ischaemic ulcer or gangrene). Prior bleeding event: transfusion during index hospitalisation or a prior diagnosis of coagulopathy or a prior primary diagnosis of major bleeding. Anaemia: presence of blood loss anaemia or deficiency anaemia or anti-anaemic medication. Dementia: presence of vascular or unspecified dementia or anti-dementia medication.

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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.[41]

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.[42] 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.[43,44]

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,[45–47] whereas a higher frequency of statin associated muscle symptoms has been reported under statin treatment in observational studies.[48] 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).[49] 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).[50] This discrepancy may be due to a selection of healthier patients in RCTs but may also be explained by nocebo effects in non-blinded studies as well as recall and other bias in observational studies[51]. 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.[52] 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.[53] 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,[54] 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.[55] 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.[56–58] 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

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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.[59–62] 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.[63] 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.[64] 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.[64–66] 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%.[67] 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.[68] 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.[69,70] 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.[71] 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.[67]

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

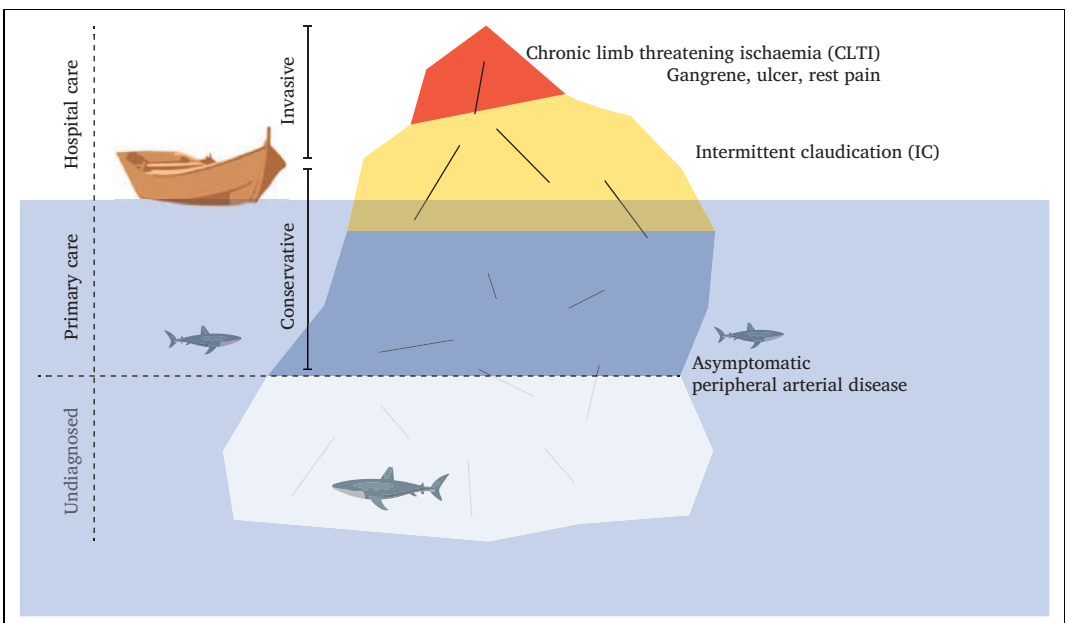

Figure 3. Schematic illustration of the lower limb peripheral arterial disease (PAD) iceberg epidemiology, indirectly illustrating the real challenges associated with reaching out to the entire patient population with any healthcare intervention. (Modified after Søgaard et al. Vasa. 2023;52:77-80.[72])

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highest or lowest recorded ankle blood pressure.[73] 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.[74]

Previous studies on PAD incidence have shown considerably varying incidence rates (3.8 to 23.0 per 1 000 person years).[75,76] 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.[77] 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.[78] 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.[79]

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.[80–82] 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.[64,65] 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.[71] 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 subpopulation 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.[83] 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).[84] 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%.[68] 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%).[85] 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.[86–88] 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.[85,89]

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.[90,91] Similar results were found in the Edinburgh Artery Study; 9.5% deteriorated within five years.[92] Mohler *et al.* prospectively followed a small sample of asymptomatic PAD patients over one year

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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.[88]

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).[93] 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.[94—96]

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.[97] 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.[16]

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,[94,98,99] while the mortality rate for post myocardial infarction patients was 13% at six years.[100] While mortality from heart disease has fallen over the past two decades, this is not the case with PAD[101] for a number of reasons, including late presentation with higher atheroma burden, underdiagnosis, and undertreatment.[94,101—104]

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.[105] 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.

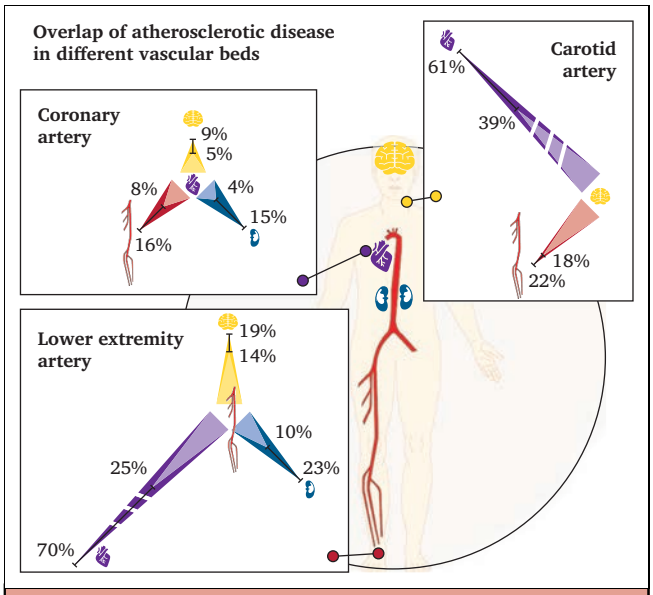

Figure 4. Reported rate range of other localisations of atherosclerosis in patients with a specific atherosclerotic disease. Percentages and lines represent reported ranges of engagement of additional vascular beds for the three common index atherosclerotic disease beds (yellow: carotid artery disease; red: lower extremity peripheral arterial disease; blue; chronic kidney disease; purple: coronary artery disease). For example, between 14% and 19% of patients with lower extremity peripheral arterial disease have concomitant carotid artery disease. The bars (in black) represent the ranges.[106—114]

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.[115—117] Patients with PAD exhibit more extensive, calcified, and progressive coronary atherosclerosis.[118] 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.[119,120] 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).[121] 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).[117] Concomitant PAD (clinical or subclinical) is also associated with a worse outcome in patients undergoing coronary revascularisation.[122,123]

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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.[124] 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.[125]

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.[126,127] 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%, $p = .010$).[127] 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.[128] 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),[108,129] 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.[107,130] 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.[107,131,132]

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^2, 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^2 and 2.06 (95% CI 1.70 — 2.48) at an eGFR of 15 mL/min per 1.73m^2. 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.[133]

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.[82,134–136] The diagnosis of PAD should focus on the past medical history including an accurate assessment of the patient's walking ability.[81] 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.[81] 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.[137,138] 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.[67,139] In one study of patients with an ABI < 0.9, 19% were asymptomatic, 49% had atypical symptoms, and 32% had typical IC symptoms.[139] 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.[140,141]

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.[142] 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.[143] Another potential explanation for lack of symptoms in asymptomatic PAD is that some patients may decrease their walking speed to avoid exertional leg symptoms.[144]

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People with asymptomatic PAD also have greater functional impairment and faster functional decline than people without PAD.[145,146] 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.[143,144]

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.[147] 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.[148] 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.[149]

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.[150] 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.[151] 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.[152] 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; $p = .060$).[153] 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.[154] 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.[154] A recent systematic review of PAD screening identified several major guidelines.[155—163] 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.[155]

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.[164] 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;

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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).[165,166] 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 *et al.* (2018)[150] Alahdab *et al.* (2015)[167] Andras *et al.* (2014)[147] Lindholt *et al.* (2022)[153]	

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 *et al.* (2017)[151] Shah *et al.* (2017)[154] Matsushita *et al.* (2017)[145] Sartipy *et al.* (2018)[94] Lindholt *et al.* (2022)[153]	

* 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.[168–171]

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 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.[172] 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.[173] Any palpable pulse abnormality (absence or reduction) should raise a suspicion of PAD.[174] 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.[173] Palpation of foot pulses may also be particularly difficult in the presence of significant foot oedema.

Table 4. Classical symptoms of intermittent claudication, modified from Rose.[81]

Exertional leg pain that:
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

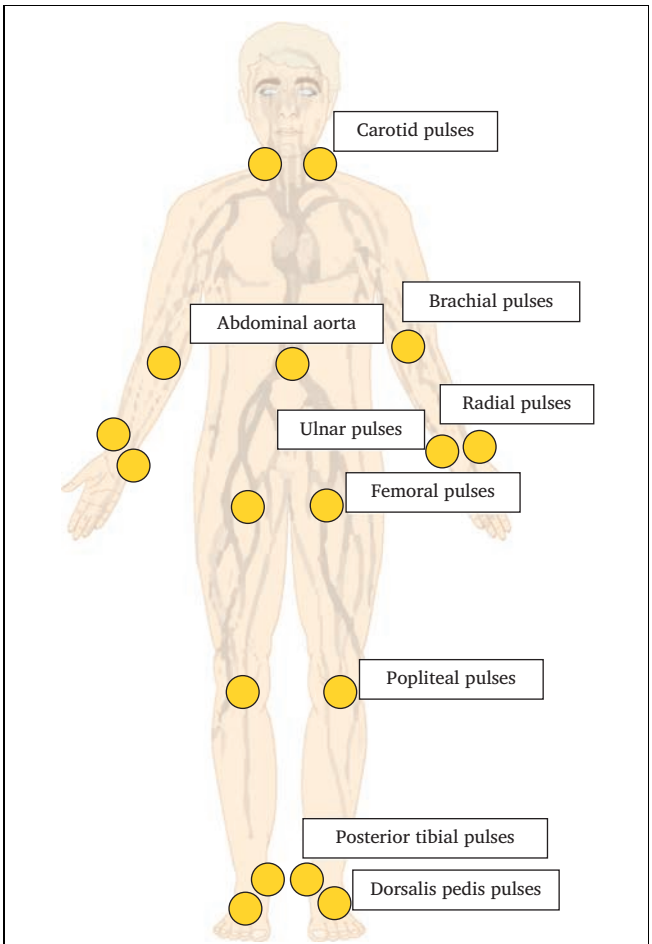

Figure 5. Pulse examination of patients with lower extremity peripheral arterial disease.

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).[174—177]

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[81] 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.[178] The Edinburgh Claudication Questionnaire included a lower extremity diagram, which enabled individuals to indicate the location of the pain directly on the diagram.[71]

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.[142,179] 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.[180] 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.[174,181]

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,[63,182,183] with an acceptable intertester and intratester reliability on average of 10%.[184] 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.[63] 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.[185—191]

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.[95,192] A similar association is shown for abnormally high ABI.[193—195] 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.[93,196]

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.[6,56,165,179,197,198] 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.[74,199—201] More subjects at risk will be identified using the lower ankle blood pressure for ABI calculation and hence should be preferred for risk stratification.[199,201—203] 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 *et al.* (2012)[63] Xu *et al.* (2013)[60] Donohue *et al.* (2020)[204] Weragoda *et al.* (2016)[205] Crawford *et al.* (2016)[206]	

Recommendation 6

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

Class	Level	References	ToE
I	C	Aboyans *et al.* (2012)[63] Weragoda *et al.* (2016)[205]	

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 *et al.* (2006)[199] Schroder *et al.* (2006)[200] Klein *et al.* (2006)[207]	

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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 *et al.* (2006)[199] Le Bivic *et al.* (2019)[202] O'Hare *et al.* (2006)[203] Espinola-Klein *et al.* (2008)[201] Pereira Fihlo *et al.* (2022)[208]	

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.[209] 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.[210] Absolute pressures of lower than 30 mmHg are diagnostic of severe ischaemia.[211,212] The intra- and interobserver reproducibility is excellent for both TP and TBI (intraclass correlation coefficient 0.85 — 0.99).[213] 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.[191,214,215] Thus, the main advantage may be the higher sensitivity for diagnosing PAD in challenging populations

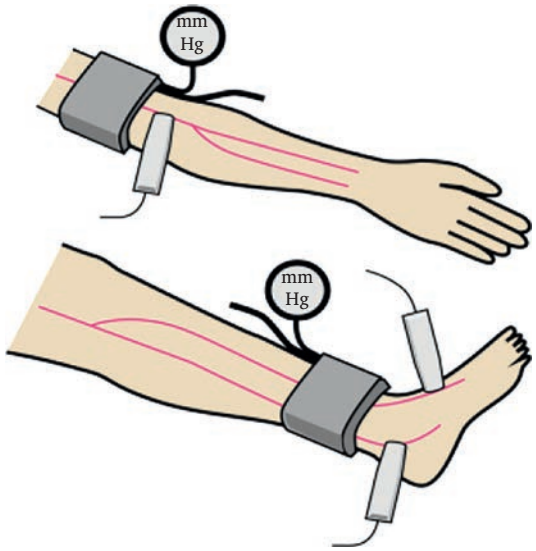

Figure 6. Measurement of the ankle brachial index (ABI): The measurement is made in the supine position and by using a manual blood pressure cuff and a pen Doppler. The cuff is placed distally at ankle level. Flow signal is identified with a pen Doppler held over the posterior tibial and dorsalis pedis 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.[189] This is of particular importance as low TPs are also associated with higher rates of cardiovascular mortality[216] 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.[216]

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 *et al.* (2020)[214] Laivuori *et al.* (2021)[216]	

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 *et al.* (2021)[216]	

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.[63,217] 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%).[218] 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.[218—220] 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 *et al.* (1991)[220] Birkett *et al.* (2021)[218] Hoogeveen *et al.* (2008)[217]	

* A post exercise ABI drop of ≥ 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 *et al.* (2009)[219] Gardner *et al.* (1991)[220]	

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Table 6. Overview of the measurement conditions, calculation, interpretation, and target populations for the ankle brachial index measurement	
Measurement	An ABI measurement requires a continuous wave Doppler probe, 8 − 10MHz, ultrasound transmission gel and a blood pressure cuff with a width ≥ 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 ≥ 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.
	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.
Calculation	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 ≤ 0.90 is the threshold for confirming the diagnosis of PAD.
	A post-exercise ABI drop of ≥ 20% or ankle pressure decrease > 30 mmHg confirms the PAD diagnosis.
	ABI ≤ 0.90 or ≥ 1.40 is associated with increased risk of CV events and death.
	If ABI ≥ 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.[221] 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.[222] 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.[223–225] Importantly, the observed maximum walking distances of corridor based walking tests and treadmill walking tests are not interchangeable measures of walking endurance.[223] For the 6MWT a very good test–retest reliability among IC patients was shown by Sandberg *et al.*[226] 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 *et al.* (2008)[224] McDermott *et al.* (2014)[221] Nordanstig *et al.* (2014)[227] McDermott *et al.* (2020)[223]	

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.

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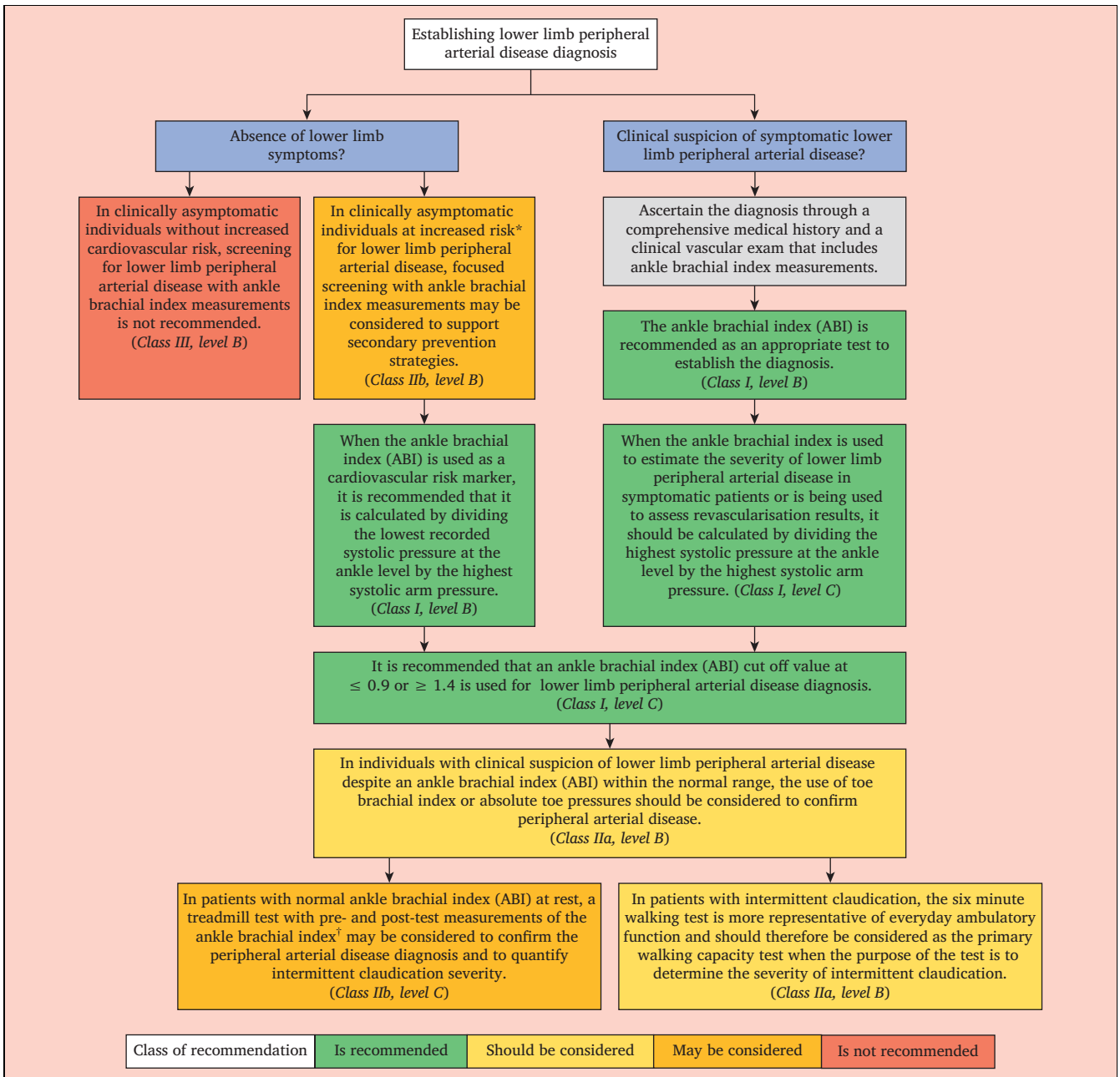

Figure 7. Flow chart describing the principal steps to establish the lower limb peripheral arterial disease (PAD) diagnosis. *Individuals 65 years or older; individuals aged 50 to 64 years with risk factors for atherosclerosis (diabetes, history of smoking, dyslipidaemia, hypertension, chronic kidney 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. †A post-exercise ABI drop of ≥ 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.[228,229] 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).[228] 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.[228] Therefore, duplex ultrasound may be used as a first modality after non-invasive bedside tests to evaluate the vascular tree for abnormalities.[229] Advantages of DUS are its non-invasive character, the absence of radiation,

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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.[228]

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.[228,230–233] Accuracy may vary slightly below and above the knee; however, these differences are neither clinically nor statistically significant.[228,232] 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^2 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.[234–236]

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.[228,230,237–239] Accuracy may vary slightly below and above the knee; however, these differences are neither clinically nor statistically significant.[228,238] 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,[230] 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.[240] A rare complication described is gadolinium induced nephrogenic systemic fibrosis,[241] although this risk seems to be minimised by using a group II gadolinium based contrast (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol).[242]

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.[243]

3.1.3.5.4. Digital subtraction angiography. Digital subtraction angiography used to be the gold standard[244–246] 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_2 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_2 angiography, including limb pain and nausea or vomiting.[247]

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.

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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 *et al.* (2013)[230] Menke *et al.* (2010)[237] Met *et al.* (2009)[231] Heijenbrok-Kal *et al.* (2007)[232] Collins *et al.* (2007)[228] Sun *et al.* (2006)[233] Koelemay *et al.* (2001)[238] Nelemans *et al.* (2000)[239] Visser *et al.* (2000)[229] Verma *et al.* (2022)[248]	

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 ($tcpO_2$, laser Doppler flowmetry, indocyanine green fluorescence angiography).[249–254] Skin perfusion assessments are advantageous mainly in CLTI patients and in wound healing disorders.[255] 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.[256–259] However, $tcpO_2$ measurement can also be used after exercise to detect buttock claudication.[260] Additionally, some studies have published thresholds for diagnosis of PAD in patients with diabetes ($< 50 - 60$ mmHg).[261] Promising methods such as multispectral opto-acoustic tomography which directly addresses muscle perfusion and therefore effectively investigate the end organ in intermittent claudication transcutaneously, are currently under evaluation (ClinicalTrials.gov Identifier: NCT04641091), as are different deep tissue perfusion MRI protocols.[259,262]

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.[59] 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.[263,264] 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).[265] 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).[266] 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.[179] 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).[267] 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 ≥ 200 m	I	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
	IIB: Claudication at a distance < 200 m		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 infrapopliteal TASC II grading.[268] 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.[269]

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.[270]

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).[271]

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.[272,273] 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.[274] 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.[275] 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 VascuQoL-6 survey and 12 optional items to be collected by trials and registries on IC treatment.[4]

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TASC A lesions
- Unilateral or bilateral CIA stenoses
- Unilateral or bilateral single short (≤ 3 cm) EIA stenosis

TASC B lesions
- Short (≤ 3 cm) stenosis of the infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totalling 3 to 10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of the internal iliac or CFA

TASC C lesions
- Bilateral CIA occlusions
- Bilateral EIA stenoses 3 to 10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion involving the origins of the internal iliac and or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of the origins of the internal iliac and or CFA

TASC D lesions
- Infrarenal aorto-iliac occlusion
- Diffuse disease involving the aorta and both iliac arteries
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral EIA occlusions
- Iliac stenoses in patients with AAA not amenable to endograft placement

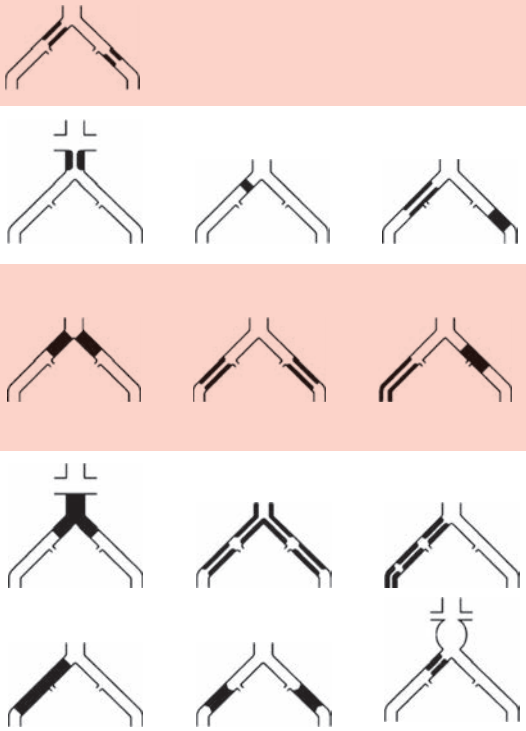

Figure 8. Overview of the Trans-Atlantic Inter-Society Consensus anatomical classification of lower limb peripheral artery disease lesion severities in aortoiliac segment.

TASC A lesions
- Single stenosis ≤ 10 cm in length
- Single occlusion ≤ 5 cm in length

TASC B lesions
- Multiple lesions (stenoses or occlusions), each ≤ 5 cm
- Single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery
- Heavily calcified occlusion ≤ 5 cm in length
- Single popliteal stenosis

TASC C lesions
- Multiple stenoses or occlusions totalling > 15 cm with or without heavy alcification
- Recurrent stenoses or occlusions after failing treatment

TASC D lesions
- Chronic total occlusions of CFA or SFA (> 20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

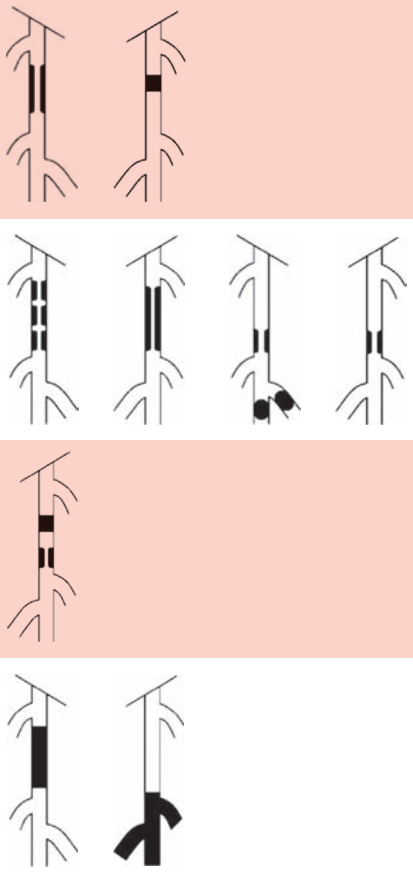

Figure 9. Overview of the Trans-Atlantic Inter-Society Consensus anatomical classification of lower limb peripheral artery disease lesion severities in femoropopliteal segment.

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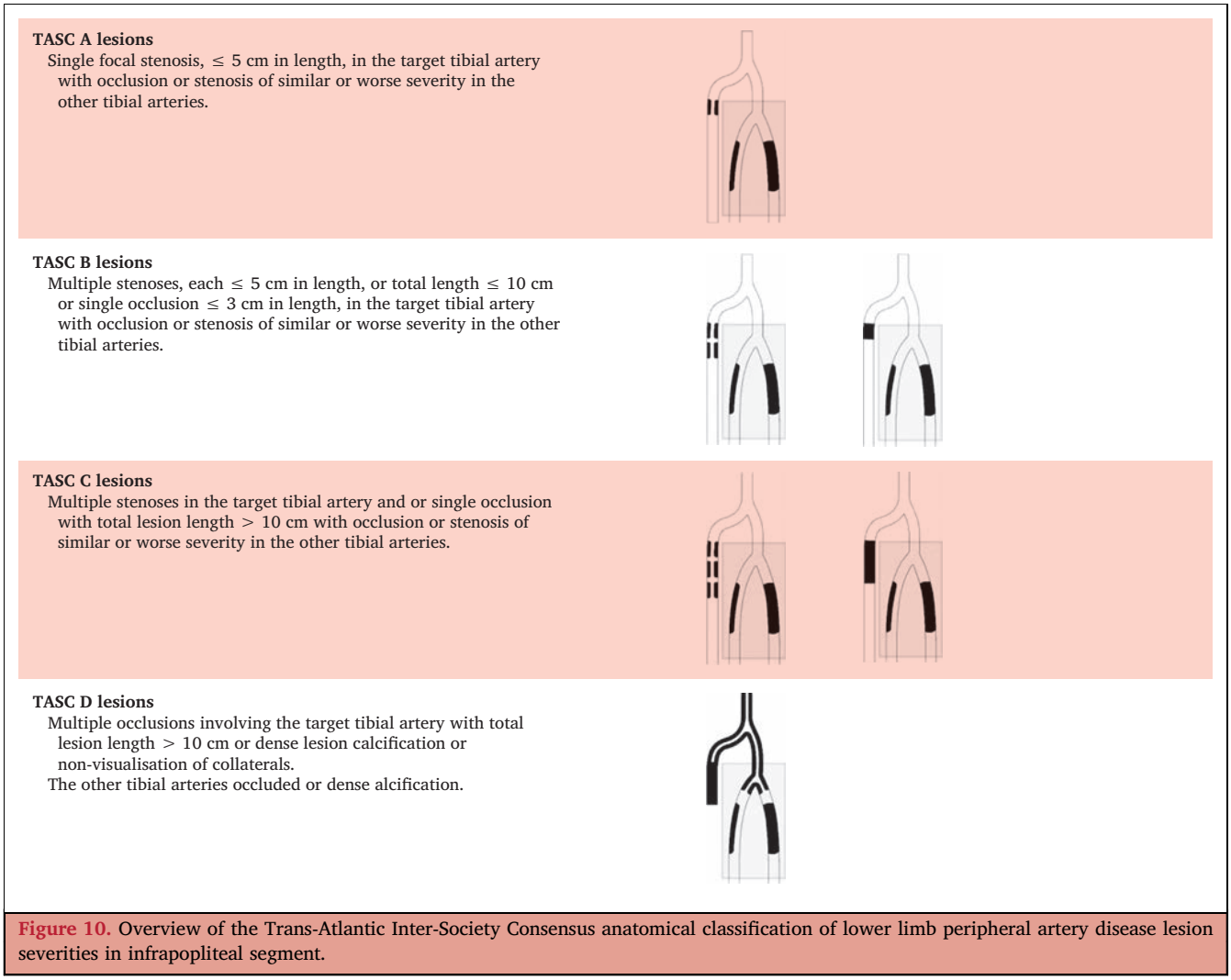

Figure 10. Overview of the Trans-Atlantic Inter-Society Consensus anatomical classification of lower limb peripheral artery disease lesion severities in infrapopliteal segment.

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.[276] 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.[277,278] 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).[277,279,280] 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.[278] 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 *et al.* (2016)[277] Mays *et al.* (2011)[276] Conijn *et al.* (2015)[278]	

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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 *et al.* (2014)[227] Kumlien *et al.* (2017)[279] Arndt *et al.* (2022)[4]	

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.[281] A direct association between inflammatory biomarkers and the development or progression of lower extremity atherosclerosis has not yet been established, however.[281] Increasing CRP levels have been associated with a higher risk of developing PAD[282,283] and greater ABI declines during follow up.[283] Elevated levels of inflammatory biomarkers are also associated with greater functional impairment and faster functional decline in people with PAD.[284–293]

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.[294] 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.[295,296]

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.[297]

Different markers of lipoprotein metabolism are also potentially useful biomarkers in PAD settings. In a prespecified 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.[298] Golledge *et al.* noted similar observations in a prospective observational study of 1 472 individuals with vascular disease.[299,300] In the CAVASIC study, Kheirkhah *et al.* reported higher PCSK-9 levels among male patients with intermittent claudication than controls without.[300] Finally, the levels of lipoprotein (a) (Lp[a]) have also been demonstrated to correlate with the angiographic severity of femoropopliteal lesions.[301]

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.[302]

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.[303] 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.[304] 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.[305] Patients with PAD who manage to successfully stop smoking enjoy improved outcomes,[306,307] 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.[308] 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%, $p = .023$).[309] 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

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use, advise them to stop smoking, and should provide behavioural interventions and approved pharmacotherapy for smoking cessation.[310] 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.[311] 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.[312,313] 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,[314] 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.[315–317]

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.[318] Bupropion is approved for a 12 week course, but treatment for 12 months reduces the relapse rate.[319] Combination therapy with nicotine patches and bupropion is more effective than either therapy alone.[320] Bupropion has also been studied in combination with varenicline, showing substantially more smoking cessation in the first few months.[321]

Varenicline is a partial agonist of α-4 and β-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.[322,323] 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 *et al.* (1996)[324] Canga *et al.* (2000)[325] Weissfeld *et al.* (1991)[326] Bock *et al.* (2013)[327] Smith *et al.* (2013)[328] Carson-Chahhoud *et al.* (2020)[329]	

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	Hennrikus *et al.* (2010)[330]	

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 *et al.* (2018)[322] Anthenelli *et al.* (2016)[323]	

Many long time smokers with PAD initiate a quit attempt but the long term effectiveness is not fully evaluated.[330,331] 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.[311] The European guidelines on prevention summarise stop smoking into five As: ask, assess, advise, assist, and lastly, arrange a schedule of follow up visits.[332]

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

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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.[333–337] Dietary changes may be performed by education, diet assessment, self monitoring, motivation, and encouragement.[338–340] 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^2. An increased CV risk is proven at BMI $>$ 30.0 kg/m^2.[332] 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.[341] In a three armed, multicentre, 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.[342]

Both metabolic syndrome and diabetes are linked to the occurrence of asymptomatic PAD[67] 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.[343] 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
IIa	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
IIa	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,[344] is known to be associated with reduced physical function and adverse outcomes in the elderly.[345,346] 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.[37]

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,[347] there is no direct evidence for asymptomatic PAD patients from clinical trials stratified for this dedicated patient subgroup.[348,349] Elevated low density lipoprotein (LDL) cholesterol values are, however, an important risk factor for the development and progression of cardiovascular disease.[350,351] 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.[352] 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).[352,353]

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.[353,354] The addition of ezetimibe to simvastatin also provided additional benefit in a trial with $>$ 18 000 high risk patients treated for acute coronary syndrome

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(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.[355,356]

Several large trials have suggested that PCSK9 inhibitors (evolocumab, alirocumab) may further reduce the risk of cardiovascular events when given in addition to statins.[357–359] 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.[359] Besides the fact that these benefits were revealed from a prespecified 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.[360] 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 *et al.* (2015)[361] Heart Protection Study Collaborative Group (2007)[362] Aung *et al.* (2007)[35] Kumbhani *et al.* (2014)[363] Mohler *et al.* (2003)[33] Peters *et al.* (2020)[364] Ramos *et al.* (2016)[365] Vogel *et al.* (2013)[366] Mills *et al.* (2011)[367] Rodriguez *et al.* (2017)[368] De Martino *et al.* (2014)[369] Cholesterol Treatment Trialists Collaborators (2005)[370] Cholesterol Treatment Trialists Collaborators (2015)[371]	

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 *et al.* (2019)[42] Leya *et al.* (2017)[372]	

* 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 *et al.* (2020)[373] Pastori *et al.* (2020)[36] Peters *et al.* (2020)[364] Sigvant *et al.* (2009)[374]	

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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 *et al.* (2020)[352] Cannon *et al.* (2015)[356] Cholesterol Treatment Trialists Collaborators (2015)[371] Sabatine *et al.* (2017)[358] Belch *et al.* (2021)[375]	

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 *et al.* (2015)[356]	

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 subtilsin-kexin type 9 inhibitors is not recommended as first line therapy.

Class	Level	Reference
III	C	Consensus

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

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 *et al.* (2020)[392] Visseren *et al.* (2021)[397] Williams *et al.* (2019)[398] Lewington *et al.* (2002)[384]	

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 *et al.* (2021)[397] Unger *et al.* (2020)[392] Yusuf *et al.* (2008)[382] Ostergren *et al.* (2004)[378] Heart Outcomes Prevention Evaluation Study Investigators (2000)[381]	

* 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.

4.1.2.3. Antihypertensive agents. Hypertension is associated with the development and progression of atherosclerosis as well as with unfavourable long term outcomes.[376–384] In line with observations regarding lipid lowering drugs, international data suggest that the prescription rates for antihypertensive medication are considerably lower than recommended.[385,386] In addition to lifestyle advice including decreased sedentary behaviour and nutritional habits which can reduce the cardiovascular risk and prevalence of hypertension,[387–390] pharmacotherapy should be initiated in accordance with multisocietal guidelines on the management of hypertension.[391,392]

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.[392,393] 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

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.[399]

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.[400,401] 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.[402]

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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.[403–405] Hence, they are recommended for use in diabetic patients with cardiovascular diseases, chronic kidney disease, and heart failure.[332,400,401]

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 SGTL-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).[406] 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.[407] 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.[408] 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.[409] 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[410] and dapagliflozin via the DECLARE-TIMI 58 trial[408] 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.[411] 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.[411] Similar effects were observed in subsequent trials such as EMPEROR.[412]

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 ≤ 7% (≤ 53 mmol/mol) to prevent vascular complications.

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

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 *et al.* (2020)[400] American Diabetes Association (2021)[401] Visseren *et al.* (2021)[397]	

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.[417] In a retrospective observational study by Peters *et al.*,[418] 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.[418] Two randomised trials on acute coronary syndrome patients determined the impact of vaccination on long term outcomes. Gurfinkel *et al.*[419] enrolled 200 patients and revealed that the incidence of the primary endpoint cardiovascular death at one year was substantially lower among patients receiving vaccination.[419] Ciszewski *et al.*[420] found that in optimally treated coronary artery disease patients influenza vaccination improved the clinical course and reduced the frequency of coronary ischaemic events.[420]

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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 *et al.* (2021)[418] Ciszewski *et al.* (2008)[420] Gurfinkel *et al.* (2004)[419]	

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.[421] Therefore, it is important to attach a high priority to vaccination against COVID-19 infection in all PAD patients.[422]

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 *et al.* (2022)[421]	

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.[423] Asymptomatic PAD confers a long subclinical phase easily detected by ABI measurements or femoral artery plaque burden assessment using duplex ultrasound.[6,352] 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.[92,94,96,424,425] 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.[62,63,66,150,196,426]

5.2. Physical activity

Although individuals with asymptomatic PAD report no exertional leg symptoms, they commonly have impaired lower extremity functioning.[144,427,428] 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.[144] 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.[144] In another study, asymptomatic PAD was associated with a greater mean annual decline in 6MWD, compared with individuals without PAD.[428]

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.[429] 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 online sedentary reduction programme, including behavioural medicine strategies and an activity tracker or to active control (the active control group received six different online 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.[430] 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.[431] 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.*,[432] 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

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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.[433] 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,[434] striving to reach the general physical activity recommendations for cardiovascular disease prevention,[435] 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.[435]

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 *et al.* (2019)[436] Powell *et al.* (2018)[437]	

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 *et al.* (2004)[429] Laslovich *et al.* (2020)[430] Farhad *et al.* (2019)[431] McDermott *et al.* (2009)[432] McDermott *et al.* (2013)[433]	

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.[438] 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.[439]

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.[440]

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 *et al.* (2008)[441] Fowkes *et al.* (2010)[439] Ambler *et al.* (2020)[440]	

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 2×2 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

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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.[378] 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.[362] 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.[6]

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.[442] 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.[434] 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.[434] 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 ≤ 0.9 or ≥ 1.4 a risk enhancing factor for a cardiovascular event and for an increased all cause mortality.

Class	Level	References	ToE
I	A	Fowkes *et al.* (2006)[110] Hajibandeh *et al.* (2017)[95] Heald *et al.* (2006)[443] Qu *et al.* (2015)[444] Pereira Filho *et al.* (2022)[208] Sigvant *et al.* (2016)[87]	

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.[6,445] 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).[446] 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

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primary revascularisation strategy led to higher HRQoL and walking distances[447,448] whereas these observed differences were lost at the five year follow up.[449] 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.[450] Comparable results in favour of SET as a first line of therapy were observed by others, with varying costs per QALY.[451–457]

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.[458] 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.[459] A stepwise care approach has been studied to a greater extent in the Netherlands, where SET is organised in a community based setting.[460] 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.[461]

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).

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 *et al.* (2021)[454] Hageman *et al.* (2017)[455] Van den Houten *et al.* (2016)[453] Reynolds *et al.* (2014)[450] Fokkenrood *et al.* (2014)[452] Mazari *et al.* (2013)[462] Spronk *et al.* (2008)[463] Treesak *et al.* (2004)[456] De Vries *et al.* (2002)[457]	

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.[464–466]

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.[467–473] 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.[464]

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.*[468] and Fakhry *et al.*,[474] SET resulted in a mean improvement in maximum and pain free walking distance, compared with usual medical care. Vemulapalli *et al.*[471] 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.*[472] 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.[472] 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.[475] Overall, the risk—benefit ratio for SET in IC is favourable with extremely low cardiovascular complication rates.[476]

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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 *et al.* (2013)[477] Hageman *et al.* (2018)[470] Parmenter *et al.* (2015)[468] Vemulapalli *et al.* (2015)[471] Gommans *et al.* (2014)[478] Fakhry *et al.* (2012)[474] Pymer *et al.* (2021)[475]	

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 *et al.* (2019)[482] Pymer *et al.* (2021)[475]	

Although SET provides benefit for patients with IC, it remains underused.[479–481] 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.[479] 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.[470] 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.[482] The most recent meta-analysis concluded that HBET was inferior to SET.[475] 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.[223]

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.[483] 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.[464] As exercise related pain is considered one potential reason for poor exercise adherence,[484] 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.[485] 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.[486]

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

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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.[487] 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.[488] 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
IIa	A	Jansen *et al.* (2020)[483]	

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.[479–481] 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.[489] 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.[481] 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.[479–481] Patient adherence to SET programmes are reported to be generally low.[490,491] 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.[492] The national integrated care network (ClaudicatioNet) 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.[493] 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.[494] 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.[494,495] Helping patients transition to long term maintenance of unsupervised exercise once SET is completed is a requisite to maintain and further improve exercise outcomes.[494]

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.[495] However, patients with PAD are currently referred to CR in only a minority of cases and often when associated with other cardiovascular conditions.[496] A recently published European position paper showed that 34% of the SET programmes are PAD dedicated, while 23% are part of a CR programme.[489]

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.[497] Several cohort studies have shown that CR attendance is associated with a similar reduction in mortality[498] and physical fitness[498–500] for patients with and without PAD. Stauber *et al.*[501] 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
IIb	B	Siercke *et al.* (2021)[497]	

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

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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.[502–509] The added benefit of SET in combination with revascularisation has been consistently shown after both open and endovascular IC treatment procedures.[506] Moreover, to offer such combination therapy reduces the number of secondary revascularisation procedures compared with revascularisation as a standalone treatment of limb symptoms.[507] 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.[503,508,510,511] 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.[512]

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 *et al.* (2019)[513] Klaphake *et al.* (2018)[503] Meneses *et al.* (2017)[504] Aherne *et al.* (2015)[506] Fakhry *et al.* (2018)[507] Doshi *et al.* (2021)[508] Bø *et al.* (2013)[514] Fakhry *et al.* (2015)[511] Thanigaimani *et al.* (2021)[512] Kruidenier *et al.* (2011)[515]	

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.[516]

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.[517]

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.[518,519]

McDermott *et al.*[433] 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.*[520] 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.[520] In another systematic review and meta-analysis on the efficacy of cilostazol, naftidrofuryl oxalate, and pentoxifylline for treatment of intermittent claudication, Stevens *et al.*[521] 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.[521] Bedenis *et al.*[522] and Brown *et al.*[523] 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.[522,523] In an updated Cochrane review on the

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effect of pentoxifylline for intermittent claudication by Salhiyyah *et al.*,[524,525] 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 *et al.* (2014)[522] Stevens *et al.* (2012)[521] Salhiyyah *et al.* (2015)[524] Salhiyyah *et al.* (2012)[525] Dawson *et al.* (2000)[526]	

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.[525,527,528] 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 *et al.* (2012)[525] Robertson *et al.* (2013)[528]	

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.[529] 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 infrapopliteal 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.[5] 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

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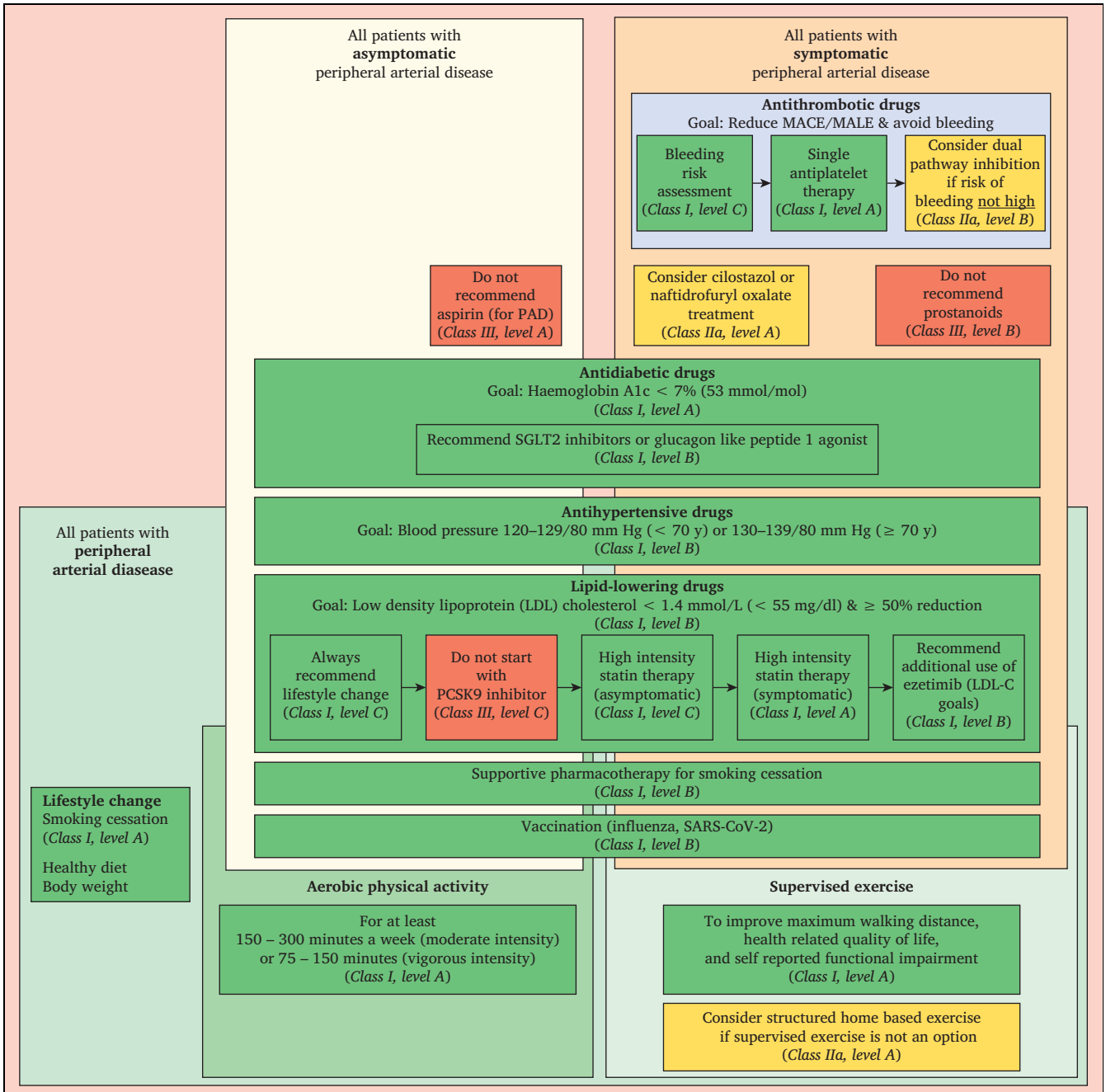

Figure 11. Schematic illustration of best medical treatment strategies in PAD patients. MALE = major adverse limb events; MACE = major adverse cardiovascular events; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; SARS-CoV-2 = severe acute respiratory syndrome 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[530] and the STAG Trial.[531] A meta-analysis including both studies concluded that there is insufficient evidence to make general conclusions about

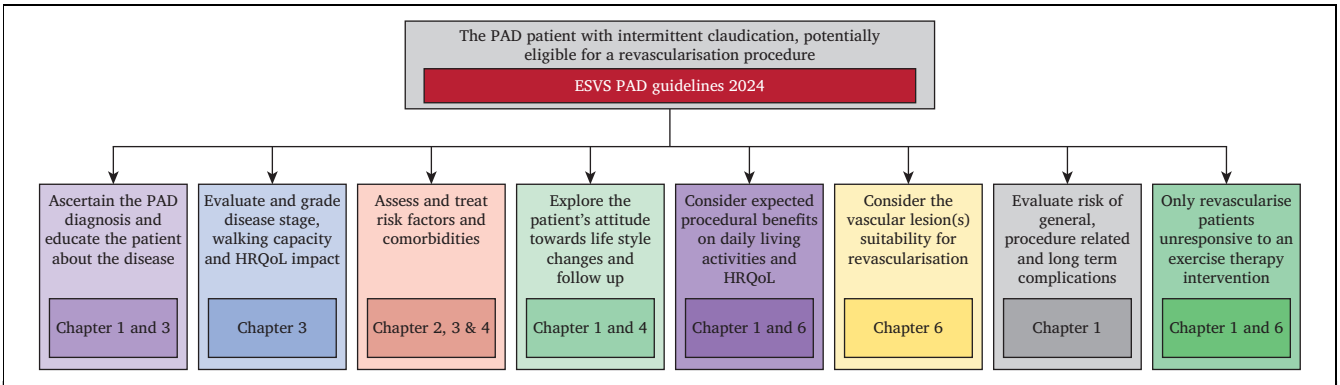

Figure 12. Important factors to consider before recommending an intermittent claudication (IC) revascularisation procedure. PAD = peripheral arterial disease; HRQoL = health related quality of life; ESVS = European Society for Vascular Surgery.

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.[532]

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
IIa	B	Koeckerling *et al.* (2023)[5] Klein *et al.* (2006)[530] Goode *et al.* (2013)[531] Jongsma *et al.* (2020)[532]	

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 *et al.* (2023)[5] Klein *et al.* (2006)[530] Goode *et al.* (2013)[531] Jongsma *et al.* (2020)[532]	

The potential benefits of specific primary stenting strategies were investigated in two randomised studies: the ICE and the COBEST trials.[533,534] 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.[533]

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 *et al.* (2023)[5] Krankenberg *et al.* (2017)[533]	

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.[534] 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.[535] Taken together, these trials lead to the conclusion that covered stents do not currently offer any treatment advantages over bare metal stents in less

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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 *et al.* (2023)[5] Mwipatayi *et al.* (2016)[534] Bekken *et al.* (2023)[535]	

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).[536] 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).[537] 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).[538] 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).[539]

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.

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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 *et al.* (2021)[536] Premaratne *et al.* (2020)[537] Indes *et al.* (2013)[538] Starodubtsev *et al.* (2022)[539]	

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, perioperative 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%.[540] 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).[541]

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 *et al.* (2010)[540] Eiberg *et al.* (2006)[541] Ricco *et al.* (2008)[542]	

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).[543] 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 be 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).[544] 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 ($p = .001$)

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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 *et al.* (2010)[545] Kang *et al.* (2008)[546]	

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 *et al.* (2019)[543] Boufi *et al.* (2021)[544]	

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
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.[547] The prospectively collected Swedvasc 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.[548]

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.[549]

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.[550]

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 *et al.* (2020)[449] Gunnarsson *et al.* (2020)[548] Howard *et al.* (2023)[549]	

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

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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%, $p = .017$).[551,552] 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.[5] 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.[553–555] The use of paclitaxel coated balloon angioplasty is also supported by recent cost effectiveness analyses.[556,557]

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
IIa	A	Koeckerling *et al.* (2023)[5]	

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.[5] 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.[558] 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
III	C	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.[5] Long term data were provided by the Zilver PTX trial, whereas the BATTLE trials provided midterm data.[559,560] 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.

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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.[561]

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.[562,563]

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 *et al.* (2023)[5] Dake *et al.* (2016)[559] Gouëffic *et al.* (2020)[560] Bausback *et al.* (2019)[562] Liistro *et al.* (2019)[563] Gouëffic *et al.* (2022)[561]	

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.[564–570]

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 *et al.* (2023)[5] Vroegindeweij *et al.* (1992)[564] Tielbeek *et al.* (1996)[565] Shammas *et al.* (2011)[566] Dattilo *et al.* (2014)[567] Ott *et al.* (2017)[568] Zeller *et al.* (2017)[569] Cai *et al.* (2020)[570]	

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.[571–573]

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.[571]

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.[572]

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 *et al.* (2023)[5] Saxon *et al.* (2008)[571] Geraghty *et al.* (2013)[572] Lammer *et al.* (2015)[573]	

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.[574–576] 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

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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 ± 5.9% at one year and 59.3 ± 7.3% at five years for above knee venous bypass *vs.* 69.5 ± 5.3% at one year and 54.5 ± 6.2% at five years for above knee prosthetic bypass.[577] 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.[578] 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
IIa	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 *et al.* (2018)[574] Vossen *et al.* (2022)[575] Kim *et al.* (2022)[577] Sharrock *et al.* (2019)[576]	

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.[579]

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%, $p = .040$).[580] 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 *et al.* (2015)[579] Rastan *et al.* (2012)[580]	

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 *et al.* (2012)[580]	

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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.[581] 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.[29] 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 *et al.* (2021)[32] Fashandi *et al.* (2018)[29]	

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.[582]

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 *et al.* (2021)[582]	

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.[41] 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.[583] In a systematic review and network meta-analysis undertaken on trials including both revascularised and non-revascularised PAD patients, a

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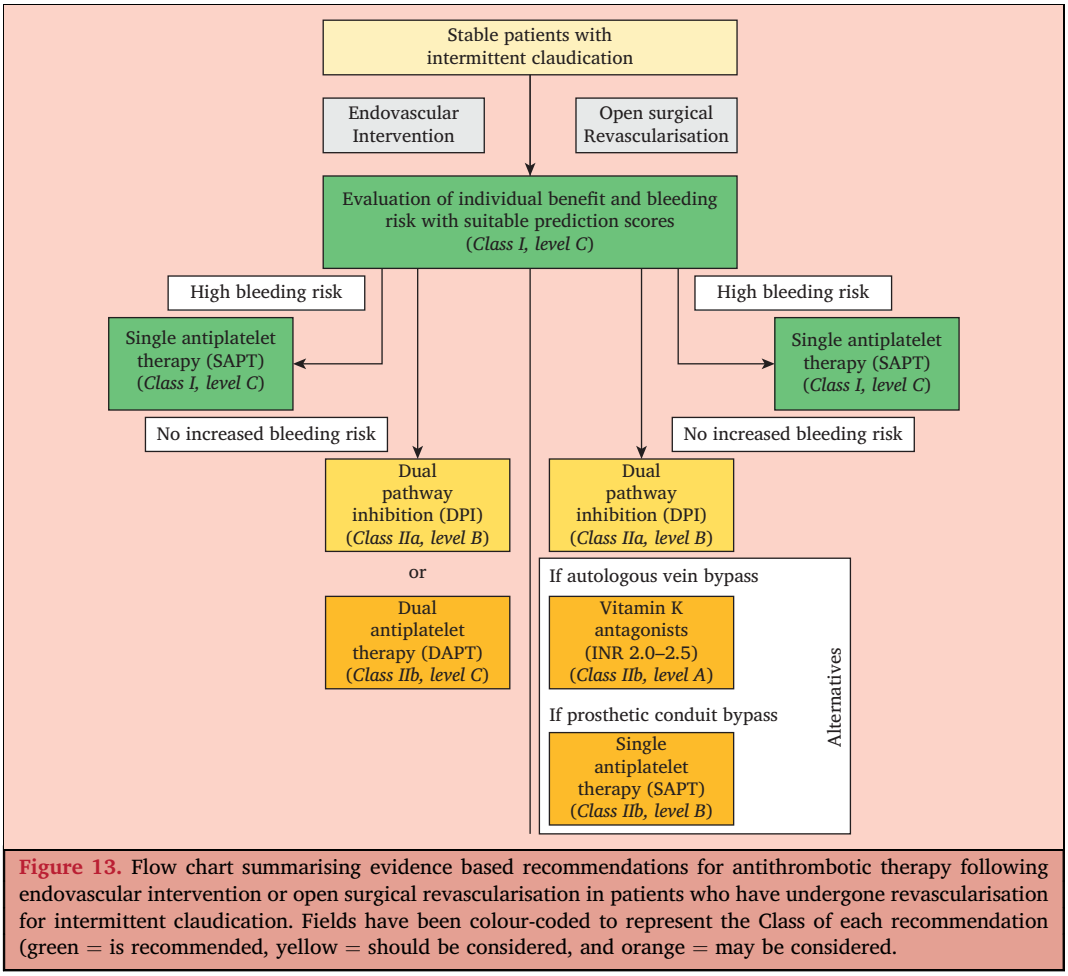

Figure 13. Flow chart summarising evidence based recommendations for antithrombotic therapy following endovascular intervention or open surgical revascularisation in patients who have undergone revascularisation for intermittent claudication. Fields have been colour-coded to represent the Class of each recommendation (green = is recommended, yellow = should be considered, and orange = may be considered.

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).[584] 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).[440] 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.[585] 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.[586] 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.[587] 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
IIb	C	Consensus

The effect of cilostazol following lower limb endovascular revascularisation was studied in a meta-analysis by Megaly *et al.*[588] 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

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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.[589]

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.[106]

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.[590] 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).[591] 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,[592–594] although it should be recognised that rivaroxaban has been poorly studied in patients with severe renal impairment (eGFR < 15 mL/min/1.73m^2) and is therefore not recommended in such patients. Even in the range of 15–30 mL/min/1.73m^2, 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).[595] Moreover, combination therapy seems to protect revascularised PAD patients from subsequent venous thrombosis.[596] 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.[587]

One additional small multicentre double blind RCT (n = 203) compared edoxaban (60 mg daily) with clopidogrel (75 mg daily) on a background of aspirin.[597] 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
IIa	B	Bonaca *et al.* (2020)[590]	

* 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 *et al.* (2020)[587]	

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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.[598] 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.[599] 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.[600,601] 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.[602]

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.[603]

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).[591,604] 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.[605] 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, $p = .046$).[606]

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 *et al.* (2020)[604] Debus *et al.* (2021)[591]	

* 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 *et al.* (2020)[587]	

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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
IIb	A	Geraghty *et al.* (2011)[607] Bedenis *et al.* (2015)[603] Monaco *et al.* (2012)[608] Tangelder *et al.* (2001)[598] van Hattum *et al.* (2009)[609] de Smit *et al.* (1992)[610]	

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
IIb	B	Bedenis *et al.* (2015)[603] Geraghty *et al.* (2011)[607] Lassila *et al.* (1991)[611] Belch *et al.* (2010)[602] McCollum *et al.* (1991)[612] Clyne *et al.* (1987)[613]	

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
IIb	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.[614–619] 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.[56,198,620–622]

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.[623,624] 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.[625–628] Graft stenoses commonly develop at sites of unrepaired defects or at early appearing conduit abnormalities.[629] 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.[630]

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.[631–633] A recently published review found a large variation in used modality, surveillance duration, and intensity.[633] 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

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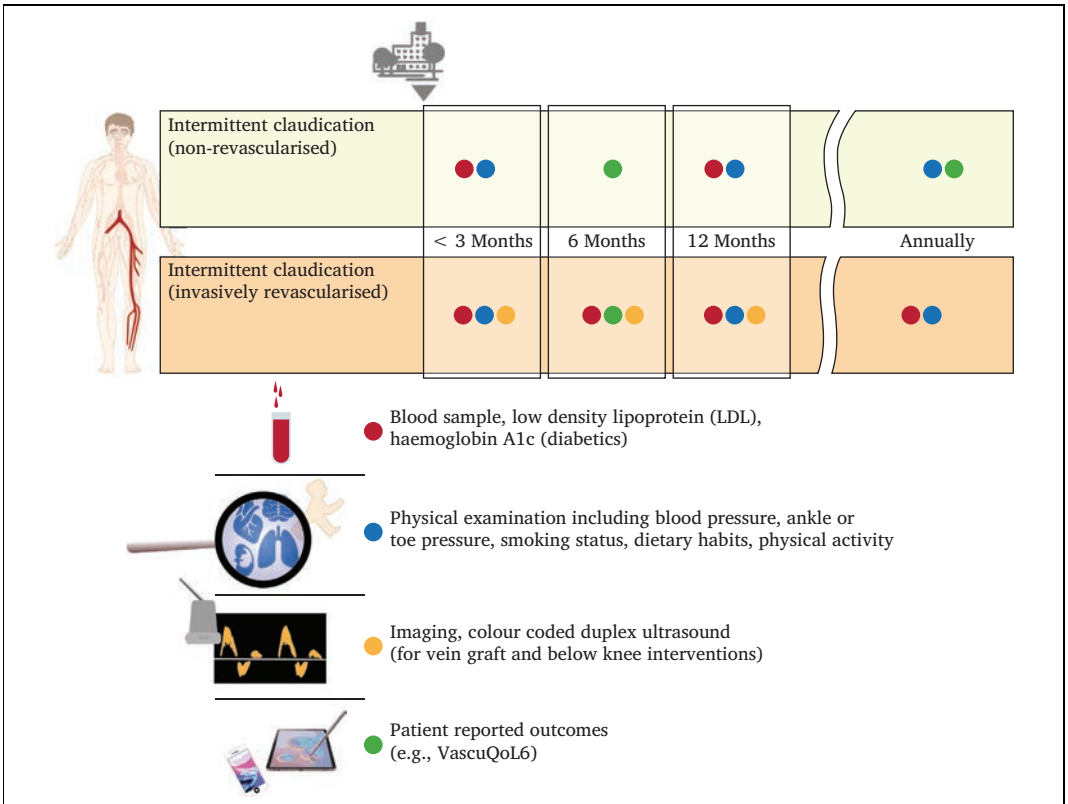

Figure 14. Suggested monitoring schedule for patients with intermittent claudication treated with or without revascularisation.

and constitute a practical way of integrating the patient's voice in the follow up, longitudinal monitoring, and overall management of IC.[634,635] 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.[636] 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).[98,637–640] 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
IIa	B	Cassar *et al.* (2003)[641] Guidon *et al.* (2010)[636] Donker *et al.* (2016)[635] Peri-Okonny *et al.* (2021)[637] Gardner *et al.* (2018)[638] Conijn *et al.* (2015)[278] Nordanstig *et al.* (2017)[640]	

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

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among screened PAD patients by a single phone call at six month follow up but not over 60 month follow up.[642] Other examples are improved blood glucose levels and medication adherence by telemedicine follow up.[643,644] 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.[645] The use of web based applications for promoting and maintaining a healthy lifestyle is increasing with promising results.[646,647] 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.[648] 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.[649]

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 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.[650] 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.[651] From these sources, only three process quality indicators from two publications[652,653] 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:[654]

- 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 *et al.* (2014)[652] Olin *et al.* (2010)[653] Rieß *et al.* (2018)[654] Hischke *et al.* (2019)[651]	

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6.7. Overall management strategy for patients with intermittent claudication

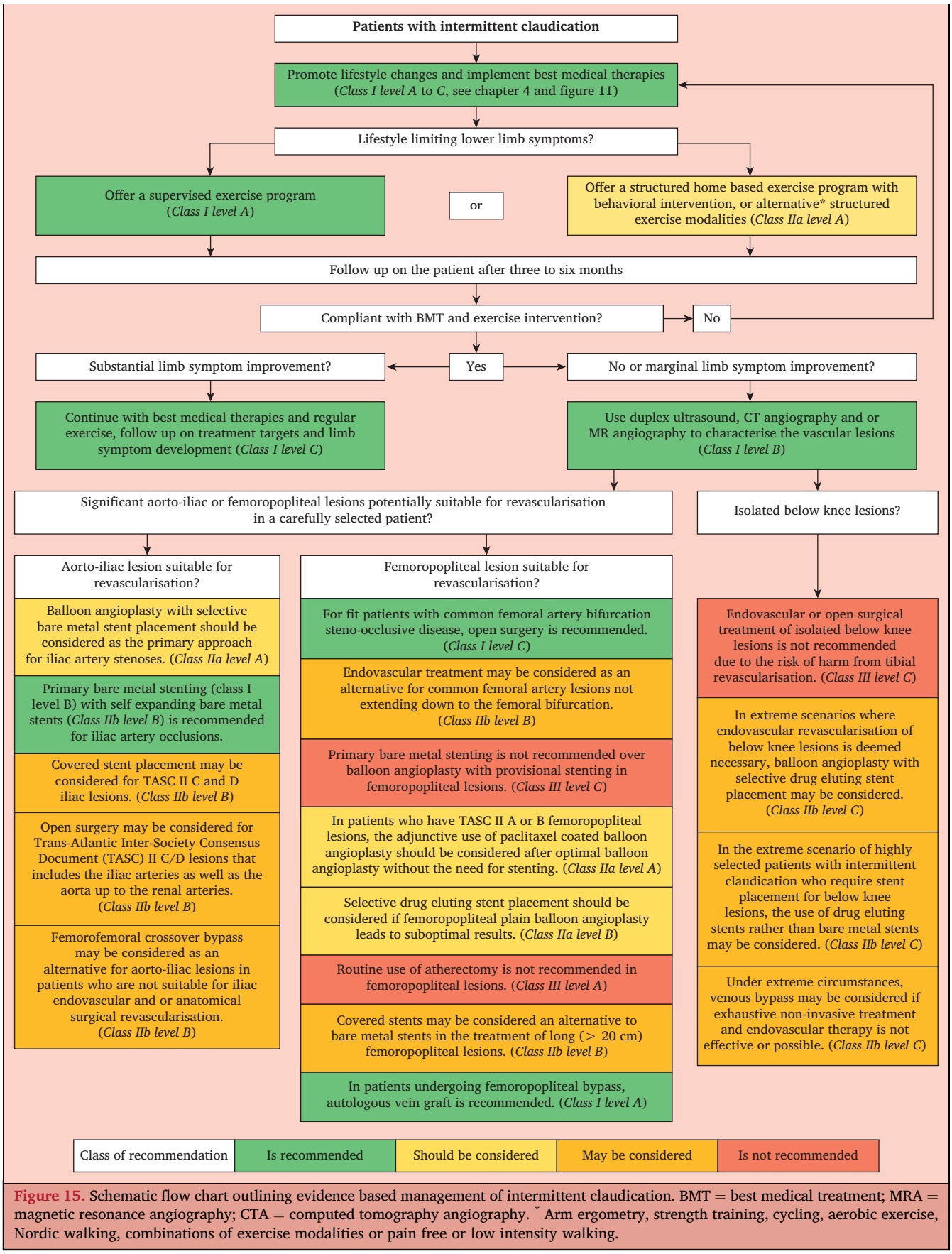

Figure 15. Schematic flow chart outlining evidence based management of intermittent claudication. BMT = best medical treatment; MRA = magnetic resonance angiography; CTA = computed tomography angiography. * Arm ergometry, strength training, cycling, aerobic exercise, Nordic walking, combinations of exercise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

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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.[655–657] 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, ≈10% in epidemiological cohorts will present with IC with an overall lower prevalence among women (range 1.0 – 12.7%).[658–661] 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.[135,143,659,662–665] 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.[666]

When compared with women, men have historically been more frequently selected for revascularisation.[615,667,668] Furthermore, women were more often treated by endovascular techniques at a more severe disease stage.[667,669–671] 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).[672] 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.[673] 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.[674] 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.[675]

Despite the increase of CV disease among postmenopausal women, hormone replacement therapy with oestrogen and progestin has not been proven beneficial.[676,677] 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.[678]

Diabetes and hyperlipidaemia are suggested to increase the risk of PAD four fold in women, as is tobacco use.[656,679,680] Smoking is more common among men; however, the overall use is decreasing, but at a slower pace among women.[374,681–683] McDermott *et al.* and Peters *et al.* found men to be more likely to be treated with intense cholesterol lowering drugs than women.[684,685] 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.[686,687]

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 *et al.* (2018)[656] Mayor *et al.* (2021)[688] Hirsch *et al.* (2012)[662]	

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 *et al.* (2002)[676] Grady *et al.* (2002)[677]	

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 *et al.* (2015)[689] Srivaratharajah *et al.* (2018)[660] Hirsch *et al.* (2012)[662] Peters *et al.* (2020)[685] Makowski *et al.* (2021)[690] Ramkumar *et al.* (2018)[691] Messiha *et al.* (2022)[692]	

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

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(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.[693] Similar associations have been reported between PAD and low educational levels.[694–696] 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.[697] 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.[698] 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.[699] Selvin *et al.* reported increased crude odds for PAD among individuals of African American ethnicity (OR 2.83, 95% CI 1.48 – 5.42).[700] 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.[701] 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.[702] Whether this is related to lower socio-economic status, lower general access to health services, or a lack of physician awareness remain unknown.[703] 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.[704–706] 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.[707–709]

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.[710,711] 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.[712–715] In addition, subjects with diabetes experience poorer lower extremity function.[711,716] Having diabetes has been shown to increase both mortality and amputation risk.[717] Among 21 197 IC patients, concomittant diabetes increased long term mortality (HR 1.3) and amputation rates by 2.3 times.[712,713] 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.[718] 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.[719–721]

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.[162,267] 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.[1] 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.

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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).[722]

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.[723] Another recent data comparison of amputation practice in 12 countries confirmed the possible impact of external factors on treatment patterns.[724] 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.[263,264] 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

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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

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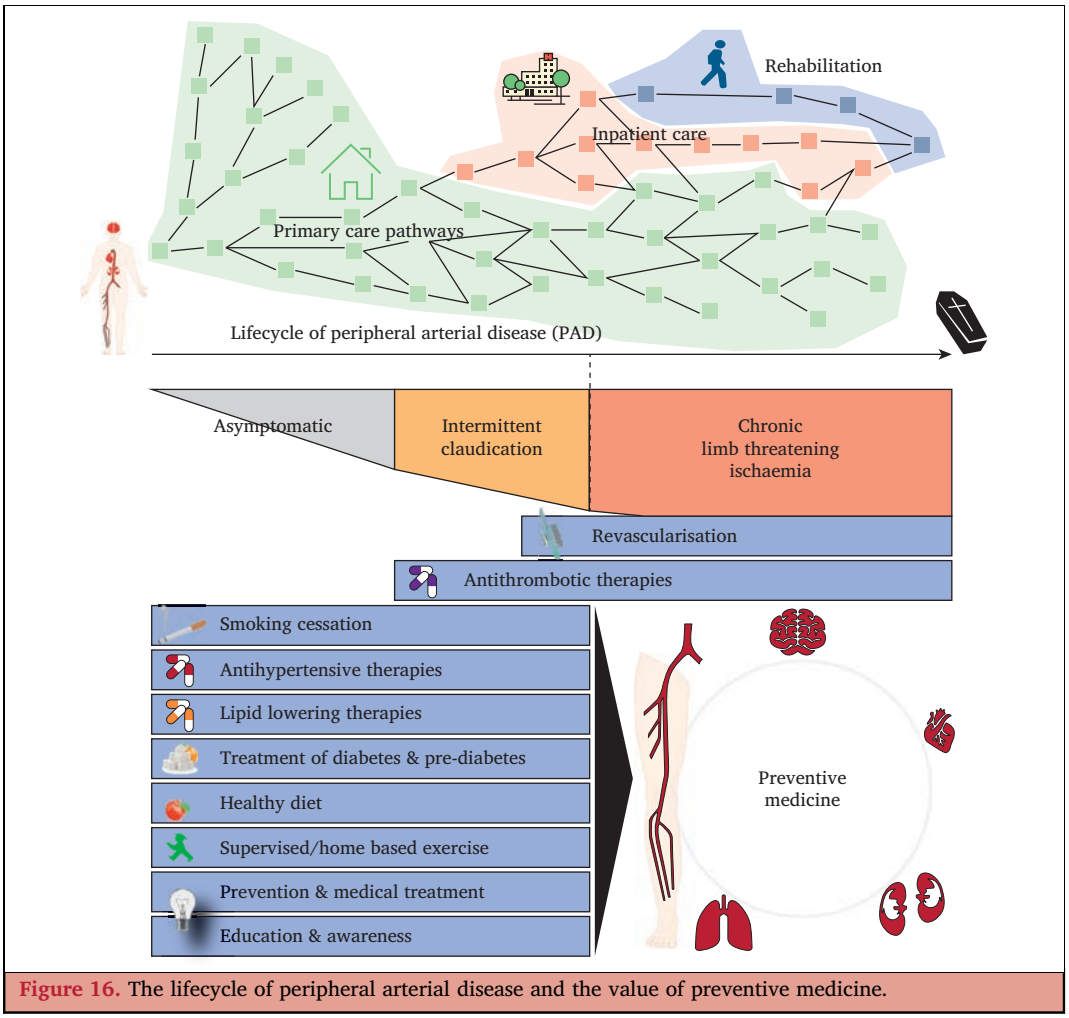

Figure 16. The lifecycle of peripheral arterial disease and the value of preventive medicine.

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.

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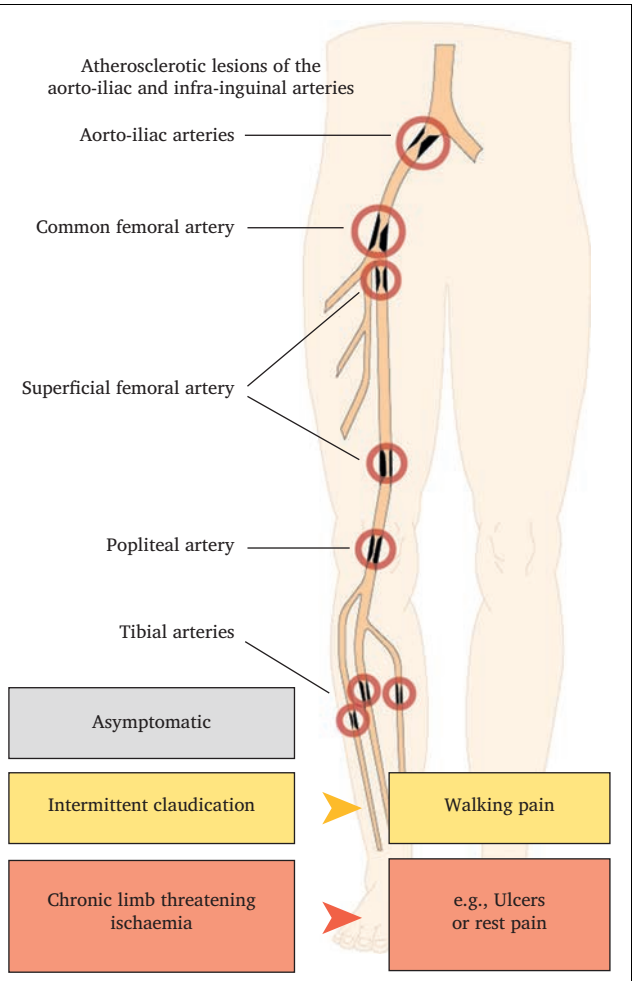

Figure 17. Typical locations for atherosclerotic lesions of the aorto-iliac and infra-inguinal arteries and stages of the disease.

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 that 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

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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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REFERENCES

1 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg* 2019;**58**:S1–109.
2 Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;**352**:i1152.
3 Antoniou GA, Bastos Goncalves F, Bjorck M, Chakfe N, Coscas R, Dias NV, et al. Editor's Choice - European Society for Vascular Surgery Clinical Practice Guideline Development Scheme: An Overview of Evidence Quality Assessment Methods, Evidence to Decision Frameworks, and Reporting Standards in Guideline Development. *Eur J Vasc Endovasc Surg* 2022;**63**:791–9.
4 Arndt H, Nordanstig J, Bertges DJ, Budtz-Lilly J, Venermo M, Espada CL, et al. A Delphi Consensus on patient reported outcomes for registries and trials including patients with intermittent claudication: recommendations and reporting standard. *Eur J Vasc Endovasc Surg* 2022;**64**:526–33.
5 Koeckerling D, Raguindin PF, Kastrati L, Bernhard S, Barker J, Quiroga Centeno AC, et al. Endovascular revascularization strategies for aortoiliac and femoropopliteal artery disease: a meta-analysis. *Eur Heart J* 2023;**44**:935–50.
6 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
7 Bjorck M, Earnshaw JJ, Acosta S, Bastos Goncalves F, Cochennec F, Debus ES, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. *Eur J Vasc Endovasc Surg* 2020;**59**:173–218.
8 Conte MS. Data, guidelines, and practice of revascularization for claudication. *J Vasc Surg* 2017;**66**:911–5.
9 Jung KS, Heo SH, Woo SY, Park YJ, Kim DI, Kim YW. Factors associated with long-term graft patency after lower extremity arterial bypasses. *Ann Surg Treat Res* 2021;**100**:175–85.
10 Martinez RA, Shnayder M, Parreco J, Gaffney L, Eby M, Cortolillo N, et al. Nationally representative readmission factors in patients with claudication and critical limb ischemia. *Ann Vasc Surg* 2018;**52**:96–107.
11 Bodewes TC, Soden PA, Ultee KH, Zettervall SL, Pothof AB, Deery SE, et al. Risk factors for 30-day unplanned readmission following infrainguinal endovascular interventions. *J Vasc Surg* 2017;**65**:484–94.
12 Smith SL, Matthews EO, Moxon JV, Golledge J. A systematic review and meta-analysis of risk factors for and incidence of 30-day readmission after revascularization for peripheral artery disease. *J Vasc Surg* 2019;**70**:996–1006.
13 Kuy S, Dua A, Desai S, Dua A, Patel B, Tondravi N, et al. Surgical site infections after lower extremity revascularization procedures involving groin incisions. *Ann Vasc Surg* 2014;**28**:53–8.
14 Groin wound Infection after Vascular Exposure Study Group. Groin wound Infection after Vascular Exposure (GIVE) multicentre cohort study. *Int Wound J* 2021;**18**:164–75.
15 Gwilym BL, Ambler GK, Saratzis A, Bosanquet DC, Groin wound Infection after Vascular Exposure Study Group. Groin wound Infection after Vascular Exposure (GIVE) risk prediction models: development, internal validation, and comparison with existing risk prediction models identified in a systematic literature review. *Eur J Vasc Endovasc Surg* 2021;**62**:258–66.
16 Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S. Long-term survival and fate of the leg in de novo intermittent claudication. *Eur Heart J Qual Care Clin Outcomes* 2017;**3**:208–15.
17 Ochoa Chaar CI, Gholitabar N, DeTrani M, Jorshery SD, Zhuo H, Zhang Y, et al. The Reintervention Index: a new outcome measure for comparative effectiveness of lower extremity revascularization. *Ann Vasc Surg* 2020;**69**:52–61.
18 Golledge J, Moxon JV, Rowbotham S, Pinchbeck J, Yip L, Velu R, et al. Risk of major amputation in patients with intermittent claudication undergoing early revascularization. *Br J Surg* 2018;**105**:699–708.
19 Djerf H, Hellman J, Baubeta Fridh E, Andersson M, Nordanstig J, Falkenberg M. Low risk of procedure related major amputation following revascularisation for intermittent claudication: a population based study. *Eur J Vasc Endovasc Surg* 2020;**59**:817–22.
20 Kim TI, Kiwan G, Mohamedali A, Zhang Y, Dardik A, Guzman RJ, et al. Multiple reinterventions for claudication are associated with progression to chronic limb-threatening ischemia. *Ann Vasc Surg* 2021;**72**:166–74.
21 Madabhushi V, Davenport D, Jones S, Khoudoud SA, Orr N, Minion D, et al. Revascularization of intermittent claudicants leads to more chronic limb-threatening ischemia and higher amputation rates. *J Vasc Surg* 2021;**74**:771–9.
22 Ubbink DT, Koelemay MJW. Shared decision making in vascular surgery. Why would you? *Eur J Vasc Endovasc Surg* 2018;**56**:749–50.
23 Bath J, Lawrence PF, Neal D, Zhao Y, Smith JB, Beck AW, et al. Endovascular interventions for claudication do not meet minimum standards for the Society for Vascular Surgery efficacy guidelines. *J Vasc Surg* 2021;**73**:1693–700.
24 Feinglass J, McCarthy WJ, Slavensky R, Manheim LM, Martin GJ. Effect of lower extremity blood pressure on physical functioning in patients who have intermittent claudication. The Chicago Claudication Outcomes Research Group. *J Vasc Surg* 1996;**24**:503–11.
25 McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med* 2002;**136**:873–83.
26 McDermott MM, Ferrucci L, Guralnik JM, Dyer AR, Liu K, Pearce WH, et al. The ankle-brachial index is associated with the magnitude of impaired walking endurance among men and women with peripheral arterial disease. *Vasc Med* 2010;**15**:251–7.
27 Anderson JD, Epstein FH, Meyer CH, Hagspiel KD, Wang H, Berr SS, et al. Multifactorial determinants of functional capacity in peripheral arterial disease: uncoupling of calf muscle perfusion and metabolism. *J Am Coll Cardiol* 2009;**54**:628–35.
28 Mullins CH, Novak Z, Axley JC, Sutzko DC, Spangler EL, Pearce BJ, et al. Prevalence and outcomes of endovascular infrapopliteal interventions for intermittent claudication. *Ann Vasc Surg* 2021;**70**:79–86.
29 Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch Jr GR, Robinson WP. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg* 2018;**68**:1817–23.
30 Zhou Y, Zhang Z, Lin S, Xiao J, Ai W, Wang J, et al. Comparative effectiveness of endovascular treatment modalities for de novo femoropopliteal lesions: a network meta-analysis of randomized controlled trials. *J Endovasc Ther* 2020;**27**:42–59.
31 Soga Y, Yokoi H, Urakawa T, Tosaka A, Iwabuchi M, Nobuyoshi M. Long-term clinical outcome after endovascular treatment in patients with intermittent claudication due to iliofemoral artery disease. *Circ J* 2010;**74**:1689–95.
32 Levin SR, Farber A, Osborne NH, Beck AW, McFarland GE, Rybin D, et al. Tibial bypass in patients with intermittent claudication is associated with poor outcomes. *J Vasc Surg* 2021;**73**:564–71.

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33 Mohler 3rd ER, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;**108**:1481–6.
34 Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;**114**:359–64.
35 Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;**2007**:CD000123.
36 Pastori D, Farcomeni A, Milanese A, Del Sole F, Menichelli D, Hiatt WR, et al. Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. *Thromb Haemost* 2020;**120**:866–75.
37 Twine CP, Kakkos SK, Aboyans V, Baumgartner I, Behrendt CA, Bellmunt-Montoya S, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases. *Eur J Vasc Endovasc Surg* 2023;**65**:627–89.
38 Behrendt CA, Kreutzburg T, Nordanstig J, Twine CP, Marschall U, Kakkos S, et al. The OAC(3)-PAD Risk Score predicts major bleeding events one year after hospitalisation for peripheral artery disease. *Eur J Vasc Endovasc Surg* 2022;**63**:503–10.
39 Peters F, Behrendt CA. External validation of the OAC3-PAD Risk Score to predict major bleeding events using the prospective GermanVasc Cohort Study. *Eur J Vasc Endovasc Surg* 2022;**64**:429–30.
40 Lareyre F, Behrendt CA, Pradier C, Settembre N, Chaudhuri A, Fabre R, et al. Nationwide study in France to predict one year major bleeding and validate the OAC3-PAD score in patients undergoing revascularisation for lower extremity arterial disease. *Eur J Vasc Endovasc Surg* 2023;**66**:213–9.
41 Twine CP, Kakkos SK, Aboyans V, Baumgartner I, Behrendt CA, Bellmunt-Montoya S, et al. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases. *Eur J Vasc Endovasc Surg* 2023;**65**:627–89.
42 Ponce OJ, Larrea-Mantilla L, Hemmingsen B, Serrano V, Rodriguez-Gutierrez R, Spencer-Bonilla G, et al. Lipid-lowering agents in older individuals: a systematic review and meta-analysis of randomized clinical trials. *J Clin Endocrinol Metab* 2019;**104**:1585–94.
43 Angelidi AM, Stambolliu E, Adamopoulou KI, Kousoulis AA. Is atorvastatin associated with new onset diabetes or deterioration of glycemic control? Systematic review using data from 1.9 million patients. *Int J Endocrinol* 2018;**2018**:8380192.
44 Neves JS, Newman C, Bostrom JA, Buysschaert M, Newman JD, Medina JL, et al. Management of dyslipidemia and atherosclerotic cardiovascular risk in prediabetes. *Diabetes Res Clin Pract* 2022;**190**:109980.
45 Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;**80**:363–71.
46 McClure DL, Valuck RJ, Glanz M, Hokanson JE. Systematic review and meta-analysis of clinically relevant adverse events from HMG CoA reductase inhibitor trials worldwide from 1982 to present. *Pharmacoepidemiol Drug Saf* 2007;**16**:132–43.
47 Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006;**114**:2788–97.
48 Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. *Nutr Metab Cardiovasc Dis* 2013;**23**:871–5.
49 Bytyci I, Penson PE, Mikhailidis DP, Wong ND, Hernandez AV, Sahebkar A, et al. Prevalence of statin intolerance: a meta-analysis. *Eur Heart J* 2022;**43**:3213–23.
50 Cholesterol Treatment Trialists Collaborators. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials. *Lancet* 2022;**400**:832–45.
51 Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* 2017;**389**:2473–81.
52 Wood FA, Howard JP, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects. *N Engl J Med* 2020;**383**:2182–4.
53 Giral P, Neumann A, Weill A, Coste J. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;**40**:3516–25.
54 Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;**346**:539–40.
55 Golledge J, Ward NC, Watts GF. Lipid management in people with peripheral artery disease. *Curr Opin Lipidol* 2019;**30**:470–6.
56 Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. *Vasa* 2019;**48**:1–79.
57 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (Lower extremity, renal, mesenteric, and abdominal aortic). *Circulation* 2006;**113**:e463–654.
58 Gordon T, Kannel WB. Predisposition to atherosclerosis in the head, heart, and legs. The Framingham study. *JAMA* 1972;**221**:661–6.
59 Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R. Overview of classification systems in peripheral artery disease. *Semin Intervent Radiol* 2014;**31**:378–88.
60 Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. *Can J Cardiol* 2013;**29**:492–8.
61 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509–26.
62 Sartipy F, Lundin F, Wahlberg E, Sigvant B. Cardiovascular long-term outcome and prophylactic treatment patterns in peripheral arterial disease in a population-based cohort. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:310–20.
63 Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:2890–909.
64 Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health* 2019;**7**:e1020–30.
65 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329–40.
66 Chen Q, Li L, Chen Q, Lin X, Li Y, Huang K, et al. Critical appraisal of international guidelines for the screening and treatment of asymptomatic peripheral artery disease: a systematic review. *BMC Cardiovasc Disord* 2019;**19**:17.
67 Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;**286**:1317–24.
68 Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 2007;**45**:1185–91.

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69 Cimminiello C, Borghi C, Kownator S, Wautrecht JC, Carvounis CP, Kranendonk SE, et al. Prevalence of peripheral arterial disease in patients at non-high cardiovascular risk. Rationale and design of the PANDORA study. *BMC Cardiovasc Disord* 2010;**10**:35.
70 Cimminiello C, Kownator S, Wautrecht JC, Carvounis CP, Kranendonk SE, Kindler B, et al. The PANDORA study: peripheral arterial disease in patients with non-high cardiovascular risk. *Intern Emerg Med* 2011;**6**:509–19.
71 Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;**20**:384–92.
72 Søgaard M, Nordanstig J, Eldrup N, Behrendt CA. A thought-provoking statement regarding the treatment of patients with peripheral arterial disease. *Vasa* 2023;**52**:77–80.
73 Kroger K, Bock E, Hohenberger T, Moysidis T, Santosa F, Pfeifer M, et al. ABI derived from the highest and lowest ankle pressure. What is the difference? *Int Angiol* 2010;**29**:482–8.
74 Allison MA, Aboyans V, Granston T, McDermott MM, Kamineni A, Ni H, et al. The relevance of different methods of calculating the ankle-brachial index: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2010;**171**:368–76.
75 Velescu A, Clara A, Penafiel J, Grau M, Degano IR, Marti R, et al. Peripheral arterial disease incidence and associated risk factors in a Mediterranean population-based cohort. The REGICOR Study. *Eur J Vasc Endovasc Surg* 2016;**51**:696–705.
76 Weiss NS, McClelland R, Criqui MH, Wassel CL, Kronmal R. Incidence and predictors of clinical peripheral artery disease in asymptomatic persons with a low ankle-brachial index. *J Med Screen* 2018;**25**:218–22.
77 Lupilov A, Krause D, Klaassen-Mielke R, Trampisch HJ, Rudolf H. Effects of three different methods defining onset of peripheral artery disease on the assessments of incidence and important predictors - results from the German Epidemiological Trial on Ankle Brachial Index (getABI). *Vasc Health Risk Manag* 2021;**17**:421–9.
78 Kreutzburg T, Peters F, Riess HC, Hischke S, Marschall U, Kriston L, et al. Editor's Choice - Comorbidity patterns among patients with peripheral arterial occlusive disease in Germany: a trend analysis of health insurance claims data. *Eur J Vasc Endovasc Surg* 2020;**59**:59–66.
79 Behrendt CA, Thomalla G, Rimmele DL, Petersen EL, Twerenbold R, Debus ES, et al. Editor's Choice - Prevalence of peripheral arterial disease, abdominal aortic aneurysm, and risk factors in the Hamburg City Health Study: a cross sectional analysis. *Eur J Vasc Endovasc Surg* 2023;**65**:590–8.
80 Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Section B: intermittent claudication. *Eur J Vasc Endovasc Surg* 2000;**19**(Suppl A):S47–114.
81 Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;**27**:645–58.
82 Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med* 1996;**1**:65–71.
83 Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of intermittent claudication. Sex-related differences have been eliminated. *Eur J Vasc Endovasc Surg* 2003;**25**:209–12.
84 Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis* 2004;**172**:95–105.
85 Krishna M, Oommen AM, Paul GJS, Abraham VJ, George K. Prevalence of intermittent claudication in rural and urban Vellore, Tamil Nadu, India: a population-based study. *Int Surg J* 2018;**5**:3.
86 Smith FB, Lee AJ, Price JF, van Wijk MC, Fowkes FG. Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. *J Vasc Surg* 2003;**38**:1323–30.
87 Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016;**51**:395–403.
88 Mohler 3rd ER, Bundens W, Denenberg J, Medenilla E, Hiatt WR, Criqui MH. Progression of asymptomatic peripheral artery disease over 1 year. *Vasc Med* 2012;**17**:10–6.
89 Gao X, Tong Z, Wu Y, Guo L, Gu Y, Dardik A. Similarities and differences in peripheral artery disease between China and Western countries. *J Vasc Surg* 2021;**74**:1417–14124 e1.
90 Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol* 2001;**153**:666–72.
91 Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol* 2004;**57**:294–300.
92 Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ* 1996;**313**:1440–4.
93 Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
94 Sartipy F, Sigvant B, Lundin F, Wahlberg E. Ten year mortality in different peripheral arterial disease stages: a population based observational study on outcome. *Eur J Vasc Endovasc Surg* 2018;**55**:529–36.
95 Hajibandeh S, Hajibandeh S, Shah S, Child E, Antoniou GA, Torella F. Prognostic significance of ankle brachial pressure index: a systematic review and meta-analysis. *Vascular* 2017;**25**:208–24.
96 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;**326**:381–6.
97 Aquino R, Johnnides C, Makaroun M, Whittle JC, Muluk VS, Kelley ME, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. *J Vasc Surg* 2001;**34**:962–70.
98 Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. *Eur J Vasc Endovasc Surg* 2017;**54**:480–6.
99 Kreutzburg T, Peters F, Kuchenbecker J, Marschall U, Lee R, Kriston L, et al. Editor's Choice - The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease. *Eur J Vasc Endovasc Surg* 2021;**61**:248–56.
100 Droz-Perroteau C, Blin P, Dureau-Pournin C, Thomas D, Danchin N, Tricoire J, et al. Six-year survival study after myocardial infarction: the EOLE prospective cohort study. Long-term survival after MI. *Therapie* 2019;**74**:459–68.
101 Goodall R, Salciccioli JD, Davies AH, Marshall D, Shalhoub J. Trends in peripheral arterial disease incidence and mortality in EU15+ countries 1990–2017. *Eur J Prev Cardiol* 2021;**28**:1201–13.
102 Malyar N, Freisinger E, Reinecke H. [Peripheral Arterial Disease - Trends in Morbidity and Mortality]. *Dtsch Med Wochenschr* 2018;**143**:766–70.
103 Brand AR, Houben E, Bezemer ID, Visseren FLJ, Bots ML, Herings RM, et al. Platelet aggregation inhibitor prescription for newly diagnosed peripheral arterial disease in the Netherlands: a cohort study. *BMJ Open* 2021;**11**:e041715.
104 Welten GM, Schouten O, Hoeks SE, Chonchol M, Vidakovic R, van Domburg RT, et al. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. *J Am Coll Cardiol* 2008;**51**:1588–96.

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105 Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol* 2013;**61**:1736–43.
106 Committee Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329–39.
107 Aboyans V, Desormais I, Magne J, Morange G, Mohty D, Lacroix P. Renal artery stenosis in patients with peripheral artery disease: prevalence, risk factors and long-term prognosis. *Eur J Vasc Endovasc Surg* 2017;**53**:380–5.
108 Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2009;**37**:262–71.
109 Durand DJ, Perler BA, Roseborough GS, Grega MA, Borowicz Jr LM, Baumgartner WA, et al. Mandatory versus selective preoperative carotid screening: a retrospective analysis. *Ann Thorac Surg* 2004;**78**:159–66.
110 Fowkes FG, Low LP, Tuta S, Kozak J, AGATHA Investigators. Ankle-brachial index and extent of atherothrombosis in 8891 patients with or at risk of vascular disease: results of the international AGATHA study. *Eur Heart J* 2006;**27**:1861–7.
111 Mukherjee D, Eagle KA, Kline-Rogers E, Feldman LJ, Juliard JM, Agnelli G, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). *Am J Cardiol* 2007;**100**:1–6.
112 Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Surg* 2002;**23**:283–94.
113 Steinvil A, Sadeh B, Arbel Y, Justo D, Belei A, Borenstein N, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011;**57**:779–83.
114 Subherwal S, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2012;**5**:541–9.
115 Kim EK, Song PS, Yang JH, Song YB, Hahn JY, Choi JH, et al. Peripheral artery disease in Korean patients undergoing percutaneous coronary intervention: prevalence and association with coronary artery disease severity. *J Korean Med Sci* 2013;**28**:87–92.
116 Imori Y, Akasaka T, Ochiai T, Oyama K, Tobita K, Shishido K, et al. Co-existence of carotid artery disease, renal artery stenosis, and lower extremity peripheral arterial disease in patients with coronary artery disease. *Am J Cardiol* 2014;**113**:30–5.
117 Saw J, Bhatt DL, Moliterno DJ, Brener SJ, Steinhubl SR, Lincoff AM, et al. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. *J Am Coll Cardiol* 2006;**48**:1567–72.
118 Hussein AA, Uno K, Wolski K, Kapadia S, Schoenhagen P, Tuzcu EM, et al. Peripheral arterial disease and progression of coronary atherosclerosis. *J Am Coll Cardiol* 2011;**57**:1220–5.
119 Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. The Coronary Artery Surgery Study (CASS) Investigators. *J Am Coll Cardiol* 1994;**23**:1091–5.
120 Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. *Vasc Med* 2013;**18**:176–84.
121 Inglis SC, Bebchuk J, Al-Suhaim SA, Case J, Pfeffer MA, Solomon SD, et al. Peripheral artery disease and outcomes after myocardial infarction: an individual-patient meta-analysis of 28,771 patients in CAPRICORN, EPEHESUS, OPTIMAAL and VALIANT. *Int J Cardiol* 2013;**168**:1094–101.
122 Aboyans V, Lacroix P, Postil A, Guilloux J, Rolle F, Cornu E, et al. Subclinical peripheral arterial disease and incompressible ankle arteries are both long-term prognostic factors in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol* 2005;**46**:815–20.
123 Rihal CS, Sutton-Tyrrell K, Guo P, Keller NM, Jandova R, Sellers MA, et al. Increased incidence of periprocedural complications among patients with peripheral vascular disease undergoing myocardial revascularization in the bypass angioplasty revascularization investigation. *Circulation* 1999;**100**:171–7.
124 Collet JP, Cayla G, Ennezat PV, Leclercq F, Cuisset T, Elhadad S, et al. Systematic detection of polyvascular disease combined with aggressive secondary prevention in patients presenting with severe coronary artery disease: the randomized AMERICA Study. *Int J Cardiol* 2018;**254**:36–42.
125 Aboyans V, Lacroix P, Guilloux J, Rolle F, Le Guyader A, Cautres M, et al. A predictive model for screening cerebrovascular disease in patient undergoing coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg* 2005;**4**:90–5.
126 Anandasundaram B, Lane DA, Apostolakis S, Lip GY. The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. *J Thromb Haemost* 2013;**11**:975–87.
127 Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 2008;**156**:855–63.
128 Olesen JB, Lip GY, Lane DA, Kober L, Hansen ML, Karasoy D, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med* 2012;**125**:826.
129 Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. *Eur J Vasc Endovasc Surg* 2023;**65**:7–111.
130 Amighi J, Schlager O, Haumer M, Dick P, Mlekusch W, Loewe C, et al. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. *Eur J Clin Invest* 2009;**39**:784–92.
131 Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**:13–22.
132 Investigators ASTRAL, Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953–62.
133 Matsushita K, Ballew SH, Coresh J, Arima H, Arnlov J, Cirillo M, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2017;**5**:718–28.
134 Gardner AW, Montgomery PS, Afaq A. Exercise performance in patients with peripheral arterial disease who have different types of exertional leg pain. *J Vasc Surg* 2007;**46**:79–86.
135 Sigvant B, Lundin F, Nilsson B, Bergqvist D, Wahlberg E. Differences in presentation of symptoms between women and men with intermittent claudication. *BMC Cardiovasc Disord* 2011;**11**:39.
136 McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Arch Intern Med* 1999;**159**:387–92.
137 Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. *Semin Vasc Surg* 1999;**12**:142–7.
138 Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, et al. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 2003;**163**:884–92.

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139 McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Liao Y, et al. Leg symptom categories and rates of mobility decline in peripheral arterial disease. *J Am Geriatr Soc* 2010;**58**:1256–62.
140 Santoro L, Flex A, Nesci A, Ferraro PM, De Matteis G, Di Giorgio A, et al. Association between peripheral arterial disease and cardiovascular risk factors: role of ultrasonography versus ankle-brachial index. *Eur Rev Med Pharmacol Sci* 2018;**22**:3160–5.
141 Serhal A, Koktzoglou I, Aouad P, Carr JC, Giri S, Morcos O, et al. Cardiovascular magnetic resonance imaging of aorto-iliac and ilio-femoral vascular calcifications using proton density-weighted in-phase stack of stars. *J Cardiovasc Magn Reson* 2018;**20**:51.
142 Tummala S, Scherbel D. Clinical assessment of peripheral arterial disease in the office: what do the guidelines say? *Semin Intervent Radiol* 2018;**35**:365–77.
143 McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;**286**:1599–606.
144 McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation* 2008;**117**:2484–91.
145 Matsushita K, Ballew SH, Sang Y, Kalbaugh C, Loehr LR, Hirsch AT, et al. Ankle-brachial index and physical function in older individuals: The Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis* 2017;**257**:208–15.
146 McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA* 2004;**292**:453–61.
147 Andras A, Ferket B. Screening for peripheral arterial disease. *Cochrane Database Syst Rev* 2014:CD010835.
148 Bendermacher BL, Teijink JA, Willigendael EM, Bartelink ML, Peters RJ, de Bie RA, et al. A clinical prediction model for the presence of peripheral arterial disease–the benefit of screening individuals before initiation of measurement of the ankle-brachial index: an observational study. *Vasc Med* 2007;**12**:5–11.
149 Ramos R, Baena-Diez JM, Quesada M, Solanas P, Subirana I, Sala J, et al. Derivation and validation of REASON: a risk score identifying candidates to screen for peripheral arterial disease using ankle brachial index. *Atherosclerosis* 2011;**214**:474–9.
150 Guirguis-Blake JM, Evans CV, Redmond N, Lin JS. Screening for peripheral artery disease using the ankle-brachial index: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2018;**320**:184–96.
151 Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet* 2017;**390**:2256–65.
152 Sogaard R, Lindholt JS. Cost-effectiveness of population-based vascular disease screening and intervention in men from the Viborg Vascular (VIVA) trial. *Br J Surg* 2018;**105**:1283–93.
153 Lindholt JS, Sogaard R, Rasmussen LM, Mejldal A, Lambrechtsen J, Steffensen FH, et al. Five-year outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial. *N Engl J Med* 2022;**387**:1385–94.
154 Shah S, Antoniou GA, Torella F. Evidence-based analysis of peripheral arterial disease screening based on the WHO criteria. *Int Angiol* 2017;**36**:299–305.
155 Ferket BS, Spronk S, Colkesen EB, Hunink MG. Systematic review of guidelines on peripheral artery disease screening. *Am J Med* 2012;**125**:198–208.
156 Abramson BL, Huckell V, Anand S, Forbes T, Gupta A, Harris K, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease - executive summary. *Can J Cardiol* 2005;**21**:997–1006.
157 Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010;**56**:e50–103.
158 Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol* 2009;**25**:567–79.
159 Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;**110**:227–39.
160 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**:e463–654.
161 National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421.
162 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;**33**(Suppl 1):S1–75.
163 U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;**151**:474–82.
164 Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015;**61**:2S–41S.
165 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;**135**:e726–79.
166 Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:1555–70.
167 Alahdab F, Wang AT, Elraiyah TA, Malgor RD, Rizvi AZ, Lane MA, et al. A systematic review for the screening for peripheral arterial disease in asymptomatic patients. *J Vasc Surg* 2015;**61**:42S–53S.

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168 Weiss DJ, Casale GP, Koutakis P, Nella AA, Swanson SA, Zhu Z, et al. Oxidative damage and myofiber degeneration in the gastrocnemius of patients with peripheral arterial disease. *J Transl Med* 2013;**11**:230.
169 Gillani S, Cao J, Suzuki T, Hak DJ. The effect of ischemia reperfusion injury on skeletal muscle. *Injury* 2012;**43**:670–5.
170 Pipinos II , Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, et al. The myopathy of peripheral arterial occlusive disease: Part 2. Oxidative stress, neuropathy, and shift in muscle fiber type. *Vasc Endovascular Surg* 2008;**42**:101–12.
171 Pipinos II, Judge AR, Zhu Z, Selsby JT, Swanson SA, Johanning JM, et al. Mitochondrial defects and oxidative damage in patients with peripheral arterial disease. *Free Radic Biol Med* 2006;**41**:262–9.
172 Woods BO. Clinical evaluation of the peripheral vasculature. *Cardiol Clin* 1991;**9**:413–27.
173 Arnold JF. Vascular assessment of the lower extremity with a chronic wound. *Surg Clin North Am* 2020;**100**:807–22.
174 Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA* 2006;**295**:536–46.
175 Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Knottnerus JA. Diagnostic value of signs and symptoms associated with peripheral arterial occlusive disease seen in general practice: a multivariable approach. *Med Decis Making* 1997;**17**:61–70.
176 Nicholson ML, Byrne RL, Steele GA, Callum KG. Predictive value of bruits and Doppler pressure measurements in detecting lower limb arterial stenosis. *Eur J Vasc Surg* 1993;**7**:59–62.
177 Carter SA. Arterial auscultation in peripheral vascular disease. *JAMA* 1981;**246**:1682–6.
178 Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992;**45**:1101–9.
179 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;**45**(Suppl S):S5–67.
180 Killewich LA, Martin R, Cramer M, Beach KW, Strandness Jr DE. Pathophysiology of venous claudication. *J Vasc Surg* 1984;**1**:507–11.
181 Zemaitis MR, Boll JM, Dreyer MA. Peripheral Arterial Disease. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright 2021, StatPearls Publishing LLC.; 2023.
182 Shabani Varaki E, Gargiulo GD, Penkala S, Breen PP. Peripheral vascular disease assessment in the lower limb: a review of current and emerging non-invasive diagnostic methods. *Biomed Eng Online* 2018;**17**:61.
183 Alagha M, Aherne TM, Hassanin A, Zafar AS, Joyce DP, Mahmood W, et al. Diagnostic performance of ankle-brachial pressure index in lower extremity arterial disease. *Surg J (N Y)* 2021;**7**:e132–7.
184 Casey S, Lanting S, Oldmeadow C, Chuter V. The reliability of the ankle brachial index: a systematic review. *J Foot Ankle Res* 2019;**12**:39.
185 Normahani P, Mustafa C, Shalhoub J, Davies AH, Norrie J, Sounderajah V, et al. A systematic review and meta-analysis of the diagnostic accuracy of point-of-care tests used to establish the presence of peripheral arterial disease in people with diabetes. *J Vasc Surg* 2021;**73**:1811–20.
186 Xu L, He R, Hua X, Zhao J, Zhao J, Zeng H, et al. The value of ankle-branchial index screening for cardiovascular disease in type 2 diabetes. *Diabetes Metab Res Rev* 2019;**35**:e3076.
187 Wukich DK, Shen W, Raspovic KM, Suder NC, Baril DT, Avgerinos E. Noninvasive arterial testing in patients with diabetes: a guide for foot and ankle surgeons. *Foot Ankle Int* 2015;**36**:1391–9.
188 Bhowmick R, Bhattacharjee P, Das P. A clinical study of peripheral arterial disease in diabetes mellitus with reference to ankle brachial pressure index and doppler sonography. *J Assoc Physicians India* 2020;**68**:51.
189 AbuRahma AF, Adams E, AbuRahma J, Mata LA, Dean LS, Caron C, et al. Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of diabetes mellitus and chronic kidney disease. *J Vasc Surg* 2020;**71**:937–45.
190 Chuter VH, Searle A, Barwick A, Golledge J, Leigh L, Oldmeadow C, et al. Estimating the diagnostic accuracy of the ankle-brachial pressure index for detecting peripheral arterial disease in people with diabetes: a systematic review and meta-analysis. *Diabet Med* 2021;**38**:e14379.
191 Brouwers J, Willems SA, Goncalves LN, Hamming JF, Schepers A. Reliability of bedside tests for diagnosing peripheral arterial disease in patients prone to medial arterial calcification: a systematic review. *EClinicalMedicine* 2022;**50**:101532.
192 Bauersachs R, Debus S, Nehler M, Huelsebeck M, Balradj J, Bowrin K, et al. A targeted literature review of the disease burden in patients with symptomatic peripheral artery disease. *Angiology* 2020;**71**:303–14.
193 Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation* 2004;**109**:733–9.
194 Velescu A, Clara A, Marti R, Ramos R, Perez-Fernandez S, Marcos L, et al. Abnormally high ankle-brachial index is associated with all-cause and cardiovascular mortality: the REGICOR Study. *Eur J Vasc Endovasc Surg* 2017;**54**:370–7.
195 Golledge J, Moxon JV, Rowbotham S, Pinchbeck J, Quigley F, Jenkins J. High ankle brachial index predicts high risk of cardiovascular events amongst people with peripheral artery disease. *PLoS One* 2020;**15**:e0242228.
196 Fowkes FG, Murray GD, Butcher I, Folsom AR, Hirsch AT, Couper DJ, et al. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. *Eur J Prev Cardiol* 2014;**21**:310–20.
197 Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development Group. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ* 2012;**345**:e4947.
198 Conte MS, Pomposelli FB. Society for Vascular Surgery Practice guidelines for atherosclerotic occlusive disease of the lower extremities management of asymptomatic disease and claudication. Introduction. *J Vasc Surg* 2015;**61**:1S.
199 Niazi K, Khan TH, Easley KA. Diagnostic utility of the two methods of ankle brachial index in the detection of peripheral arterial disease of lower extremities. *Catheter Cardiovasc Interv* 2006;**68**:788–92.
200 Schroder F, Diehm N, Kareem S, Ames M, Pira A, Zwettler U, et al. A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease. *J Vasc Surg* 2006;**44**:531–6.
201 Espinola-Klein C, Rupprecht HJ, Bickel C, Lackner K, Savvidis S, Messow CM, et al. Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. *Circulation* 2008;**118**:961–7.
202 Le Bivic L, Magne J, Guy-Moyat B, Wojtyna H, Lacroix P, Blossier JD, et al. The intrinsic prognostic value of the ankle–brachial index is independent from its mode of calculation. *Vasc Med* 2019;**24**:23–31.
203 O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. *Circulation* 2006;**113**:388–93.
204 Donohue CM, Adler JV, Bolton LL. Peripheral arterial disease screening and diagnostic practice: a scoping review. *Int Wound J* 2020;**17**:32–44.
205 Weragoda J, Seneviratne R, Weerasinghe MC, Wijeyaratne SM. ABPI against colour duplex scan: a screening tool for detection of

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peripheral arterial disease in low resource setting approach to validation. *Int J Vasc Med* 2016;**2016**:1390475.
206 Crawford F, Welch K, Andras A, Chappell FM. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. *Cochrane Database Syst Rev* 2016;**9**:CD010680.
207 Klein S, Hage JJ. Measurement, calculation, and normal range of the ankle-arm index: a bibliometric analysis and recommendation for standardization. *Ann Vasc Surg* 2006;**20**:282–92.
208 Pereira Filho AJG, Sartipy F, Lundin F, Wahlberg E, Sigvant B. Impact of ankle brachial index calculations on peripheral arterial disease prevalence and as a predictor of cardiovascular risk. *Eur J Vasc Endovasc Surg* 2022;**64**:217–24.
209 Chuter VH, Casey SL. Pre-measurement rest time affects magnitude and reliability of toe pressure measurements. *Blood Press* 2015;**24**:185–8.
210 Hoyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. *J Vasc Surg* 2013;**58**:231–8.
211 Tyrrell MR, Wolfe JH. Critical leg ischaemia: an appraisal of clinical definitions. Joint Vascular Research Group. *Br J Surg* 1993;**80**:177–80.
212 Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg* 2014;**59**:220–34.
213 de Graaff JC, Ubbink DT, Legemate DA, de Haan RJ, Jacobs MJ. Interobserver and intraobserver reproducibility of peripheral blood and oxygen pressure measurements in the assessment of lower extremity arterial disease. *J Vasc Surg* 2001;**33**:1033–40.
214 Herraiz-Adillo A, Cavero-Redondo I, Alvarez-Bueno C, Pozuelo-Carrascosa DP, Solera-Martinez M. The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: a systematic review and meta-analysis. *Atherosclerosis* 2020;**315**:81–92.
215 Tehan PE, Santos D, Chuter VH. A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral artery disease. *Vasc Med* 2016;**21**:382–9.
216 Laivuori M, Hakovirta H, Kauhanen P, Sinisalo J, Sund R, Alback A, et al. Toe pressure should be part of a vascular surgeon's first-line investigation in the assessment of lower extremity artery disease and cardiovascular risk of a patient. *J Vasc Surg* 2021;**73**:641–9.
217 Hoogeveen EK, Mackaay AJ, Beks PJ, Kostense PJ, Dekker JM, Heine RJ, et al. Evaluation of the one-minute exercise test to detect peripheral arterial disease. *Eur J Clin Invest* 2008;**38**:290–5.
218 Birkett ST, Harwood AE, Caldow E, Ibeggazene S, Ingle L, Pymer S. A systematic review of exercise testing in patients with intermittent claudication: A focus on test standardisation and reporting quality in randomised controlled trials of exercise interventions. *PLoS One* 2021;**16**:e0249277.
219 Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg* 2009;**50**:322–9.
220 Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991;**23**:402–8.
221 McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation* 2014;**130**:61–8.
222 Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;**47**:1019–24.
223 McDermott MM, Guralnik JM, Tian L, Zhao L, Polonsky TS, Kibbe MR, et al. Comparing 6-minute walk versus treadmill walking distance as outcomes in randomized trials of peripheral artery disease. *J Vasc Surg* 2020;**71**:988–1001.
224 McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. *J Vasc Surg* 2008;**48**:1231–7.
225 Nordanstig J, Broeren M, Hensater M, Perlander A, Osterberg K, Jivegard L. Six-minute walk test closely correlates to "real-life" outdoor walking capacity and quality of life in patients with intermittent claudication. *J Vasc Surg* 2014;**60**:404–9.
226 Sandberg A, Cider A, Jivegard L, Nordanstig J, Wittboldt S, Back M. Test-retest reliability, agreement, and minimal detectable change in the 6-minute walk test in patients with intermittent claudication. *J Vasc Surg* 2020;**71**:197–203.
227 Nordanstig J, Wann-Hansson C, Karlsson J, Lundstrom M, Pettersson M, Morgan MB. Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg* 2014;**59**:700–7.
228 Collins R, Cranny G, Burch J, Aguiar-Ibanez R, Craig D, Wright K, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. *Health Technol Assess* 2007;**11**, iii–iv, xi–xiii, 1–184.
229 Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US–a meta-analysis. *Radiology* 2000;**216**:67–77.
230 Jens S, Koelemay MJ, Reekers JA, Bipat S. Diagnostic performance of computed tomography angiography and contrast-enhanced magnetic resonance angiography in patients with critical limb ischaemia and intermittent claudication: systematic review and meta-analysis. *Eur Radiol* 2013;**23**:3104–14.
231 Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 2009;**301**:415–24.
232 Heijenbrok-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: multidetector CT angiography meta-analysis. *Radiology* 2007;**245**:433–9.
233 Sun Z. Diagnostic accuracy of multislice CT angiography in peripheral arterial disease. *J Vasc Interv Radiol* 2006;**17**:1915–21.
234 van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury - Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors: recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2018;**28**:2845–55.
235 Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet* 2017;**389**:1312–22.
236 van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients: recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2018;**28**:2856–69.
237 Menke J, Larsen J. Meta-analysis: accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. *Ann Intern Med* 2010;**153**:325–34.
238 Koelemay MJ, Lijmer JG, Stoker J, Legemate DA, Bossuyt PM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. *JAMA* 2001;**285**:1338–45.
239 Nelemans PJ, Leiner T, de Vet HC, van Engelshoven JM. Peripheral arterial disease: meta-analysis of the diagnostic performance of MR angiography. *Radiology* 2000;**217**:105–14.

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240 Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. [2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA)]. *G Ital Cardiol (Rome)* 2022;**23**:e1–94.
241 Kallen AJ, Jhung MA, Cheng S, Hess T, Turabelidze G, Abramova L, et al. Gadolinium-containing magnetic resonance imaging contrast and nephrogenic systemic fibrosis: a case-control study. *Am J Kidney Dis* 2008;**51**:966–75.
242 Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a Group II gadolinium-based contrast agent: a systematic review and meta-analysis. *JAMA Intern Med* 2020;**180**:223–30.
243 Cavallo AU, Koktzoglou I, Edelman RR, Gilkeson R, Mihai G, Shin T, et al. Noncontrast magnetic resonance angiography for the diagnosis of peripheral vascular disease. *Circ Cardiovasc Imaging* 2019;**12**:e008844.
244 Takahashi M, Koga Y, Bussaka H, Miyawaki M. The value of digital subtraction angiography in peripheral vascular diseases. *Br J Radiol* 1984;**57**:123–32.
245 Blakeman BM, Littooy FN, Baker WH. Intra-arterial digital subtraction angiography as a method to study peripheral vascular disease. *J Vasc Surg* 1986;**4**:168–73.
246 Yong OY, Ma HP, Gu SB, Zhou QH, Zhang SL, Liu PZ, et al. Clinical application of DSA and evaluation of its methods: analysis of 160 cases and review of literature. *Radiat Med* 1990;**8**:71–8.
247 Ghumman SS, Weinerman J, Khan A, Cheema MS, Garcia M, Levin D, et al. Contrast induced-acute kidney injury following peripheral angiography with carbon dioxide versus iodinated contrast media: a meta-analysis and systematic review of current literature. *Catheter Cardiovasc Interv* 2017;**90**:437–48.
248 Verma M, Pandey NN, Singh V, Jagia P. A meta-analysis of the diagnostic performance of quiescent-interval-single-shot magnetic resonance angiography in peripheral arterial disease. *Eur Radiol* 2022;**32**:2393–403.
249 de Graaff JC, Ubbink DT, Legemate DA, Tijssen JG, Jacobs MJ. Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischemia: a diagnostic randomized clinical trial. *J Vasc Surg* 2003;**38**:528–34.
250 Rother U, Lang W, Horch RE, Ludolph I, Meyer A, Gefeller O, et al. Pilot assessment of the angiosome concept by intra-operative fluorescence angiography after tibial bypass surgery. *Eur J Vasc Endovasc Surg* 2018;**55**:215–21.
251 Rother U, Krenz K, Lang W, Horch RE, Schmid A, Heinz M, et al. Immediate changes of angiosome perfusion during tibial angioplasty. *J Vasc Surg* 2017;**65**:422–30.
252 Castronuovo Jr JJ, Adera HM, Smiell JM, Price RM. Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. *J Vasc Surg* 1997;**26**:629–37.
253 Eiken FL, Pedersen BL, Baekgaard N, Eiberg JP. Diagnostic methods for measurement of peripheral blood flow during exercise in patients with type 2 diabetes and peripheral artery disease: a systematic review. *Int Angiol* 2019;**38**:62–9.
254 Eslahpazir BA, Allemang MT, Lakin RO, Carman TL, Trivonovich MR, Wong VL, et al. Pulse volume recording does not enhance segmental pressure readings for peripheral arterial disease stratification. *Ann Vasc Surg* 2014;**28**:18–27.
255 Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev* 2020;**36**(Suppl 1):e3278.
256 Leenstra B, Wijnand J, Verhoeven B, Koning O, Teraa M, Verhaar MC, et al. Applicability of transcutaneous oxygen tension measurement in the assessment of chronic limb-threatening ischemia. *Angiology* 2020;**71**:208–16.
257 Ma KF, Kleiss SF, Schuurmann RCL, Bokkers RPH, Unlu C, De Vries JPM. A systematic review of diagnostic techniques to determine tissue perfusion in patients with peripheral arterial disease. *Expert Rev Med Devices* 2019;**16**:697–710.
258 Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diabetes Metab Res Rev* 2020;**36**(Suppl 1):e3279.
259 Wermelink B, Ma KF, Haalboom M, El Moumni M, de Vries JPM, Geelkerken RH. A systematic review and critical appraisal of peri-procedural tissue perfusion techniques and their clinical value in patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2021;**62**:896–908.
260 Abraham P, Colas-Ribas C, Signolet I, Ammi M, Feuilloy M, Picquet J, et al. Transcutaneous exercise oximetry for patients with claudication - a retrospective review of approximately 5,000 consecutive tests over 15 years. *Circ J* 2018;**82**:1161–7.
261 Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. *Diabetes Metab Res Rev* 2020;**36**(Suppl 1):e3277.
262 Torngren K, Eriksson S, Arvidsson J, Falkenberg M, Johnsson AA, Sjoberg C, et al. A reperfusion BOLD-MRI tissue perfusion protocol reliably differentiate patients with peripheral arterial occlusive disease from healthy controls. *J Clin Med* 2021;**10**:3643.
263 Behrendt CA, Bjorck M, Schwaneberg T, Debus ES, Cronenwett J, Sigvant B, et al. Editor's Choice - Recommendations for Registry Data Collection for Revascularisations of Acute Limb Ischaemia: A Delphi Consensus from the International Consortium of Vascular Registries. *Eur J Vasc Endovasc Surg* 2019;**57**:816–21.
264 Behrendt CA, Bertges D, Eldrup N, Beck AW, Mani K, Venermo M, et al. International Consortium of Vascular Registries Consensus Recommendations for Peripheral Revascularisation Registry Data Collection. *Eur J Vasc Endovasc Surg* 2018;**56**:217–37.
265 Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta* 1954;**21**:499–533.
266 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;**26**:517–38.
267 Committee TS, Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Endovasc Ther* 2015;**22**:663–77.
268 Fridh EB, Ludwigs K, Svalkvist A, Andersson M, Nordanstig J, Falkenberg M, et al. Comparison of magnetic resonance angiography and digital subtraction angiography for the assessment of infrapopliteal arterial occlusive lesions, based on the TASC II Classification Criteria. *Diagnostics (Basel)* 2020;**10**:892.
269 Bollinger A, Breddin K, Hess H, Heystraten FM, Kollath J, Konttila A, et al. Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. *Atherosclerosis* 1981;**38**:339–46.
270 Rondinelli RD, Genovese E, Katz RT, Mayer TG, Mueller KL, Ranavaya MI, et al. *AMA Guides to the Evaluation of Permanent Impairment*. 6th Edition 2008.
271 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg* 2019;**58**:S1–109.

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272 Nehler MR, McDermott MM, Treat-Jacobson D, Chetter I, Regensteiner JG. Functional outcomes and quality of life in peripheral arterial disease: current status. *Vasc Med* 2003;**8**:115–26.
273 Aber A, Lumley E, Phillips P, Woods HB, Jones G, Michaels J. Themes that determine quality of life in patients with peripheral arterial disease: a systematic review. *Patient* 2018;**11**:489–502.
274 Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2021. Version 6.2.
275 Rymer JA, Mulder H, Smolderen KG, Hiatt WR, Conte MS, Berger JS, et al. Association of Health Status Scores with cardiovascular and limb outcomes in patients with symptomatic peripheral artery disease: insights from the EUCLID (Examining Use of Ticagrelor in Symptomatic Peripheral Artery Disease) Trial. *J Am Heart Assoc* 2020;**9**:e016573.
276 Mays RJ, Casserly IP, Kohrt WM, Ho PM, Hiatt WR, Nehler MR, et al. Assessment of functional status and quality of life in claudication. *J Vasc Surg* 2011;**53**:1410–21.
277 Poku E, Duncan R, Keetharuth A, Essat M, Phillips P, Woods HB, et al. Patient-reported outcome measures in patients with peripheral arterial disease: a systematic review of psychometric properties. *Health Qual Life Outcomes* 2016;**14**:161.
278 Conijn AP, Jens S, Terwee CB, Breek JC, Koelemay MJ. Assessing the quality of available patient reported outcome measures for intermittent claudication: a systematic review using the COSMIN checklist. *Eur J Vasc Endovasc Surg* 2015;**49**:316–34.
279 Kumlien C, Nordanstig J, Lundstrom M, Pettersson M. Validity and test retest reliability of the vascular quality of life Questionnaire-6: a short form of a disease-specific health-related quality of life instrument for patients with peripheral arterial disease. *Health Qual Life Outcomes* 2017;**15**:187.
280 Larsen ASF, Reiersen AT, Jacobsen MB, Klow NE, Nordanstig J, Morgan M, et al. Validation of the Vascular quality of life questionnaire - 6 for clinical use in patients with lower limb peripheral arterial disease. *Health Qual Life Outcomes* 2017;**15**:184.
281 McDermott MM, Lloyd-Jones DM. The role of biomarkers and genetics in peripheral arterial disease. *J Am Coll Cardiol* 2009;**54**:1228–37.
282 Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. *J Periodontol* 2008;**79**:1544–51.
283 Pradhan AD, Shrivastava S, Cook NR, Rifai N, Creager MA, Ridker PM. Symptomatic peripheral arterial disease in women: nontraditional biomarkers of elevated risk. *Circulation* 2008;**117**:823–31.
284 McDermott MM, Ferrucci L, Guralnik JM, Tian L, Green D, Liu K, et al. Elevated levels of inflammation, d-dimer, and homocysteine are associated with adverse calf muscle characteristics and reduced calf strength in peripheral arterial disease. *J Am Coll Cardiol* 2007;**50**:897–905.
285 Goodman MN. Interleukin-6 induces skeletal muscle protein breakdown in rats. *Proc Soc Exp Biol Med* 1994;**205**:182–5.
286 McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Green D, et al. Circulating blood markers and functional impairment in peripheral arterial disease. *J Am Geriatr Soc* 2008;**56**:1504–10.
287 Igari K, Kudo T, Toyofuku T, Inoue Y. Relationship of inflammatory biomarkers with severity of peripheral arterial disease. *Int J Vasc Med* 2016;**2016**:6015701.
288 Signorelli SS, Anzaldi M, Libra M, Navolanic PM, Malaponte G, Mangano K, et al. Plasma levels of inflammatory biomarkers in peripheral arterial disease: results of a cohort study. *Angiology* 2016;**67**:870–4.
289 Signorelli SS, Mazzarino MC, Di Pino L, Malaponte G, Porto C, Pennisi G, et al. High circulating levels of cytokines (IL-6 and TNFalpha), adhesion molecules (VCAM-1 and ICAM-1) and selectins in patients with peripheral arterial disease at rest and after a treadmill test. *Vasc Med* 2003;**8**:15–9.
290 Engelberger RP, Limacher A, Kucher N, Baumann F, Silbernagel G, Benghozi R, et al. Biological variation of established and novel biomarkers for atherosclerosis: results from a prospective, parallel-group cohort study. *Clin Chim Acta* 2015;**447**:16–22.
291 Pande RL, Brown J, Buck S, Redline W, Doyle J, Plutzky J, et al. Association of monocyte tumor necrosis factor alpha expression and serum inflammatory biomarkers with walking impairment in peripheral artery disease. *J Vasc Surg* 2015;**61**:155–61.
292 Valkova M, Lazurova I, Petrasova D, Frankovicova M, Dravecka I. Humoral predictors of ankle-brachial index in patients with peripheral arterial disease and controls. *Bratisl Lek Listy* 2018;**119**:646–50.
293 Saenz-Pipaon G, San Martin P, Planell N, Maillo A, Ravassa S, Vilas-Zornoza A, et al. Functional and transcriptomic analysis of extracellular vesicles identifies calprotectin as a new prognostic marker in peripheral arterial disease (PAD). *J Extracell Vesicles* 2020;**9**:1729646.
294 Signorelli SS, Anzaldi M, Fiore V, Simili M, Puccia G, Libra M, et al. Patients with unrecognized peripheral arterial disease (PAD) assessed by ankle-brachial index (ABI) present a defined profile of proinflammatory markers compared to healthy subjects. *Cytokine* 2012;**59**:294–8.
295 Matsushita K, Kwak L, Yang C, Pang Y, Ballew SH, Sang Y, et al. High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Eur Heart J* 2018;**39**:2412–9.
296 Fatemi S, Acosta S, Gottsater A, Melander O, Engstrom G, Dakhel A, et al. Copeptin, B-type natriuretic peptide and cystatin C are associated with incident symptomatic PAD. *Biomarkers* 2019;**24**:615–21.
297 Zhou SS, Jin JP, Wang JQ, Zhang ZG, Freedman JH, Zheng Y, et al. miRNAS in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. *Acta Pharmacol Sin* 2018;**39**:1073–84.
298 Schwartz GG, Steg PG, Szarek M, Bittner VA, Diaz R, Goodman SG, et al. Peripheral artery disease and venous thromboembolic events after acute coronary syndrome: role of lipoprotein(a) and modification by alirocumab: prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial. *Circulation* 2020;**141**:1608–17.
299 Golledge J, Rowbotham S, Velu R, Quigley F, Jenkins J, Bourke M, et al. Association of serum lipoprotein (a) with the requirement for a peripheral artery operation and the incidence of major adverse cardiovascular events in people with peripheral artery disease. *J Am Heart Assoc* 2020;**9**:e015355.
300 Kheirkhah A, Lamina C, Rantner B, Kollerits B, Stadler M, Pohlhammer J, et al. Elevated levels of serum PCSK9 in male patients with symptomatic peripheral artery disease: the CAVASIC study. *Atherosclerosis* 2021;**316**:41–7.
301 Yanaka K, Akahori H, Imanaka T, Miki K, Yoshihara N, Kimura T, et al. Relationship between lipoprotein(a) and angiographic severity of femoropopliteal lesions. *J Atheroscler Thromb* 2021;**28**:555–61.
302 Kremers B, Wubbeke L, Mees B, Ten Cate H, Spronk H, Ten Cate-Hoek A. Plasma biomarkers to predict cardiovascular outcome in patients with peripheral artery disease: a systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol* 2020;**40**:2018–32.
303 GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* 2017;**389**:1885–906.
304 Young JC, Paul NJ, Karatas TB, Kondrasov SA, McGinigle KL, Crowner JR, et al. Cigarette smoking intensity informs outcomes after open revascularization for peripheral artery disease. *J Vasc Surg* 2019;**70**:1973–1983 e5.
305 Kaschwich M, Peters F, Hischke S, Riess HC, Gansel M, Marschall U, et al. Long-term incidence of cancer after index

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treatment for symptomatic peripheral arterial disease - a health insurance claims data analysis. *Vasa* 2020;**49**:493–9.

306 Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg* 2014;**60**:1565–71.

307 Reitz KM, Althouse AD, Meyer J, Arya S, Goodney PP, Shireman PK, et al. Association of smoking with postprocedural complications following open and endovascular interventions for intermittent claudication. *JAMA Cardiol* 2022;**7**:45–54.

308 Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;**163**:608–21.

309 Hennrikus D, Joseph AM, Lando HA, Duval S, Ukestad L, Kodl M, et al. Effectiveness of a smoking cessation program for peripheral artery disease patients: a randomized controlled trial. *J Am Coll Cardiol* 2010;**56**:2105–12.

310 US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Interventions for tobacco smoking cessation in adults, including pregnant persons: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021;**325**:265–79.

311 Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2018;**72**:3332–65.

312 Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med* 2015;**175**:504–11.

313 Wayne GF, Connolly G, Henningfield J. Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents. *Tobacco Control* 2006;**15**:189–98.

314 McNeill A, Simonavicius E, Brose L, Taylor E, East K, Zuikova E, et al. Nicotine vaping in England: an evidence update including health risks and perceptions, 2022. *A report commissioned by the Office for Health Improvement and Disparities*. London: Office for Health Improvement and Disparities 2022; 2022.

315 Peruzzi M, Biondi-Zoccai G, Carnevale R, Cavarretta E, Frati G, Versaci F. Vaping cardiovascular health risks: an updated umbrella review. *Curr Emerg Hosp Med Rep* 2020;**8**:103–9.

316 Wilson N, Summers JA, Ait Ouakrim D, Hoek J, Edwards R, Blakely T. Improving on estimates of the potential relative harm to health from using modern ENDS (vaping) compared to tobacco smoking. *BMC Public Health* 2021;**21**:2038.

317 Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2021;**9**:CD010216.

318 Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**:685–91.

319 Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Ann Intern Med* 2001;**135**:423–33.

320 Suissa K, Lariviere J, Eisenberg MJ, Eberg M, Gore GC, Grad R, et al. Efficacy and safety of smoking cessation interventions in patients with cardiovascular disease: a network meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2017;**10**:e002458.

321 Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA* 2014;**311**:155–63.

322 Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri M-A, Morris PB, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2018;**72**:3332–65.

323 Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;**387**:2507–20.

324 Morgan GD, Noll EL, Orleans CT, Rimer BK, Amfoh K, Bonney G. Reaching midlife and older smokers: tailored interventions for routine medical care. *Prev Med* 1996;**25**:346–54.

325 Canga N, De Irala J, Vara E, Duaso MJ, Ferrer A, Martinez-Gonzalez MA. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. *Diabetes Care* 2000;**23**:1455–60.

326 Weissfeld JL, Holloway JL. Treatment for cigarette smoking in a Department of Veterans Affairs outpatient clinic. *Arch Intern Med* 1991;**151**:973–7.

327 Bock B, Heron K, Jennings E, Morrow K, Cobb V, Magee J, et al. A text message delivered smoking cessation intervention: the initial trial of TXT-2-Quit: randomized controlled trial. *JMIR Mhealth Uhealth* 2013;**1**:e17.

328 Smith BJ, Carson KV, Brinn MP, Labiszewski NA, Peters MJ, Fitridge R, et al. Smoking Termination Opportunity for in-Patients (STOP): superiority of a course of varenicline tartrate plus counselling over counselling alone for smoking cessation: a 12-month randomised controlled trial for inpatients. *Thorax* 2013;**68**:485–6.

329 Carson-Chahhoud KV, Smith BJ, Peters MJ, Brinn MP, Ameer F, Singh K, et al. Two-year efficacy of varenicline tartrate and counselling for inpatient smoking cessation (STOP study): a randomized controlled clinical trial. *PLoS One* 2020;**15**:e0231095.

330 Hennrikus D, Joseph AM, Lando HA, Duval S, Ukestad L, Kodl M, et al. Effectiveness of a smoking cessation program for peripheral artery disease patients: a randomized controlled trial. *J Am Coll Cardiol* 2010;**56**:2105–12.

331 Goodney PP, Spangler EL, Newhall K, Brooke BS, Schanzer A, Tan TW, et al. Feasibility and pilot efficacy of a brief smoking cessation intervention delivered by vascular surgeons in the Vascular Physician Offer and Report (VAPOR) Trial. *J Vasc Surg* 2017;**65**:1152–11560 e2.

332 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol* 2022;**29**:5–115.

333 Lopez-Laguna N, Martinez-Gonzalez MA, Toledo E, Babio N, Sorli JV, Ros E, et al. Risk of peripheral artery disease according to a healthy lifestyle score: the PREDIMED study. *Atherosclerosis* 2018;**275**:133–40.

334 Nosova EV, Conte MS, Grenon SM. Advancing beyond the "heart-healthy diet" for peripheral arterial disease. *J Vasc Surg* 2015;**61**:265–74.

335 Tharrey M, Mariotti F, Mashchak A, Barbillon P, Delattre M, Fraser GE. Patterns of plant and animal protein intake are strongly associated with cardiovascular mortality: the Adventist Health Study-2 cohort. *Int J Epidemiol* 2018;**47**:1603–12.

336 Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med* 2017;**377**:143–53.

337 Adegbola A, Behrendt CA, Zyriax BC, Windler E, Kreutzburg T. The impact of nutrition on the development and progression of peripheral artery disease: a systematic review. *Clin Nutr* 2022;**41**:49–70.

338 Mahe G, Carsin M, Zeeny M, De Bosschere JP. Dietary pattern, a modifiable risk factor that can be easily assessed for

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atherosclerosis vascular disease prevention in clinical practice. *Public Health Nutr* 2011;**14**:319–26.

339 Lee WW, Choi KC, Yum RW, Yu DS, Chair SY. Effectiveness of motivational interviewing on lifestyle modification and health outcomes of clients at risk or diagnosed with cardiovascular diseases: a systematic review. *Int J Nurs Stud* 2016;**53**:331–41.

340 Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al. Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: a Scientific Statement From the American Heart Association. *Circulation* 2016;**134**:e505–29.

341 Mattioli AV, Coppi F, Migaldi M, Scicchitano P, Ciccone MM, Farinetti A. Relationship between Mediterranean diet and asymptomatic peripheral arterial disease in a population of premenopausal women. *Nutr Metab Cardiovasc Dis* 2017;**27**:985–90.

342 Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, Corella D, Fito M, Ros E, et al. Benefits of the Mediterranean Diet: insights from the PREDIMED Study. *Prog Cardiovasc Dis* 2015;**58**:50–60.

343 Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329–40.

344 Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. *Drugs Aging* 2003;**20**:817–32.

345 Katsimpris A, Linseisen J, Meisinger C, Volaklis K. The association between polypharmacy and physical function in older adults: a systematic review. *J Gen Intern Med* 2019;**34**:1865–73.

346 Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse outcomes of polypharmacy in older people: systematic review of reviews. *J Am Med Dir Assoc* 2020;**21**:181–7.

347 Masson W, Lobo M, Barbagelata L, Molinero G, Bluro I. Effects of lipid-lowering therapy on major adverse limb events in patients with peripheral arterial disease: a meta-analysis of randomized clinical trials. *Vascular* 2022;**30**:1134–41.

348 Nastasi DR, Moxon JV, Norman R, Trollope AF, Rowbotham S, Quigley F, et al. The cost-effectiveness of intensive low-density lipoprotein cholesterol lowering in people with peripheral artery disease. *J Vasc Surg* 2021;**73**:1396–13403 e3.

349 Hess CN, Cannon CP, Beckman JA, Goodney PP, Patel MR, Hiatt WR, et al. Effectiveness of blood lipid management in patients with peripheral artery disease. *J Am Coll Cardiol* 2021;**77**:3016–27.

350 Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–72.

351 Boren J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2020;**41**:2313–30.

352 Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–88.

353 Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–61.

354 Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, et al. High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease. *J Am Heart Assoc* 2017;**6**:e005699.

355 Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018;**137**:1571–82.

356 Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–97.

357 Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–22.

358 Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:941–50.

359 Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* 2018;**137**:338–50.

360 Laschkolnig A, Kollerits B, Lamina C, Meisinger C, Rantner B, Stadler M, et al. Lipoprotein (a) concentrations, apolipoprotein (a) phenotypes, and peripheral arterial disease in three independent cohorts. *Cardiovasc Res* 2014;**103**:28–36.

361 Antoniou GA, Hajibandeh S, Hajibandeh S, Vallabhaneni SR, Brennan JA, Torella F. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. *J Vasc Surg* 2015;**61**:519–532 e1.

362 Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007;**45**:645–54, discussion 653–4.

363 Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith Jr SC, Goto S, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;**35**:2864–72.

364 Peters F, Kuchenbecker J, Kreutzburg T, Marschall U, Debus ES, Behrendt CA. Long-term effectiveness and safety of initiating statin therapy after index revascularization in patients with peripheral arterial occlusive disease. *J Am Heart Assoc* 2020;**9**:e018338.

365 Ramos R, Garcia-Gil M, Comas-Cufi M, Quesada M, Marrugat J, Elosua R, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol* 2016;**67**:630–40.

366 Vogel TR, Dombrovskiy VY, Galinanes EL, Kruse RL. Preoperative statins and limb salvage after lower extremity revascularization in the Medicare population. *Circ Cardiovasc Interv* 2013;**6**:694–700.

367 Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011;**104**:109–24.

368 Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2017;**2**:47–54.

369 De Martino RR, Eldrup-Jorgensen J, Nolan BW, Stone DH, Adams J, Bertges DJ, et al. Perioperative management with antiplatelet and statin medication is associated with reduced

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mortality following vascular surgery. *J Vasc Surg* 2014;**59**:1615–21. 21 e1.

370 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–78.

371 Cholesterol Treatment Trialists Collaborators, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–405.

372 Leya M, Stone NJ. Statin prescribing in the elderly: special considerations. *Curr Atheroscler Rep* 2017;**19**:47.

373 Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, Katsaros I, Jawaid O, Jonnalagadda AK, et al. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: a systematic review and meta-analysis. *Vasc Med* 2020;**25**:106–17.

374 Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Wahlberg E. Risk factor profiles and use of cardiovascular drug prevention in women and men with peripheral arterial disease. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:39–46.

375 Belch JJF, Brodmann M, Baumgartner I, Binder CJ, Casula M, Heiss C, et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease. *Vasa* 2021;**50**:401–11.

376 Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, et al. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. *Hypertension* 2010;**55**:48–53.

377 Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O, et al. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. *J Am Coll Cardiol* 2006;**47**:1182–7.

378 Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 2004;**25**:17–24.

379 Otterstad JE, Sleight P. The HOPE study: comparison with other trials of secondary prevention. *Eur Heart J* 2001;**22**:1307–10.

380 Sleight P. The HOPE Study (Heart Outcomes Prevention Evaluation). *J Renin Angiotensin Aldosterone Syst* 2000;**1**:18–20.

381 Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.

382 Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;**359**:1225–37.

383 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;**288**:2981–97.

384 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–13.

385 Geldsetzer P, Manne-Goehler J, Marcus ME, Ebert C, Zhumadilov Z, Wesseh CS, et al. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet* 2019;**394**:652–62.

386 NCD Risk Factor Collaboration. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet* 2019;**394**:639–51.

387 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–81.

388 He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ* 2013;**346**:f1325.

389 Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of different dietary interventions on blood pressure: systematic review and meta-analysis of randomized controlled trials. *Hypertension* 2016;**67**:733–9.

390 Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Health* 2017;**2**:e108–20.

391 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.

392 Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* 2020;**75**:1334–57.

393 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Blood Press* 2018;**27**:314–40.

394 Diehm C, Pittrow D, Lawall H. Effect of nebivolol vs. hydrochlorothiazide on the walking capacity in hypertensive patients with intermittent claudication. *J Hypertens* 2011;**29**:1448–56.

395 Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev* 2013;**2013**:CD005508.

396 Espinola-Klein C, Weisser G, Jagodzinski A, Savvidis S, Warnholtz A, Ostad MA, et al. beta-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial. *Hypertension* 2011;**58**:148–54.

397 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337.

398 Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. [2018 ESC/ESH Guidelines for the management of arterial hypertension]. *Kardiol Pol* 2019;**77**:71–159.

399 Kleinherenbrink W, Osei E, den Hertog HM, Zandbergen AAM. Prediabetes and macrovascular disease: review of the association, influence on outcome and effect of treatment. *Eur J Intern Med* 2018;**55**:6–11.

400 Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.

401 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. *Diabetes Care* 2021;**44**:S111–24.

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402 Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016;**316**:313–24.
403 Escobar C, Barrios V, Cosin J, Gamez Martinez JM, Huelmos Rodrigo AI, Ortiz Cortes C, et al. SGLT2 inhibitors and GLP1 agonists administered without metformin compared to other glucose-lowering drugs in patients with type 2 diabetes mellitus to prevent cardiovascular events: a systematic review. *Diabet Med* 2021;**38**:e14502.
404 Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019;**139**:2022–31.
405 Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;**7**:776–85.
406 Marchiori E, Rodionov RN, Peters F, Magnussen C, Nordanstig J, Gombert A, et al. SGLT2 inhibitors and peripheral vascular events: a review of the literature. *Heart Fail Clin* 2022;**18**:609–23.
407 Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46.
408 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–57.
409 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57.
410 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28.
411 McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
412 Vlachopoulos C, Terentes-Printzios D, Tsioufis K. Do SGLT2 inhibitors increase the risk of amputation? Make haste slowly. *Eur Heart J* 2021;**42**:1739–41.
413 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:837–53.
414 Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
415 Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008;**359**:1565–76.
416 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89.
417 Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2018;**2**:CD004876.
418 Peters F, Marschall U, Behrendt CA. Prevalence of COVID-19 risk factors and risks of severe acute respiratory disease are markedly higher in patients with symptomatic peripheral arterial occlusive disease. *Eur J Vasc Endovasc Surg* 2021;**61**:859–60.
419 Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J* 2004;**25**:25–31.
420 Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J* 2008;**29**:1350–8.
421 Smolderen KG, Lee M, Arora T, Simonov M, Mena-Hurtado C. Peripheral artery disease and COVID-19 outcomes: insights from the Yale DOM-CovX Registry. *Curr Probl Cardiol* 2022;**47**:101007.
422 Jongkind V, Earnshaw JJ, Bastos Goncalves F, Cochennec F, Debus ES, Hinchliffe R, et al. Editor's Choice - Update of the European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia in light of the COVID-19 pandemic, based on a scoping review of the literature. *Eur J Vasc Endovasc Surg* 2022;**63**:80–9.
423 Gal D, Thijs B, Glanzel W, Sipido KR. Hot topics and trends in cardiovascular research. *Eur Heart J* 2019;**40**:2363–74.
424 Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017;**14**:156–70.
425 Suarez C, Zeymer U, Limbourg T, Baumgartner I, Cacoub P, Poldermans D, et al. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. *Vasc Med* 2010;**15**:259–65.
426 Mahe G, Boge G, Bura-Riviere A, Chakfe N, Constans J, Goueffic Y, et al. Disparities between international guidelines (AHA/ESC/ESVS/ESVM/SVS) concerning lower extremity arterial disease: Consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE). *Ann Vasc Surg* 2021;**72**:1–56.
427 McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the Women's Health and Aging Study. *Circulation* 2000;**101**:1007–12.
428 McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA* 2004;**292**:453–61.
429 McDermott MM, Tiukinhoy S, Greenland P, Liu K, Pearce WH, Guralnik JM, et al. A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication. *J Cardiopulm Rehabil* 2004;**24**:187–96.
430 Laslovich S, Alvar BA, Allison M, Rauh MJ. Effects of lifestyle physical activity on vascular function in asymptomatic peripheral arterial disease. *Med Sci Sports Exerc* 2020;**52**:8–15.
431 Farhad A, Farooqui SI, Amjad S, Khan AA. Role of structured and supervised exercise programmes in peripheral artery disease patients with and without claudication - a systematic review and metaanalysis. *J Pak Med Assoc* 2019;**69**:874–8.
432 McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA* 2009;**301**:165–74.
433 McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA* 2013;**310**:57–65.
434 Itoga NK, Minami HR, Chelvakumar M, Pearson K, Mell MM, Bendavid E, et al. Cost-effectiveness analysis of asymptomatic peripheral artery disease screening with the ABI test. *Vasc Med* 2018;**23**:97–106.
435 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337.

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436 Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc* 2019;**51**:1270–81.
437 Powell KE, King AC, Buchner DM, Campbell WW, DiPietro L, Erickson KI, et al. The Scientific Foundation for the Physical Activity Guidelines for Americans, 2nd Edition. *J Phys Act Health* 2018:1–11.
438 Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;**337**:a1840.
439 Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 2010;**303**:841–8.
440 Ambler GK, Waldron CA, Contractor UB, Hinchliffe RJ, Twine CP. Umbrella review and meta-analysis of antiplatelet therapy for peripheral artery disease. *Br J Surg* 2020;**107**:20–32.
441 Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;**337**:a1840.
442 Sigvant B, Henriksson M, Lundin F, Wahlberg E. Asymptomatic peripheral arterial disease: is pharmacological prevention of cardiovascular risk cost-effective? *Eur J Cardiovasc Prev Rehabil* 2011;**18**:254–61.
443 Heald CL, Fowkes FG, Murray GD, Price JF, Ankle Brachial Index C. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis* 2006;**189**:61–9.
444 Qu B, Liu Q, Li J. Systematic review of association between low ankle-brachial index and all-cause cardiovascular, or non-cardiovascular mortality. *Cell Biochem Biophys* 2015;**73**:571–5.
445 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;**135**:e686–725.
446 Mazari FA, Khan JA, Carradice D, Samuel N, Gohil R, McCollum PT, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg* 2013;**100**:1172–9.
447 Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. *Circulation* 2014;**130**:939–47.
448 Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Two-year results from a randomized clinical trial of revascularization in patients with intermittent claudication. *Br J Surg* 2016;**103**:1290–9.
449 Djerf H, Millinger J, Falkenberg M, Jivegard L, Svensson M, Nordanstig J. Absence of long-term benefit of revascularization in patients with intermittent claudication: five-year results from the IRONIC randomized controlled trial. *Circ Cardiovasc Interv* 2020;**13**:e008450.
450 Reynolds MR, Apruzzese P, Galper BZ, Murphy TP, Hirsch AT, Cutlip DE, et al. Cost-effectiveness of supervised exercise, stenting, and optimal medical care for claudication: results from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial. *J Am Heart Assoc* 2014;**3**:e001233.
451 Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg* 2008;**48**:1472–80.
452 Fokkenrood HJ, Scheltinga MR, Koelemay MJ, Breek JC, Hasaart F, Vahl AC, et al. Significant savings with a stepped care model for treatment of patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2014;**48**:423–9.
453 van den Houten MM, Lauret GJ, Fakhry F, Fokkenrood HJ, van Asselt AD, Hunink MG, et al. Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. *Br J Surg* 2016;**103**:1616–25.
454 Fakhry F, Rouwet EV, Spillenaar Bilgen R, van der Laan L, Wever JJ, Teijink JAW, et al. Endovascular revascularization plus supervised exercise versus supervised exercise only for intermittent claudication: a cost-effectiveness analysis. *Circ Cardiovasc Interv* 2021;**14**:e010703.
455 Hageman D, Fokkenrood HJP, Essers PPM, Koelemay MJW, Breek JC, Vahl AC, et al. Improved adherence to a stepped-care model reduces costs of intermittent claudication treatment in the Netherlands. *Eur J Vasc Endovasc Surg* 2017;**54**:51–7.
456 Treesak C, Kasemsup V, Treat-Jacobson D, Nyman JA, Hirsch AT. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. *Vasc Med* 2004;**9**:279–85.
457 de Vries SO, Visser K, de Vries JA, Wong JB, Donaldson MC, Hunink MG. Intermittent claudication: cost-effectiveness of revascularization versus exercise therapy. *Radiology* 2002;**222**:25–36.
458 Koelemay MJW, van Reijen NS, van Dieren S, Frans FA, Vermeulen EJG, Buscher H, et al. Editor's Choice - Randomised clinical trial of supervised exercise therapy vs. endovascular revascularisation for intermittent claudication caused by iliac artery obstruction: the SUPER study. *Eur J Vasc Endovasc Surg* 2022;**63**:421–9.
459 van Reijen NS, van Dieren S, Frans FA, Reekers JA, Metz R, Buscher H, et al. Cost effectiveness of endovascular revascularisation vs. exercise therapy for intermittent claudication due to iliac artery obstruction. *Eur J Vasc Endovasc Surg* 2022;**63**:430–7.
460 Lauret GJ, Gijsbers HJ, Hendriks EJ, Bartelink ML, de Bie RA, Teijink JA. The ClaudicatioNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vasc Health Risk Manag* 2012;**8**:495–503.
461 Jansen SCP, van Nistelrooij LPJ, Scheltinga MRM, Rouwet EV, Teijink JAW, Vahl AC. Successful implementation of the exercise first approach for intermittent claudication in the Netherlands is associated with few lower limb revascularisations. *Eur J Vasc Endovasc Surg* 2020;**60**:881–7.
462 Mazari FAK, Khan JA, Carradice D, Samuel N, Gohil R, McCollum PT, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg* 2013;**100**:1172–9.
463 Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PMT, Hunink MGM. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg* 2008;**48**:1472–80.
464 Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, et al. Optimal exercise programs for patients with peripheral artery disease: a Scientific Statement from the American Heart Association. *Circulation* 2019;**139**:e10–33.
465 Rodrigues E, Silva I. Supervised exercise therapy in intermittent claudication: a systematic review of clinical impact and limitations. *Int Angiol* 2020;**39**:60–75.
466 Harwood AE, Cayton T, Sarvanandan R, Lane R, Chetter I. A review of the potential local mechanisms by which exercise

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improves functional outcomes in intermittent claudication. *Ann Vasc Surg* 2016;**30**:312–20.
467 Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2017;**12**:CD000990.
468 Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. *Sports Med* 2015;**45**:231–44.
469 Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2013:CD005263.
470 Hageman D, Fokkenrood HJ, Gommans LN, van den Houten MM, Teijink JA. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database Syst Rev* 2018;**4**:CD005263.
471 Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised vs unsupervised exercise for intermittent claudication: a systematic review and meta-analysis. *Am Heart J* 2015;**169**:924–937 e3.
472 Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice–The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg* 2014;**48**:169–84.
473 Parmenter BJ, Dieberg G, Phipps G, Smart NA. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. *Vasc Med* 2015;**20**:30–40.
474 Fakhry F, van de Luijtgaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012;**56**:1132–42.
475 Pymer S, Ibeggazene S, Palmer J, Tew GA, Ingle L, Smith GE, et al. An updated systematic review and meta-analysis of home-based exercise programs for individuals with intermittent claudication. *J Vasc Surg* 2021;**74**:2076–2085 e20.
476 Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg* 2015;**61**:512–518 e2.
477 Fokkenrood HJP, Bendermacher BLW, Lauret GJ, Willigendael EM, Prins MH, Teijink JAW. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2013;**8**.
478 Gommans LNM, Saarloos R, Scheltinga MRM, Houterman S, de Bie RA, Fokkenrood HJP, et al. Editor's choice–The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg* 2014;**48**:169–84.
479 Makris GC, Lattimer CR, Lavida A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2012;**44**:569–75, discussion 76.
480 Dua A, Gologorsky R, Savage D, Rens N, Gandhi N, Brooke B, et al. National assessment of availability, awareness, and utilization of supervised exercise therapy for peripheral artery disease patients with intermittent claudication. *J Vasc Surg* 2020;**71**:1702–7.
481 Abaraogu UO, Abaraogu OD, Dall PM, Tew G, Stuart W, Brittenden J, et al. Exercise therapy in routine management of peripheral arterial disease and intermittent claudication: a scoping review. *Ther Adv Cardiovasc Dis* 2020;**14**:1753944720924270.
482 Golledge J, Singh TP, Alahakoon C, Pinchbeck J, Yip L, Moxon JV, et al. Meta-analysis of clinical trials examining the benefit of structured home exercise in patients with peripheral artery disease. *Br J Surg* 2019;**106**:319–31.
483 Jansen SC, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJ, Teijink JA. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev* 2020;**8**:CD009638.
484 Galea MN, Bray SR, Ginis KA. Barriers and facilitators for walking in individuals with intermittent claudication. *J Aging Phys Act* 2008;**16**:69–83, quiz 84.
485 Seed SA, Harwood AE, Sinclair J, Pymer S, Caldow E, Ingle L, et al. A systematic review of exercise prescription in patients with intermittent claudication: does pain matter? *Ann Vasc Surg* 2021;**77**:315–23.
486 Perks J, Zaccardi F, Paterson C, Houghton JSM, Nickinson ATO, Pepper CJ, et al. Effect of high-pain versus low-pain structured exercise on walking ability in people with intermittent claudication: meta-analysis. *Br J Surg* 2022;**109**:686–94.
487 Fassora M, Calanca L, Jaques C, Mazzolai L, Kayser B, Lanzi S. Intensity-dependent effects of exercise therapy on walking performance and aerobic fitness in symptomatic patients with lower-extremity peripheral artery disease: a systematic review and meta-analysis. *Vasc Med* 2022;**27**:158–70.
488 McDermott MM, Spring B, Tian L, Treat-Jacobson D, Ferrucci L, Lloyd-Jones D, et al. Effect of low-intensity vs high-intensity home-based walking exercise on walk distance in patients with peripheral artery disease: the LITE randomized clinical trial. *JAMA* 2021;**325**:1266–76.
489 Lanzi S, Belch J, Brodmann M, Madaric J, Bura-Riviere A, Visona A, et al. Supervised exercise training in patients with lower extremity peripheral artery disease. *Vasa* 2022;**51**:267–74.
490 Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication. *Ann Vasc Surg* 2016;**34**:280–9.
491 Sandberg A, Back M, Cider A, Jivegard L, Sigvant B, Wittboldt S, et al. Effectiveness of supervised exercise, home-based exercise, or walk advice strategies on walking performance and muscle endurance in patients with intermittent claudication (SUNFIT trial): a randomized clinical trial. *Eur J Cardiovasc Nurs* 2023;**22**:400–11.
492 Lauret GJ, van Dalen DC, Willigendael EM, Hendriks EJ, de Bie RA, Spronk S, et al. Supervised exercise therapy for intermittent claudication: current status and future perspectives. *Vascular* 2012;**20**:12–9.
493 Hageman D, van den Houten MM, Spruijt S, Gommans LN, Scheltinga MR, Teijink JA. Supervised exercise therapy: it does work, but how to set up a program? *J Cardiovasc Surg (Torino)* 2017;**58**:305–12.
494 Treat-Jacobson D, McDermott MM, Beckman JA, Burt MA, Creager MA, Ehrman JK, et al. Implementation of supervised exercise therapy for patients with symptomatic peripheral artery disease: a Science Advisory from the American Heart Association. *Circulation* 2019;**140**:e700–10.
495 Ambrosetti M, Abreu A, Corra U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2021;**28**:460–95.
496 Ambrosetti M, Temporelli PL, Faggiano P, Febo O, Diaco T, Favretto G, et al. Lower extremities peripheral arterial disease among patients admitted to cardiac rehabilitation: the THINK-PAD registry. *Int J Cardiol* 2014;**171**:192–8.
497 Siercke M, Jorgensen LP, Missel M, Thygesen LC, Moller SP, Sillesen H, et al. Cardiovascular rehabilitation increases walking distance in patients with intermittent claudication. results of the CIPIC Rehab Study: a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2021;**62**:768–76.
498 Devrome AN, Aggarwal S, McMurtry MS, Southern D, Hauer T, Lamb B, et al. Cardiac rehabilitation in people with peripheral arterial disease: a higher risk population that benefits from completion. *Int J Cardiol* 2019;**285**:108–14.
499 Nguyen CH, Marzolini S, Oh P, Thomas SG. A retrospective comparison of fitness and exercise progression in patients with

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coronary and peripheral artery disease in cardiac rehabilitation. *Can J Cardiol* 2021;**37**:260–8.

500 Jeger RV, Rickenbacher P, Pfisterer ME, Hoffmann A. Outpatient rehabilitation in patients with coronary artery and peripheral arterial occlusive disease. *Arch Phys Med Rehabil* 2008;**89**:618–21.

501 Stauber S, Guera V, Barth J, Schmid JP, Saner H, Znoj H, et al. Psychosocial outcome in cardiovascular rehabilitation of peripheral artery disease and coronary artery disease patients. *Vasc Med* 2013;**18**:257–62.

502 Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2019;**12**:1125–36.

503 Klaphake S, Buettner S, Ultee KH, van Rijn MJ, Hoeks SE, Verhagen HJ. Combination of endovascular revascularization and supervised exercise therapy for intermittent claudication: a systematic review and meta-analysis. *J Cardiovasc Surg (Torino)* 2018;**59**:150–7.

504 Meneses AL, Ritti-Dias RM, Parmenter B, Golledge J, Askew CD. Combined lower limb revascularisation and supervised exercise training for patients with peripheral arterial disease: a systematic review of randomised controlled trials. *Sports Med* 2017;**47**:987–1002.

505 Vemulapalli S. Revascularisation plus supervised exercise is superior to supervised exercise alone for the treatment of intermittent claudication. *Evid Based Med* 2016;**21**:91.

506 Aherne T, McHugh S, Kheirelseid EA, Lee MJ, McCaffrey N, Moneley D, et al. Comparing supervised exercise therapy to invasive measures in the management of symptomatic peripheral arterial disease. *Surg Res Pract* 2015;**2015**:960402.

507 Fakhry F, Fokkenrood HJ, Spronk S, Teijink JA, Rouwet EV, Hunink MGM. Endovascular revascularisation versus conservative management for intermittent claudication. *Cochrane Database Syst Rev* 2018;**3**:CD010512.

508 Doshi R, Shah P, Majmundar M, Kumar A, Vallabhajosyula S. Comparison of supervised exercise therapy with or without revascularization for the management of intermittent claudication: SET in PAD. *Eur J Intern Med* 2021;**92**:131–3.

509 Bo E, Hisdal J, Cvancarova M, Stranden E, Jorgensen JJ, Sandbaek G, et al. Twelve-months follow-up of supervised exercise after percutaneous transluminal angioplasty for intermittent claudication: a randomised clinical trial. *Int J Environ Res Public Health* 2013;**10**:5998–6014.

510 Klaphake S, Fakhry F, Rouwet EV, van der Laan L, Wever JJ, Teijink JA, et al. Long-term follow-up of a randomized clinical trial comparing endovascular revascularization plus supervised exercise with supervised exercise only for intermittent claudication. *Ann Surg* 2022;**276**:e1035–43.

511 Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. *JAMA* 2015;**314**:1936–44.

512 Thanigaimani S, Phie J, Sharma C, Wong S, Ibrahim M, Huynh P, et al. Network meta-analysis comparing the outcomes of treatments for intermittent claudication tested in randomized controlled trials. *J Am Heart Assoc* 2021;**10**:e019672.

513 Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2019;**12**:1125–36.

514 Bø E, Hisdal J, Cvancarova M, Stranden E, Jørgensen JJ, Sandbæk G, et al. Twelve-months follow-up of supervised exercise after percutaneous transluminal angioplasty for intermittent claudication: a randomised clinical trial. *Int J Environ Res Public Health* 2013;**10**:5998–6014.

515 Kruidenier LM, Nicolai SP, Rouwet EV, Peters RJ, Prins MH, Teijink JA. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. *J Vasc Interv Radiol* 2011;**22**:961–8.

516 Abaraogu UO, Dall PM, Seenan CA. The effect of structured patient education on physical activity in patients with peripheral arterial disease and intermittent claudication: a systematic review. *Eur J Vasc Endovasc Surg* 2017;**54**:58–68.

517 McCallum M, Cooper B, Matson S, Renwick B, Messeder SJ. Improving health behaviors in patients with peripheral arterial disease - a pilot study of supported self-management. *J Vasc Nurs* 2021;**39**:11–6.

518 Cunningham MA, Swanson V, Holdsworth RJ, O'Carroll RE. Late effects of a brief psychological intervention in patients with intermittent claudication in a randomized clinical trial. *Br J Surg* 2013;**100**:756–60.

519 Cunningham MA, Swanson V, O'Carroll RE, Holdsworth RJ. Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *Br J Surg* 2012;**99**:49–56.

520 Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg* 2009;**38**:463–74.

521 Stevens JW, Simpson E, Harnan S, Squires H, Meng Y, Thomas S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. *Br J Surg* 2012;**99**:1630–8.

522 Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev* 2014;**2014**:CD003748.

523 Brown T, Forster RB, Cleanthis M, Mikhailidis DP, Stansby G, Stewart M. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev* 2021;**6**:CD003748.

524 Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev* 2015;**9**:CD005262.

525 Salhiyyah K, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev* 2012;**1**:CD005262.

526 Dawson DL, Cutler BS, Hiatt WR, Hobson 2nd RW, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000;**109**:523–30.

527 Ruffolo AJ, Romano M, Ciapponi A. *Prostanoids for critical limb ischaemia*. Cochrane Database Syst Rev; 2010CD006544.

528 Robertson L, Andras A. *Prostanoids for intermittent claudication*. Cochrane Database Syst Rev; 2013CD000986.

529 Levin SR, Farber A, Cheng TW, Arinze N, Jones DW, Rybin D, et al. Patients undergoing interventions for claudication experience low perioperative morbidity but are at risk for worsening functional status and limb loss. *J Vasc Surg* 2020;**72**:241–9.

530 Klein WM, van der Graaf Y, Seegers J, Spithoven JH, Buskens E, van Baal JG, et al. Dutch iliac stent trial: long-term results in patients randomized for primary or selective stent placement. *Radiology* 2006;**238**:734–44.

531 Goode SD, Cleveland TJ, Gaines PA, collaborators St. Randomized clinical trial of stents versus angioplasty for the treatment of iliac artery occlusions (STAG trial). *Br J Surg* 2013;**100**:1148–53.

532 Jongsma H, Bekken J, Ayez N, Hoogewerf CJ, Van Weel V, Fioole B. Angioplasty versus stenting for iliac artery lesions. *Cochrane Database Syst Rev* 2020;**12**:CD007561.

533 Krankenberg H, Zeller T, Ingwersen M, Schmalstieg J, Gissler HM, Nikol S, et al. Self-expanding versus balloon-expandable stents for iliac artery occlusive disease: the randomized ICE trial. *JACC Cardiovasc Interv* 2017;**10**:1694–704.

534 Mwipatayi BP, Sharma S, Daneshmand A, Thomas SD, Vijayan V, Altaf N, et al. Durability of the balloon-expandable covered

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versus bare-metal stents in the Covered versus Balloon Expandable Stent Trial (COBEST) for the treatment of aortoiliac occlusive disease. *J Vasc Surg* 2016;**64**:83–94 e1.

535 Bekken JA, Vroegindeweij D, Vos JA, de Vries JPM, Lardenoije J, Petri BJ, et al. Editor's Choice - Two year results of the randomised DISCOVER trial comparing covered versus bare metal stents in the common iliac artery. *Eur J Vasc Endovasc Surg* 2023;**65**:359–68.

536 Salem M, Hosny MS, Francia F, Sallam M, Saratzis A, Saha P, et al. Management of extensive aorto-iliac disease: a systematic review and meta-analysis of 9319 patients. *Cardiovasc Intervent Radiol* 2021;**44**:1518–35.

537 Premaratne S, Newman J, Hobbs S, Garnham A, Wall M. Meta-analysis of direct surgical versus endovascular revascularization for aortoiliac occlusive disease. *J Vasc Surg* 2020;**72**:726–37.

538 Indes JE, Pfaff MJ, Farrokhyar F, Brown H, Hashim P, Cheung K, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. *J Endovasc Ther* 2013;**20**:443–55.

539 Starodubtsev V, Mitrofanov V, Ignatenko P, Gostev A, Preece R, Rabtsun A, et al. Editor's Choice - Hybrid vs. open surgical reconstruction for iliofemoral occlusive disease: a prospective randomised trial. *Eur J Vasc Endovasc Surg* 2022;**63**:557–65.

540 Capoccia L, Riambau V, da Rocha M. Is femorofemoral crossover bypass an option in claudication? *Ann Vasc Surg* 2010;**24**:828–32.

541 Eiberg JP, Roder O, Stahl-Madsen M, Eldrup N, Qvarfordt P, Laursen A, et al. Fluoropolymer-coated dacron versus PTFE grafts for femorofemoral crossover bypass: randomised trial. *Eur J Vasc Endovasc Surg* 2006;**32**:431–8.

542 Ricco JB, Probst H, French University Surgeons A. Long-term results of a multicenter randomized study on direct versus crossover bypass for unilateral iliac artery occlusive disease. *J Vasc Surg* 2008;**47**:45–53, discussion 53–4.

543 Changal KH, Syed MA, Dar T, Mangi MA, Sheikh MA. Systematic review and proportional meta-analysis of endarterectomy and endovascular therapy with routine or selective stenting for common femoral artery atherosclerotic disease. *J Interv Cardiol* 2019;**2019**:1593401.

544 Boufi M, Ejargue M, Gaye M, Boyer L, Alimi Y, Loundou AD. Systematic review and meta-analysis of endovascular versus open repair for common femoral artery atherosclerosis treatment. *J Vasc Surg* 2021;**73**:1445–55.

545 Ballotta E, Gruppo M, Mazzalai F, Martella B, Terranova O, Da Giau G. Infrapopliteal arterial reconstructions for limb salvage in patients aged > or =80 years according to preoperative ambulatory function and residential status. *Surgery* 2010;**148**:119–28.

546 Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP. Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. *J Vasc Surg* 2008;**48**:872–7.

547 Djerf H, Millinger J, Falkenberg M, Jivegard L, Svensson M, Nordanstig J. Absence of long-term benefit of revascularization in patients with intermittent claudication: five-year results from the IRONIC randomized controlled trial. *J Vasc Surg* 2020;**72**. 747-47.

548 Gunnarsson T, Gottsater A, Bergman S, Troeng T, Lindgren H. Eight-year outcome after invasive treatment of infrainguinal intermittent claudication: a population-based analysis from the Swedish vascular register (Swedvasc). *SAGE Open Med* 2020;**8**: 2050312120926782.

549 Howard R, Albright J, Fleckenstein R, Forrest A, Osborne N, Corriere MA, et al. Identifying potentially avoidable femoral to popliteal expanded polytetrafluoroethylene bypass for claudication using cross-site blinded peer review. *J Vasc Surg* 2023;**77**: 490–496 e8.

550 Baumgartner I, Norgren L, Fowkes FGR, Mulder H, Patel MR, Berger JS, et al. Cardiovascular outcomes after lower extremity endovascular or surgical revascularization: the EUCLID Trial. *J Am Coll Cardiol* 2018;**72**:1563–72.

551 Tepe G, Brodmann M, Werner M, Bachinsky W, Holden A, Zeller T, et al. Intravascular lithotripsy for peripheral artery calcification: 30-day outcomes from the randomized disrupt PAD III Trial. *JACC Cardiovasc Interv* 2021;**14**:1352–61.

552 Tepe G, Brodmann M, Bachinsky W, Holden A, Zeller T, Mangalmurti S, et al. Intravascular lithotripsy for peripheral artery calcification: mid-term outcomes from the randomized disrupt PAD III Trial. *J Soc Cardiovasc Angiogr Interv* 2022;**1**: 100341.

553 Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med* 2020;**383**:2538–46.

554 Dinh K, Limmer AM, Chen AZL, Thomas SD, Holden A, Schneider PA, et al. Mortality rates after paclitaxel-coated device use in patients with occlusive femoropopliteal disease: an updated systematic review and meta-analysis of randomized controlled trials. *J Endovasc Ther* 2021;**28**:755–77.

555 Zhang C, Yin G. Safety of paclitaxel-coated devices in the femoropopliteal arteries: a systematic review and meta-analysis. *PLoS One* 2022;**17**:e0275888.

556 Sridharan ND, Boitet A, Smith K, Noorbakhsh K, Avgerinos E, Eslami MH, et al. Cost-effectiveness analysis of drug-coated therapies in the superficial femoral artery. *J Vasc Surg* 2018;**67**: 343–52.

557 Katsanos K, Geisler BP, Garner AM, Zayed H, Cleveland T, Pietzsch JB. Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK. *BMJ Open* 2016;**6**:e011245.

558 Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. *J Am Coll Cardiol* 2012;**59**:16–23.

559 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation* 2016;**133**:1472–83, discussion 1483.

560 Goueffic Y, Sauguet A, Desgranges P, Feugier P, Rosset E, Ducasse E, et al. A polymer-free paclitaxel-eluting stent versus a bare-metal stent for de novo femoropopliteal lesions: the BATTLE Trial. *JACC Cardiovasc Interv* 2020;**13**:447–57.

561 Goueffic Y, Torsello G, Zeller T, Esposito G, Vermassen F, Hausegger KA, et al. Efficacy of a drug-eluting stent versus bare metal stents for symptomatic femoropopliteal peripheral artery disease: primary results of the EMINENT randomized trial. *Circulation* 2022;**146**:1564–76.

562 Bausback Y, Wittig T, Schmidt A, Zeller T, Bosiers M, Peeters P, et al. Drug-eluting stent versus drug-coated balloon revascularization in patients with femoropopliteal arterial disease. *J Am Coll Cardiol* 2019;**73**:667–79.

563 Liistro F, Angioli P, Porto I, Ducci K, Falsini G, Ventoruzzo G, et al. Drug-eluting balloon versus drug-eluting stent for complex femoropopliteal arterial lesions: the DRASTICO Study. *J Am Coll Cardiol* 2019;**74**:205–15.

564 Vroegindeweij D, Kemper FJ, Tielbeek AV, Buth J, Landman G. Recurrence of stenoses following balloon angioplasty and Simpson atherectomy of the femoro-popliteal segment. A randomised comparative 1-year follow-up study using colour flow duplex. *Eur J Vasc Surg* 1992;**6**:164–71.

565 Tielbeek AV, Vroegindeweij D, Buth J, Landman GH. Comparison of balloon angioplasty and Simpson atherectomy for lesions in the femoropopliteal artery: angiographic and clinical results of a prospective randomized trial. *J Vasc Interv Radiol* 1996;**7**: 837–44.

566 Shammas NW, Coiner D, Shammas GA, Dippel EJ, Christensen L, Jerin M. Percutaneous lower-extremity arterial interventions with primary balloon angioplasty versus Silverhawk atherectomy and adjunctive balloon angioplasty: randomized trial. *J Vasc Interv Radiol* 2011;**22**:1223–8.

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567 Dattilo R, Himmelstein SI, Cuff RF. The COMPLIANCE 360 degrees Trial: a randomized, prospective, multicenter, pilot study comparing acute and long-term results of orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. *J Invasive Cardiol* 2014;**26**:355–60.

568 Ott I, Cassese S, Groha P, Steppich B, Hadamitzky M, Ibrahim T, et al. Randomized comparison of paclitaxel-eluting balloon and stenting versus plain balloon plus stenting versus directional atherectomy for femoral artery disease (ISAR-STATH). *Circulation* 2017;**135**:2218–26.

569 Zeller T, Langhoff R, Rocha-Singh KJ, Jaff MR, Blessing E, Amann-Vesti B, et al. Directional atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis and maintain vessel patency: twelve-month results of the DEFINITIVE AR Study. *Circ Cardiovasc Interv* 2017;**10**:e004848.

570 Cai Z, Guo L, Qi L, Cui S, Tong Z, Guo J, et al. Midterm outcome of directional atherectomy combined with drug-coated balloon angioplasty versus drug-coated balloon angioplasty alone for femoropopliteal arteriosclerosis obliterans. *Ann Vasc Surg* 2020;**64**:181–7.

571 Saxon RR, Dake MD, Volgelzang RL, Katzen BT, Becker GJ. Randomized, multicenter study comparing expanded polytetrafluoroethylene-covered endoprosthesis placement with percutaneous transluminal angioplasty in the treatment of superficial femoral artery occlusive disease. *J Vasc Interv Radiol* 2008;**19**:823–32.

572 Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM, VIBRANT Investigators. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. *J Vasc Surg* 2013;**58**:386–395 e4.

573 Lammer J, Zeller T, Hausegger KA, Schaefer PJ, Gschwendtner M, Mueller-Huelsbeck S, et al. Sustained benefit at 2 years for covered stents versus bare-metal stents in long SFA lesions: the VIASTAR trial. *Cardiovasc Intervent Radiol* 2015;**38**:25–32.

574 Ambler GK, Twine CP. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev* 2018;**2**:CD001487.

575 Vossen RJ, Fokkema TM, Vahl AC, Balm R. Systematic review and meta-analysis comparing the autogenous vein bypass versus a prosthetic graft for above-the-knee femoropopliteal bypass surgery in patients with intermittent claudication. *Vascular* 2022:17085381221124701.

576 Sharrock M, Antoniou SA, Antoniou GA. Vein versus prosthetic graft for femoropopliteal bypass above the knee: a systematic review and meta-analysis of randomized controlled trials. *Angiology* 2019;**70**:649–61.

577 Kim Y, Thangappan K, DeCarlo CS, Jessula S, Majumdar M, Patel SS, et al. Outcomes of femoropopliteal bypass for lifestyle-limiting claudication in the endovascular era. *J Surg Res* 2022;**279**:323–9.

578 Bosiers M, Setacci C, De Donato G, Torsello G, Silveira PG, Deloose K, et al. ZILVERPASS Study: ZILVER PTX stent vs bypass surgery in femoropopliteal lesions. *J Endovasc Ther* 2020;**27**:287–95.

579 Zeller T, Beschorner U, Pilger E, Bosiers M, Deloose K, Peeters P, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (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 revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv* 2015;**8**:1614–22.

580 Rastan A, Brechtel K, Krankenberg H, Zahorsky R, Tepe G, Noory E, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. *J Am Coll Cardiol* 2012;**60**:587–91.

581 Levin SR, Farber A, Osborne NH, Beck AW, McFarland GE, Rybin D, et al. Tibial bypass in patients with intermittent claudication is associated with poor outcomes. *J Vasc Surg* 2021;**73**:564–571.e1.

582 Kobayashi T, Hamamoto M, Okazaki T, Honma T, Takahashi S. Long-term results of distal bypass for intermittent claudication. *Vasc Endovascular Surg* 2021;**55**:5–10.

583 Qureshi MI, Li HL, Ambler GK, Wong KHF, Dawson S, Chaplin K, et al. Antiplatelet and anticoagulant use in randomised trials of patients undergoing endovascular intervention for peripheral arterial disease: systematic review and narrative synthesis. *Eur J Vasc Endovasc Surg* 2020;**60**:77–87.

584 Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M, et al. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One* 2015;**10**:e0135692.

585 Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy–the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol* 2012;**22**:1998–2006.

586 Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. *J Endovasc Ther* 2013;**20**:699–706.

587 Hiatt WR, Bonaca MP, Patel MR, Nehler MR, Debus ES, Anand SS, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: impact of concomitant clopidogrel on efficacy and safety. *Circulation* 2020;**142**:2219–30.

588 Megaly M, Abraham B, Saad M, Mekaiel A, Soukas P, Banerjee S, et al. Outcomes with cilostazol after endovascular therapy of peripheral artery disease. *Vasc Med* 2019;**24**:313–23.

589 Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). *J Vasc Surg* 2008;**47**:330–6.

590 Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020;**382**:1994–2004.

591 Debus ES, Nehler MR, Govsyeyev N, Bauersachs RM, Anand SS, Patel MR, et al. Effect of rivaroxaban and aspirin in patients with peripheral artery disease undergoing surgical revascularization: insights from the VOYAGER PAD Trial. *Circulation* 2021;**144**:1104–16.

592 Krantz M, Hiatt W, Anand S, Debus ES, Patel M, Nehler M, et al. Efficacy and safety of rivaroxaban in elderly patients with symptomatic PAD undergoing revascularization: insights from VOYAGER PAD. *J Am Coll Cardiol* 2021;**77**:1783.

593 Morrison J, Hiatt W, Patel M, Anand S, Debus ES, Nehler M, et al. Efficacy and safety of low-dose rivaroxaban in symptomatic PAD patients undergoing revascularization currently smoking: insights from VOYAGER PAD. *J Am Coll Cardiol* 2021;**77**:1808.

594 Hsia J, Nehler MR, Anand S, Patel MR, Hiatt WR, Debus S, et al. Rivaroxaban reduces major cardiovascular and limb events in patients with CKD and peripheral artery disease with recent lower extremity revascularization: insights from VOYAGER PAD. *J Am Soc Nephrol* 2020;**31**:649.

595 Bauersachs RM, Szarek M, Brodmann M, Gudz I, Debus ES, Nehler MR, et al. Total ischemic event reduction with rivaroxaban after peripheral arterial revascularization in the VOYAGER PAD Trial. *J Am Coll Cardiol* 2021;**78**:317–26.

596 Hess CN, Anand S, Bauersachs R, Patel MR, Debus ES, Nehler MR, et al. Reduction in venous thromboembolism with rivaroxaban versus placebo in peripheral artery disease after lower extremity revascularization: insights from VOYAGER PAD. *Circulation* 2020:142.

597 Moll F, Baumgartner I, Jaff M, Nwachuku C, Tangelder M, Ansel G, et al. Edoxaban plus aspirin vs dual antiplatelet therapy

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in endovascular treatment of patients with peripheral artery disease: results of the ePAD Trial. *J Endovasc Ther* 2018;**25**:158–68.

598 Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;**355**:346–51.

599 Tangelder MJ, Algra A, Lawson JA, Hennekes S, Eikelboom BC. Optimal oral anticoagulant intensity to prevent secondary ischemic and hemorrhagic events in patients after infrainguinal bypass graft surgery. Dutch BOA Study Group. *J Vasc Surg* 2001;**33**:522–7.

600 Johnson WC, Williford WO, Corson JD, Padberg Jr FT. Hemorrhagic complications during long-term postoperative warfarin administration in patients undergoing lower extremity arterial bypass surgery. *Vascular* 2004;**12**:362–8.

601 Johnson WC, Williford WO. Department of Veterans Affairs Cooperative Study #362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002;**35**:413–21.

602 Belch JJ, Dormandy J, Committee CW, Biasi GM, Cairols M, Diehm C, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg* 2010;**52**:825–33. 33 e1–2.

603 Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2015;**2015**:CD000535.

604 Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020;**382**:1994–2004.

605 Govsyeyev N, Nehler MR, Debus S, Bauersachs R, Patel M, Anand S, et al. Efficacy of rivaroxaban and aspirin in patients with peripheral artery disease with venous and prosthetic surgical bypass conduits: insights from the VOYAGER PAD Trial. *J Vasc Surg* 2021;**74**:e24–5.

606 Bonaca MP, Szarek M, Debus ES, Nehler MR, Patel MR, Anand SS, et al. Efficacy and safety of rivaroxaban versus placebo after lower extremity bypass surgery: a post hoc analysis of a "CASPAR like" outcome from VOYAGER PAD. *Clin Cardiol* 2022;**45**:1143–6.

607 Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. *Cochrane Database Syst Rev* 2011;**2011**:CD000536.

608 Monaco M, Di Tommaso L, Pinna GB, Lillo S, Schiavone V, Stassano P. Combination therapy with warfarin plus clopidogrel improves outcomes in femoropopliteal bypass surgery patients. *J Vasc Surg* 2012;**56**:96–105.

609 van Hattum ES, Algra A, Lawson JA, Eikelboom BC, Moll FL, Tangelder MJ. Bleeding increases the risk of ischemic events in patients with peripheral arterial disease. *Circulation* 2009;**120**:1569–76.

610 de Smit P, Urk H. Dutch oral anticoagulation trial. *Acta Chir Austriaca* 1992;**24**:5–7.

611 Lassila R, Lepantalo M, Lindfors O. The effect of acetylsalicylic acid on the outcome after lower limb arterial surgery with special reference to cigarette smoking. *World J Surg* 1991;**15**:378–82.

612 McCollum C, Alexander C, Kenchington G, Franks PJ, Greenhalgh R. Antiplatelet drugs in femoropopliteal vein bypasses: a multicenter trial. *J Vasc Surg* 1991;**13**:150–61, discussion 161–2.

613 Clyne CA, Archer TJ, Atuhaire LK, Chant AD, Webster JH. Random control trial of a short course of aspirin and dipyridamole (Persantin) for femorodistal grafts. *Br J Surg* 1987;**74**:246–8.

614 Shalaeva EV, Saner H, Janabaev BB, Shalaeva AV. Tenfold risk increase of major cardiovascular events after high limb amputation with non-compliance for secondary prevention measures. *Eur J Prev Cardiol* 2017;**24**:708–16.

615 Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016;**64**:1009–10017 e3.

616 Cugusi L, Manca A, Yeo TJ, Bassareo PP, Mercuro G, Kaski JC. Nordic walking for individuals with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2017;**24**:1938–55.

617 Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;**3**:e000697.

618 Hobaus C, Herz CT, Obendorf F, Howanietz MT, Wrba T, Koppensteiner R, et al. Center-based patient care enhances survival of elderly patients suffering from peripheral arterial disease. *Ann Med* 2017;**49**:291–8.

619 Hussain MA, Al-Omran M, Mamdani M, Eisenberg N, Premji A, Saldanha L, et al. Efficacy of a guideline-recommended risk-reduction program to improve cardiovascular and limb outcomes in patients with peripheral arterial disease. *JAMA Surg* 2016;**151**:742–50.

620 Aboyans V, Ricco JB, Bartelink ML, Bjorck M, Brodmann M, Cohner T, et al. [2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)]. *Kardiol Pol* 2017;**75**:1065–160.

621 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary. *Vasc Med* 2017;**22**:NP1–43.

622 Venermo M, Sprynger M, Desormais I, Bjorck M, Brodmann M, Cohnert T, et al. Follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur J Prev Cardiol* 2019;**26**:1971–84.

623 Mills JL. Mechanisms of vein graft failure: the location, distribution, and characteristics of lesions that predispose to graft failure. *Semin Vasc Surg* 1993;**6**:78–91.

624 Shah DM, Darling 3rd RC, Chang BB, Fitzgerald KM, Paty PS, Leather RP. Long-term results of in situ saphenous vein bypass. Analysis of 2058 cases. *Ann Surg* 1995;**222**:438–46, discussion 446–8.

625 Disselhoff B, Buth J, Jakimowicz J. Early detection of stenosis of femoro-distal grafts. A surveillance study using colour-duplex scanning. *Eur J Vasc Surg* 1989;**3**:43–8.

626 Ihlberg L, Luther M, Alback A, Kantonen I, Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein-graft failure? *Eur J Vasc Endovasc Surg* 1999;**18**:395–400.

627 Griffin NM, Wright IA, Buckenham TM. Comparison of duplex ultrasound with digital subtraction angiography in the assessment of infra-inguinal autologous vein bypass grafts. *ANZ J Surg* 2006;**76**:966–9.

628 Green RM, McNamara J, Ouriel K, DeWeese JA. Comparison of infrainguinal graft surveillance techniques. *J Vasc Surg* 1990;**11**:207–14, discussion 214–5.

629 Mills JL, Bandyk DF, Gahtan V, Esses GE. The origin of infrainguinal vein graft stenosis: a prospective study based on duplex surveillance. *J Vasc Surg* 1995;**21**:16–22, discussion 22–5.

630 Wixon CL, Mills JL, Westerband A, Hughes JD, Ihnat DM. An economic appraisal of lower extremity bypass graft maintenance. *J Vasc Surg* 2000;**32**:1–12.

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631 Bui TD, Mills JL, Sr , Ihnat DM, Gruessner AC, Goshima KR, Hughes JD. The natural history of duplex-detected stenosis after femoropopliteal endovascular therapy suggests questionable clinical utility of routine duplex surveillance. *J Vasc Surg* 2012;**55**:346–52.
632 Tielbeek AV, Rietjens E, Buth J, Vroegindeweij D, Schol FP. The value of duplex surveillance after endovascular intervention for femoropopliteal obstructive disease. *Eur J Vasc Endovasc Surg* 1996;**12**:145–50.
633 Wong KHF, Zucker BE, Wardle BG, Coughlin PA, Chaplin K, Cheng HY, et al. Systematic review and narrative synthesis of surveillance practices after endovascular intervention for lower limb peripheral arterial disease. *J Vasc Surg* 2022;**75**:372–80 e15.
634 Kornowski R. Patient-reported outcome measures in cardiovascular disease. *Eur Heart J Qual Care Clin Outcomes* 2023;**9**:119–27.
635 Donker J, de Vries J, Ho GH, Goncalves FB, Hoeks SE, Verhagen HJ, et al. Review: Quality of life in lower limb peripheral vascular surgery. *Vascular* 2016;**24**:88–95.
636 Guidon M, McGee H. Exercise-based interventions and health-related quality of life in intermittent claudication: a 20-year (1989–2008) review. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:140–54.
637 Peri-Okonny PA, Wang J, Gosch KL, Patel MR, Shishehbor MH, Safley DL, et al. Establishing thresholds for minimal clinically important differences for the Peripheral Artery Disease Questionnaire. *Circ Cardiovasc Qual Outcomes* 2021;**14**:e007232.
638 Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. *Vasc Med* 2018;**23**:349–57.
639 Conijn AP, Jonkers W, Rouwet EV, Vahl AC, Reekers JA, Koelemay MJ. Introducing the concept of the minimally important difference to determine a clinically relevant change on patient-reported outcome measures in patients with intermittent claudication. *Cardiovasc Intervent Radiol* 2015;**38**:1112–8.
640 Nordanstig J, Pettersson M, Morgan M, Falkenberg M, Kumlien C. Assessment of minimum important difference and substantial clinical benefit with the Vascular Quality of Life Questionnaire-6 when evaluating revascularisation procedures in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2017;**54**:340–7.
641 Cassar K, Bachoo P, Brittenden J. The effect of peripheral percutaneous transluminal angioplasty on quality of life in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2003;**26**:130–6.
642 Qvist I, Lindholt JS, Sogaard R, Lorentzen V, Hallas J, Frost L. Randomised trial of telephone counselling to improve participants' adherence to prescribed drugs in a vascular screening trial. *Basic Clin Pharmacol Toxicol* 2020;**127**:477–87.
643 Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2015;**2015**:CD002098.
644 Gandapur Y, Kianoush S, Kelli HM, Misra S, Urrea B, Blaha MJ, et al. The role of mHealth for improving medication adherence in patients with cardiovascular disease: a systematic review. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:237–44.
645 Medina D, Zil EAA, Daoud D, Brooke J, Lee Chester-Paul K, Aziz F. Implementation of transitional care planning is associated with reduced readmission rates in patients undergoing lower extremity bypass surgery for peripheral arterial disease. *Ann Vasc Surg* 2022;**84**:28–39.
646 Safran Naimark J, Madar Z, Shahar DR. The impact of a web-based app (eBalance) in promoting healthy lifestyles: randomized controlled trial. *J Med Internet Res* 2015;**17**:e56.
647 Michaud TL, Ern J, Scoggins D, Su D. Assessing the impact of telemonitoring-facilitated lifestyle modifications on diabetes outcomes: a systematic review and meta-analysis. *Telemed J E Health* 2021;**27**:124–36.
648 Carter T, O'Neill S, Johns N, Brady RR. Contemporary vascular smartphone medical applications. *Ann Vasc Surg* 2013;**27**:804–9.
649 Alushi K, Hinterseher I, Peters F, Rother U, Bischoff MS, Mylonas S, et al. Distribution of mobile health applications amongst patients with symptomatic peripheral arterial disease in Germany: a cross-sectional survey study. *J Clin Med* 2022;**11**.
650 Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q* 1966;**44**(Suppl):166–206.
651 Hischke S, Riess HC, Bublitz MK, Kriston L, Schwaneberg T, Harter M, et al. Quality indicators in peripheral arterial occlusive disease treatment: a systematic review. *Eur J Vasc Endovasc Surg* 2019;**58**:738–45.
652 Bellmunt S, Roque M, Osorio D, Pardo H, Escudero JR, Bonfill X. Healthcare quality indicators of peripheral artery disease based on systematic reviews. *Eur J Vasc Endovasc Surg* 2014;**48**:60–9.
653 Olin JW, Allie DE, Belkin M, Bonow RO, Casey Jr DE, Creager MA, et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). *J Am Coll Cardiol* 2010;**56**:2147–81.
654 Riess HC, Debus ES, Schwaneberg T, Hischke S, Maier J, Bublitz M, et al. Indicators of outcome quality in peripheral arterial disease revascularisations - a Delphi expert consensus. *Vasa* 2018;**47**:491–7.
655 Vyas MV, Mrkobrada M, Donner A, Hackam DG. Underrepresentation of peripheral artery disease in modern cardiovascular trials: systematic review and meta-analysis. *Int J Cardiol* 2013;**168**:4875–6.
656 Jelani QU, Petrov M, Martinez SC, Holmvang L, Al-Shaibi K, Alasnag M. Peripheral arterial disease in women: an overview of risk factor profile, clinical features, and outcomes. *Curr Atheroscler Rep* 2018;**20**:40.
657 Mayor JM, Preventza O, McGinigle K, Mills JL, Sr , Montero-Baker M, Gilani R, et al. Persistent under-representation of female patients in United States trials of common vascular diseases from 2008 to 2020. *J Vasc Surg* 2022;**75**:30–6.
658 Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. *J Epidemiol* 2003;**13**:1–14.
659 Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health (Lond)* 2009;**5**:669–83.
660 Srivaratharajah K, Abramson BL. Women and peripheral arterial disease: a review of sex differences in epidemiology, clinical manifestations, and outcomes. *Can J Cardiol* 2018;**34**:356–61.
661 Porras CP, Teraa M, Bots ML, de Boer AR, Peters SAE, van Doorn S, et al. The frequency of primary healthcare contacts preceding the diagnosis of lower-extremity arterial disease: do women consult general practice differently? *J Clin Med* 2022;**11**:24.
662 Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation* 2012;**125**:1449–72.
663 Gardner AW. Sex differences in claudication pain in subjects with peripheral arterial disease. *Med Sci Sports Exerc* 2002;**34**:1695–8.
664 Gardner AW, Parker DE, Montgomery PS, Khurana A, Ritti-Dias RM, Blevins SM. Gender differences in daily ambulatory activity patterns in patients with intermittent claudication. *J Vasc Surg* 2010;**52**:1204–10.

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665 Wang JC, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in patients with and without peripheral arterial disease. *Circulation* 2005;**112**:3501–8.
666 Singh N, Liu K, Tian L, Criqui MH, Guralnik JM, Ferrucci L, et al. Leg strength predicts mortality in men but not in women with peripheral arterial disease. *J Vasc Surg* 2010;**52**:624–31.
667 Egorova N, Vouyouka AG, Quin J, Guillerme S, Moskowitz A, Marin M, et al. Analysis of gender-related differences in lower extremity peripheral arterial disease. *J Vasc Surg* 2010;**51**:372–378 e1, discussion 378–9.
668 Freisinger E, Malyar NM, Reinecke H, Unrath M. Low rate of revascularization procedures and poor prognosis particularly in male patients with peripheral artery disease - a propensity score matched analysis. *Int J Cardiol* 2018;**255**:188–94.
669 Behrendt CA, Sigvant B, Kuchenbecker J, Grima MJ, Schermerhorn M, Thomson IA, et al. Editor's Choice - International variations and sex disparities in the treatment of peripheral arterial occlusive disease: a report from VASCUNET and the International Consortium of Vascular Registries. *Eur J Vasc Endovasc Surg* 2020;**60**:873–80.
670 Lee MH, Li PY, Li B, Shakespeare A, Samarasinghe Y, Feridooni T, et al. A systematic review and meta-analysis of sex- and gender-based differences in presentation severity and outcomes in adults undergoing major vascular surgery. *J Vasc Surg* 2022;**76**:581–94 e25.
671 Correia R, Catarino J, Vieira I, Bento R, Garcia R, Pais F, et al. Gender differences in chronic lower limb ischemia presentation and revascularization outcomes. *Angiologia e Cirurgia Vascular* 2021;**17**:110–6.
672 Parvar SL, Thiyagarajah A, Nerlekar N, King P, Nicholls SJ. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. *J Vasc Surg* 2021;**73**:1456–14565 e7.
673 Wang J, He Y, Shu C, Zhao J, Dubois L. The effect of gender on outcomes after lower extremity revascularization. *J Vasc Surg* 2017;**65**:889–906 e4.
674 Altin SE, Gitto M, Secemsky EA, Rao SV, Hess CN. Sex-based differences in periprocedural complications following lower extremity peripheral vascular intervention. *Circ Cardiovasc Interv* 2022;**15**:e011768.
675 Haine A, Kavanagh S, Berger JS, Hess CN, Norgren L, Fowkes FGR, et al. Sex-specific risks of major cardiovascular and limb events in patients with symptomatic peripheral artery disease. *J Am Coll Cardiol* 2020;**75**:608–17.
676 Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.
677 Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;**288**:49–57.
678 Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;**297**:1465–77.
679 Simmons A, Steffen K. Peripheral arterial disease in women. *Rev Cardiovasc Med* 2011;**12**:123–31.
680 Schramm K, Rochon PJ. Gender differences in peripheral vascular disease. *Semin Intervent Radiol* 2018;**35**:9–16.
681 World Health Organization. *Regional Office for Europe. Through a gender lens: women and tobacco in the WHO European Region. World Health Organization. Regional Office for Europe.* 2021 https://apps.who.int/iris/handle/10665/339328.
682 Gabel J, Jabo B, Patel S, Kiang S, Bianchi C, Chiriano J, et al. Smoking habits of patients undergoing treatment for intermittent claudication in the Vascular Quality Initiative. *Ann Vasc Surg* 2017;**44**:261–8.
683 Bolego C, Poli A, Paoletti R. Smoking and gender. *Cardiovasc Res* 2002;**53**:568–76.
684 McDermott MM, Greenland P, Reed G, Mazor KM, Merriam PA, Graff R, et al. Gender differences in cholesterol-lowering medication prescribing in peripheral artery disease. *Vasc Med* 2011;**16**:428–35.
685 Peters F, Kreutzburg T, Riess HC, Heidemann F, Marschall U, L'Hoest H, et al. Editor's Choice - Optimal pharmacological treatment of symptomatic peripheral arterial occlusive disease and evidence of female patient disadvantage: an analysis of health insurance claims data. *Eur J Vasc Endovasc Surg* 2020;**60**:421–9.
686 Campesi I, Franconi F, Seghieri G, Meloni M. Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes. *Pharmacol Res* 2017;**119**:195–207.
687 Alfredsson J, Green JB, Stevens SR, Reed SD, Armstrong PW, Angelyn Bethel M, et al. Sex differences in management and outcomes of patients with type 2 diabetes and cardiovascular disease: a report from TECOS. *Diabetes Obes Metab* 2018;**20**:2379–88.
688 Mayor J, Preventza O, Mills JL, Montero-Baker M, Gilani R, Pallister Z, et al. Persistent underrepresentation of female patients in US trials of common vascular diseases since 2008. *J Vasc Surg* 2021;**73**:e23.
689 Jain RK, Laiteerapong N. Strategies for improving cardiovascular health in women with diabetes mellitus: a review of the evidence. *Curr Diab Rep* 2015;**15**:98.
690 Makowski L, Feld J, Koppe J, Illner J, Kuhnemund L, Wiederhold A, et al. Sex related differences in therapy and outcome of patients with intermittent claudication in a real-world cohort. *Atherosclerosis* 2021;**325**:75–82.
691 Ramkumar N, Suckow BD, Brown JR, Sedrakyan A, Cronenwett JL, Goodney PP. Sex-based assessment of patient presentation, lesion characteristics, and treatment modalities in patients undergoing peripheral vascular intervention. *Circ Cardiovasc Interv* 2018;**11**:e005749.
692 Messiha D, Petrikhovich O, Lortz J, Mahabadi AA, Hering R, Schulz M, et al. Gender differences in outpatient peripheral artery disease management in Germany: a population based study 2009–2018. *Eur J Vasc Endovasc Surg* 2022;**63**:714–20.
693 Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults. *Circ Cardiovasc Qual Outcomes* 2014;**7**:532–9.
694 Rudolf H, Kreutzer J, Klaassen-Mielke R, Timmesfeld N, Trampisch HJ, Krause DMJ. Socioeconomic factors and the onset of peripheral artery disease in older adults. *Vasa* 2021;**50**:341–7.
695 Vart P, Coresh J, Kwak L, Ballew SH, Heiss G, Matsushita K. Socioeconomic status and incidence of hospitalization with lower-extremity peripheral artery disease: atherosclerosis risk in communities study. *J Am Heart Assoc* 2017;**6**:e004995.
696 Kroger K, Dragano N, Stang A, Moebus S, Mohlenkamp S, Mann K, et al. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vasc Med* 2009;**14**:289–96.
697 Subherwal S, Patel MR, Tang F, Smolderen KG, Jones WS, Tsai TT, et al. Socioeconomic disparities in the use of cardioprotective medications among patients with peripheral artery disease: an analysis of the American College of Cardiology's NCDR PINNACLE Registry. *J Am Coll Cardiol* 2013;**62**:51–7.
698 Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag* 2008;**4**:269–86.
699 Vitalis A, Lip GY, Kay M, Vohra RK, Shantsila A. Ethnic differences in the prevalence of peripheral arterial disease: a systematic review and meta-analysis. *Expert Rev Cardiovasc Ther* 2017;**15**:327–38.

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700 Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 2004;**110**:738–43.
701 Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol* 2006;**48**:1190–7.
702 Sabatine MS, Blake GJ, Drazner MH, Morrow DA, Scirica BM, Murphy SA, et al. Influence of race on death and ischemic complications in patients with non-ST-elevation acute coronary syndromes despite modern, protocol-guided treatment. *Circulation* 2005;**111**:1217–24.
703 Lurie N, Fremont A, Jain AK, Taylor SL, McLaughlin R, Peterson E, et al. Racial and ethnic disparities in care: the perspectives of cardiologists. *Circulation* 2005;**111**:1264–9.
704 Hutchinson RG, Watson RL, Davis CE, Barnes R, Brown S, Romm F, et al. Racial differences in risk factors for atherosclerosis. The ARIC Study. Atherosclerosis Risk in Communities. *Angiology* 1997;**48**:279–90.
705 Abbasi F, Brown Jr BW, Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol* 2002;**40**:937–43.
706 Jones DW, Chambless LE, Folsom AR, Heiss G, Hutchinson RG, Sharrett AR, et al. Risk factors for coronary heart disease in African Americans: the atherosclerosis risk in communities study, 1987–1997. *Arch Intern Med* 2002;**162**:2565–71.
707 Eslami MH, Zayaruzny M, Fitzgerald GA. The adverse effects of race, insurance status, and low income on the rate of amputation in patients presenting with lower extremity ischemia. *J Vasc Surg* 2007;**45**:55–9.
708 Rowe VL, Weaver FA, Lane JS, Etzioni DA. Racial and ethnic differences in patterns of treatment for acute peripheral arterial disease in the United States, 1998–2006. *J Vasc Surg* 2010;**51**:21S–6S.
709 Hughes K, Boyd C, Oyetunji T, Tran D, Chang D, Rose D, et al. Racial/ethnic disparities in revascularization for limb salvage: an analysis of the National Surgical Quality Improvement Program database. *Vasc Endovascular Surg* 2014;**48**:402–5.
710 Strain WD, Paldanius PM. Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc Diabetol* 2018;**17**:57.
711 Yang SL, Zhu LY, Han R, Sun LL, Li JX, Dou JT. Pathophysiology of peripheral arterial disease in diabetes mellitus. *J Diabetes* 2017;**9**:133–40.
712 Stalling P, Engelbertz C, Luders F, Meyborg M, Gebauer K, Waltenberger J, et al. Unmet medical needs in intermittent claudication with diabetes and coronary artery disease - a "real-world" analysis on 21 197 PAD patients. *Clin Cardiol* 2019;**42**:629–36.
713 Fowkes FGR, Aboyans V, Fowkes FJI, McDermott MM, Sampson UKA, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017;**14**:156–70.
714 Jensen SA, Vatten LJ, Myhre HO. The association between diabetes mellitus and the prevalence of intermittent claudication: the HUNT study. *Vasc Med* 2008;**13**:239–44.
715 Wilcox T, Newman JD, Maldonado TS, Rockman C, Berger JS. Peripheral vascular disease risk in diabetic individuals without coronary heart disease. *Atherosclerosis* 2018;**275**:419–25.
716 Hageman D, Gommans LN, Scheltinga MR, Teijink JA. Effect of diabetes mellitus on walking distance parameters after supervised exercise therapy for intermittent claudication: a systematic review. *Vasc Med* 2017;**22**:21–7.
717 Stoberock K, Kaschwich M, Nicolay SS, Mahmoud N, Heidemann F, Riess HC, et al. The interrelationship between diabetes mellitus and peripheral arterial disease. *Vasa* 2021;**50**:323–30.
718 Dakhel A, Zarrouk M, Ekelund J, Acosta S, Nilsson P, Miftaraj M, et al. Worse cardiovascular prognosis after endovascular surgery for intermittent claudication caused by infrainguinal atherosclerotic disease in patients with diabetes. *Ther Adv Endocrinol Metab* 2020;**11**:2042018820960294.
719 Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care* 2002;**25**:894–9.
720 Vijan S, Stevens DL, Herman WH, Funnell MM, Standiford CJ. Screening, prevention, counseling, and treatment for the complications of type II diabetes mellitus. Putting evidence into practice. *J Gen Intern Med* 1997;**12**:567–80.
721 Dakhel A, Zarrouk M, Ekelund J, Acosta S, Miftaraj M, Eliasson B, et al. Higher long-term cardiovascular morbidity after open surgery for intermittent claudication caused by infrainguinal atherosclerotic disease in patients with diabetes - a nationwide observational cohort study. *Vasa* 2021;**50**:224–30.
722 Behrendt CA, Venermo M, Cronenwett JL, Sedrakyan A, Beck AW, Eldrup-Jorgensen J, et al. VASCUNET, VQI, and the International Consortium of Vascular Registries - unique collaborations for quality improvement in vascular surgery. *Eur J Vasc Endovasc Surg* 2019;**58**:792–3.
723 Lees T, Troeng T, Thomson IA, Menyhei G, Simo G, Beiles B, et al. International variations in infrainguinal bypass surgery - a VASCUNET report. *Eur J Vasc Endovasc Surg* 2012;**44**:185–92.
724 Behrendt CA, Sigvant B, Szeberin Z, Beiles B, Eldrup N, Thomson IA, et al. International variations in amputation practice: a VASCUNET report. *Eur J Vasc Endovasc Surg* 2018;**56**:391–9.

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