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Review Article

Medical Management of Peripheral Arterial Disease: Deciphering the Intricacies of Therapeutic Options

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ABSTRACT

Due to the pathophysiology of atherosclerosis, the management for coronary artery disease and peripheral arterial disease (PAD) were considered homogenous, with therapies focused on the use of lipid-lowering medications, antiplatelet therapy, glucose control, and blood pressure management. However, more recently, studies have supported the use of tailored therapeutics and medical targets for patients with PAD that sometimes differ from those for coronary artery disease. Moreover, we are now witnessing large randomized PAD-specific trials that have altered therapeutic regimens and targets. Given these updates, dissemination of knowledge is lacking, as evidenced by discordant guideline recommendations. This comprehensive review provides an overview of contemporary therapeutic options for secondary prevention for patients with PAD.

RÉSUMÉ

En raison de la physiopathologie de l'athérosclérose, les stratégies de prise en charge de la coronaropathie et de la maladie artérielle périphérique (MAP) étaient considérées comme homogènes, les traitements étant axés sur l'utilisation d'agents hypolipidémiants et d'agents antiplaquettaires, sur l'équilibre glycémique et sur la maîtrise de la pression artérielle. Toutefois, des études plus récentes sont venues appuyer l'utilisation de cibles thérapeutiques et médicales adaptées pour la MAP qui diffèrent parfois de celles qui sont définies pour la coronaropathie. Ainsi, nous voyons maintenant de vastes essais à répartition aléatoire portant expressément sur la MAP dans lesquels les schémas et cibles thérapeutiques ont été modifiés. Compte tenu de ces mises à jour, la diffusion des connaissances est déficiente, comme en témoignent les recommandations divergentes dans les lignes directrices. Cette revue exhaustive fournit un survol des options thérapeutiques actuelles pour la prévention secondaire chez les patients atteints de MAP.

Peripheral arterial disease (PAD) is a common vascular condition seen more often in older patients with cardiovascular (CV) risk.[1] Although all extremities may be affected, lower limbs and carotid arteries are more commonly involved due to atherosclerosis.[2] Even though roughly 50% of PAD patients are asymptomatic, the presence of PAD is associated with decreased functional capability, increased CV morbidity, and increased mortality.[2]

Due to their common atherosclerotic pathway, coronary artery disease (CAD) and PAD are often grouped together.[3,4] As a result, the standard management for secondary prevention is often thought to be the same.[3] More recently, differences in therapeutic management have been identified. This narrative review builds upon the therapeutic strategies for CAD and discusses the contemporary pharmacologic management for patients with PAD.

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See page 946 for disclosure information.

Search Strategy

Our intent was to focus on the pharmacotherapy of stable PAD, defined as having any one of the following: an ankle-brachial index (ABI) < 0.9, occlusion of lower extremities documented on imaging, intermittent claudication (IC), limb ischemia, or a prior history of lower-extremity revascularization or amputation.[5] Patients undergoing current revascularization or amputation due to critical limb ischemia were excluded. A search of PubMed and Embase was conducted in October 2020 using the following search terms (and related terms): peripheral arterial disease, risk reduction/ secondary prevention, and medical management. Filters were set to include clinical trials, meta-analyses, randomized controlled trials (RCTs; subgroup analyses), systematic reviews, and reviews written in English (high-quality studies). Additional articles were identified through cross-referencing of the screened articles. In total, 501 articles were identified and screened, with 62 forming the basis of the review and proposed recommendations for treatment. There was no bias in article selection, and the articles selected were reviewed and determined to be highly relevant to our systematic review. Full details of our search strategy can be found in Supplemental Appendix S1.

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PAD Background

Epidemiology and pathophysiology of PAD

PAD affects more than 202 million people worldwide.[6] In Western countries, the prevalence is estimated to be 5% in women and men aged 45-49 years, and it increases to 18% at 85-89 years of age.[7] The annual incidence of PAD is estimated[8] to be 2.4%. Across all populations, the occurrence of PAD is on the rise, with a 25% increase observed between 2000 and 2010.[6,7]

The traditional CV risk factors (smoking, hypertension, dyslipidemia, diabetes mellitus, family history, etc.) undoubtedly are associated with increased incidence of PAD.[2] Smoking in particular (along with diabetes mellitus and hypertension) has a strong association.[4,7] Among those without a smoking history, elevated body mass index was a strong predictor of PAD.[9] As for lipids, the ratio of total cholesterol to high-density lipoprotein cholesterol best correlates with PAD.[4,7] Several studies have found an increased risk in African-American populations.[4] In a 2014 systematic review, South Asians, compared with White Europeans, were found to be at lower risk of developing PAD.[10] Gender differences have been observed as well. In one study of low-middle income countries, women had higher rates of PAD than men, and this effect was more pronounced at younger ages.[7] In a systematic review and meta-analysis, men with PAD had a higher risk of mortality and major adverse cardiovascular events (MACE) compared to women.[11] Women with critical leg ischemia are less likely to receive statins or undergo revascularization.[12] In a cohort analysis from the Women's Health Study (absence of cardiovascular disease), the metabolic syndrome (obesity, lipid abnormalities, hypertension, and insulin resistance) was strongly associated with the development of symptomatic PAD.[13] Although the relationship is still controversial, elevated biomarkers such as homocysteine, c-reactive protein, and fibrinogen often correlate with PAD.[4,7]

Clinical manifestations

The majority of PAD patients are asymptomatic, as defined by an ABI < 0.90 without the presence of other symptoms.[2] However, roughly one-quarter present with the classic symptoms of IC,[14] defined as pain within the calf that is brought on by walking and relieved by rest.[1] Others may present with atypical leg pain symptoms, such as non-calf lower limb pain on walking, or pain while standing or sitting. In diabetics, these symptoms may be accompanied by peripheral neuropathy and altered pain perception. These symptoms can be screened using patient questionnaires such as the Edinburgh Claudication Questionnaire[15] and the San Diego Claudication Questionnaire.[16] For many PAD patients, risk factor profile, clinical symptoms, and physical examination findings are sufficient for diagnosis. However, the use of an abnormal ABI in the clinical context may prove useful (ABI of < 0.9 is strongly associated with an angiographic stenosis of ≥ 50%). Lower-extremity arterial imaging (invasive angiography or computed tomography imaging) can provide supplementary information. In this context, the Bollinger score has proven useful as a scoring method for assessment of lower limb atherosclerosis, including scoring for plaques, stenoses, and occlusions—which has been shown to provide prognostic outcome.[17,18] critical limb ischemia is the most severe form of PAD, as it is associated with severe resting leg pain, with or without tissue necrosis.[2,14] A subset of critical limb ischemia is acute limb ischemia, which is defined as the rapid onset of ischemic symptoms characterized by the "six Ps"—pain, pallor, pulselessness, paraesthesia, paralysis, poikilothermia ("inability to maintain core limb temperature").[1,2] Acute limb ischemia is rare and deemed to be a medical emergency requiring urgent revascularization or amputation.

The natural progression of PAD is varied and not well understood. For example, although it is estimated that 9.3% of asymptomatic patients will progress to IC over 5 years, others will remain asymptomatic or progress directly to critical limb ischemia.[7] Although a decrease in ABI occurs for most PAD patients, it does not always result in increased symptom severity or progression.[4] Thus, the progression of PAD and its symptoms is difficult to predict.

Conversely, PAD is an established harbinger of cardiovascular disease (CVD), morbidity, and mortality. A 2008 meta-analysis, which adjusted for Framingham risk score, found that asymptomatic PAD (ABI < 0.90) was associated with increased 10-year cardiovascular mortality (hazard ratio [HR] of 2.9 for men and 3.0 for women); similar results were found for all-cause mortality and major coronary events.[19] Similarly, patients with IC or atypical leg pain had a heightened risk of CV death (relative risk [RR]: 2.7) after adjustment for CV risk factors.[7,20] Critical limb ischemia is associated with a 25% risk of amputation within 1 year, and 1-, 5-, and 10-year mortality rates of 20%-45%, 40%-70%, and 80%-95%, respectively.[21,22] Moreover, PAD has a strong association with an increased prevalence of CVD such as myocardial infarction (MI), angina, congestive heart failure, and stroke; in fact, roughly 60% of PAD patients have either concomitant CAD or cerebrovascular disease.[4,7] Regardless of symptomology, PAD is an established risk factor for increased CVD morbidity and worsened prognosis—all of which underscores the importance of effectively managing secondary prevention.

Pharmacologic Therapy for PAD

Risk factor management

In the past, there was a lack of high-quality literature focused on the pharmacologic treatment of PAD,[23] mainly due to the paucity of clinical data in a condition that was less commonly diagnosed and underappreciated.[24] Over time, we have developed therapeutic treatment strategies based upon subgroup analyses of larger RCTs focused on CAD risk factor management. More recently, dedicated studies focused on PAD have been performed. An overview according to risk factor profile is provided in Tables 1–4.

Lipid-lowering drugs. For patients with stable ischemic heart disease, statin use is uniformly supported by European,[25] Canadian,[26] and American[27] guidelines. Furthermore, the European and Canadian guidelines support a target-based approach that focuses on either reducing low-density

Table 1. Cardiovascular outcome trials relevant to lipid management in PAD patients

Study (year)	Study design	Sample size	Patient population	PAD definition	Intervention	Median ollow-up time, y	Main result (95% CI)	Interpretation
4S[28,29] (1998)	RCT (PAD subgroup)	4444	Prior MI, or angina and hypercholesteremia	n/a	Simvastatin vs placebo	5.4	IC RR: 0.62 (0.44−0.88)	Statin therapy may prevent progression of PAD
HPS[30,31] (2007)	RCT (PAD subgroup)	6748	History of CVD or DM	History of IC, previous revascularization, amputation, or aneurysm repair	Simvastatin vs placebo	5	MACE RR: 0.22 (0.15−0.29)	Statin therapy provides benefit to all patients with PAD, regardless of initial presenting features
Antoniou et al.[32] (2014)	Meta-analysis	19,368	12 observational and 2 RCTs	Symptomatic PAD	Statin vs placebo	n/a	MACE OR: 0.91 (0.81−1.03) ACM OR: 0.77 (0.68−0.86) MI OR: 0.62 (0.38−1.01) Stroke OR: 0.77 (0.67−0.89)	Statins proven to significantly reduce ACM and stroke in PAD patients. A trend toward decreased MACE and MI was found
FOURIER[33,34] (2017; 2018)	RCT (PAD subgroup)	3642	Clinically evident atherosclerotic CVD while on high-intensity statin	Symptomatic PAD: IC, and ABI < 0.85; history of peripheral artery revascularization, or a history of amputation attributable to atherosclerosis	Evolocumab + statin vs placebo + statin	2.2	MACE HR: 0.79 (0.66−0.94)	Evolocumab is associated with a significant decrease in MACE for PAD patients, even beyond guideline-recommended LDL-C targets
		1505	Clinically evident atherosclerotic CVD while on high-intensity statin	Above definition except patients with prior history of MI and stroke were excluded	Evolocumab + statin vs placebo + statin	2.2	MACE HR: 0.67 (0.47−0.96)	The subgroup analyzed was at less risk of MACE, which indicates that aggressive lipid-lowering therapy may be appropriate at any stage of PAD
ODYSSEY OUTCOME[35] (2019)	RCT (PAD subgroup)	610	Dyslipidemia and ACS 1-12 months prior	Arterial disease of the extremities or abdominal aortic aneurysm	Alirocumab vs placebo	2.8	MACE HR: 0.93 (0.76−1.30)	Alirocumab is not associated with a decreased MACE risk in PAD patients with a recent ACS event

ABI, ankle-brachial index; ACM, all-cause mortality; ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval;.CVD, cardiovascular disease; DM, diabetes mellitus; FOURIER, **F**urther Cardiovascular **Ou**tcomes **R**esearch with PCSK9 **I**nhibition in Subjects with **E**levated **R**isk) trial; HR, hazard ratio; HPS, heart protection study; IC, intermittent claudication; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events (nonfatal stroke or MI, or CVD); MI, myocardial infarction; n/a, not applicable; ODYSSEY OUTCOME, Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome Study; OR, odds ratio; PAD, peripheral arterial disease; RCT, randomized controlled trial; RR, risk reduction; T2DM, type 2 diabetes mellitus.

Table 2. Cardiovascular outcome trials relevant to glucose regulation in PAD patients

Study (year)	Study design	Sample size	Patient population	PAD definition	Intervention	Median follow-up time, y	Main result (95% CI)	Interpretation
EMPA-REG [42,43](2015; 2018)	RCT (PAD subgroup)	1461 (7020 total)	T2DM and established CVD	Prior lower-limb revascularization, amputation, or peripheral arterial stenosis with ABI < 0.9	Empagliflozin vs placebo	3.1	MACE HR: 0.84 (0.62−1.14) ACM HR: 0.62 (0.35−0.92) CVM HR: 0.57 (0.37−0.88)	Empagliflozin (SGLT2i) improve mortality in PAD patients, and there is a nonsignificant trend towardsdecreased adverse events
CANVAS (2017)	RCT	10,142	T2DM with either a history of atherosclerotic CVD or at least 2 risk factors for CVD	N/A	Canagliflozin vs placebo	2.4	MACE HR: 0.86 (0.75−0.97) Amputation HR: 1.97 (1.41 −2.75)	Canagliflozin (SGLT2i) decrease MACE in CVD patients, but are associated with a significant increase in amputation risk
DECLARE-TIMI 58[45] (2020)	RCT (PAD subgroup)	1025	T2DM and established CVD or multiple atherosclerotic risk factors	Current claudication + ABI < 0.9, or history of revascularization or amputation	Dapagliflozin vs placebo	4.2	MACE HR: 1.05 (0.77−1.42) Amputation HR: 1.09 (0.84 −1.40)	Dapagliflozin (SGLT2i) is not associated with increased amputation, but no decrease in MACE
Harmony Outcomes[48] (2018)	RCT (PAD subgroup)	2354 (9463 total)	T2DM and established CVD and > 40 years old	IC and ABI < 0.9, non-traumatic amputation, or previous revascularization	Albiglutide vs placebo	1.6	MACE HR: 0.96 (0.73−1.25)	Albiglutide (GLP1 agonist) is not associated with decreased MACE in PAD patients, as compared to the larger CVD disease population
EXSCEL[49] (2019)	RCT (PAD subgroup)	2800 (14,752 total)	Adults with T2DM	Nontraumatic amputation, IC & ABI < 0.9, previous revascularization	Exenatide vs placebo	3.2	MACE HR: 0.85 (0.69−1.04)	Exenatide (GLP1 agonist) is not associated with decreased MACE in PAD patients

ABI, ankle-brachial index; ACM, all-cause mortality; CANVAS, **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy; CI, confidence interval; CVD, cardiovascular disease; CVM, cardiovascular mortality; DECLARE-TIMI 58, **D**apagliflozin **E**ffect on **C**ardiovascu**lar** **E**vents—Thrombolysis in Myocardial Infarction 58; DM, diabetes mellitus; EMPA-REG, **Empa**gliflozin Cardiovascular **Outcome** Event Trial in Type 2 Diabetes Mellitus Patients—**R**emoving **E**xcess **G**lucose) trial; EXSCEL, **Ex**enatide **S**tudy of **C**ardiovascular **E**vent **L**owering trial; GLP, glucagon-like peptide; Harmony Outcomes, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; HR, hazard ratio; IC, intermittent claudication; MACE, major adverse cardiovascular events (nonfatal stroke or myocardial infarction, or CVD); N/A, not applicable; PAD, peripheral arterial disease; RCT, randomized controlled trial; SGLT2i, sodium glucose transport protein 2 inhibitors; T2DM, type 2 diabetes mellitus.

Table 3. Cardiovascular outcome trials relevant to blood pressure management in PAD patients

Study (year)	Study design	Sample size	Patient population	PAD definition	4pc2>Intervention	Median follow-up, y	Main result (95% CI)	Interpretation
HOPE[34] (2004)	RCT (PAD subgroup)	3099	CVD, without heart failure with reduced ejection fraction	ABI < 0.9 and asymptomatic	Ramipril vs placebo	4.5	MACE HR: 0.75 (0.61−0.92)	Ramipril (ACEi) associated with a significant decrease in MACE for asymptomatic PAD patients
		1715	CVD, without heart failure with reduced ejection fraction	IC with ABI < 0.90, or previous vascular intervention/ amputation	Ramipril vs placebo	4.5	MACE HR: 0.73 (0.60−0.90)	Ramipril (ACEi) associated with a significant decrease in MACE for symptomatic PAD patients
INVEST[35] (2010)	RCT (PAD subgroup)	2699	CAD and hypertension	History of PAD based on patient questionnaire	Verapamil ± trandolapril vs atenolol ± HCT	2.7	SBP < 110; HR: 1.69 SBP = 135; HR: 1.02 SBP = 145; HR: 1.01 SBP = 170; HR: 1.65	Among PAD patients, a SBP range between 135 and 145 mm Hg was associated with best outcomes. Note, an optimal DBP range of 60 −90 mm Hg was also determined

ABI, ankle−brachial index; ACEi, angiotensin-converting enzyme inhibitor; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HCT, hydrochlorothiazide; HR, hazard ratio; HOPE, **H**eart **O**utcomes **P**revention **E**valuation; INVEST, **In**ternational **Ve**rapamil-SR/Trandolapril **St**udy; IC, intermittent claudication; MACE, major adverse cardiovascular events; PAD, peripheral arterial disease; RCT, randomized controlled trial; SBP, systolic blood pressure.

lipoprotein cholesterol (LDL-C) levels by 50% or to below 2.0 mmol/L (1.4 mmol/L for European guidelines). Alternative lipid-lowering pharmacologic therapy should be considered only when LDL-C target levels have not been reached while on the maximum-tolerated statin therapy.[25-27]

The 4S (**S**candinavian **S**imvastatin **S**urvival **S**tudy) trial (n = 4444) formed the foundation for use of statins in patients with coronary heart disease.[28] In a post-hoc analysis from the 4S study, simvastatin (10-40 mg) reduced IC by 38% (RR: 0.62, 95% confidence interval [CI]: 0.44-0.88).[29] The 2007 Heart Protection Study (HPS) randomized 20,536 individuals with atherosclerotic disease (or at high risk) to receive 40 mg simvastatin or placebo; the primary outcome measured was the occurrence of MACE over 5 years.[30] In a subset analysis of 6748 PAD patients, a 78% reduction in MACE (RR: 0.22, 95% CI: 0.15-0.29) was demonstrated in patients allocated to simvastatin therapy.[31] In a 2014 meta-analysis, statin-treated PAD patients had lower all-cause-mortality (odds ratio [OR]: 0.77, 95% CI: 0.68-0.86), lower non-fatal stroke (OR: 0.77, 95% CI: 0.67-0.89), and trends toward lower rates of MI (OR: 0.62, 95% CI: 0.38-1.01) and MACE (OR: 0.91, 95% CI: 0.81-1.03).[32]

More recently, the FOURIER (**F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk) trial investigated the use of evolocumab in adults with clinically evident atherosclerotic disease who were already on optimized lipid-lowering therapy (high-intensity statin +/- ezetimibe). Over a duration of 2.2 years, evolocumab use was associated with a significant reduction in MACE (HR: 0.85, 95% CI: 0.73-0.88) with median LDL-C levels in the evolocumab arm of 0.78 mmol/L—and no concerning safety signals.[33] A PAD subgroup analysis of symptomatic PAD patients (n = 3642) found similar reductions in MACE (HR: 0.79, 95% CI: 0.66-0.94). Within the same subgroup, those with symptomatic PAD but without a history of MI or stroke showed similar reductions in MACE (HR: 0.67, 95% CI: 0.47-0.96)[34]—hence, the addition of evolocumab therapy may be beneficial even in the early stages of PAD and in those without concomitant CAD. The 2018 ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) study randomized patients with a recent acute coronary syndrome (n = 18,924) event to receive alirocumab or placebo. Over 2.8 years, alirocumab reduced MACE (HR: 0.85, 95% CI: 0.73-0.98)—however a PAD subanalysis found that alirocumab did not alter MACE in patients with PAD and a recent acute coronary syndrome event (HR: 0.93, 95% CI: 0.67-1.30).[35] These trials showcase a need for future RCTs to: (i) be specifically powered for both symptomatic and asymptomatic PAD patients; (ii) assess whether the primary benefit from lipid-management therapy is a result of specific medications or an overall reduction in LDL-C levels.

Anti-diabetic drugs. For patients with stable CAD and diabetes, guidelines support the use of a hemoglobin A1c (HbA1c) target of 7.0 mmol/L and recommend the use of angiotensin-converting enzyme inhibitors, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide-1 agonists in addition to metformin, due to their cardioprotective effects.[25,36,37]

Table 4. Cardiovascular outcome trials relevant to the antithrombotic management of peripheral arterial disease (PAD) patients

Study (year)	Study design	Sample size	Patient population	PAD definition	Intervention	Median follow-up, y	Main result (95% CI)	Interpretation
Antiplatelet monotherapy								
CAPRIE[60] (1996)	RCT (PAD subgroup)	6452	Ischemic stroke, MI, or symptomatic PAD	IC and ABI < 0.85, or a history of previous IC with previous leg amputation or revascularization	Clopidogrel vs aspirin	1.9	MACE OR: 23% (8.9%−36.2%)	Clopidogrel use in symptomatic PAD patients may be more beneficial as a first-line monotherapy than aspirin
ATC[58] (2002)	Meta-analysis	9214	Patients at high risk of CV complications	Symptomatic PAD: IC or revascularization	Various AP vs placebo	N/A	MACE OR: 0.80 (0.68−0.94)	Various AP agents proven to reduce MACE occurrence in PAD patients
CLIPS[59] (2007)	RCT	366	Symptomatic and asymptomatic PAD	Symptomatic PAD: IC Asymptomatic PAD: occlusion documented by angiography or ultrasound, and ABI < 0.85 or TBI < 0.6	Aspirin vs placebo	1.7	MACE HR: 0.35 (0.15−0.82)	Aspirin was associated with a decreased occurrence of MACE in a heterogenous PAD group
POPADAD[62] (2008)	RCT	1276	DM and asymptomatic PAD	Asymptomatic with ABI < 0.99	Aspirin vs placebo	6.7	MACE HR: 0.98 (0.76−1.26)	Aspirin not shown to decrease MACE in asymptomatic PAD and DM
AAA[63] (2010)	RCT	3350	No clinical CVD and low ABI	Asymptomatic with ABI < 0.95	Aspirin vs placebo	8.2	MACE HR: 1.03 (0.84−1.27)	Aspirin not shown to decrease MACE in asymptomatic PAD
EUCLID[61] (2017)	RCT	13,885	Symptomatic PAD	Previous revascularization of lower limbs for symptomatic PAD or ABI < 0.80	Ticagrelor vs clopidogrel	2.5	MACE HR: 1.02 (0.92−1.13)	Ticagrelor not superior to clopidogrel in reducing MACE for PAD patients
DAPT								
CHARISMA[65] (2009)	RCT (PAD subgroup)	3096	Stable CVD, PAD, or multiple atherothrombotic risk factors	Symptomatic PAD: IC + ABI < 0.8, or a history of IC with previous intervention Asymptomatic PAD: ABI < 0.90	Clopidogrel + aspirin vs aspirin	2.3	MACE HR: 0.85 (0.66−1.08) MI HR: 0.63 (0.42−0.96) CVD hospitalization HR: 0.81 (0.68−0.95)	DAPT use in stable PAD patients not significantly associated with decreased MACE, but decreases MI and CVD hospitalization rates
TRA 2°P-TIMI 50[67] (2020)	RCT (PAD subgroup)	6136 (26,449 total)	Previous MI, stroke, or PAD	IC and ABI < 0.85, or a history of previous revascularization. Patients with concomitant CAD included	Vorapaxar vs placebo	2	MACE HR: 0.85 (0.73−0.99)	Vorapaxar associated with decreased MACE in PAD patients with concomitant CAD
PEGASUS_TIMI 54[66] (2016)	RCT (PAD subgroup)	1143	Prior MI and an atherosclerotic risk factor	ABI < 0.90, history of peripheral revascularization, or a history of IC	Ticagrelor + aspirin vs aspirin + placebo	2.8	MACE HR: 0.69 (0.44−0.99)	DAPT with ticagrelor + aspirin reduced rates of MACE in PAD patients
Oral anticoagulation								
WAVE[68] (2007)	RCT	2161	Proven atherosclerosis of the lower extremity, carotid, or subclavian arteries	IC with objective evidence of PAD (ischemic pain, gangrene, previous amputation, revascularization)	Warfarin or acenocoumarol + AP vs AP	2.9	MACE RR: 0.92 (0.73−1.16) Bleeding RR: 3.41 (1.84−6.35)	Warfarin/acenocoumarol plus antiplatelet was not more effective than antiplatelet alone in preventing MACE and increased bleeding risk
COMPASS[69,70] (2017; 2018)	RCT (PAD subgroup)	5551	Patients with CVD	Lower-limb revascularization, prior amputation, IC with diagnostic confirmation, or ABI < 0.90	Rivaroxaban + aspirin vs aspirin	1.8	MACE HR: 0.72 (0.57−0.90) Bleeding HR: 1.75 (1.16−2.65)	Low-dose rivaroxaban + aspirin was superior to aspirin alone in reducing MACE
VOYAGER PAD[85] (2020)	RCT	6547	Patients with PAD and recent revascularization	Lower-extremity PAD with recent revascularization	Rivaroxaban + aspirin vs aspirin	3	MACE HR: 0.85 (0.76−0.96) Bleeding HR: 1.43 (0.97−2.10)	Low-dose rivaroxaban + aspirin was superior to aspirin alone in reducing MACE.

AAA, **A**spirin for **A**symptomatic **A**therosclerosis; ABI, ankle-brachial index; AP, antiplatelet; ATC, Antithrombotic Trialists' Collaboration; CAD, coronary artery disease; CAPRIE, **C**lopidogrel versus **A**spirin in **P**atients at **R**isk of **I**schaemic **E**vents; CHARISMA, **C**lopidogrel for **H**igh **A**therothrombotic **R**isk and **I**schemic **S**tabilization, **M**anagement, and **A**voidance; CI, confidence interval; CLIPS, **C**ritical **L**eg **I**schemia **P**revention **S**tudy; COMPASS, **C**ardiovascular **O**utcom**e**s for **P**eople Using **A**nticoagulation **S**trategie**s**; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; EUCLID, **E**xamining **U**se of Ti**c**agre**l**or **i**n PA**D**; HR, hazard ratio; IC, intermittent claudication; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not applicable; OAC, oral anticoagulation; OR, odds ratio; PAD, peripheral arterial disease; PEGASUS-TIMI 54, **P**revention of Cardiovascular **E**vents in Patients With Prior Heart Attack Using Tica**g**relor T**a**blet**s** Compared to Placebo on a Backgro**u**nd of A**s**pirin−**T**hrombolysis **i**n **M**yocardial **I**nfarction 54; POPADAD, **P**revention **o**f **P**rogression of **A**rterial **D**isease **a**nd **D**iabetes; RCT, randomized controlled trial; RR, risk reduction; TBI, toe-brachial index; TRA 2°P-TIMI 50, **T**hrombin **R**eceptor **A**ntagonist in Secondary **P**revention of Atherothrombotic Ischemic Events−**T**hrombolysis **i**n **M**yocardial **I**nfarction 50; VOYAGER, **V**ascular **O**utcomes Stud**y** of **A**SA Alon**g** with Rivaroxaban in **E**ndovascular or Surgical Limb **R**evascularization for **PAD**; WAVE, **W**arfarin **A**ntiplatelet **V**ascular **E**valuation.

A large majority of evidence supporting glucose management in PAD comes from studies that assess hyperglycemia as a risk factor for atherosclerotic disease.[38] In a subgroup analysis of patients from the **UK P**rospective **D**iabetes **S**tudy (UKPDS; randomized study to address the impact of optimal glucose control on diabetic complications), 3834 PAD-naïve patients were followed for 6 years; the study found a 28% increase in PAD (OR: 1.28, 95% CI: 1.12-1.46) for each 1% increase in HbA1c.[39] In a subgroup analysis of PAD diabetics from the **E**xamining **U**se of Ti**c**agre**l**or **i**n Pa**d** (EUCLID) trial, every 1% increase in HbA1c was associated with a 14.2% risk of MACE.[40] However, in a meta-analysis of RCTs investigating the cardiovascular effects of optimal glucose control in type 2 diabetes mellitus, intensive glucose control did not reduce the risk of PAD.[41]

Recently, sodium-glucose cotransporter 2 inhibitors have shown promise in diabetics with CV risk their effects on PAD outcomes have been somewhat unclear. A subanalysis of 1431 PAD patients from the EMPA-REG OUTCOME (**Empa**gliflozin Cardiovascular **Outcome** Event Trial in Type 2 Diabetes Mellitus Patients—**R**emoving **E**xcess **G**lucose) trial[42] found empagliflozin decreased all-cause mortality (HR: 0.62; 95% CI: 0.35-0.92) and CV death (HR: 0.57, 95% CI: 0.37-0.88) while demonstrating a nonsignificant reduction in MACE (HR: 0.84, 95% CI: 0.62-1.14) and lower-limb amputation (HR: 0.84, 95% CI: 0.54-1.32).[42,43] However, the **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) found a significant increase in limb amputation in diabetics with high cardiovascular risk (HR: 1.97, 95% CI: 1.41-2.75).[44] Most recently, the **D**apagliflozin **E**ffect on **C**ardiovascu**lar** **E**vents—**T**hrombolysis **i**n **M**yocardial **I**nfarction 58 (DECLARE-TIMI 58) trial evaluated the effects of dapagliflozin on type-2 diabetes mellitus patients with CVD (or associated risk factors), and found no significant difference in amputation (HR: 1.09, 95% CI: 0.84-1.40)—but a subgroup analysis of 1025 PAD patients found no reduction in MACE (HR: 1.05, 95% CI: 0.77-1.42).[45] Two recent meta-analyses[46,47] found that the increased risk of amputation is likely drug-specific—related to canagliflozin. Nevertheless, further research and RCT data are required to determine the risk/benefit profile of sodium-glucose cotransporter 2 inhibitor therapy in PAD patients.[46,47]

The effect of glucagon-like peptide-1 agonists have also been assessed in PAD patients through the recent Harmony Outcomes (Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease)[48] and **Ex**enatide **S**tudy of **C**ardiovascular **E**vent **L**owering (EXSCEL) trials.[49] In Harmony Outcomes, albiglutide was associated with decreased MACE (HR: 0.79, 95% CI: 0.68-0.90) for type 2 diabetes mellitus patients with established CVD (n = 9463); however, no difference was seen in the PAD subgroup (HR: 0.85, 95% CI: 0.73-1.25).[42] The EXSCEL trial evaluated the effects of exenatide on MACE in type 2 diabetes mellitus patients (n = 14,752), with a trend toward benefit (HR: 0.91, 95% CI: 0.83-1.00); however, a subgroup analysis in the PAD group found no significant reduction in MACE (HR: 0.85, 95% CI: 0.69-1.04).

Broadly, it appears that glucose regulation is an important parameter in the risk-reduction treatment of PAD, yet the choice of a specific pharmacologic agent has yet to be determined.

Anti-hypertensive drugs. For patients with stable CAD and hypertension, Canadian guidelines recommend a systolic blood pressure target of < 120 mm Hg,[50] whereas American[51] and European[25] guidelines recommend a target systolic blood pressure of < 130 mm Hg and a target diastolic blood pressure of < 80 mm Hg. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended as first-line therapy for all patients with stable CAD and hypertension, in the Canadian guidelines.[50] Conversely, the American and European guidelines recommend these as first-line therapies only in patients with hypertension and recent MI.[25,51]

Although it is widely understood that hypertensioncontributes to the development of PAD,[52] few studies have addressed treatment with therapeutic targets. In a PAD subset from the **A**ppropriate **B**lood Pressure **C**ontrol in **D**iabetes (ABCD) trial (53 patients), patients with intensive blood pressure lowering (average of 128/75 mm Hg) had fewer CV events (compared to moderate treatment).[53] In a PAD subgroup analysis from the **H**eart **O**utcomes **P**revention **E**valuation (HOPE) trial (n = 8986), an ABI of < 0.9 was found to be a strong predictor of adverse outcome regardless of symptoms—yet the absolute benefit of ramipril (vs placebo) was twice as large (50 per 1000 events prevented) compared to the benefit for those with a normal ABI (> 0.9).[54] In an important post hoc analysis of the **In**ternational **Ve**rapamil-SR/Trandolapril **St**udy (INVEST) trial, those with CAD and PAD had lower MACE with an average systolic blood pressure of 135-145 mm Hg and an average diastolic blood pressure of 60-90 mm Hg, but with an important J-shape relationship demonstrated with lower blood pressure having deleterious limb effects (ie, balance of necessary perfusion in the setting of limb ischemia).[55]

Overall, it is clear that blood pressure management is an essential intervention required in preventing MACE in PAD patients; however, the preferred use of a specific pharmacologic agent and absolute target (threshold limit given the J-shape relationship) remains to be determined.

Inhibitors of coagulation and platelet activation

Guideline recommendations support the indefinite use of aspirin for secondary prevention in CAD. For those who are unable to tolerate aspirin therapy, clopidogrel therapy is recommended.[25,56,57] Oral anticoagulation alone for CAD has not been recommended.

Antiplatelet monotherapy in patients with symptomatic PAD. The contemporary basis of antiplatelet use in PAD patients was developed from the 2002 Antithrombotic Trialists' Collaboration (ATC) meta-analysis, which studied antiplatelet regimens vs placebo in high-risk atherosclerotic patients. In the symptomatic PAD subgroup, reduction in MACE was demonstrated with antiplatelet therapy (OR: 0.80, 95% CI: 0.68-0.94).[58] The 2007 **C**ritical **L**eg **I**schemia **P**revention **S**tudy (CLIPS) study compared the efficacy of aspirin against placebo in 366 PAD patients. Aspirin was associated with a significant decrease in MACE (HR: 0.35, 95% CI: 0.15-0.82).[59] In the **C**lopidogrel versus **A**spirin in **P**atients at **R**isk of **I**schaemic **E**vents (CAPRIE) trial, clopidogrel monotherapy was shown to be more effective than

aspirin monotherapy in reducing cardiovascular events over 3 years—an effect magnified in those with symptomatic PAD.[60] Recently, the EUCLID trial examined the efficacy and safety of ticagrelor against clopidogrel monotherapy in patients with symptomatic PAD. In 13,885 patients, there was no significant difference in MACE at 30 months.[61] Taken together, these studies suggest a benefit of antiplatelet monotherapy (aspirin or clopidogrel) in symptomatic PAD.

Antiplatelet monotherapy in patients with asymptomatic PAD. The 2008 **P**revention **o**f **P**rogression of **A**rterial **D**isease **a**nd **D**iabetes (POPADAD)[62] and 2010 **A**spirin for **A**symptomatic **A**therosclerosis (AAA)[63] trials sought to assess the efficacy of aspirin in asymptomatic PAD. The POPADAD trial did not find a significant reduction in the composite of death from coronary heart disease or stroke, non-fatal MI or stroke, or above-ankle amputation for critical limb ischemia in those taking aspirin (HR: 0.98, 95% CI: 0.76-1.26). Likewise, the AAA trial did not find a significant reduction in MACE for PAD patients taking aspirin (HR: 1.03, 95% CI: 0.84-1.27). Reminiscent of the controversy for aspirin in primary prevention for CAD, antiplatelet monotherapy cannot be recommended for asymptomatic PAD patients.

DAPT in patients with PAD or CAD. The use of dual antiplatelet therapy (DAPT) in stable CAD patients who have had a recent acute coronary syndrome event and/or are undergoing concomitant coronary revascularization is well studied and has an established role.[25,56,64] Given the incremental risk, studies have explored the use of DAPT in patients with PAD and CAD. In an important subgroup analysis of the 3096 PAD patients from the **C**lopidogrel for **H**igh **A**therothrombotic **R**isk and **I**schemic **S**tabilization, **M**anagement, and **A**voidance (CHARISMA) trial (examining the efficacy of a clopidogrel plus aspirin regimen vs aspirin alone in preventing MACE for those at high risk for atherothrombotic events), no difference in MACE was demonstrated (HR: 0.85, 95% CI: 0.66-1.08), but the rates of MI (HR: 0.63, 95% CI: 0.42-0.96) and hospitalization for ischemic events (HR: 0.81, 95% CI: 0.68-0.95) were reduced with DAPT (at the cost of increased bleeding).[65] In a subgroup analysis of 1143 PAD patients from the **P**revention of Cardiovascular **E**vents in Patients With Prior Heart Attack Using Tica**g**relor T**a**blet**s** Compared to Placebo on a Backgro**u**nd of A**s**pirin−**T**hrombolysis **i**n **M**yocardial **I**nfarction 54 (PEGASUS-TIMI 54) trial (comparing DAPT therapy [ticagrelor and aspirin] with aspirin monotherapy in stable CAD patients with a history of MI), MACE was reduced with DAPT (HR: 0.69, 95% CI: 0.47-0.99)—with greater absolute reduction compared to those without PAD. Additionally, a 35% reduction in major adverse limb events was demonstrated with ticagrelor-based DAPT.[66]

In a sub-group analysis of 6136 PAD patients from the **T**hrombin **R**eceptor **A**ntagonist in Secondary **P**revention of Atherothrombotic Ischemic Events−**T**hrombolysis **i**n **M**yocardial **I**nfarction 50 (TRA 2°P−TIMI 50) trial (assessing the addition of vorapaxar [PAR-1 platelet antagonist] to standard treatment of patients with established CVD), MACE and major adverse limb events were reduced with the addition of vorapaxar (HR: 0.85, 95% CI: 0.73-0.99) with absolute risk reduction greater in patients with PAD and CAD.[67] Overall, it appears there are long-term benefits with DAPT in patients with PAD and CAD (particularly with prior MI).

Vitamin K inhibitors, aspirin, and rivaroxaban therapy in patients with PAD. The 2007 **W**arfarin **A**ntiplatelet **V**ascular **E**valuation (WAVE) trial was a primary RCT that investigated the use of warfarin and aspirin combination therapy against aspirin monotherapy in 2161 patients with stable (mainly symptomatic) PAD.[68] No significant reduction in MACE was found with combination therapy (RR: 0.92, 95% CI: 0.73-1.16), and a significant increase in life-threatening bleeding was demonstrated (RR: 3.41, 95% CI: 1.84-6.35).

The **C**ardiovascular **O**utco**m**es for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial enrolled 27,395 participants with stable atherosclerotic vascular disease (CAD and/or PAD) comparing low-dose rivaroxaban, with or without aspirin, against aspirin alone.[69] The combination of low-dose rivaroxaban (2.5 mg twice daily) and low-dose aspirin significantly decreased MACE (and mortality alone) compared to aspirin monotherapy (HR: 0.76, 95% CI: 0.66-0.86). Although a higher frequency of major bleeding events occurred for patients taking both aspirin and rivaroxaban (HR: 1.70, 95% CI: 1.40-2.05), no significant differences were seen with life-threatening or fatal bleeds. A prespecified PAD subgroup analysis from COMPASS was conducted as well.[70] In total, 5551 participants from the original cohort were identified as having lower-extremity PAD, defined as: previous aorto-femoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization of the iliac, or infrainguinal arteries; or limb or foot amputation for arterial vascular disease; or IC and one or more of either an ABI of less than 0.90 or a peripheral artery stenosis ($\geq$ 50%) documented by angiography or duplex ultrasound; or asymptomatic PAD defined as patients with CAD, who had an ABI $<$ 0.90. Results showed that dual pathway inhibition with low-dose rivaroxaban (2.5 mg twice daily) and low-dose aspirin significantly decreased MACE (HR: 0.72, 95% CI: 0.57-0.90). Equally impressive was a near 50% reduction in major adverse limb events (HR: 0.54, 95% CI: 0.35-0.82). Although major bleeding was increased (HR: 1.75, 95% CI: 1.16-2.25), there was no excess in fatal bleeding, intracranial bleeding, or bleeding into critical organs.[71]

Most recently, the **V**ascular **O**utcomes Stud**y** of **A**SA Alon**g** with Rivaroxaban in **E**ndovascular or Surgical Limb **R**evascularization for **PAD** (VOYAGER PAD) trial evaluated the effects of vascular dose rivaroxaban (2.5 mg twice daily) and aspirin vs placebo and aspirin in PAD patients who had undergone successful revascularization within the previous 10 days from symptoms. This is the first randomized study to address this therapy in those with lower-extremity revascularization—a population known for a heightened risk of MACE and major adverse limb events. Of the 6564 patients enrolled, the composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes (primary efficacy outcome) was modestly reduced with rivaroxaban and aspirin at 3 years (17.3% vs 19.9%; HR: 0.85, 95% CI: 0.76-0.96, P = 0.009) with a trend toward higher risk of thrombolysis in myocardial infarction major bleeding (primary safety outcome; 2.65% vs 1.87%; HR: 1.43, 95% CI: 0.97-2.10, P = 0.07) and significantly higher risk of International Society on Thrombosis and Haemostasis major bleeding.[72] Given these data, oral

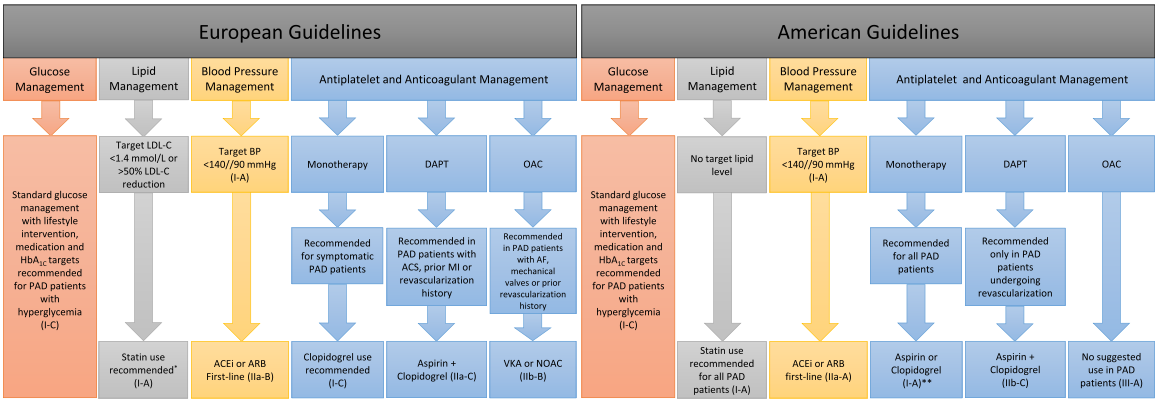

Figure 1. Overview of European and American Guidelines for Peripheral Arterial Disease (PAD) Secondary Prevention. Recommendation class (eg, I-A) provided in parentheses. ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; DAPT, dual antiplatelet therapy; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NOAC, non–vitamin k antagonist oral anticoagulation; OAC, oral anticoagulation; VKA, vitamin K antagonist. *Use of statins recommended until LDL-C < 1.4 mmol/L for patients with baseline LDL-C levels > 2.8 mmol/L or until > 50% reduction in LDL-C levels for patients with LDL-C levels between 1.4 and 2.8 mmol/L. If the targets are not met, ezetimibe is recommended as second-line therapy (I-B), and evolocumab is recommended as third-line therapy (I-A). **A Class I-A recommendation was provided for antiplatelet monotherapy use in symptomatic PAD patients, and a Class IIa-C recommendation was provided for asymptomatic PAD patients with ankle-brachial index < 0.9.

anticoagulation with vascular dose rivaroxaban (2.5 mg twice daily) and aspirin is a reasonable option and should be considered in patients with PAD with or without recent lower-limb revascularization.

Secondary Prevention Involving Patient Participation

Smoking cessation

All patients should be counselled to quit smoking, as it is an established modifiable risk factor associated with an 11-fold increased risk of PAD progression.[7] A Cochrane systematic review of (n = 64,640) on nicotine replacement therapy found that it significantly increased smoking abstinence rates compared to a control group not using nicotine replacement therapy (OR: 1.55, 95% CI: 1.49-1.61).[73] An additional meta-analysis found that bupropion (RR: 1.42, 95% CI: 1.01-2.01), varenicline (RR: 2.64, 95% CI: 1.34 -5.21), telephone therapy (RR: 1.47, 95% CI: 1.15-1.88), and individual counselling (RR: 1.64, 95% CI: 0.72-2.06) were all effective intervention for increasing smoking cessation.[74]

Regular physical activity

Increased physical activity is associated with decreased disease progression and all-cause-mortality in PAD patients.[75] Meta-analyses have demonstrated that structured home-based exercise programs are effective in improving maximum walking distance, IC onset distance, and physical activity.[76,77] An additional meta-analysis found that such programs were associated with decreased LDL-C, total cholesterol, systolic blood pressure, and diastolic blood pressure.[78] However, European countries found that the implementation and utilization of structured home-based exercise programs was still suboptimal.[79] Given the overwhelming body of evidence supporting the benefits of exercise programs for PAD over the past 30 years, the American Heart Association (AHA) has endorsed supervised exercise programs (ie, supervised treadmill exercise therapy) for patients with claudication with a Class of Recommendation (COR) I - Level of Evidence (LOE) A recommendation.[80] Alternative strategies for exercise therapy (upper body ergometry, cycling, pain-free/low-intensity walking) are listed as COR IIa - LOE A.[80] In Canada, physical activity recommendations include 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of 10 minutes or more (also beneficial are muscle- and bone-strengthening exercises at least 2 days per week).[81]

Review of the Guidelines

Existing evidence from RCT studies, meta-analyses, and registry data have supported the development of American and European guidelines for the management of patients with stable PAD (Fig. 1).

European guidelines

The 2017 European Society of Cardiology guidelines provide a review on all non-coronary atherosclerotic vascular diseases, with specific sections being dedicated to the medical management of lower-extremity artery disease.[82] Additionally, the 2019 European Society of Cardiology lipid guidelines provided updated lipid targets.[83] Overall, the guidelines provide recommendations for all therapies and interventions discussed in this review.

Physical activity is recommended in all patients (COR I - LOE C), and supervised exercise training is recommended in patients with IC (COR I - LOE A). Smoking cessation is recommended in all PAD patients (COR I - LOE A). Standard glucose control, with no specific medication preference, was recommended for patients with diabetes and PAD (COR I - LOE C). The guidelines advocate for the use of statins in lowering LDL-C levels below 1.4 mmol/L, or for patients with an LDL-C between 1.4 and 2.8 mmol/L, by greater than 50% (COR I - LOE A). If the lipid targets are not met, ezetimibe is recommended as a second-line therapy (COR I - LOE B),

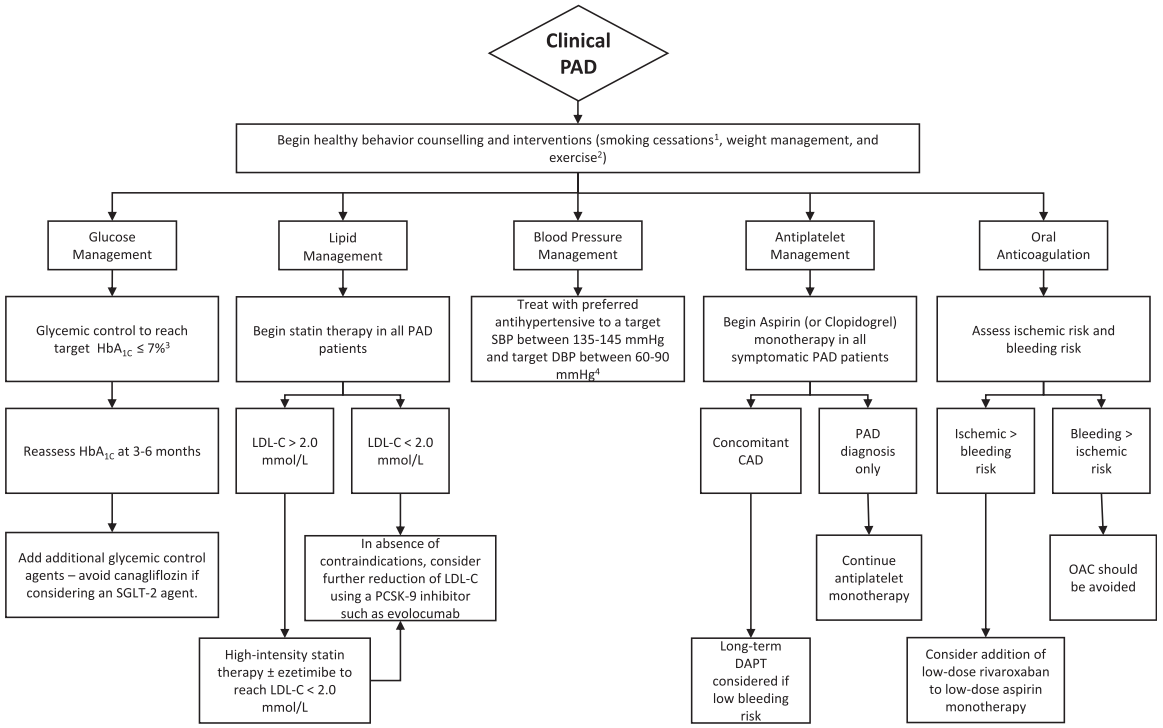

Figure 2. Treatment algorithm for peripheral arterial disease (PAD) patients. CAD, coronary artery disease; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; PCSK-9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2. * Consider addition of nicotine replacement therapy, bupropion, varenicline, or telephone therapy. † Consider referral for a structured home-based exercise program, if available. ‡ HbA1c targets may increase or decrease depending on patient's functional capacity, risk for hypoglycemia, and risk of microvascular complications. § Target blood pressure range may vary based on patient comorbidities such as diabetes mellitus, kidney disease, cardiomyopathy, and CAD.

and evolocumab is recommended as a third-line therapy (COR I - LOE A). A blood pressure target of < 140/90 mm Hg in stable PAD patients is recommended (COR I - LOE A). Moreover, for lower-extremity artery disease patients, either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is recommended as first-line therapy due to their beneficial effect on walking distance and claudication symptoms (COR IIa - LOE B). Lastly, recommendations on antiplatelet therapy and use of DAPT or oral anticoagulation therapy are provided. Antiplatelet therapy is recommended in all patients with symptomatic PAD (COR I - LOE C), and clopidogrel is the recommended choice of monotherapy. No antiplatelet therapy is recommended for asymptomatic PAD patients (COR III - LOE A). DAPT is only recommended in patients with a recent acute coronary syndrome event, revascularization, or with a prior history of MI (COR II - LOE C). Interestingly, when needed, DAPT consisting of aspirin and clopidogrel is recommended. The guideline makes note of the COMPASS trial, but it does not make suggestions based upon it as the trial's data had not been released. Consequently, oral anticoagulation is only recommended for PAD patients who have concomitant atrial fibrillation, have a mechanical prosthetic valve, or are undergoing revascularization (COR IIb - LOE B).

American guidelines

The 2016 American College of Cardiology Foundation (ACCF)/AHA guidelines provide a focused review on lower-extremity PAD.[84] The American guidelines provide specific recommendations for all therapies discussed in this review.

Smoking cessation is recommended in all PAD patients (COR I - LOE A); these patients should be assisted in quitting through the use of pharmacotherapy and/or referral to a smoking cessation program (COR I - LOE A). A supervised exercise program is recommended in all patients with claudication (COR I - LOE A), and a structured community-based or home-based program with behavioural change techniques is recommended in all other PAD patients (COR IIa - LOE A). It is acknowledged that diabetes mellitus is an important risk factor for PAD and that its management should be coordinated among all members of the healthcare team (COR I - LOE C). However, no specific medications or HbA1c goals are set, except those used in standard care. Statin use is also recommended for both symptomatic and asymptomatic PAD patients; however, no LDL-C or other lipid targets are provided within the guidelines (COR I - LOE A). Antihypertensives are recommended for all patients diagnosed with hypertension, and PAD-specific blood pressure targets are not provided (COR I - LOE A). Furthermore, no specific antihypertensive medication is suggested for superior blood pressure lowering, but a weaker recommendation for the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is suggested to reduce the risk of cardiovascular ischemic events (COR IIa - LOE A). Antiplatelet therapy with aspirin or clopidogrel is recommended for patients with symptomatic PAD to reduce MI, stroke, and vascular death (COR I - LOE A). A weaker recommendation for the use of

antiplatelet therapy in asymptomatic PAD patients (ABI < 0.9) is also suggested (COR IIa - LOE C). It is also suggested that the overall effectiveness of DAPT is not well established, but that it may be reasonable in patients after revascularization (COR IIb - LOE C). When indicated, the suggested DAPT is aspirin plus clopidogrel. Lastly, a strong recommendation against the use of anticoagulation as a risk reduction medication in PAD patients is provided (COR III - LOE A). Again, these guidelines were released prior to the COMPASS study.

Proposed clinical pathway

Although we recognize the importance of clinical guidelines, important to note is the lack of contemporary recommendations based on current evidence. This becomes paramount, given the recognition of PAD as an important disease state within the spectrum of atherosclerosis, and with the development of clinical trials focused on PAD management. Moreover, there are no contemporary Canadian guidelines for the management of PAD. So we have developed a clinical PAD pathway based on the best available high-quality evidence (Fig. 2).

Conclusion

Current guideline recommendations concur on the use of exercise therapy, smoking cessation, statins, blood pressure management, glucose management, and antithrombotic use for PAD patients. Yet, important distinctions exist. Our review identifies contemporary pharmacotherapies from high-quality studies, providing further direction for clinicians. Still, fundamental efforts are warranted in establishing Canadian guidelines for management of PAD.

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References

1. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ 2018;360:j5842.
2. Conte SM, Vale PR. Peripheral arterial disease. Heart Lung Circ 2018;27:427–32.
3. Hira RS, Cowart JB, Akeroyd JM, et al. Risk factor optimization and guideline-directed medical therapy in US veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. Am J Cardiol 2016;118:1144–9.
4. Criqui MH, Aboyans V. Epidemiology of peripheral arterial disease. Circ Res 2015;116:1509–26.
5. Patel MR, Conte MS, Cutlip DE, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from peripheral academic research consortium (PARC). J Am Coll Cardiol 2015;65:931–41.
6. 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.
7. Fowkes FGR, Aboyans V, Fowkes FJI, et al. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 2016;14:156–70.
8. Dua A, Lee CJ. Epidemiology of peripheral arterial disease and critical limb ischemia. Tech Vasc Interv Radiol 2016;19:91–5.
9. Ix JH, Biggs ML, Kizer JR. Association of body mass index with peripheral arterial disease in older adults: the cardiovascular health study. J Vasc Surg 2012;55:614.
10. 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 2014;100:100–5.
11. 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;73:1456–65.
12. Mentias A, Vaughan-Sarrazin M, Saad M, Girotra S. Sex differences in management and outcomes of critical limb ischemia in the Medicare population. Circ Cardiovasc Interv 2020;13:e009459.
13. Conen D, Rexrode KM, Creager MA, Ridker PM, Pradhan AD. Metabolic syndrome, inflammation, and risk of symptomatic peripheral artery disease in women: a prospective study. Circulation 2009;120:1041–7.
14. Schorr EN, Treat-Jacobson D. Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: a review. Vasc Med 2013;18:95–111.
15. Lend GC, Fowkes FGR. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. J Clin Epidemiol 1992;45:1101–9.
16. Criqui MH, Denenberg JO, Bird CE, et al. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. Vasc Med 1996;1:65–71.
17. Bollinger A, Breddin K, Hess H, et al. Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. Atherosclerosis 1981;38:339–46.
18. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial: a description of the severity and extent of disease using the Bollinger angiogram scoring method and the Trans-Atlantic Inter-Society Consensus II classification. J Vasc Surg 2010;51:32S–42S.
19. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197–208.

20. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall study. Circulation 1990;82:1925–31.

21. Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. Semin Vasc Surg 1999;12:142–7.

22. Long-term mortality and its predictors in patients with critical leg ischaemia. The I.C.A.I. Group (Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori). The Study Group of Criticial Chronic Ischemia of the Lower Exremities. Eur J Vasc Endovasc Surg 1997;14:91–5.

23. Hussain MA, Al-Omran M, Creager MA, et al. Antithrombotic therapy for peripheral artery disease: recent advances. J Am Coll Cardiol 2018;71:2450–67.

24. Hiatt WR, Rogers RK. The treatment gap in peripheral artery disease. J Am Coll Cardiol 2017;69:2301–3.

25. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2019;41:407–77.

26. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32:1263–82.

27. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:3168–209.

28. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

29. Pedersen TR, Kjekshus J, Pyörälä K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 1998;81:333–5.

30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.

31. 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.

32. Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis. Vascul Pharmacol 2014;63:79–87.

33. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

34. Bonaca M, Nault P, Giugliano R, 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.

35. Jukema JW, Szarek M, Zijlstra LE, et al. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY OUTCOMES trial. J Am Coll Cardiol 2019;74:1167–76.

36. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2020. Diabetes Care 2020;43:S111–34.

37. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2018;42:S1–S325.

38. Parvar SL, Fitridge R, Dawson J, Nicholls SJ. Medical and lifestyle management of peripheral arterial disease. J Vasc Surg 2018;68:1595–606.

39. Adler AI, Stevens RJ, Neil A, et al. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002;25:894–9.

40. Low Wang CC, Blomster JI, Heizer G, et al. Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: the EUCLID trial. J Am Coll Cardiol 2018;72:3274–84.

41. Yudkin JS, Richter B. Concerns about meta-analysis of glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2010;52:63–4.

42. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.

43. Subodh V, David MC, Mohammed Al-Omran, et al. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease. Circulation 2018;137:405–7.

44. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.

45. Bonaca M, Wiviott S, Zelniker T, et al. Dapagliflozin and cardiac, kidney and limb outcomes in patients with and without peripheral artery disease in DECLARE-TIMI 58. Circulation 2020;142:734–47.

46. Dicembrini I, Tomberli B, Nreu B, et al. Peripheral artery disease and amputations with sodium-glucose co-transporter-2 (SGLT-2) inhibitors: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2019;153:138–44.

47. Heyward J, Mansour O, Olson L, Singh S, Alexander GC. Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: a systematic review and meta-analysis. PLoS One 2020;15:e0234065.

48. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–29.

49. Badjatiya A, Merrill P, Buse J, et al. Clinical outcomes in patients with type 2 diabetes mellitus and peripheral artery disease: results from the EXSCEL trial. Circ Cardiovasc Interv 2019;12:e008018.

50. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol 2020;36:596–624.

51. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–248.

52. Makin A, Lip GYH, Silverman S, Beevers DG. Peripheral vascular disease and hypertension: A forgotten association? J Hum Hypertens 2001;15:447.

53. Mehler PS, Coll JR, Estacio R, et al. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. Circulation 2003;107:753–6.

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

55. Bavry AA, Anderson RD, Gong Y, 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.

56. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. Can J Cardiol 2018;34:214–33.

57. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–164.

58. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.

59. Critical Leg Ischaemia Prevention Study (CLIPS) Group. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. J Intern Med 2007;261:276–84.

60. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39.

61. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017;376:32–40.

62. Belch J, MacCuish A, Campbell I, 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;337:1030–4.

63. Fowkes FGR, Price JF, Stewart MCW, 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.

64. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

65. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J 2009;30:192–201.

66. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol 2016;67:2719–28.

67. Qamar A, Morrow DA, Creager MA, et al. Effect of vorapaxar on cardiovascular and limb outcomes in patients with peripheral artery disease with and without coronary artery disease: analysis from the TRA 2°P-TIMI 50 trial. Vasc Med 2020;25:124–32.

68. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med 2007;357:217–27.

69. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319–30.

70. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:219–29.

71. Hussain MA, Verma S, Al-Omran M. Rivaroxaban in peripheral artery disease: the new kid on the block? J Vasc Surg 2018;67:985–6.

72. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382:1994–2004.

73. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. Cochrane Database Syst Rev 2018;2019:CD000146.

74. Suissa K, Larivière J, Eisenberg MJ, 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.

75. Chang P, Nead KT, Olin JW, et al. Effect of physical activity assessment on prognostication for peripheral artery disease and mortality. Mayo Clin Proc 2015;90:339–45.

76. Golledge J, Singh TP, Alahakoon C, 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.

77. Li Y, Li Z, Chang G, et al. Effect of structured home-based exercise on walking ability in patients with peripheral arterial disease: a meta-analysis. Ann Vasc Surg 2015;29:597–606.

78. Jansen SCP, Hoorweg BBN, Hoeks SE, et al. A systematic review and meta-analysis of the effects of supervised exercise therapy on modifiable cardiovascular risk factors in intermittent claudication. J Vasc Surg 2019;69:1293–308. e2.

79. Abaraogu UO, Abaraogu OD, Dall PM, et al. Exercise therapy in routine management of peripheral arterial disease and intermittent claudication: a scoping review. Ther Adv Cardiovasc Dis 2020;14 :1753944720924270.

80. Treat-Jacobson D, McDermott MM, Bronas UG, et al. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. Circulation 2019;139:e10–33.

81. Tremblay MS, Warburton DER, Janssen I, et al. New Canadian physical activity guidelines. Appl Physiol Nutr Metab 2011;36:36–46.

82. Aboyans V, Ricco J, Bartelink MEL, 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.

83. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. The task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2020;41: 111–88.

84. Gerhard-Herman M, Gornik H, Barrett C, 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.

85. Hiatt WR, Bonaca MP, Patel MR, 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.

Supplementary Material

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