

Evidence-Based Recommendations for Medical Management of Peripheral Artery Disease

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Patients with lower limb artery stenosis or occlusion (peripheral artery disease; PAD) have been determined to be at very high risk of both major adverse cardiovascular events, such as myocardial infarction and stroke, and major adverse limb events, such as amputation and requirement for artery surgery.

Effective medical management has been identified as key in reducing this risk; however, this is often poorly implemented in clinical practice. Thus, the aim of this narrative review was to summarize the current evidence on the medical management of PAD in order to inform clinicians and highlight recommendations for clinical practice. International guidelines, randomized controlled trials, and relevant systematic reviews and meta-analyses have been included in this study. The focus was the management of the key modifiable risk factors to mitigate possible adverse events through prescription of anti-platelet and anticoagulation drugs and medications to control low-density lipoprotein cholesterol, blood pressure, and diabetes and aid smoking cessation. The available evidence from randomized clinical trials provide a strong rationale for the need for holistic medical management programs that are effective in achieving uptake of these medical therapies in patients with PAD. In conclusion, people with PAD have some of the highest adverse event rates among those with cardiovascular diseases. Secondary preventive measures have been proven effective in reducing these adverse events; however, they remain to be adequately implemented. Thus, the need for an effective implementation program has emerged to reduce adverse events in this patient group.

Key words: Secondary prevention, Modifiable risk factors, Medical management

Background

Peripheral artery disease (PAD) has been defined as an atherothrombotic occlusive disease of the lower limb arteries estimated to affect over 220 million people worldwide¹. PAD can lead to leg pain brought on by walking, known as intermittent claudication, or in severe cases constant pain in the foot, or ischemic ulcers or gangrene, collectively known as chronic limb-threatening ischemia². PAD may also be asymptomatic or associated with atypical symptoms such as a burning sensation in the leg³. PAD is associated with poor health-related quality of life⁴ and a high risk of major adverse cardiovascular events

(myocardial infarction, stroke, or cardiovascular death; MACE) and major adverse limb events (peripheral revascularization or major amputation; MALE)^{5, 6}. The risk of adverse events is particularly high for people with chronic limb-threatening ischemia^{7, 8}.

PAD, as diagnosed by ankle-brachial pressure index (ABPI) <0.9, has been estimated to affect nearly 10% of the population worldwide, affecting 6%, 9%, 12%, and 16% of 50-, 60-, 70-, and 80-year-olds, respectively¹. Given the aging of the world population, particularly in developed countries, PAD is projected to represent an important cause of morbidity and mortality in the future⁹. The frequency of adverse events due to PAD is substantial. Recent

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Received: January 3, 2021 Accepted for publication: February 8, 2021

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series report an incidence of MACE of approximately 25% over 5 years in people referred to hospital with PAD^{10, 11}), with outcomes being particularly poor for people presenting with chronic limb-threatening ischemia, with MACE rates of approximately 10% per year⁷. Mortality rates of approximately 20% within 5 years of diagnosis have also been reported¹²). The health service costs of managing PAD-related adverse events have also been deemed significant^{13, 14}). Multiple clinical trials have highlighted that the incidence of MACE is higher in people presenting with PAD than those with some other presentations of cardiovascular disease such as coronary artery or cerebrovascular disease^{5, 15}). This highlights the importance of implementing medical treatments effective at improving outcomes in PAD patients^{5, 15}).

The main strategy to reduce MACE and MALE is the medical management of atherosclerosis risk factors, including appropriate prescription of anti-platelet and anti-thrombotic drugs; control of lipids, blood pressure, and diabetes; and smoking cessation where relevant. However, a growing body of published literature has demonstrated that the implementation of these treatments remains poor due to multiple interrelated issues^{11, 16-20}). Firstly, in many countries, the medical management of people with PAD is managed by a combination of general practitioners and vascular surgeons^{21, 22}), who may have not received specific and up-to-date training on the medical management of atherosclerosis, which has become increasingly complex. Furthermore, published evidence that these health professionals rely on have been limited or have presented conflicting results with regard to safe and appropriate targets^{16, 17, 23-25}). Finally, current international guidelines that include or are focused on PAD do not comprehensively describe how to implement the medical management of PAD, since they aim to cover all aspects of arterial disease diagnosis and management^{2, 26-28}).

There is, therefore, a need for an up-to-date review of the rationales and suggested pathways to implement optimal medical management of PAD. This review focuses on the current evidence from randomized controlled trials (RCTs) and meta-analyses regarding the most appropriate medical management of PAD in order to reduce the risk of MACE and MALE. The review aimed to guide health professionals who manage patients with PAD in identifying relevant risk factors and implementing appropriate medical therapies. **Table 1** briefly summarizes the modifiable medical risk factors of importance from each key international guideline, including specific targets and overall medication recommendations where described. The risk factors

discussed are as follows: preventing thrombus formation, lowering low-density lipoprotein cholesterol (LDL-c), blood pressure control, blood glucose control, and cessation of tobacco smoking. Failure to control these risk factors has been found to be associated with an increased risk of adverse events. For example, high blood pressure (systolic blood pressure >140) has been associated with increased risk of MACE of 1.23 (95% confidence intervals, CI, 1.00–1.51)¹¹). Diabetes, particularly insulin treated, has been associated with increased mortality among people with PAD (hazard ratio, HR, 2.94, 95% CI 1.86–4.66)¹⁶). Prescription of a statin has been associated with a 30% reduction (HR 0.70, 95% CI 0.61–0.82) in the incidence of MALE in a previous systematic review²⁹). Similarly, having no diabetes and the prescription of a statin have been associated with a lower risk of major amputation in people with PAD³⁰). This review does not focus on the management of the leg symptoms of PAD, such as intermittent claudication. Readers are referred to previously published reviews on exercise therapy and revascularization used to treat the leg symptoms of PAD³¹⁻³³).

1. Anti-Platelet and Anti-Coagulant Treatments

1a. Overall Recommendations

Current international PAD guidelines have strongly recommended the prescription of an anti-platelet medication to people with symptomatic PAD to prevent MACE^{2, 26-28}). The two anti-platelet medications recommended are aspirin (75–325 mg daily) or clopidogrel (75 mg daily). The American, Asia-Pacific and European guidelines recommend either of these drugs^{27, 28}). The global vascular guidelines on the management of chronic limb-threatening ischemia favors the use of clopidogrel²). Recent guidelines recommend low-dose rivaroxaban, in addition to low-dose aspirin, in patients at high risk of events after considering the risk of bleeding.

1b. Summary of Evidence

Several meta-analyses of RCTs have examined the risks and benefits of anti-platelet drugs in people with PAD³⁴⁻³⁷). A Cochrane meta-analysis showed that an anti-platelet drug compared to placebo, reduced all-cause (relative risk, RR, 0.76, 95% CI 0.60–0.98) and cardiovascular mortality (RR 0.54, 95% CI 0.32–0.93) in patients with intermittent claudication³⁴). A more recent meta-analysis supports clopidogrel as the anti-platelet of choice to limit MACE. The network meta-analysis of 49 RCTs involving 34,518 PAD patients examined the relative benefits of different

Table 1. Overall recommendations for medical management of peripheral artery disease by key guideline

Risk factor	Asian Pacific Society of Atherosclerosis and Vascular Diseases ²⁸⁾	European Society of Cardiology ²⁷⁾	Global CLTI ²⁾	American College of Cardiology & American Heart Association ²⁶⁾
Anti-platelet treatments	Aspirin alone (75-325mg daily) or clopidogrel alone (75mg daily) in patients with symptomatic PAD.	Antiplatelet therapy is recommended in all patients with symptomatic PAD (no specific medications recommended).	Treat all patients with CLTI with an anti-platelet agent; consider clopidogrel as the agent of choice.	Aspirin alone (75-325mg daily) or clopidogrel alone (75mg daily) in patients with symptomatic PAD. Antiplatelet therapy is reasonable in asymptomatic PAD.
Anticoagulation treatments	Aspirin (100mg daily) plus rivaroxaban (2.5mg twice daily) may be considered in symptomatic PAD.	No specific recommendations provided.	Consider low-dose aspirin and rivaroxaban (2.5mg twice daily) in patients with CLTI.	Anticoagulation should not be used in patients with PAD to reduce the risk of cardiovascular ischaemic events.
Control of low density lipoprotein	A statin is recommended for all patients with PAD.	Statin are recommended in all patients with PAD. Serum LDL-c should be reduced to <1.8mmol/L or decreased by ≥ 50% if initial LDL-c level is 1.8-3.5mmol/L.	Use moderate or high intensity statin therapy in patients with CLTI.	A statin medication is indicated for all patients with PAD.
Control of blood pressure	Antihypertensive therapy for patients with PAD and hypertension; ACEI or ARB can reduce cardiovascular ischemic events.	Control blood pressure to <140/90mmHg in PAD patients with hypertension; ACEI or ARB should be considered first-line.	Control systolic blood pressure to <140mmHg and diastolic <90mmHg in patients with CLTI.	Antihypertensive therapy for all patients with hypertension and PAD; ACEI or ARB can reduce the risk of cardiovascular ischaemic events.
Control of diabetes	Management should be coordinated between a healthcare team (no specific medication recommendations).	Strict glycaemic control is recommended in all diabetic patients with PAD (no specific medication recommendations).	Control T2DM in CLTI patients to <7% HbA1c; use metformin as primary hypoglycaemic agent.	Management should be coordinated between a healthcare team (no specific medication recommendations).
Smoking Cessation	PAD patients who smoke should be advised to quit at every visit; assist in developing a quit plan including pharmacotherapy and/or referral to a smoking cessation program. Patients should avoid exposure to environmental tobacco smoke.	Smoking cessation is recommended for all PAD patients. No specific medications or other interventions provided.	Offer smoking cessation interventions (pharmacotherapy, counselling, or behaviour modification therapy) to all patients with CLTI. Ask smokers and former smokers about status of tobacco use at every visit.	PAD patients who smoke should be advised to quit at every visit; assist in developing a quit plan including pharmacotherapy and/or referral to a smoking cessation program. Patients should avoid exposure to environmental tobacco smoke.

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-2 receptor blocker; CLTI: chronic limb-threatening ischemia; HbA1c: haemoglobin A1c (glycated haemoglobin); LDL-c: low-density lipoprotein-c; PAD: peripheral artery disease; T2DM: type-2 diabetes mellitus

anti-platelets³⁵). It was reported that aspirin was not effective at reducing MACE compared to placebo³⁵, while clopidogrel did (RR 0.72; 95% CI 0.58–0.91, number needed to treat, NNT, 80). Clopidogrel also showed the most favorable benefit-harm profile (79% cumulative rank probability best and 77% cumulative rank probability safest)³⁵). These findings were consistent with an earlier conventional smaller meta-analysis, which reported that aspirin did not significantly reduce MACE but did reduce the risk of nonfatal stroke (RR 0.64, 95% CI 0.42–0.99)³⁶). The preference for clopidogrel is also supported by the CAPRIE trial³⁷), which reported that from 6,452 patients that had PAD, there was an RR reduction in events of 23.8% (95% CI 8.9, 36.2) in those administered with clopidogrel (75 mg daily) compared to aspirin (325 mg daily)³⁷).

Another consideration is the benefit of anti-platelet medications on the patency of lower limb endovascular or open surgical revascularization performed in people with PAD. In the network meta-analysis discussed above, dual anti-platelet therapy with clopidogrel plus aspirin significantly reduced major amputations following leg revascularization compared to aspirin alone (RR 0.68; 95% CI 0.46, 0.99, NNT 94), though the risk of severe bleeding was determined to be significantly higher (RR 1.48; 95% CI 1.05, 2.10, number needed to harm 215)³⁵). This has led to a weak recommendation in current guidelines that dual anti-platelet therapy (clopidogrel and aspirin) may reduce the risk of limb-related events after lower extremity revascularization for up to 6 months^{2, 27, 28}).

There have been few trials of warfarin in people with PAD undergoing peripheral revascularization; overall, these have not provided convincing evidence of benefit, and current guidelines recommend against its use to reduce MACE and MALE in people with PAD^{2, 26-28, 38}). Two recent trials have tested the benefit of low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily) in people with PAD³⁹⁻⁴²). The COMPASS trial tested whether this combination reduced the risk of MACE compared with low-dose aspirin alone⁴¹). Among 6,391 patients with PAD, the combination significantly reduced the risk of MALE (HR 0.57, 95% CI 0.37, 0.88) and major amputation (HR 0.33, 95% CI 0.12, 0.92), although major bleeding was more common (HR 1.61, 95% CI 1.09, 2.36)³⁹). Combination therapy also significantly reduced the risk of MACE compared to aspirin alone, although this was reported for a larger group of vascular disease patients including those with carotid artery disease (HR 0.72, 95% CI 0.57, 0.90)⁴²). Meanwhile, the VOYAGER PAD trial tested if the

same combination compared with aspirin alone reduced the incidence of acute limb ischemia, major amputation from vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes in 6,564 people recently having peripheral revascularization⁴⁰). People given aspirin and rivaroxaban had a significant reduction in the primary end-point (HR 0.85, 95% CI, 0.76, 0.96), with an increased risk of major bleeding (HR 1.42, 95% CI 1.10, 1.84).

Overall, these trials provide evidence that low-dose rivaroxaban plus low-dose aspirin is superior to aspirin alone in reducing the risk of MACE and MALE among people with PAD, but with increased risk of major bleeding. As a result, recent guidelines have weakly recommended that low-dose rivaroxaban plus low dose-aspirin may be considered to reduce MACE and MALE in people with symptomatic PAD, having considered the associated risk of bleeding²⁸). Whether rivaroxaban and aspirin are superior to clopidogrel alone remains undetermined.

2. Control of Lipids

2a. Overall Recommendations

Current PAD guidelines strongly recommend the prescription of statin in all PAD patients, although there is a lack of clarity on the exact statin choice and other agent choice if statins are not tolerated or contraindicated^{2, 26-28}). Some guidelines focus on LDL-c targets rather than recommending specific agents, as there is no evidence on ezetimibe in PAD and limited but increasing evidence on the effectiveness of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The recent European Society of Cardiology and European Atherosclerosis Society guidelines suggest people with PAD should receive the maximum tolerated dose of a statin, plus ezetimibe, or a PCSK9 inhibitor⁴³).

These guidelines also indicate that all people with PAD should be considered at very high risk of MACE; thus, treatment should target a LDL-c <1.4 mmol/L, which is more intensive than targets recommended in PAD-focused guidelines^{2, 26-28, 43}). The likely benefit of LDL-c-lowering treatments, as with other medical management interventions, depends on absolute risk. While all people with PAD have a substantial risk of MACE and MALE, this is particularly high for some groups, such as people with chronic limb-threatening ischemia, or evidence of more severe peripheral ischemia or physical impairment^{2, 7, 44-46}). None of the PAD guidelines provide recommendations for treatments to lower triglycerides.

2b. Summary of Evidence

Two previous RCTs have tested the benefit of treatments to lower LDL-c among people with PAD^{15, 47}. The UK Heart Protection Study randomized 6,748 people with PAD or abdominal aortic aneurysm to simvastatin 40 mg or placebo¹⁵. Simvastatin led to an average lower LDL-c of 1 mmol/L compared to placebo, resulting in a significant reduction in major vascular events (HR 0.78, 95% CI 0.71, 0.85)¹⁵ and peripheral revascularization events, but not amputations¹⁵. None of the other large statin trials have reported findings restricted to people with PAD⁴⁸.

The FOURIER trial tested the PCSK9 inhibitor evolocumab in 3,642 people with PAD⁴⁷. Evolocumab significantly reduced median LDL-c by about 1.6 mmol/L and the risk of MACE (HR 0.73, 95% CI 0.59, 0.91) and MALE (HR 0.58, 95% CI 0.38, 0.88)⁴⁷. No increase in adverse events in participants administered with evolocumab was reported. There is current debate on whether PCSK9 inhibitors are a cost-effective therapy given the significant cost associated with their use^{7, 49}. A recent analysis modeled the effect of a PCSK9 inhibitor, using the data from the FOURIER trial, based on the incidence of MACE and MALE among a group of Australian patients with PAD⁷. It was estimated that intensive LDL-c lowering using a PCSK9 inhibitor would lead to an absolute risk reduction in MACE of 6.1% (95% CI 2.0, 9.3, NNT 16) and MALE of 13.1% (95% CI 4.1, 20.5, NNT 8) in people with chronic limb-threatening ischemia compared to 3.2% (95% CI 1.1, 4.8, NNT 32) and 5.3% (1.7, 8.3, NNT 19) in people with intermittent claudication⁷. This illustrates the potential advantage of intensive management in people at highest risk, such as those with chronic limb-threatening ischemia. The JELIS trial reported that people with PAD ($n=223$) randomized to eicosapentaenoic acid (EPA) had a significant reduction in major coronary events (HR 0.44, 95% CI 0.19, 0.97)⁵⁰. The REDUCE-IT trial, which included people with PAD, reported that EPA significantly reduced the risk of MACE (HR 0.74, 95% CI 0.65, 0.83)⁵¹. These findings suggest that there may also be benefit in lowering triglycerides in people with PAD.

3. Control of Blood Pressure

3a. Overall Recommendations

Current PAD guidelines strongly recommend people with PAD who also suffer from hypertension should receive an antihypertensive medication, favoring the use of angiotensin-converting enzyme

inhibitors or angiotensin receptor blockers^{26, 28}. Some guidelines recommend a blood pressure target of less than 140/90 mmHg^{2, 27}.

3b. Summary of Evidence

Depending on the definition and study entry criteria, between 38 and 86% of people with PAD have been determined to have hypertension¹⁷. The HOPE study is the only large trial that has examined whether a medication for hypertension reduces MACE in people with PAD, which included 1,715 people with symptomatic PAD⁵². Randomization to a 2.5 mg dose of ramipril was found to reduce the risk of MACE, in comparison to placebo (HR 0.75, 95% CI 0.61, 0.92)⁵². In contrast, the SPRINT trial reported that among a group 9,361 people with blood pressure ≥ 130 mmHg, including some participants with PAD, intensive blood pressure lowering aimed to achieve systolic blood pressure <120 mmHg significantly reduced vascular events (myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death: HR 0.75, 95% CI 0.64, 0.89) and all-cause mortality (HR 0.73, 95% CI 0.60, 0.90)²⁴. The trial excluded people with diabetes and reported a significantly increased rate of serious adverse events believed to be related to intensive blood pressure lowering²⁴. To the best of our knowledge, the trial has not separately reported the results for the participants with PAD. One observational study reported an increased rate of MACE in PAD patients with systolic blood pressure <120 mmHg¹¹. Furthermore, the ACCORD trial reported that intensive blood pressure lowering in people with diabetes did not significantly reduce MACE (HR 0.88, 95% CI 0.73, 1.06) or all-cause mortality (HR 1.07, 95% CI 0.85, 1.35)²⁵. As a result, further evidence is needed before intensive lowering of blood pressure can be recommended for people with PAD.

4. Control of Diabetes

4a. Overall Recommendations

Most current diabetes treatments have not been tested in RCTs in people with PAD. Current PAD guidelines have emphasized the importance of glucose control in people with diabetes and PAD, although they do not have clear recommendation of how to achieve this²⁸. In the absence of clear evidence, it is appropriate to use national and international guidelines for the management of diabetes. These guidelines recommend an algorithm of management to achieve the desired HbA1c target, which is usually $<7\%$ ⁵³. Metformin is recommended as the first-line treatment unless contraindicated or not tolerated.

Second-line treatments include sodium/glucose cotransport-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulphonylureas, glucagon-like peptide 1 receptor agonists, and insulin⁵³).

4b. Summary of Evidence

Depending on the study entry criteria and testing, between 14 and 60% of people with PAD have been reported to have diabetes¹⁷), which is associated with increased mortality¹⁶). Furthermore, poorly controlled diabetes, as estimated by high HbA1c concentrations, has been associated with an increased risk of MACE, MALE, and all-cause mortality in people with PAD^{54, 55}). The ACCORD trial reported that intensive glucose control, as compared to standard glucose control, significantly reduced the risk of lower extremity amputation (HR 0.69, 95% CI 0.48, 0.99) in participants with diabetes⁵⁶). These findings emphasize the importance of tight control of diabetes among people with PAD. The novel SGLT-2 inhibitor empagliflozin has recently been reported to improve outcomes among people with diabetes and PAD in a randomized placebo-controlled trial⁵⁷). Among the 1,461 participants with PAD and diabetes, empagliflozin was found to reduce the risk of cardiovascular death (HR 0.57, 95% CI 0.37, 0.88) and all-cause mortality (HR 0.62, 95% CI 0.44, 0.88), with no excess of lower limb amputation⁵⁷).

Meanwhile, the CANVAS trial has reported on the effect of another SGLT2 inhibitor (canagliflozin) in people with diabetes, but it did not specifically report on people with PAD. It was determined that canagliflozin reduced MACE (HR 0.86, 95% CI 0.75, 0.97), but there was also a significant excess of lower limb amputations⁵⁷). Whether the latter is a chance or repeatable findings remains unclear, but caution in the use of canagliflozin for people with PAD is currently warranted. As a result, previous lower limb amputation, foot ulcers, and chronic limb-threatening ischemia are currently considered relative contraindications to canagliflozin.

5. Smoking Cessation

5a. Overall Recommendations

Smoking cessation is recommended for all PAD patients, with recommended treatments as follows: counseling, varenicline (a partial nicotine receptor agonist), nicotine replacement therapy, and bupropion (a combined nicotine receptor antagonist and norepinephrine-dopamine reuptake inhibitor)⁵⁸⁻⁶⁰). Recommended counseling approaches include brief

advice tailored to the patient's degree of readiness to quit, use of nonjudgmental communication, motivational interviewing techniques, and intensive behavior counseling^{59, 60}). Guideline-recommended interventions are informed by patient preferences and experiences in quitting.

5b. Summary of Evidence

Smoking has been identified as an important risk factor for PAD, and over 30% of people referred to hospital with PAD are current smokers^{11, 16, 61}). Continued smoking is associated with worse outcomes, including reduced patency of peripheral revascularization⁶² and increased risk of MACE and MALE (combined HR 1.77, 95% CI 1.30, 2.41)^{63, 64}). Quitting smoking has been associated with reduced mortality and amputation risks⁶⁵). Previous studies suggest that current smokers value programs which allow them autonomy, which are delivered by familiar counselors with excellent communication skills, and which include printed material and safe drugs they can access for no or low cost⁶⁶).

Few RCTs have tested the success of these smoking cessation methods in PAD patients⁶⁷⁻⁷⁰). The largest trial included 124 smokers with PAD who wanted to quit, being randomized to an intensive tailored counseling intervention or minimal advice⁶⁷). The intervention consisted of physician-delivered advice and smoking cessation counseling focused on the link between smoking and PAD, motivational interviewing, cognitive behavior counseling to develop a quit plan, and provision of drug information to aid quitting. A minimum of six sessions over 5 months were provided. The control group received verbal advice from their physician and a list of available smoking cessation programs. At 6 months, 54% of the intervention group reported using varenicline to aid smoking cessation compared to 31% of the control group ($p=0.019$) and 21% compared to 7% had confirmed smoking abstinence ($p=0.023$)⁶⁷). The findings suggest that a combination of counseling and medications, particularly varenicline, can improve smoking cessation at 6 months in PAD patients. Quitting was, however, ineffective in over three-quarter of participants, and no long-term outcomes were reported.

A more recent randomized trial examined the effect of a 5-minute PowerPoint presentation by a junior vascular surgeon on the benefits of smoking cessation⁶⁸). The presentation used a gain-framed approach to outline the benefits of quitting in terms of reducing the risk of cardiovascular, lung, mouth and throat complications and provided information about the available methods and support to quit

smoking⁶⁸). The presentation was delivered in an outpatient clinic or hospital individually to patients on an electronic notebook. The control group did not receive the presentation, but both groups received 2 weeks free nicotine replacement therapy. The trial only managed to recruit 59 of the planned 68 (87%) participants. At 6 months, 7 (29%) of the intervention group and 9 (32%) of the control group had quit smoking ($p=1.0$), whereas 14 (58%) vs. 10 (36%) had reportedly reduced their number of cigarettes smoked by at least 50% of that reported at entry. None of the participants included in this trial were reported to have used varenicline.

A cluster RCT examined the effect of very brief advice from a physician about smoking cessation, prescription of nicotine replacement therapy, and referral to telephone-based smoking cessation counseling⁶⁹). Eight vascular centers were randomly allocated one by one to the intervention or standard care. Centers allocated to the intervention group received training in providing the smoking cessation approach via two 2-hour-long web-based seminars delivered to study site leaders. At 3 months, 23 of 57 (40%) patients attending the centers trained to provide the smoking cessation intervention, and 26 of 84 (31%) patients attending the control centers had quit smoking ($p=0.250$)⁶⁹). Finally, a RCT tested a program of five counseling sessions over 6 weeks. The sessions were based on motivational conversations, advice on and free provision of nicotine replacement therapy, and education on the benefits of quitting⁷⁰. The control group received limited advice about quitting and free nicotine replacement therapy. Only 32 of the planned 144 (22%) participants were recruited. Four patients were excluded shortly after randomization since they did not meet entry criteria. At 6 weeks, 3 of 11 (27%) patients in the intervention group and 3 of 17 (18%) in the control group had quit smoking⁷⁰. Overall these past trials emphasize the challenges of assisting people with PAD to quit smoking, but provide some evidence that a combination of counseling and smoking cessation medications, particularly varenicline, can aid quitting.

Integrated Programs of Medical Management

Ideally, any intervention to improve healthcare should be able to be integrated into existing systems to facilitate efficient care. Patients with PAD are typically cared for by a combination of primary healthcare physicians and vascular specialists. Thus, interventions that effectively enable both specialties to better implement the optimal medical management

discussed above are of great potential value. A limited number of clinical trials that have included some participants with PAD have examined the effect of such interventions.

The BRIDGE Cardiovascular Prevention study tested whether a quality improvement intervention could improve the prescription of evidence-based therapies in 1,619 people with cardiovascular disease through a cluster RCT⁷¹). The program included case management, audit and feedback, decision support tools based on current guidelines, and distribution of educational materials. Participants in the intervention clusters were more likely to receive a prescription of evidence-based therapies than those in control clusters (odds ratio 2.30; 95% CI 1.14, 4.65) although risk factor control was not significantly improved⁷¹). Another randomized trial tested the benefit of a personalized website along with communication with a nurse practitioner for education among 330 participants with coronary, cerebral, or peripheral atherosclerosis⁷²). After 1 year, the relative reduction in the Framingham risk score was 14% (95% CI 2 to 25%)⁷²). A currently ongoing trial is examining the effect of a nurse-led, person-centered, health-promoting program among 210 people with intermittent claudication that have recently had surgical treatment of intermittent claudication⁷³). Approaches which have had success in people at risk of cardiovascular disease include practice facilitators⁷⁴, community health workers⁷⁵, online education programs⁷⁶, and community forums⁷⁶). Another important consideration is whether interventions to improve implementation of medical management should be provided through in-person consultation or can be provided by remote means, such as telehealth. A recent systematic review⁷⁷ suggests that telehealth can be effective at improving secondary prevention in people with coronary artery disease.

Conclusion

People with PAD have some of the highest adverse event rates among those with cardiovascular disease. Secondary preventive measures for key modifiable risk factors have proven their efficacy, but they remain to be adequately implemented in clinical practice. Thus, effective implementation programs are required to achieve optimal medical management for PAD patients and to reduce adverse events in this patient group.

Acknowledgments

None.

Financial Support

Funding from the National Health and Medical Research Council (1063476 and 1022752), James Cook University, the Townsville Hospital and Health Services Study, Education and Research Trust Fund, and Queensland Government supported this work. JG holds a Practitioner Fellowships from the National Health and Medical Research Council (1117061) and a Senior Clinical Research Fellowship from the Queensland Government, Australia.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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