Peripheral arterial disease (PAD) is a common vascular condition seen more often in older patients with cardiovascular (CV) risk. Although all extremities may be affected, lower limbs and carotid arteries are more commonly involved due to atherosclerosis. 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.

Due to their common atherosclerotic pathway, coronary artery disease (CAD) and PAD are often grouped together. As a result, the standard management for secondary prevention is often thought to be the same. 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.

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. 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.
PAD Background

Epidemiology and pathophysiology of PAD

PAD affects more than 202 million people worldwide. 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. The annual incidence of PAD is estimated 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. Smoking in particular (along with diabetes mellitus and hypertension) has a strong association.8 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.10 Several studies have found an increased risk in African-American populations. 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.11 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.12 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. However, roughly one-quarter present with the classic symptoms of IC, defined as pain within the calf that is brought on by walking and relieved by rest. 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, and the San Diego Claudication Questionnaire. 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. Critical limb ischemia is the most severe form of PAD, as it is associated with severe resting leg pain, with or without tissue necrosis. 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, palsy, paraesthesia, paralysis, poikilothermia (“inability to maintain core limb temperature”). 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. Although a decrease in ABI occurs for most PAD patients, it does not always result in increased symptom severity or progression. 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. 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. 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. 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. 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, mainly due to the paucity of clinical data in a condition that was less commonly diagnosed and underappreciated. 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, Canadian, and American 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 follow-up time, y | Main result (95% CI) | Interpretation |
|--------------|--------------|-------------|--------------------|----------------|--------------|--------------------------|----------------------|----------------|----------------------------------|
| 4S28,29 (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 |
| HPS30,31 (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) | Statins proven to significantly reduce ACM and stroke in PAD patients. A trend toward decreased MACE and MI was found |
| FOURIER33,34 (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 OUTCOME35 (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, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk 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.
| 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     | 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 towards decreased 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    | 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   | RCT (PAD subgroup)      | 2354 (9463 total) | T2DM and established CVD and > 40 years old                                        | IC and ABI < 0.9, nontraumatic 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 (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, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CVD, cardiovascular disease; CVM, cardiovascular mortality; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58; DM, diabetes mellitus; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose) trial; EXSCEL, Exenatide Study of Cardiovascular Event Lowering 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 | Intervention | Follow-up, y | Main result (95% CI) | Interpretation |
|--------------|--------------|-------------|-------------------|----------------|--------------|--------------|----------------------|---------------|
| HOPE 54 (2004) | RCT (PAD subgroup) | 3099 CVD, without heart < ABI 0.9 and < 0.92 | Ramipril (ACEi) associated with reduced asymptomatic PAD failure with reduced ejection fraction in MACE for asymptomatic PAD patients | Randomized, double-blind, placebo-controlled trial | 4.5 MACE HR: 0.73 (0.60–0.90) | Reduced MACE in asymptomatic PAD patients; (i) significantly lower non-fatal MI or stroke showed similar reductions in MACE (HR: 0.79, 95% CI: 0.66–0.94). Within the same PD subgroup analysis of symptomatic PAD patients (n = 3642) found similar reductions in MACE (HR: 0.79, 95% CI: 0.66–0.94) 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). |
| INVEST 55 (2010) | RCT (PAD subgroup) | 2699 CAD and hypertension History of PAD based on questionnaire | Verapamil § trandolapril vs atenolol | Randomized controlled trial | 2.7 SBP < 110; HR: 1.69 | 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. 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 treatment. 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). |

More recently, the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) 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. 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: 0.79, 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: 0.79, 95% CI: 0.66-0.94) — 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: 0.73-0.89) — 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). 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.

Notes:
- 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, Heart Outcomes Prevention Evaluation; INVEST, International Vascular SR/Translational Study; IC, intermittent claudication; MACE, major adverse cardiovascular events; PAD, peripheral arterial disease; RCT, randomized controlled trial; SBP, systolic blood pressure.
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 |
|--------------|--------------|-------------|--------------------|----------------|--------------|--------------------|----------------------|------------------|
| **Antithrombotic monotherapy** |
| CAPRIE18 (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** (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** (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 heterogeneous PAD group |
| **POPADAD** (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** (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** (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** (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) | DAPT use in stable PAD patients not significantly associated with decreased MACE, but decreases MI and CVD hospitalization rates |
| **TRA 2°P-TIMI 50** (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** (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** (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) | Warfarin/acenocoumarol plus antplatelet was not more effective than antplatelets alone in preventing MACE and increased bleeding risk |
| **COMPASS** (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) | Low-dose rivaroxaban + aspirin was superior to aspirin alone in reducing MACE |
| **VOYAGER PAD** (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) | Low-dose rivaroxaban + aspirin was superior to aspirin alone in reducing MACE |

**Note:**IC, intermittent claudication; P, padding; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TBI, toe-brachial index; CVD, cardiovascular disease; RR, risk ratio; CI, confidence interval; OR, odds ratio; MI, myocardial infarction; CAD, coronary artery disease; DM, diabetes mellitus; COP, critical Limb ischemia Prevention Study; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antplatelet therapy; MI, myocardial infarction; N/A, not applicable; OAC, oral anticoagulation; RR, risk ratio; TBI, toe-brachial index; TRA 2°P-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50; VOYAGER, Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD; WAVE, Warfarin Antiplatelet Vacular Evaluation.
A large majority of evidence supporting glucose management in PAD comes from studies that assess hyperglycemia as a risk factor for atherosclerotic disease. In a subgroup analysis of patients from the UK Prospective Diabetes Study (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. In a subgroup analysis of PAD diabetics from the Examining Use of Ticagrelor in PAd (EUCLID) trial, every 1% increase in HbA1c was associated with a 14.2% risk of MACE. 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.

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 1341 PAD patients from the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetics Mellitus Patients—Removing Excess Glucose) trial 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). However, the Canagliflozin Cardiovascular Assessment Study (CANVAS) found a significant increase in limb amputation in diabetics with high cardiovascular risk (HR: 1.97; 95% CI: 1.41-2.75). Most recently, the Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 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). Two recent meta-analyses 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.

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) and Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trials. 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). 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, whereas American and European 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. Conversely, the American and European guidelines recommend these as first-line therapies only in patients with hypertension and recent MI.

Although it is widely understood that hypertension contributes to the development of PAD, fewer studies have addressed treatment with therapeutic targets. In a PAD subset from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (53 patients), patients with intensive blood pressure lowering (average of 128/75 mm Hg) had fewer CV events (compared to moderate treatment). In a PAD subgroup analysis from the Heart Outcomes Prevention Evaluation (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). In an important post hoc analysis of the International Verapamil-SR/Trandolapril Study (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).

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. 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 Trials' 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). The 2007 Critical Leg Ischemia Prevention Study (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). In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (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. 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. 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 Prevention of Progression of Arterial Disease and Diabetes (POPADAD) and 2010 Aspirin for Asymptomatic Atherosclerosis (AAA) trials sought to assess the efficacy of aspirin in asymptomatic PAD. The POPADAD trial did not find a significant reduction in the composite outcome 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. 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 Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (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). In a subgroup analysis of 1143 PAD patients from the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Tablets Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 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.

In a sub-group analysis of 6136 PAD patients from the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction 50 (TRA 2P–TIMI 50) trial (assessing the addition of vorapaxar [P2Y12 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. 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 Warfarin Antiplatelet Vascular Evaluation (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. 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 Cardiovascular Outcomes for People Using Anticoagulation Strategies (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. 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. 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 infrapopliteal 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 (≥ 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.

Most recently, the Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization 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 thrombosis 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. Given these data, oral
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. 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). 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.

Regular physical activity

Increased physical activity is associated with decreased disease progression and all-cause-mortality in PAD patients. Meta-analyses have demonstrated that structured home-based exercise programs are effective in improving maximum walking distance, IC onset distance, and physical activity. An additional meta-analysis found that such programs were associated with decreased LDL-C, total cholesterol, systolic blood pressure, and diastolic blood pressure. However, European countries found that the implementation and utilization of structured home-based exercise programs was still suboptimal. 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. Alternative strategies for exercise therapy (upper body ergometry, cycling, pain-free/low-intensity walking) are listed as COR IIa - LOE A. 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).

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. Additionally, the 2019 European Society of Cardiology lipid guidelines provided updated lipid targets. 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), and evolocumab is recommended as third-line therapy (i.e., a Class IIa 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).
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 A), 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. 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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Supplementary Material
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