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Review

Building Your Peripheral Artery Disease Toolkit: Medical Management of Peripheral Artery Disease in 2022

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ABSTRACT

Peripheral artery disease (PAD) is associated with substantial morbidity, including a high risk of cardiovascular and limb events and death. A growing body of evidence has demonstrated the benefits of antithrombotic therapy, lipid lowering, blood pressure control, diabetes management, smoking cessation, and exercise programs on improving symptoms and reducing these complications. Guidelines make specific recommendations on how to use these strategies to prevent adverse cardiovascular and limb outcomes in patients with PAD. Unfortunately, antithrombotic therapies, statins, optimal antihypertensives, smoking cessation counselling and therapies, and exercise programs have all been consistently shown to be underutilised in PAD patients both in Canada and globally. A variety of barriers to optimal utilisation of evidence-based medical therapies have been described at the patient, health care provider, and system levels. These include lack of

RÉSUMÉ

La maladie artérielle périphérique (MAP) est associée à une morbidité substantielle, avec notamment un risque élevé d'événements cardiovasculaires et d'événements touchant les membres, ainsi que de décès. De plus en plus d'évidences ont démontré les avantages d'un traitement antithrombotique, d'une réduction des taux lipidiques, du contrôle de la pression artérielle, d'une prise en charge du diabète, de l'arrêt du tabac et des programmes d'exercice physique pour atténuer les symptômes et en réduire les complications. Les lignes directrices font des recommandations spécifiques sur la façon d'utiliser ces stratégies pour prévenir les effets indésirables au niveau des membres et du système cardiovasculaire chez les patients atteints de MAP. Malheureusement, il a été démontré que les traitements antithrombotiques, les statines, les meilleurs antihypertenseurs, les conseils et les thérapies de désaccoutumance au tabac et les

Peripheral artery disease (PAD) is defined by the narrowing and obstruction of the noncoronary and nonintracranial arteries, and it is estimated to affect more than 200 million people worldwide.[1] In Canada, it has been estimated that 1 in 20 people over the age of 50 years have PAD,[2] with prevalence likely to be rising with increasing age and rates of diabetes.[3] Manifestations of PAD in the lower extremities include intermittent claudication, which causes significant functional impairment and a reduction in health-related quality of life.[4] Patients may also develop critical limb ischemia (CLI), which is characterised by resting leg pain and tissue loss (ulcers, gangrene) and often requires surgical intervention (ie, revascularisation or amputation).[5] One year after revascularisation for CLI in Canada, more than 25% of patients undergo amputation or die.[6] Even in the absence of symptoms, the development of PAD indicates the presence of more widespread atherosclerosis.[7] For this reason, in addition to major adverse limb events (MALE), PAD patients are also at risk for major adverse cardiovascular (CV) events (MACE) and increased mortality.[8] The cumulative incidence risk of MACE among patients with PAD alone is similar to those with established coronary artery disease (CAD), and this risk is increased 2-fold in patients with both PAD and CAD.[9] Canadian data reveal that age-adjusted mortality is higher for patients with PAD than for patients with CAD or ischemic stroke in this country.[3]

The morbidity and mortality associated with PAD can be combatted with the effective use of secondary preventative therapies including lifestyle modification and medications such as antithrombotic, lipid-lowering, and antihypertensive drugs (Table 1). However, these therapies are underutilised, both in Canada and globally.[6,10] Barriers to implementation of therapies can be classified as occurring at the level of the patient, health care provider, or health system (Fig. 1). Patients and health care providers may face capability barriers

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knowledge among patients and health care providers, and lack of access to secondary prevention programs. We review the evidence for preventive therapies in PAD, evidence for underutilisation of these therapies, and barriers to their use. Core elements of PAD secondary prevention clinics are proposed, and a summary of optimal medical therapies and relevant tools is provided. This review may help clinicians who treat patients with PAD to develop a toolkit to overcome these barriers in order to improve utilisation of medical therapies, with the ultimate goal of improving outcomes for PAD patients.

programmes d'activité physique sont autant d'outils sous-utilisés chez les patients atteints de MAP, tant au Canada que dans le monde. Divers obstacles à l'utilisation optimale des thérapies médicales, fondées sur des données probantes, ont été détaillés au niveau des patients, des fournisseurs de soins de santé et du système. Cela inclut le manque de connaissances des patients et des fournisseurs de soins de santé, et du manque d'accès aux programmes de prévention secondaire. Nous réalisons la synthèse des évidences concernant les thérapies préventives dans la MAP, les preuves de la sous-utilisation de ces thérapies et les obstacles à leur utilisation. Les éléments fondamentaux des cliniques de prévention secondaire pour la prise en charge de la MAP sont proposés, et un résumé des thérapies médicales optimales et des outils pertinents est proposé. Cet examen peut aider les cliniciens qui traitent les patients atteints de MAP à développer une boîte à outils pour surmonter ces obstacles afin d'améliorer l'utilisation des thérapies médicales, dans le but ultime d'améliorer le pronostic des patients atteints de MAP.

related to knowledge or capacity to act, and intention barriers related to attitudes or motivations.[11] This narrative review outlines the current evidence supporting the use of medical therapies for prevention of adverse CV and limb events in patients with PAD, and barriers to their implementation. Strategies are then suggested to build a PAD toolkit to deliver better preventive care to this population.

Lifestyle Modification

Smoking cessation

All PAD patients who smoke should be encouraged to quit.[12,13] Continued smoking is associated with increased mortality and decreased amputation-free survival[14] and can have negative impacts on postsurgical outcomes.[15] The use of nicotine replacement therapy or other medications (eg, bupropion, varenicline) is safe and effective, and can be offered in conjunction with intensive counselling and/or a referral to a smoking cessation program.[12,13] A recent systematic review of smoking cessation trials in PAD found that methods previously tested in other populations may not necessarily be effective for patients with PAD,[16] although more intensive counselling and use of varenicline may improve chances of success.[17] Guidelines recommend that PAD patients who smoke should be advised to quit, and assisted with a smoking cessation plan that includes pharmacotherapy.[12,13]

Barriers to smoking cessation

Implementation of smoking cessation counselling is suboptimal. Even in specialised vascular specialty clinics, only 75.2% of newly referred PAD patients who were current smokers were counselled on smoking cessation.[18] Rates of counselling are worse for patients without comorbid CAD. Berger and Ladapo found that PAD patients with comorbid CAD were more likely to receive smoking cessation counseling (odds ratio 4.4) at a given visit, compared with patients with PAD alone.[19]

Possible patient-level explanations for reduced effectiveness of smoking cessation interventions in PAD patients include lack of knowledge regarding smoking as a causative factor,[20] a higher level of addiction in this population, and environmental factors such as higher smoking rates among other members of the household and social circle.[17] Innovative interventions, such as SMS- or app-based counseling strategies, have been shown to be beneficial,[21] but their effectiveness may vary in different populations.[22] Although these potential patient-level barriers should motivate increased attempts by health care systems to encourage smoking cessation, we find that the opposite is true, with PAD patients receiving less counselling on smoking cessation than patients with CAD.[19] The high site-by-site variability in implementation of smoking cessation counselling suggests that health system factors, such as access to smoking cessation programs, play a role.[18] A review of smoking cessation interventions found that published interventions were less successful in women than in men, suggesting a need to consider gender when designing and implementing smoking cessation interventions.[23]

Structured exercise therapy

Exercise therapy in the form of a supervised exercise program is an additional lifestyle modification that should be encouraged in PAD patients experiencing claudication.[12,13] These programs are typically more effective than home-based programs,[24] perhaps because of differences in intensity or opportunity for encouragement/motivation. However, logistical obstacles (eg, transportation to the facility) exist for some patients, and unsupervised programs should still be considered if those are more practical for a given patient.[25] The benefits of exercise are numerous; regular physical activity is associated with reduced all-cause mortality,[26] and exercise programs result in significant improvements in functional capacity.[27] In the **Cl**audication: **E**xercise **V**ersus **E**ndoluminal **R**evascularization (CLEVER) trial, the difference in peak walking time between patients receiving supervised exercise vs stent revascularisation was nonsignificant ($P = 0.16$) at 18-month follow-up.[28] This highlights that noninvasive approaches can be considered even in the treatment of function-limiting claudication. Guidelines recommend structured exercise programs to improve symptoms and function.[12,13]

Barriers to structured exercise therapy

Studies have found that patients with PAD are less likely to start and complete exercise therapy programs,[29] and patients with PAD experience less improvement in cardiorespiratory fitness than those with CAD alone.[30] A few studies have qualitatively examined barriers to PAD patients' use of preventive therapies. At the patient level, claudication pain itself is a barrier. The pain that is associated with walking for people with claudication discourages participation in exercise programs.[31,32] A systematic review suggests that alternative exercise regimens that do not involve development of maximal claudication pain improve adherence and completion rates.[33] Transportation to supervised exercise program sites may be more difficult for people with PAD, which may be alleviated by use of home-based exercise programs that use pedometers.[34] Women are less likely to complete the therapy than men owing to unaddressed patient-level barriers including difficulty with transportation and family responsibilities.[35] At the provider level, surveys have found that health care practitioners lack knowledge regarding PAD-specific exercise protocols.[36] Health care providers appear to refer women with cardiac disease less frequently than men to exercise programs.[35]

The biggest barrier is systemic lack of access to exercise programs. Surveys and systematic reviews demonstrate that most PAD patients do not have access to supervised exercise programs.[36-38] Where they do have access, the programs often do not have PAD-specific protocols, education among staff is often limited, and funding is poor.[36] Referral for supervised exercise therapy was found to be especially sensitive to site-by-site availability of exercise programs for these patients, even in specialised vascular clinics.[18]

Diet

The body of literature investigating the role of diet in the generation and propagation of PAD is heterogeneous. Most of these studies lack impact owing to their small sizes or observational designs. Previous studies, such as the **No**rthern **Ma**nhattan **S**tudy (NOMAS)[39] and the **Cor**onary **D**iet **I**ntervention With **O**live Oil and Cardiovascular **Prev**ention (CORDIOPREV) study,[40] among others, have suggested that the Mediterranean diet may reduce the progression of carotid atherosclerosis as measured by carotid intimal medial thickness (CIMT). However, this remains a surrogate marker, and the role of serial CIMT assessments has not been established in clinical practice, nor has it been shown to affect clinical outcomes. The effect of dietary intake on plaque development and progression has not been well studied in the PAD cohort.

The only randomised controlled trial which has reported on the role of diet and the presence of PAD is a subgroup analysis of the **Pre**vención con **Die**ta **Med**iterránea (PREDIMED) study.[41] In this primary prevention study, randomisation to a Mediterranean diet was associated with a significantly lower risk of PAD development. However, the trial suffered from inconsistencies in methodology leading to the subsequent retraction and republication of the overall study.[42] The Lyon Diet Heart Study was a randomised trial of secondary prevention in patients with prior myocardial infarction (MI).[43] Although the Mediterranean diet was shown to improve the rate of CV death and nonfatal MI, PAD-specific outcomes have not been reported. Further randomised controlled trials are required to clarify the role of the Mediterranean diet in the development and progression of PAD.

The limited evidence for dietary interventions in PAD patients is reflected in the absence of recommendations for dietary counselling in PAD guidelines.[12,13]

Medications

Antiplatelet agents

The rationale for the use of antiplatelet therapy in PAD is derived from the role of platelets in atherothrombosis, and the proven efficacy of these drugs in other atherosclerotic disease states (ischemic stroke, CAD).[7] Current European and American guidelines for the treatment of PAD recommend the use of single antiplatelet therapy (SAPT; 75-325 mg/day aspirin or 75 mg/day clopidogrel) in symptomatic PAD patients.[12,13] This guidance is supported by a meta-analysis of 18 prospective randomised trials (5269 PAD patients) assessing the effectiveness of aspirin (alone or with dipyridamole) vs placebo in which a reduction in odds for cardiac events (pooled relative risk [RR] 0.88, 95% confidence interval [CI] 0.76-1.04) was observed.[44] Previous data from the Antithrombotic Trialists' Collaboration demonstrated that the use of antiplatelet therapy in general (aspirin or other drugs) is associated with a 23% relative risk reduction (8% absolute) of serious vascular events in PAD patients ($P = 0.004$).[45] The **C**lopidogrel vs **A**spirin in **P**atients at **R**isk of **I**schaemic **E**vents (CAPRIE) trial forms the basis for inclusion of clopidogrel into guidelines, in which a PAD subgroup on clopidogrel rather than aspirin experienced a 23.8% relative risk reduction (95% CI 8.9-36.2; $P = 0.0028$) in stroke, MI, or vascular death with a similar safety profile.[46] The **E**xamining **U**se of **T**i**c**agre**l**or **i**n PA**D** (EUCLID) trial did not find a benefit of ticagrelor over clopidogrel for either MACE or MALE.[47] The efficacy of SAPT in asymptomatic PAD patients is not well established.[48] Studies investigating the use of dual antiplatelet therapy (DAPT) in stable PAD, with the addition of either clopidogrel, ticagrelor, or vorapaxar to aspirin, suggest that while there are some benefits in terms of reducing CV and limb events, these are counterbalanced by an excess major bleeding risk.[48-50]

Anticoagulants

Oral anticoagulants have proven benefit in reducing CV events in CAD[51] and have since been studied in patients with PAD in combination with antiplatelet therapy. In the **W**arfarin **A**ntiplatelet **V**ascular **E**valuation (WAVE) trial, which assessed the combination of warfarin (target international normalized ratio 2-3) and antiplatelet therapy vs antiplatelet alone, no significant difference in MI, stoke, or death from CV causes was observed (RR 0.92, 95% CI 0.73-1.16; $P = 0.48$).[52] Furthermore, a significant increase in life-threatening bleeding was noted in the combination group (RR 3.41, 95% CI 1.84-6.35), limiting the utility of adding warfarin. These findings were consistent with the **Dutch** **B**ypass, **O**ral Anticoagulants or **A**spirin (Dutch BOA) trial of moderate- to high-intensity warfarin compared with aspirin

Table 1. Summary of optimal evidence-based medical therapy for reduction of vascular events in stable symptomatic PAD, with selected published guidelines* and tools

Smoking cessation	• Review of smoking status at each visit • Counselling to quit at each visit • Offer smoking cessation pharmacotherapy to those interested ○ Centers for Disease Control and Prevention clinical cessation tools: https://www.cdc.gov/tobacco/basic_information/for-health-care-providers/clinical-tools/index.html ○ Ottawa Model for Smoking Cessation: https://ottawamodel.ottawaheart.ca/about-omsc ○ Canadian Cancer Society Smokers' Helpline: +1-866-366-3667, https://smokershelpline.ca/
Structured exercise therapy	• Interested patients should be referred to an evidence-based exercise therapy program ○ Vascular Disease Foundation/American Association of Cardiovascular and Pulmonary Rehabilitation PAD exercise training toolkit: a guide for health care professionals: http://www.nccraonline.org/wp-content/uploads/2017/03/pad-exercise-training-toolkit-AACVPR.pdf
Antithrombotics	• Single antiplatelet therapy (eg, 75 mg clopidogrel daily) or combination low-dose aspirin daily and 2.5 mg rivaroxaban twice daily in patients with symptomatic PAD, with preference for combination therapy in those at higher risk of ischemic events without high risk of bleeding
Lipid-lowering therapy	• Statin therapy (eg, 40 mg rosuvastatin daily) • Consider adding PCSK9 inhibitor in patients at high risk of ischemic events with LDL-C > 1.8 mmol/L despite maximal tolerated statin
Antihypertensives	• Hypertension should be controlled according to current guidelines • Consider ACEi or ARB first line ○ Hypertension Canada's 2020 comprehensive hypertension guidelines[70]
Diabetes management	• Comprehensive coordinated care plan for diabetes control • Guideline-based pharmacotherapy including SGLT2 inhibitor or GLP-1 receptor agonist ○ 2019 European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) guideline on diabetes, prediabetes, and cardiovascular diseases[110] • Regular foot screening ○ International Working Group on the Diabetic Foot 2019 prevention guideline: https://iwgdfguidelines.org/prevention-guideline/

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; SGLT2, sodium-glucose cotransporter 2.

*The following guidelines provide recommendations on all of the categories in this table: 2017 European Society of Cardiology guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery[13]; and 2016 American Heart Association/American College of Cardiology guideline on the management of patients with lower extremity peripheral artery disease.[12]

alone in patients after infrainguinal open surgical revascularisation, which found no clear evidence of efficacy and an excess of life-threatening bleeding.[53]

A strategy of adding a low dose of direct oral anticoagulants to antiplatelet therapy was proven to reduce MACE in patients with recent coronary events.[54] In the subsequent **C**ardiovascular **O**utco**m**es for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial, patients with stable atherosclerotic disease (PAD or CAD) were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily) alone (1:1:1).[9] Among the subgroup of 7470 patients with PAD the combination of low-dose rivaroxaban and aspirin was associated with a reduction in MACE (hazard ratio [HR] 0.72, 95% CI 0.57-0.90) and MALE (HR 0.54, 95% CI 0.35-0.84) compared with aspirin alone.[55] An increased risk of major bleeding was observed in patients receiving the combination therapy, but no excess in severe bleeding, including fatal bleeding, symptomatic bleeding into a critical organ, or surgical site bleeding requiring reoperation, was observed. Even when MALE did occur, combination therapy reduced recurrent MALE by 43% ($P = 0.01$) and, total vascular amputations by 58% ($P = 0.01$).[56] Patients at high risk of MACE and MALE, such as those with concomitant heart failure, diabetes, renal insufficiency, and polyvascular disease, experienced the greatest risk reduction from rivaroxaban plus aspirin therapy.[57] These findings are applicable to many real-world PAD patients; in the **Re**duction of **A**therothrombosis for **C**ontinued **H**ealth (REACH) registry, 68.4% of real-world PAD patients met eligibility for the COMPASS trial.[58] The predominant reasons for exclusion included high bleeding risk (contraindication to rivaroxaban), need for full-dose anticoagulant use, and requirement for DAPT (after acute coronary syndrome [ACS], or percutaneous coronary intervention with stent).[58]

Kaplovitch et al. summarises best antithrombotic therapy for stable symptomatic PAD considering the newest clinical evidence (ie, COMPASS).[48] SAPT in the form of aspirin or clopidogrel remains standard in mild disease, with the evidence for clopidogrel being slightly superior. The use of rivaroxaban (2.5 mg twice daily) in combination with aspirin should now be considered in patients who are at high risk for MACE and MALE and at low risk for bleeding.[48] Patients with PAD who endure an ACS or an acute cerebrovascular event should be managed according to those corresponding guidelines.[59] For example, in patients with PAD and CAD, DAPT (aspirin and ticagrelor) is often used in the 6-12 months following ACS. There is evidence to support the continuation of long-term DAPT in those patients,[60] but given the benefit of low-dose rivaroxaban and aspirin in reducing MACE and MALE, returning to the COMPASS regimen after 6 or 12 months is reasonable.[61]

The use of antithrombotic therapy after vascular surgery for PAD patients is less well defined, but a course of DAPT after peripheral revascularisation is reasonable, according to the 2017 American Heart Association guidelines.[12] However, after those guidelines were published, strong evidence from 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 revealed similar benefits and risks for

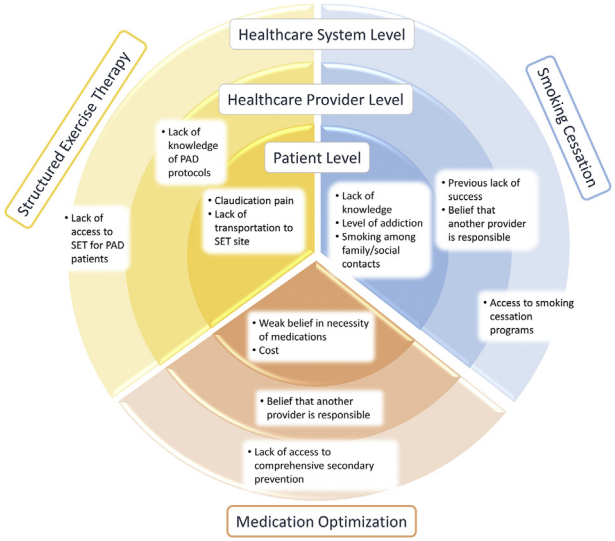

Figure 1. Barriers to optimal utilisation of evidence-based secondary preventive therapies for patients with peripheral artery disease (PAD). SET, structured exercise therapy.

PAD patients after lower-extremity infrainguinal peripheral revascularisation (endovascular or surgical) as found for stable patients in the COMPASS trial. Acute limb ischemia, major amputation, MI, ischemic stroke, or death from CV events occurred less frequently in the rivaroxaban plus aspirin group at 3 years (17.3% vs 19.9%, HR 0.85, 95% CI 0.76-0.96; $P = 0.009$).[62] Meta-analysis of the 2 trials revealed consistent beneficial effects with the use of that combination.[63]

Statins

The initiation of statin therapy in all patients with PAD is supported by current guidelines.[12,13] In the Heart Protection Study, 20,536 adults with vascular disease (6748 PAD patients) were randomly assigned to receive either 40 mg simvastatin daily or placebo.[64] In those patients with PAD receiving simvastatin, a 22% relative reduction (95% CI 15%-29%) in the rate of first major vascular event (MI, coronary death, stroke, or revascularisation) was observed, and this effect was significant across different PAD subgroups.[64] Observational data from the REACH registry demonstrates that statin users have a significantly lower risk of adverse limb outcomes (worsening claudication/new episode of CLI, new percutaneous/surgical revascularisation, or amputation) at 4 years compared with non−statin users (HR 0.82, 95% CI 0.72-0.92; $P = 0.0013$).[65] The impact of unmeasured confounding, such as the "healthy user" effect, cannot be overlooked. However, this was thought to play a minor role, because the patients receiving statins had more comorbidities and a greater severity of disease.

PCSK-9 inhibitors

Newly developed PCSK-9 inhibitors have emerged as an additional tool that can be used to lower low-density lipoprotein cholesterol (LDL-C). Forty-eight weeks after randomisation to either evolocumab (either 140 mg every 2 weeks or 420 mg monthly, subcutaneous injection) or placebo in the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial, patients in the treatment arm experienced a reduction in the risk of CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation (HR 0.85, 95% CI 0.79-0.92; $P < 0.001$).[66] The reduction in the primary end point was consistent across different baseline LDL-C levels, even in the quartile of participants with a low baseline median LDL-C of 1.9 mmol/L. A subanalysis of the 3642 patients with PAD revealed a 27% composite relative risk reduction in MACE and MALE among PAD patients (HR 0.73, 95% CI 0.60-0.88; 10.9% vs 15.0%, absolute risk reduction 4.1%; no. needed to treat: 25).[67] Strikingly, there appeared to be an approximately linear relationship between LDL-C levels and reduction of MACE/MALE, all the way down to an LDL-C of 10 mg/dL (0.6 mmol/L). PCSK-9 inhibition with alirocumab also reduced limb events in patients after acute coronary syndrome (HR 0.69, 95% CI 0.54-0.89; $P = 0.004$), and the benefit was associated with baseline lipoprotein(a) but not LDL-C levels.[68]

Blood pressure control

Elevated blood pressure (BP) is one of the main risk factors for the development of PAD, and PAD patients who are hypertensive have poorer outcomes.[69] Current guidelines endorse the use of blood pressure−lowering medications in PAD patients with hypertension to reduce the risk of MI, stroke, heart failure, and CV death.[12,13,70] Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) are typically used as first-line therapies owing to their beneficial effects in this population. In the **H**eart **O**utcomes **P**revention **E**valuation (HOPE) trial, patients with vascular disease or diabetes who were randomised to receive ramipril (10 mg daily) rather than placebo experienced a 22% relative reduction in MACE (RR 0.78, 95% CI 0.70-0.86; $P < 0.001$).[71] A subgroup analysis revealed that ramipril was beneficial in both clinical and subclinical (ankle-brachial index [ABI] < 0.9, no symptoms) PAD, and the absolute benefit of ramipril was twice as large in those with a low ABI (50 vs 24 per 1000 events prevented).[72] ARBs are a safe and effective alternative, and a trial that investigated the use of telmisartan vs ramipril in patients with vascular disease found no significant difference in CV outcomes.[73] High-quality evidence to inform the optimal BP target specifically in PAD patients is lacking. A subgroup analysis of **S**ystolic Blood **P**ressure **In**tervention **T**rial (SPRINT) trial found a reduction in the composite of MACE and heart failure, but an increase in serious adverse events, with intensive BP control (systolic BP target < 120 vs 135-139 mm Hg) in the PAD subpopulation.[74] A *post hoc* analysis of the **In**ternational **Ve**rapamil SR/Trandolapril **St**udy (INVEST) trial, which was designed to compare hypertension treatment strategies in CAD, included 2699 patients with PAD. A J-shape relationship was observed between systolic BP achieved and the primary outcome of all-cause mortality, MI, or stroke, with the lowest frequency of the outcome observed in patients with a BP of 135-145/60-90 mm Hg.[75]

Glycemic control

Diabetes is a strong risk factor for PAD, and increasing rates of diabetes may be driving an increasing share of

hospitalisations for PAD.[76] A subanalysis of the EUCLID trial revealed that each 1% elevation of HbA_{1c} was associated with a 14.2% increased risk of MACE.[77] In diabetic patients undergoing infrapopliteal balloon angioplasty, lower rates of primary patency (16% vs 46%; $P = 0.005$) and higher rates of MALE (35% vs 23%; $P = 0.05$) were observed among patients with a fasting blood glucose above the median.[78]

In terms of choice of medication, sodium-glucose cotransporter 2 (SGLT2) inhibitors have beneficial effects in diabetics with high CV risk. In the **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) trial, which assessed the efficacy of canagliflozin vs placebo in participants with type 2 diabetes and high CV risk, a reduction in MI, stroke, or CV mortality (HR 0.86, 95% CI 0.75-0.97; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority) but increase in amputation rate (HR 1.97, 95% CI 1.41-2.75) was observed.[79] The mechanistic explanation for this particular finding is unknown.[80] However, no difference in amputation rate was observed in the **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation (CREDENCE) trial among patients with type 2 diabetes and chronic kidney disease taking canagliflozin vs placebo (HR 1.11, 95% CI 0.79-1.56).[81] One observational study suggests that in adults over 65 years of age with baseline CVD who start taking canagliflozin vs a glucagon-like peptide 1 (GLP-1) receptor agonist, the number needed to treat for an additional harmful outcome is high (556 patients at 6 months).[82] The magnitude of this risk may be outweighed by the immense cardioprotective effects of these medications. The concern regarding amputation and SGLT2 inhibitors appears to be specific to canagliflozin,[83] and a recent analysis of dapagliflozin revealed that it has clinical benefits in CV outcomes regardless of PAD status, without an incremental risk of amputation.[84] In the subgroup of PAD patients from the **Empa**gliflozin Cardiovascular **Outcome** Event Trial in Type 2 Diabetes Mellitus Patients—**R**emoving **E**xcess **G**lucose (EMPA-REG OUTCOME) trial, treatment with empagliflozin vs placebo resulted in statistically significant reductions in all-cause mortality (HR 0.62, 95% CI 0.44-0.88) and CV death (HR 0.57, 95% CI 0.37-0.88).[85] GLP-1 receptor agonists are other glucose-lowering medications that also reduce adverse cardiac outcomes in high-risk diabetic patients.[86] Guidelines recommend comprehensive care plans coordinated among team members for patients with PAD and comorbid diabetes.[12]

Therapies to improve walking distance

There is some evidence to support the use of cilostazol, a vasodilator, to improve walking distance in patients with stable intermittent claudication, but no benefit in reducing CV events has been found for it, and it is contraindicated in patients with left ventricular dysfunction and heart failure.[87] Cilostazol's clinical utility is limited by side-effects (headache), contraindications (heart failure), and marginal benefit compared with distance gained through supervised exercise.[88] Pentoxifylline is a medication that increases red cell deformability, and theoretically may improve peripheral blood flow, but current guidelines do not endorse its use in improving walking distance, owing to limited conclusive evidence.[89]

Barriers to implementation of recommended medications

Despite evidence-based guidelines espousing the use of preventive medications for PAD patients,[12,13] studies have revealed persistently low adherence to these guidelines over decades. Of 647 patients with PAD included in an analysis of the U.S. National Health and Nutrition Examination Survey database from 1999 to 2004, only 30.5% were using a statin, 35.8% were using aspirin, and 24.9% were using an ACEi or ARB.[90] Similarly, in an analysis of 1982 visits of patients with PAD in national outpatient databases in the U.S. from 2005 to 2012, a statin was used in 33.1%, any antiplatelet therapy was used in 35.7%, and an ACEi or ARB in 28.4%.[19] Data from Denmark reveal better adherence to guidelines, although utilisation was still suboptimal, with 53% of patients on antiplatelet agents, 40% on a statin, and 20% on an ACEi or ARB.[91] Adherence rates may be higher in specialised vascular clinics, with prospective data from the **P**atient-Centered **O**utcomes **R**elated to **Tr**eatment Practices in Peripheral **A**rterial Disease: **I**nvestigating **T**rajectories (PORTRAIT) study of PAD patients treated at vascular care sites in the U.S., The Netherlands, and Australia revealing that 89% patients were on antiplatelets and 83% on statins.[18]

Data also reveal that patients with PAD are less likely than similar patients with CAD to use these therapies, despite equal or greater benefit with their use. For example, Berger et al. found that PAD patients with comorbid CAD were more likely to receive antiplatelets, statin, and ACEi/ARB (odds ratio 2.6 for each) at a given visit compared with patients with PAD alone.[19]

At the patient level, although there is little data specific to PAD, one study found that more than 30% of patients with PAD older than 65 years were no longer taking antiplatelet therapy 5 years after initial prescription,[92] and among those who did persist with therapy, 15% had less than 80% of days covered.[93] Several factors may contribute to poor adherence to prescribed therapy. Awareness of PAD as a diagnosis and understanding of the disease has been found to be poor even among patients attending clinics for PAD.[94,95] Descriptive studies show that many patients with PAD, even in the context of recent hospitalisation for limb ischemia, express weak belief in the necessity of medication.[20] Patient education can improve utilisation of guideline-based therapies, and a network meta-analysis found that patient education as a component of cardiac rehabilitation reduced the hazards of MI and hospitalisation. However, there is a lack of standardisation of patient education interventions, likely related to the heterogeneous preferences and needs of patients, leading to difficulty in delivering evidence-based patient education in PAD.[94] Cost may also affect the use of medications, as patients with PAD have lower socioeconomic status than patients with CAD.[96] In a Canadian survey, 70% of vascular surgeons cited cost as their principal concern regarding prescription of combination low-dose rivaroxaban and aspirin.[97] Providing medications at no cost improved adherence among patients who cited cost as a barrier in a randomised controlled trial.[98]

Research into health care provider—level barriers to medication prescription in PAD is limited, but may include capability barriers (such as lack of knowledge and skills) and

Table 2. Proposed core elements for PAD secondary prevention clinics

1) Access to a secondary prevention program
A clinic with an explicit mandate to optimise preventive therapy for PAD patients should be identified and made accessible for PAD patients.
2) Referral system
A system to prompt and accept referrals from inpatient and outpatient environments should be established. Clear criteria for referrals should be communicated.
3) Intake assessment
Screening for smoking status, hypertension, diabetes, current activity levels and limitations, lipid profile, and diet should occur at intake.
4) Patient education
Patients should be educated about PAD manifestations, risk factors, and therapies, with consideration of their individual learning needs and preferences.
5) Medication optimisation
Procedures for medication reconciliation, recognition of suboptimal prescribing, and optimisation should be followed.
6) Smoking cessation
Smoking status should be reviewed, smokers should be counselled to quit at every visit, and those who are interested should be offered pharmacotherapy.
7) Diabetes care
Patients with diabetes should receive comprehensive coordinated care, including guideline-based foot screening.
8) Exercise
Patients should be referred to a PAD-specific structured exercise program, which may take place in collaboration with a cardiac rehabilitation program.
9) Communication with health team members
The intake assessment and any recommended changes to the medical plan should be documented and communicated to other members of the patient's health team. At discharge from the clinic, clear follow-up instructions should be communicated.
10) Quality assurance
Data on the proportion of patients offered and utilising each component of evidence-based secondary prevention should be collected and regularly reviewed.

PAD, peripheral artery disease.

intention barriers (lack of motivation owing to previous failed attempts, doubts about the efficacy or importance of preventive therapies, and habits).[99] "Diffusion of responsibility," in which there is lack of clarity regarding who will be ensuring optimisation of secondary prevention of vascular outcomes, may act as another barrier for primary care physicians and vascular surgeons,[100] as has been shown in other disease states.[101] In a Canadian study, hospitalisation for PAD resulted in high rates of antithrombotics use at discharge, but no improvement was seen in prescription of statins (60.8% vs 56.3%; $P = 0.23$) or ACEis/ARBs (48.7% vs 50.6%; $P = 0.58$) when comparing preadmission and postdischarge prescriptions.[10] This suggests that inpatient providers may focus on certain medications, assuming others will be managed by outpatient providers. Lack of access to comprehensive secondary prevention programs, such as exists for cardiac rehabilitation, limits opportunities to provide comprehensive secondary prevention for PAD patients.

Of particular concern is the low rate of prescription of evidence-based therapies for women with PAD. Although these data are limited, there are parallels with women with CAD, who also are less likely to receive prescriptions for guideline-recommended antiplatelet or statin therapy, and are less likely to have their hypertension controlled, despite similar observed benefits in trials as for men.[102] Although all of the reasons for these sex differences are poorly understood, underrepresentation of women in clinical trials may result in therapies that are optimised and marketed for men more than for women.[35]

How can barriers to optimal use of secondary prevention therapies in PAD be overcome?

Strategies to optimise secondary prevention therapies in PAD should address barriers at patient, health care provider, and system levels. An approach similar to that of the Ontario Core Elements for Stroke Prevention Clinics,[103] and consistent with the Cardiac Care Network of Ontario Standards for the Provision of Cardiovascular Rehabilitation,[104] can be taken. The following core elements for PAD secondary prevention clinics are proposed: 1) access to a secondary prevention program; 2) an established system for referral to the program; 3) intake assessment that includes risk factor screening; 4) patient education on manifestations, risk factors, and therapies for PAD; 5) medication optimisation; 6) a smoking cessation plan; 7) access to comprehensive diabetes care; 8) access to an evidence-based exercise program; 9) communication and coordination with other health care team members; and 10) quality assurance (Table 2).

The first step is to identify a clinic that can see patients specifically to optimise preventive therapy for PAD patients. This may be a vascular surgery clinic, vascular medicine clinic, or part of a cardiac rehabilitation program. Accessibility for PAD patients, including transportation options and distance from parking to the site, should be considered.[31,32]

A system to prompt and accept referrals from vascular surgery wards, vascular surgery clinics, and primary care clinics should be established and clearly communicated. Patients who have undergone revascularisation or amputation are at highest risk of CV events and may be targeted for more intensive secondary prevention efforts. We are currently studying the use of a discharge checklist to be used after revascularisation that includes assessment of major risk factors, ensures consideration of antithrombotic therapy, statins, and counselling on smoking cessation, and referral to a comprehensive secondary prevention program (Medical Care **GAP**s in **P**eripheral **A**rterial **D**isease − **Check**list implementation Pilot Trial) GAP-PAD Check Pilot Trial.

Once patients are seen in the prevention clinic, their intake assessment should include screening for smoking status, hypertension, diabetes, current activity levels and limitations, lipid profile, and diet.[104]

Patients should receive educational materials in print or electronically about PAD manifestations, risk factors, and therapies.

The clinic should use a medication reconciliation procedure to accurately capture current medications. Tools for medication reconciliation are available from the Institute for Safe Medication Practices Canada.[105] Patients who are not prescribed or on suboptimal doses of statin, ACEi or ARB, and antithrombotics, should receive evidence-based therapy as outlined above. Prescription of lower-cost brands of approved medications may improve adherence.[106] Adherence to, and tolerance of, guideline-recommended therapies should be routinely assessed.

Smoking status should be reviewed with every PAD patient, and those who are currently smoking and interested in quitting should be offered nicotine replacement therapy, bupropion, or varenicline. The Centers for Disease Control and Prevention website hosts tools for clinicians to help patients with smoking cessation,[107] and in Canada, the Ottawa Model for Smoking Cessation[108] can help to improve provision of smoking cessation services. A free smokers' helpline is available in Canada at +1-866-366-3667 and SmokersHelpline.ca.[109]

Patients with diabetes should receive coordinated and comprehensive management, especially those with CLI, in whom improved glycemic control reduces the risk of amputation and failure of revascularisation.[13,110] Guideline-based regular foot screening should be ensured.[111]

Interested patients should be referred to an evidence-based exercise program. The Vascular Disease Foundation (VDF) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have produced a toolkit that outlines protocols and considerations to set up supervised exercise programs tailored to PAD patients.[112]

Other providers involved in care of the patient should be routinely identified. Notes from the secondary prevention clinic should be communicated to these team members, and a mechanism should be created to ensure handover of ongoing secondary prevention efforts once the patient is discharged from the clinic.[12]

Finally, performance should be regularly reviewed for adherence to guidelines; ideally, data on the proportion of patients who are offered each component of evidence-based secondary prevention should be collected. Patient satisfaction surveys can provide data on how to improve adherence.

Conclusion

Although evidence-based guidelines identify life-saving therapies to prevent adverse CV events in PAD patients, these therapies are underutilised. A variety of patient-, provider-, and system-level barriers contribute to this underutilisation. By building a PAD toolkit, some of these barriers can be overcome, and morbidity and mortality can be reduced for patients with PAD.

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