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Society Guidelines

Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease

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ABSTRACT

Patients with widespread atherosclerosis such as peripheral artery disease (PAD) have a high risk of cardiovascular and limb symptoms and complications, which affects their quality of life and longevity. Over the past 2 decades there have been substantial advances in

RÉSUMÉ

Les patients atteints d'athérosclérose généralisée telle que la maladie artérielle périphérique (MAP) présentent un risque élevé de symptômes et de complications cardiovasculaires et au niveau des membres, ce qui affecte leur qualité de vie et leur longévité. Au cours des

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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diagnostics, pharmacotherapy, and interventions including endovascular and open surgical to aid in the management of PAD patients. To summarize the evidence regarding approaches to diagnosis, risk stratification, medical and intervention treatments for patients with PAD, guided by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, evidence was synthesized, and assessed for quality, and recommendations provided—categorized as weak or strong for each prespecified research question. Fifty-six recommendations were made, with 27% (15/56) graded as strong recommendations with high-quality evidence, 14% (8/56) were designated as strong recommendations with moderate-quality evidence, and 20% (11/56) were strong recommendations with low quality of evidence. Conversely 39% (22/56) were classified as weak recommendations. For PAD patients, strong recommendations on the basis of high-quality evidence, include smoking cessation interventions, structured exercise programs for claudication, lipid-modifying therapy, antithrombotic therapy with a single antiplatelet agent or dual pathway inhibition with low-dose rivaroxaban and aspirin; treatment of hypertension with an angiotensin converting enzyme or angiotensin receptor blocker; and for those with diabetes, a sodium-glucose cotransporter 2 inhibitor should be considered. Furthermore, autogenous grafts are more effective than prosthetic grafts for surgical bypasses for claudication or chronic limb-threatening ischemia involving the popliteal or distal arteries. Other recommendations indicated that new endovascular techniques and hybrid procedures be considered in patients with favourable anatomy and patient factors, and finally, the evidence for perioperative risk stratification for PAD patients who undergo surgery remains weak.

20 dernières années, des progrès considérables ont été réalisés en matière de diagnostic, de pharmacothérapie et d'interventions, notamment endovasculaires et chirurgicales à ciel ouvert, pour faciliter la prise en charge des patients atteints de MAP. Pour récapituler les données probantes relatives aux approches de diagnostic, à la stratification du risque, aux traitements médicaux et interventionnels pour les patients atteints de MAP, éclairé selon le cadre *Grading of Recommendations, Assessment, Development, and Evaluation* (GRADE), ces évidences ont été synthétisées et évaluées en fonction de critères de qualité, puis des recommandations ont été exposées - classées comme faibles ou fortes pour chacune des questions de recherche préspécifiées. Cinquante-six recommandations ont été formulées, dont 27 % (15/56) ont été classées en tant que fortes recommandations avec des donnnées probantes de haute qualité, 14 % (8/56) ont été désignées en tant que fortes recommandations avec des donnnées probantes de qualité modérée, et 20 % (11/56) étaient des recommandations fortes avec des donnnées probantes de faible qualité. Inversement, 39 % (22/56) ont été classées comme faibles recommandations. Pour les patients atteints de MAP, les fortes recommandations, basées sur des donnnées probantes de haute qualité, comprennent des interventions de sevrage tabagique, des programmes d'exercices structurés pour la claudication, un traitement modulant les taux lipidiques, un traitement antithrombotique avec un seul agent antiplaquettaire ou une inhibition duale avec de faibles doses de rivaroxaban et d'aspirine; un traitement contre l'hypertension par une enzyme de conversion de l'angiotensine ou un bloqueur des récepteurs de l'angiotensine; et pour les diabétiques, un inhibiteur du cotransporteur sodium-glucose de type 2 devrait être envisagé. En outre, les greffes de matériel autogène sont plus efficaces que les greffons prothétiques pour les pontages chirurgicaux dans le cas de claudication ou d'ischémie chronique menaçant un membre et impliquant les artères poplitées ou distales. D'autres recommandations attestent que les nouvelles techniques endovasculaires et les procédures hybrides doivent être envisagées chez les patients présentant une anatomie et des facteurs favorables. Enfin, les évidences restent fragiles dans le cas d'une stratification du risque péri-opératoire pour les patients atteints de MAP et subissant une intervention chirurgicale.

Peripheral arterial disease (PAD) is often asymptomatic, and is underdiagnosed, under-recognized, and undertreated. It is associated with significant cardiovascular (CV) and cerebrovascular morbidity and mortality. Since the 2005 Canadian Cardiovascular Congress Consensus Conference on PAD, newer data are available to inform clinicians on best practices to manage patients with PAD.

Section 1 of this guideline provides evidence-based recommendations on the diagnosis and screening of patients with PAD, with a focus primarily on lower-extremity PAD. We discuss the most accurate signs, symptoms, and tests for detecting PAD in symptomatic and asymptomatic individuals. We review whether routine screening of patients at high risk for, or with established atherosclerosis, benefit from routine screening for PAD to reduce limb ischemia and global CV outcomes. We also review the evidence for screening patients with PAD for coronary artery disease (CAD) or cerebrovascular disease, to determine if this improves prognosis.

Section 2 provides evidence-based recommendations and highlights the recent substantial advancements in the medical management of patients with PAD. We provide recommendations for clinicians who care for PAD patients regarding smoking cessation and exercise therapy. We also review the key evidence that supports risk factor modification and drug therapy including: (1) blood pressure (BP) diagnosis, lowering, and targets, and selection of BP medications; (2) the use of glucose-lowering medications; (3) the effectiveness of lipid-lowering agents including statins, proprotein convertase subtilisin/Kexin-9 (PCSK-9) inhibitors, and the role of icosapent ethyl. A substantial body of literature regarding the efficacy and safety of antithrombotic therapy in patients with PAD is reviewed, integrating recent evidence for low-dose rivaroxaban and aspirin to reduce major adverse CV and major adverse limb events (MALE). Use of antithrombotics in a broad range of PAD patients is discussed, from outpatients to those with lower extremity revascularization, including endovascular and open surgical approaches.

Section 3 provides guidance on revascularization procedures for patients with PAD. Preoperative assessment and risk stratification, and indications for revascularization are also

reviewed. Significant advancements in technology and techniques of revascularization, particularly for endovascular procedures, are discussed to inform the nonsurgeon clinician caring for the patient with PAD. For surgeons and interventionalists, evidence for choosing between open surgical and endovascular procedures are reviewed.

Please refer to the Supplementary Material for expanded information on the topics that follow.

Methodology

The topics and scope were chosen by the 3 co-chairs. Aortic diseases were explicitly excluded. The primary and secondary panelists were assigned to each of the topic areas on the basis of consideration of their research and clinical expertise, with consideration for geography and gender. Primary panelists were asked to develop the health care questions and outline Population, Intervention, Comparison, Outcome (PICO) questions, if applicable. Evidence reviews were led by the primary panelists and supported by a targeted scan for on-topic systematic reviews and meta-analyses from 2016 to 2021 for the topics, identified by the McMaster Evidence Review Synthesis Team (MERST). The search was conducted in PubMed using keywords: "peripheral artery disease" and "diagnosis," and "meta-analysis." This search resulted in 369 citations, which were reviewed for each of the guideline topics. This initial search was augmented for each PICO question, the results of which can be found on ccs.ca. For sections on lipid-lowering, glucose-lowering, and antithrombotic therapy, which were dominated by multiple recent randomized controlled trials (RCTs), MERST completed a more detailed literature review (see ccs.ca). The **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment, and **E**valuation (GRADE) scale for rating the strength of recommendations and the quality of evidence was applied.[1] When each section was complete, the primary panelists voted on the recommendations and if more than two-thirds of the members agreed, it was confirmed. Secondary panelists were then asked to read the entire document and provide comments. The recommendation discussions are prefaced by the PICO points we considered in their development.

1. Diagnosis and Screening

1.1. Diagnosis of PAD

PICO 1.1a: What are the most accurate signs, symptoms, and tests for detecting asymptomatic PAD in adults at risk of PAD?

*PICO 1.1b: What are the most accurate signs, symptoms, and tests (**A**nkle-**B**rachial **I**ndex [ABI], **T**oe-**B**rachial **I**ndex [TBI], transcutanous oxygen pressure [$TcP0_2$], plethysmographic waveforms, magnetic resonance angiography [MRA], computed tomography angiography [CTA], etc) for detecting PAD in adult men and women who present with lower limb symptoms?*

PICO 1.1c: What are the most accurate signs, symptoms, and tests (ABI, TBI, $TcPO_2$, plethysmographic waveforms, MRA, CTA, etc) for detecting PAD in adult men and women with diabetes or chronic kidney disease who present with lower limb symptoms?

Table 1. Differential diagnosis for leg pain or claudication[2]

Neurogenic	• Spinal stenosis • Peripheral neuropathy • Peripheral nerve pain (eg, radiculopathy) • Spondylolisthesis
Musculoskeletal	• Arthritis of the hip or knee • Symptomatic Baker cyst • Chronic exertional compartment syndrome • Stress fracture • Muscle spasms or cramps
Vascular	• Peripheral arterial disease • Chronic limb-threatening ischemia • Venous insufficiency • Deep venous thrombosis • Nonatherosclerotic arterial disease (eg, popliteal entrapment syndrome)
Other	• Restless leg syndrome • Malignancy

Lower extremity PAD is prevalent among people aged 50 years and older. Among those with lower limb symptoms suggestive of claudication, it is important for clinicians to distinguish PAD from other causes of leg pain (Table 1), starting with a thorough clinical history and physical examination focused on relevant signs and symptoms. A validated diagnostic questionnaire for PAD used in epidemiological studies is the Edinburgh Claudication Questionnaire (Table 2), which has a 91.3% (95% confidence interval [CI], 88.1%-94.5%) sensitivity and 99.3% (95% CI, 98.9%-100%) specificity.[3]

Only 5%-10% of patients with PAD present with classical symptoms of intermittent claudication.[4] Other patients present with nonspecific back, buttocks, or leg discomfort, whereas some are asymptomatic. Classic features of claudication include: (1) muscle pain, typically involving calf muscles or the muscle group distal to an arterial tenosis or occlusion and often described as cramping in nature; (2) pain that develops only when the muscle is exercised; and (3) pain that resolves usually within 10 minutes of discontinuation of exercise or resting. Typically, patients with vasculogenic claudication experience cramping muscle pain after walking a similar distance. Intermittent claudication differs from chronic limb-threatening ischemia, which includes ischemic rest pain, gangrene, or ulceration on the lower extremity.

After a thorough clinical history, clinicians should conduct a focused peripheral vascular examination. Confirmation of the diagnosis of PAD then requires specific tests, considering the broad differential for leg pain (see section 1.1 of the Supplementary Material for more information).

Table 2. Edinburgh Claudication Questionnaire

1. Do you get a pain or discomfort in your leg(s) when you walk?
2. Does this pain ever begin when you are standing still or sitting?
3. Do you get it if you walk uphill or hurry?
4. Do you get it when you walk at an ordinary pace on the level?
5. What happens to it if you stand still?
Usually continues more than 10 minutes
Usually disappears in 10 minutes or less
6. Where do you get this pain or discomfort?

There are a number of confirmatory diagnostic tests that help establish the diagnosis of PAD. Some of these tests are more invasive and others are specialized and/or centre-specific. The most widely used test is the ABI.

The ABI is an inexpensive, noninvasive test that involves measuring the systolic BP at the arm (or over the brachial artery) and ankle (or over the dorsal pedis or posterior tibial artery) while the patient is supine, using a continuous-wave Doppler device (Fig. 1). The higher value of systolic pressure at the ankle is divided by the higher of the arm pressures (right or left) to obtain the ABI.[5,6] The most widely used and accepted ABI calculation is shown in Figure 1. An ABI < 0.9 suggests PAD.[5]

The incidence of PAD varies according to the prevalence of risk factors for the disease such as smoking, hypertension, hypercholesterolemia, and diabetes mellitus.[4] Medial arterial calcinosis, which is more prevalent in patients with diabetes, chronic kidney disease, and advanced age, results in poorly compressible arteries.[7] This might falsely normalize or artificially elevate ABI to a value exceeding 1.4, rendering this test less reliable.

Many studies have investigated the accuracy of ABI, oscillometric ABI, TBI, near-infrared technology, pulse oximetry, pulse wave velocity, transcutaneous oxygenation, computed tomography, magnetic resonance imaging, and conventional angiography for diagnosing PAD. The TBI can be calculated with arm and great toe arterial BP measurements. The great toe systolic pressures are divided by the highest arm pressure to establish a TBI measurement for each leg. ABI and TBI are the most studied, but there is a paucity of data for most other tests for the diagnosis of PAD. From these accuracy studies, test characteristics have a very wide range depending on symptoms and risk factors of the population (eg, sensitivity of 45%-100% and specificity of 16%-100% for TBI).[7] There is also a lack of consistency with respect to how to perform an ABI or TBI. With TBI, the diagnostic cutoff for PAD is variable among studies, although < 0.60 is commonly used.

Data suggest that ABI is a reliable way to diagnose PAD. Table 3 shows a comparison of general sensitivity and specificity ranges for these test modalities.

An ABI might be insufficient to be used alone for the detection of PAD in people with diabetes and chronic kidney disease because of the higher probability of medial calcification. The literature is limited on diagnosis in patients with chronic kidney disease. Other tests such as the TBI, tibial waveform, and/or transcutaneous oxygenation should be considered for diagnosing PAD in the case that ABI > 1.4, suggestive of calcified arteries.

1.1.1. Sex/gender differences

Although population-based studies suggest higher prevalence of asymptomatic disease and more complex or multilevel and severe disease at the time of diagnosis for women, there is a paucity of studies that specifically examined sex differences in diagnosis of PAD.[11-13] However, inclusion of the ABI in CV risk stratification resulted in reclassification of the risk category and modification of treatment in approximately 19% of men and 36% of women.[14] The effect of sex and gender on PAD presentation and diagnostic tools such as ABI and TBI warrant further study.

RECOMMENDATION

1. We suggest using the ABI for asymptomatic adults, older than age 50 years, who have risk factors for PAD (such as smoking or diabetes), to screen for PAD (Weak Recommendation; Low-Quality Evidence).
2. We recommend using an ABI and/or a TBI study to confirm the diagnosis of PAD in patients with symptoms of PAD (Strong Recommendation; Moderate-Quality Evidence).
3. We suggest using a TBI with tibial waveforms and/or transcutaneous oxygen pressure as adjuncts for patients with symptoms of PAD with calcified arteries to confirm the diagnosis of PAD (Weak Recommendation; Low-Quality Evidence).

Values and preferences. To improve patient's quality and quantity of life in the long-term, it is important to diagnose PAD in at-risk asymptomatic, and symptomatic patients to initiate appropriate best, evidence-based, medical therapy.

Practical tip. The ABI used in the diagnosis of PAD can be easily classified and measured. See Figure 1 and video links provided in the legend.

1.2. Asymptomatic PAD Screening

PICO 1.2a: In patients without claudication symptoms, but at high risk for clinically apparent atherosclerotic disease, would routine systematic screening for PAD improve lower limb ischemia outcomes?

PICO 1.2b: In patients without claudication symptoms, but who have documented atherosclerosis in another vascular bed, would routine systematic screening for PAD improve global CV outcomes?

The ideal characteristics for a successful population-based screening strategy would include use of a test with high sensitivity that leads to efficacious therapy, if used early in the disease state. Although ABI measurement has very high specificity for detecting PAD, there are no current recommendations for intervention on asymptomatic disease because there has been no demonstration of benefit.[15,16] The Society for Vascular Surgery and the Canadian Society for Vascular Surgery recommend against invasive treatments for asymptomatic PAD (percutaneous or surgery), regardless of ABI or other test results that indicate PAD.[17,18] A recent systematic review including studies of asymptomatic patients demonstrated no benefit in major adverse CV events (MACE) or quality of life measures with intervention.[18] A meta-analysis commissioned by the Society for Vascular Surgery did not yield evidence of either cost-effectiveness for ABI screening of asymptomatic patients, or any clear reduction in morbidity or mortality.[14]

Individuals with multiple vascular territory involvement or polyvascular disease carry worse prognosis when identified

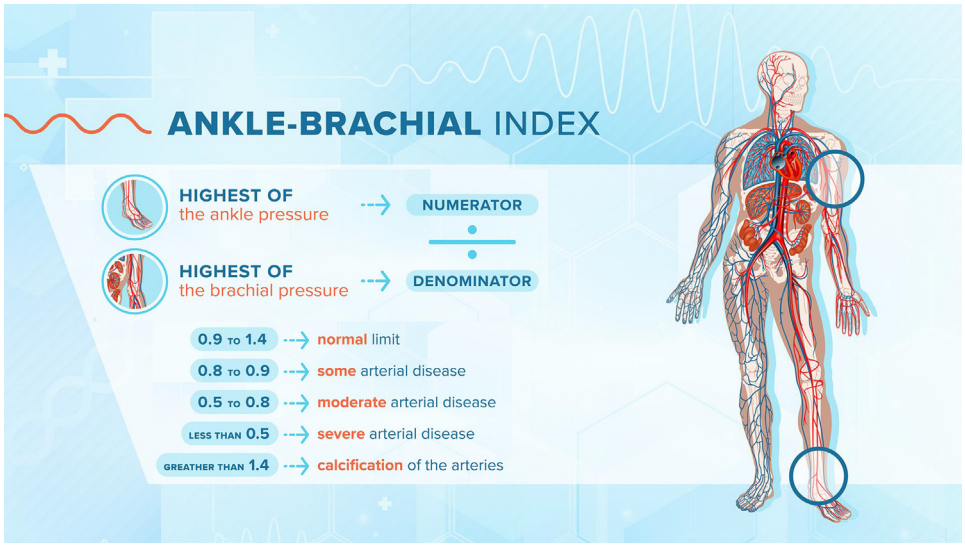

Figure 1. Calculating **A**nkle-**B**rachial **I**ndex (ABI). Image from the video "How to Detect Peripheral Arterial Disease (PAD)." Reproduced with permission from the Quebec Society of Vascular Sciences (QSVS) / Société des sciences vasculaires du Québec (SSVQ). See the video in English "How to Detect Peripheral Arterial Disease (PAD)" (https://youtu.be/5ux13-XjzgQ) and in French "Comment détecter la maladie artérielle périphérique (MAP)" (https://www.youtube.com/watch?v=MX4fAqL_15g).

(Fig. 2).[19-22] To date, there has been no RCT to suggest that the strategy of systematic screening in this setting is effective in lowering rates of CV events, or MALE (evolution to limb-threatening ischemia or limb loss).[18] This is likely because risk factor management and pharmacotherapy are not vastly different when single or multiple vascular beds are involved. Similarly, current guidelines for dyslipidemia, hypertension, or antithrombotic agents have not delineated different treatment streams for patients with vascular disease in multiple vascular territories. However, novel agents, such as PCSK-9 inhibitors and low-dose direct oral anticoagulation were not used in previous studies. It is unknown if diagnosing those at higher risk for events would change management strategies and outcomes.

As we move to precision medicine, the use of the ABI might further refine global CV risk assessment. An abnormal ABI is prognostic, regardless of symptoms. The utility of such a strategy might be dependent on the stage of a patient's disease. ABIs and CTA delineate flow-limiting lesions. Abnormal results would be a sign of late disease. They are less helpful when trying to detect preclinical or early-stage atherosclerosis in a relatively low risk primary prevention population. However, further refinement of risk estimates in secondary prevention populations could assist in determining the risk-benefit of certain pharmacotherapies and optimize prescription of high-cost treatments. A higher absolute CV risk in a patient with polyvascular disease might justify prescription of a more potent antithrombotic that has a greater bleeding risk,[19,21,22] or expensive agents such as PCSK-9 inhibitors. Thus far, we do not have a global vascular risk-estimate tool that has led to ischemic event reduction. A recent cost effectiveness analysis tested the use of ABI screening to detect asymptomatic PAD in patients with recently symptomatic CAD. The analysis showed that patients with asymptomatic PAD had minimal quality of life years gained, with significantly high incremental cost, much above usual willingness to pay thresholds.[23]

Table 3. Pooled estimates of sensitivity and specificity for diagnosis of PAD reported in systematic reviews[8-10]

Study population	Test modality	Sensitivity (95% CI), %	Specificity (95% CI), %
PAD	ABI < 0.9	61 (55-69)	92 (89-95)
	TBI < 0.6	81 (70-94)	77 (66-90)
PAD and diabetes	ABI < 0.9	60-65 (48-71)	87 (78-92)
	TBI < 0.6	83 (59-94)	66 (41-84)
	Tibial waveform	83 (73-89)	87 (76-93)

ABI, **A**nkle-**B**rachial **I**ndex; CI, confidence interval; PAD, peripheral arterial disease; TBI, **T**oe-**B**rachial **I**ndex.

RECOMMENDATION

4. We recommend **against** implementing a broad, population-based screening strategy for PAD, in patients without signs or symptoms of claudication (Strong Recommendation; High-Quality Evidence).

Values and preferences. In contrast to general population screening, individual patients with high-risk features such as smoking and diabetes, might benefit from identification of PAD and more aggressive medical management. However, patients do not benefit from revascularization with asymptomatic PAD. Patients' interest in their future vascular risk should be considered when determining if ABI testing will be undertaken.

Practical tip. Patients should be assessed and managed for vascular risk factors. Focus should be on the management of CV risk factors rather than the pursuit of

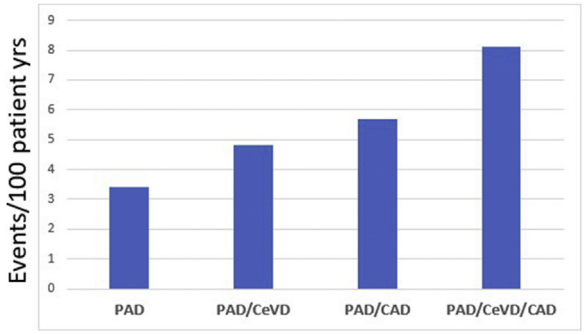

Figure 2. Risk of cardiovascular event (screening for coronary artery disease [CAD] and carotid disease in peripheral arterial disease [PAD] patients [death/myocardial infarction/stroke]) in patients with disease in multiple vascular beds (data from a secondary data analysis of the **E**xamining **U**se of Ti**c**agrel**o**r **i**n Pa**d** [EUCLID] trial).[24] CeVD, cerebrovascular disease.

revascularization. Currently available tests for PAD do not assess for preclinical disease. Other modalities to assess preclinical disease in coronary and carotid arteries have greater evidence to assist in global CV risk assessment in a primary prevention setting.

RECOMMENDATION

5. We suggest **against** routine PAD testing for inferring global CV risk, in patients without symptoms of PAD, who have clinically symptomatic atherosclerosis in another vascular territory (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. For patients with polyvascular disease, strong evidence for routine screening of other vascular territories is lacking. There is lack of consensus on how this screening would differentiate treatment. We could not recommend this practice. However, the committee recognizes that in select patients, identifying a second vascular bed might change management and assist in overcoming financial barriers for certain pharmaceuticals.

Practical tip. Global CV risk reduction should focus on risk factor management as suggested in respective risk factor guidelines.

1.3. Screening for CAD and carotid disease in PAD patients

PICO 1.3: Does screening patients with PAD for CAD or cerebrovascular disease reduce myocardial infarction (MI), stroke, or CV death?

RECOMMENDATION

6. We suggest **against** routine screening for asymptomatic carotid artery stenosis or asymptomatic CAD, among patients with documented PAD (Weak Recommendation; Low-Quality Evidence).

Values and preferences. Most patients with PAD require aggressive CV risk factor management to improve long-term outcomes. This is on the basis of the strong epidemiological evidence linking PAD with incident MI and stroke.

Practical tip. Patients with PAD have a high incidence of concomitant disease in other vascular beds and should be questioned about symptoms attributable to those vascular beds. Patients with polyvascular disease are a particularly high-risk group for future CV events and warrant aggressive management of standard atherosclerotic risk factors, including smoking, hypertension, dyslipidemia, and diabetes.

2. Management of PAD

2.1. Smoking cessation

PICO 2.1: Which smoking cessation interventions (behavioural and drug therapy) are efficacious at reducing MACE and MALE among patients with PAD?

Of all CV risk factors, tobacco exposure through cigarette smoking is the most strongly associated with the development and progression of PAD and its complications: MACE such as MI, stroke, CV death, and MALE.

There is a solid foundation of data supporting a variety of smoking cessation interventions. Smoking cessation can prevent PAD and reduce MACE and MALE when PAD becomes symptomatic. Aside from behavioural counselling, pharmacological therapy should be considered, from nicotine replacement therapy (NRT) such as gum and patches, to bupropion and varenicline. Nicotine-containing e-cigarettes (EC) should also be given consideration.

Behavioural therapy supporting pharmacotherapy does augment the 6-month quitting rate, but the relative risk (RR) is only 1.05-1.20, translating to a 20% quit rate compared with 17% when patients receive no support.[25] Behavioural therapy effectiveness is immensely variable in the literature and has been extensively reviewed in a recent Cochrane review of 312 RCTs with 250,563 participants. The RR of smoking cessation at 6 months is 1.44, ranging from 1.22 to 1.70 with a 6% background rate of quitting.[25]

Drug therapies are few and the data are limited mainly to bupropion and varenicline. Bupropion shows an effect on quitting with a RR of 1.64 (additional 6 quitters per 100 after 6 months compared with a nonpharmacological approach).[26] This effect seems less than with varenicline (RR of 0.71).[26] Psychiatric adverse events seem more frequent with bupropion than with placebo (RR, 1.25).[26] A combination of bupropion with NRT or with varenicline marginally appears

to enhance the quitting rate but the RRs are respectively 1.19 and 1.21, which are not significant.[27] In a network meta-analysis of 267 trials with 101,804 participants, varenicline and combination NRT (ie, combining 2 types of NRT such as patches, tablets, sprays, lozenges, and inhalers) vs placebo were most effective of all drug interventions (varenicline vs placebo odds ratio [OR], 2.88 [95% CI, 2.40-3.47]), accepting nausea as a frequent side effect. This translates to 1 extra quitter for 11 treated people.[28] Varenicline is similar to combination NRT (OR, 1.06 [95% CI, 0.75-1.48]), and superior to bupropion or single-use NRT, although each of these were superior to placebo (OR for bupropion vs placebo, 1.82 [95% CI, 1.60-2.06]) and NRT vs placebo (OR, 1.84 [95% CI, 1.71-1.99]).

More recently, nicotine EC have been advocated to reduce smoking addiction. The most recent Cochrane review that compared nicotine EC with NRT showed a positive effect of nicotine EC on quitting with a RR of 1.53 (95% CI, 1.21-1.93) resulting in additional 3 quitters per 100 after 6 months. This effect was higher when compared with behavioural support only/no support, with a RR of 2.61 (95% CI, 1.44-4.74) resulting in additional 6 quitters per 100.[29]

Among patients with PAD, a recent meta-analysis of 6 randomized trials involving 558 patients with PAD in which smoking interventions (behavioural counselling with or without NRT or a community intervention program promoting smoking reduction) were evaluated, suggested smoking cessation interventions increased the chance of quitting smoking (RR, 1.48 [95% CI, 0.84-2.61]),[30] although the wide CIs indicate a need for more RCTs. Furthermore, a high-quality trial of 124 patients with PAD included in this meta-analysis, in which intensive counselling with a minimum of 6 sessions was tested, was associated with a 2.97 (95% CI, 1.27-6.93) odds of smoking cessation, which was statistically significant.[31] Considering this, together with the positive effect of individual counselling, compared with usual care groups observed in a meta-analysis of smokers from the general population, which included 27 trials involving 11,100 people in which intensive counselling was effective at bringing about smoking cessation (RR, 1.57; 95% CI, 1.40-1.77), suggests this is an important and effective consideration for smoking cessation strategy for patients with PAD.[32]

RECOMMENDATION

7. We recommend smoking cessation to prevent PAD, and to prevent MACE and MALE in patients with PAD (Strong Recommendation; Moderate-Quality Evidence).
8. We recommend smoking cessation interventions ranging from intensive counselling, NRT, bupropion, varenicline, and sometimes nicotine EC (Strong Recommendation; High-Quality Evidence).

Values and preferences. Smoking is one of the most potent risk factors for PAD and is associated with MACE and MALE complications. Studies were selected irrespective of whether the effect of smoking and smoking cessation were specifically focused on PAD patients but also CAD and cardiovascular disease patients or all of these regrouped subpopulations. High value was given to any intervention that led to a significant reduction or cessation of smoking, although the success rate of any given intervention was low compared with treatment of hypertension and dyslipidemia. The value of smoking cessation is considered high not only because of its effect on vascular disease, but also because of the profound effect on preventing many cancers and chronic obstructive pulmonary disease.

Practical tip. Inquire at every clinical visit about the patient's smoking status, even if abstinence has been achieved, and offer behavioural support, and present therapeutic options for smoking reduction, and how to access them to patients, because smoking is a major risk factor for CAD and PAD and smoking reduction decreases the risk of MACE and MALE.

2.2. Glucose control, diabetes, and PAD

2.2.1. Glucose control and PAD

PICO 2.2a: Does tight glycemic control (hemoglobin A1c < 7%) reduce incidence of MALE or need for revascularization in patients with PAD?

Patients with concurrent diabetes and PAD have a three- to fourfold increase in mortality and have a rate of amputation that is 5 times higher than patients with PAD without diabetes.[33-35] Although promising, no clear association between strict hemoglobin A1c control and reduction in MACE, MALE, or death in patients with PAD has been reported.

RECOMMENDATION

9. We suggest that tight glycemic control might be beneficial for patients with PAD and diabetes in preventing MALE or need for revascularization (Weak Recommendation; Low-Quality Evidence).

2.2.2. Diabetes medications and PAD

PICO 2.2b: Do antihyperglycemic agents result in a reduction in MALE, revascularization, amputation, or MACE, in patients with PAD and diabetes?

The choice of antihyperglycemic agents in patients with PAD should be individualized to the patient's wishes, preferences, and financial support/drug coverage. However, diabetes medication should be chosen to provide the optimal CV protection and reduction in MALE.[36] Unfortunately, very few hypoglycemic medications have been studied in patients with PAD, although some have shown more promise than others.

Incretin-based selective inhibitors of dipeptidyl peptidase 4 (DPP-4) medications used in diabetes have not shown a reduction in MACE or MALE in PAD patients. However, a large observational trial of 82,169 patients who started receiving DPP-4 medication did show a 16% reduction in the development of PAD in patients with type 2 diabetes, and a subsequent 35% reduction in amputations among those with established PAD and type 2 diabetes.[37] This vascular

protection was only shown in patients receiving combination therapy with metformin. A recent observational study reported a reduction in adverse limb outcomes with glucagon-like peptide 1 (GLP-1) agonists or DPP-4 inhibitors.[38]

There is now a large body of evidence to support the use of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors in patients with PAD and diabetes, in reducing mortality and MACE, and also MALE. In **D**apagliflozin **E**ffect on **C**ardiovascu**l**ar **E**vents—**T**hrombolysis **i**n **M**yocardial **I**nfarction (DECLARE-TIMI), the effects of dapagliflozin was examined in 17,160 patients with diabetes of whom 1025 had concurrent PAD. Patients with PAD and diabetes had higher baseline risk of MACE, hospitalization for heart failure, progression of renal disease, and MALE compared with patients without PAD. The benefit of dapagliflozin in reducing MACE, MALE, and death was consistent regardless of PAD diagnosis in this population. Furthermore, there was no increased risk of adverse limb outcomes in patients with PAD and diabetes randomized to dapagliflozin.[39] In the **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) trial, canagliflozin was associated with an increased risk of amputation among patients with diabetes and PAD, but this has not been observed with other SGLT-2 inhibitors such as empagliflozin and dapagliflozin. Two large meta-analyses reported no overall significant increased risk of amputation with SGLT-2 inhibitors as a class, with the only signal coming from canagliflozin but not the other agents (eg, empagliflozin, dapagliflozin).[40,41]

RECOMMENDATION

10. We recommend that patients with PAD and type 2 diabetes should be offered a SGLT-2 inhibitor compared with usual diabetic control because of the reduction in MACE without any risk of increased amputation (Strong Recommendation; High-Quality Evidence).
11. We suggest that patients with PAD and diabetes might benefit from use of a GLP-1 agonist or DPP-4 inhibitor (Weak Recommendation; Low-Quality Evidence).

Practical tip. Presently, there is no reason to suspect that empagliflozin or dapagliflozin increase the risk of PAD or lower limb amputations. The risk, or lack of risk, associated with canagliflozin remains to be established.

2.3. Lipid-lowering and PAD

PICO 2.3a: In patients with PAD, what is the role of cholesterol-lowering with statins, ezetimibe, niacin, or resins compared with placebo for the reduction of death, CV death, nonfatal MI, nonfatal stroke, or MALE?

PICO 2.3b: In patients with PAD, what is the role of PCSK-9 inhibitors compared with use of statins with or without ezetimibe for the reduction of death, CV death, nonfatal MI, nonfatal stroke, or MALE?

Patients with PAD constitute a very high-risk subset of patients with atherosclerotic vascular disease. There is strong and high-quality evidence supporting aggressive lipid-lowering with statins to reduce overall and CV mortality as well as major adverse CV and cerebrovascular events. There is also strong evidence to support this intervention for the purpose of avoiding MALE. There is moderate-quality evidence that aggressive lipid-lowering might improve patient outcomes such as pain-free walking time and overall ambulatory ability. See section 2.3 of the Supplementary Material for further evidence and explanation.

PAD cohorts have been shown consistently to have high risk and high absolute event reductions with PCSK-9 inhibitors.[20] They benefit from significant event reductions, including adverse limb events, within 3 years, probably because of their far more substantial lipid-lowering compared with ezetimibe, and possibly because of additional benefit when lipoprotein(a) level is elevated. Patient outcomes such as pain-free walk time and overall ambulatory activity are not extensively studied but represent potential additional benefits that might promote acceptance and adherence to these lipid-lowering therapies.

Evidence for reduction of MALE or PAD patient-relevant outcomes is not yet available for icosapent ethyl. The additional use of this agent has been compared with placebo, not to additional use of ezetimibe or PCSK-9 inhibitors. Moreover, a decision to intensify lipid-lowering using the latter agents in patients receiving maximally tolerated statins might also affect triglycerides, thereby altering the criterion for consideration of icosapent ethyl, which is proven to reduce MACE in the absence of ezetimibe or PCSK-9 inhibitors. Accordingly, for the reduction of MACE, patient-physician decisions that accommodate patient preferences, priorities, and access issues will determine when it is appropriate to consider icosapent ethyl for the PAD patient. See section 2.3 of the Supplementary Material for further evidence and explanation.

RECOMMENDATION

12. We recommend that patients with PAD qualify as statin-indicated patients and should receive lipid-modifying therapy for the reduction of death, CV death, nonfatal MI, nonfatal stroke (MACE), and MALE concordant with the recommendations in the 2021 Canadian Cardiovascular Society (CCS) guidelines for the management of dyslipidemia[42] (Strong Recommendation; High-Quality Evidence).
    a. Maximally tolerated dose of statin therapy
    b. Statin add-on therapies (ezetimibe and/or PCSK-9 inhibitors) if receiving maximally tolerated dose of statin therapy and the low-density lipoprotein cholesterol is $\geq$ 1.8 mmol/L, non-high-density lipoprotein cholesterol $\geq$ 2.4 mmol/L or apolipoprotein B_{100} $\geq$ 0.7 mg/dL.
13. We recommend that patients with PAD, who, despite maximally tolerated dose of statin therapy have a triglyceride level of 1.5-5.6 mmol/L, should be considered for use of icosapent ethyl for the reduction CV death, nonfatal MI, and nonfatal stroke concordant with the

recommendations in the 2021 CCS guidelines for the management of dyslipidemia[42] (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. Statin add-on therapy and icosapent ethyl present numerous challenges with respect to cost and access for many patients. They also contribute to the burden of medications and complexity of therapy. Any decision to implement them should be made through open patient-physician discussion. Although not specifically validated in clinical trials, it is reasonable to approach the recommendations for statin add-on therapy in sequence with consideration of ezetimibe followed by PCSK-9 inhibitors if lipid thresholds are not met. But, as emphasized in the 2021 CCS guidelines for the management of dyslipidemia, patients whose levels are significantly above threshold in whom the typical reduction of low-density lipoprotein cholesterol by ezetimibe is not likely to achieve cholesterol levels below threshold might be served more effectively and efficiently by use of a PCSK-9 inhibitor as the add-on of choice while reserving ezetimibe if needed as a third, lipid-lowering agent.[42]

2.4. Hypertension

PICO 2.4a: How should hypertension be diagnosed in patients with lower extremity PAD*?*

Because patients with PAD are at high risk of CV events, hypertension diagnosis and treatment is important as a risk reduction strategy.

Most clinical studies that described the association between BP control and CV outcomes have used a 24-hour ambulatory BP monitoring (ABPM) assessment to establish a clinical diagnosis of hypertension.[43-45] Sequential home BP monitoring (HBPM) spaced throughout the day can be used as an alternative. The greater the number of recordings, the more accurately this reflects the true BP when averaged over multiple assessments.[46]

Out-of-office BP measurements have a better prognostic value compared with office-based assessments.[43,47] Moreover, 24-hour ABPM improves CV risk stratification compared with office-based BP assessments.[43,48] Hence, the Hypertension Canada 2020 guidelines advocate for a standardized protocol in which BP is measured at 20- to 30-minute intervals throughout the day.[44] If ABPM monitoring is unavailable or not tolerated, HBPM can be used as an alternative.

Hypertension can be diagnosed after multiple out-of-office assessments. Hypertension is diagnosed if the mean ambulatory daytime BP is $\geq$ 135/85 mm Hg, or if the 24-hour mean BP is $\geq$ 130/80 mm Hg (Fig. 3).

Patients with PAD are at an elevated risk of future vascular events, and a target of $\geq$ 140/90 mm Hg should be considered as the treatment threshold.[49]

PICO 2.4b: In patients with PAD without an indication for a specific antihypertensive agent, what is the ideal BP target?

Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and CV death.[50,51]

There are no large-scale RCTs that specifically assessed BP targets in patients with lower extremity PAD.

In a subgroup of patients with PAD from the **S**ystolic Blood **Pr**essure **In**tervention **T**rial (SPRINT),[52] intensive BP lowering to a systolic BP target < 120 mm Hg was associated with a reduction in the primary outcome of CV death and all-cause mortality. Because of the higher baseline risk among patients with PAD, the absolute risk reduction was larger in patients with PAD compared with those without PAD. However, intensive BP control also led to a greater absolute increased risk of adverse events in patients with PAD.

RECOMMENDATION

14. We suggest favouring HBPM measurement or a 24-hour ABPM over office BP measurement for diagnosis and management of hypertension in patients with PAD. If there is a difference in BP measurements between arms, the higher value should be used for diagnosis and treatment considerations (Weak Recommendation; Low-Quality Evidence).
15. We suggest that the approach to initiation and titration of antihypertensive agents should follow the Hypertension Canada guidelines[44] (Weak Recommendation; Low-Quality Evidence).
16. We suggest treating hypertension to a target of less than 140/90 mm Hg in patients with PAD without compelling indications for specific agents or targets (Weak Recommendation; Low-Quality Evidence).

Practical tip. In select patients, intensive systolic BP targets (< 120 mm Hg) might be considered. However, we suggest that caution be exercised if systolic BP is < 110 mm Hg because this is associated with an increase rate of adverse events (eg, MACE and MALE) in patients with PAD.

PICO 2.4c: In patients with PAD without an indication for a specific antihypertensive agent, what is the preferred approach to achieve optimal BP control?

Optimal hypertension management requires a holistic approach. Lifestyle modifications and pharmacological agents are the mainstay of treatment.

2.4.1. Lifestyle modification

Diet, exercise, weight management, alcohol reduction, stress management, and self-monitoring play an important role in managing BP. See Supplemental Table S1 for targets.

2.4.2. Pharmacological

Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium antagonists, and diuretics are all suited for BP-lowering treatment in patients with PAD[53,54]; see Figure 4, from Hypertension Canada.

In the absence of contraindications, we recommend that patients with PAD and hypertension be treated with ACE

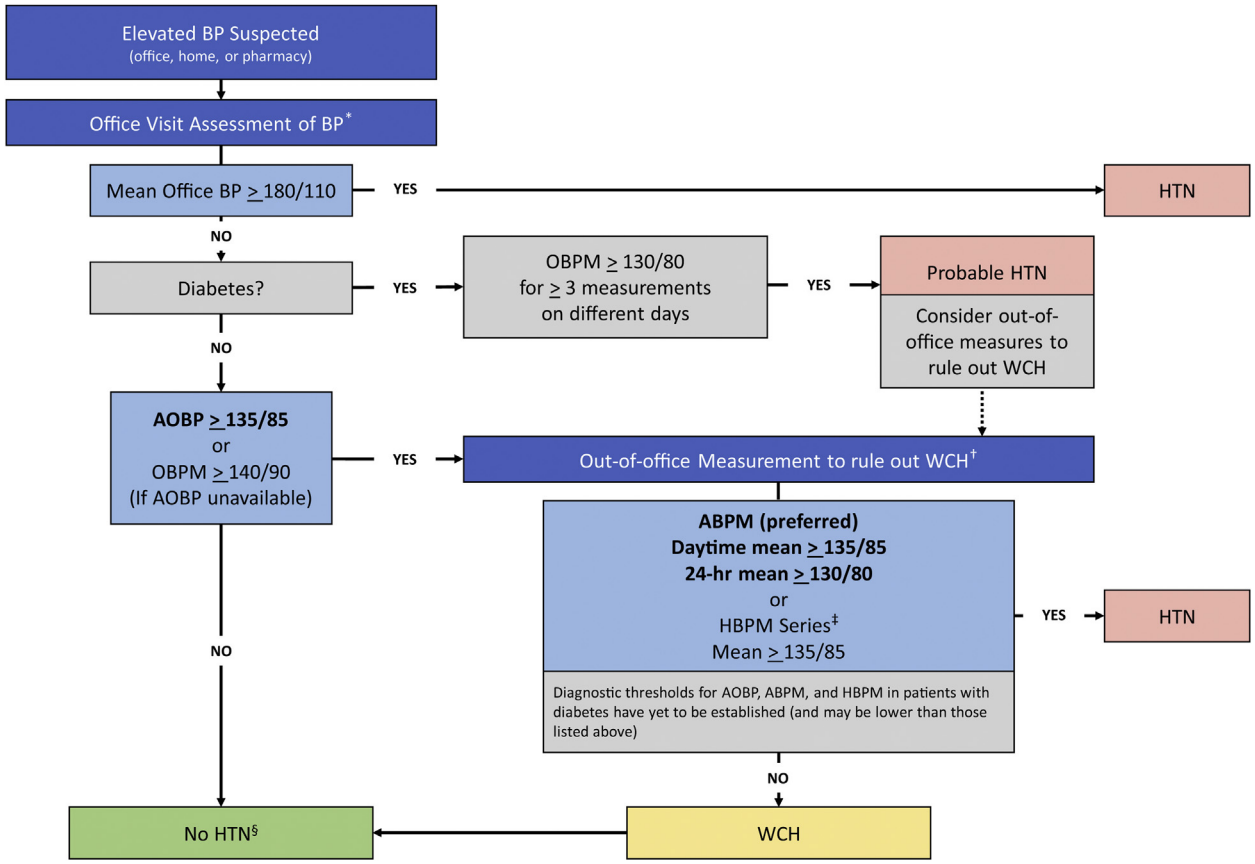

Figure 3. Diagnostic algorithm for hypertension as per the Hypertension Canada guidelines.[44] All measurement values in the algorithm are reported as mm Hg. * If AOBP is used, use the mean calculated and displayed by the device. If OBPM is used, take at least 3 readings, discard the first and calculate the mean of the remaining measurements. A history and physical exam should be performed and diagnostic tests ordered. † Serial office measurements over 3-5 visits can be used if ABPM or HBPM are not available. ‡ Home BP series: 2 readings are taken each morning and evening for 7 days (28 total). Discard first-day readings and average the last 6 days' readings. § In patients with suspected masked HTN, ABPM or HBPM could be considered to rule out masked HTN. ABPM, ambulatory blood pressure monitoring; AOBP, automated office blood pressure; BP, blood pressure; HBPM, home blood pressure monitoring; HTN, hypertension; OBPM, office blood pressure measurement; WCH, white coat hypertension. Reproduced from Rabi et al.[44] with permission from Elsevier.

inhibitors or ARBs as first choice agents. ACE inhibitors and ARBs have been shown to reduce MACE in patients with arterial peripheral vascular diseases.[55] ACE inhibitor or ARB use is also associated with reduced MACE among patients with critical limb ischemia.[56]

Most patients with hypertension require multiple agents for optimal BP control. Use of combination pills therapy improves adherence, BP, and CV outcomes compared with usual pharmacological care.[55,57]

RECOMMENDATION

17. We recommend that PAD patients with hypertension be treated with ACE inhibitors or ARBs as the first choice in the absence of contraindications (Strong Recommendation; Moderate-Quality Evidence).

2.4.3. Special considerations in PAD patients

As mentioned previously, in the SPRINT trial, aggressive BP control among patients with PAD was associated with an increased risk of the primary outcome, CV death, and all-cause mortality compared with patients without PAD. As such, the optimal target is likely between 120 mm Hg and 140 mm Hg.

A theoretical risk exists with the use of β-blockers in patients with limb ischemia. Previous guidelines have suggested avoiding the use of β-blockers in those with severe PAD. However, large systematic reviews on the topic have not shown increased harm with the use of β-blockers among patients with PAD. As such, they are not contraindicated and might be useful in PAD patients with concomitant CV disorders, where they are indicated as a second-line option.[59,60]

2.5. Antithrombotic therapy

A substantial amount of evidence has emerged since the 2005 Canadian Cardiovascular Congress Consensus

Conference for the management of PAD. The advent of newer thienopyridines and direct oral anticoagulants (DOACs), as well as their investigation within atherosclerotic PAD, has vastly expanded the tools available to practitioners. This has come with a concomitant shift in the understanding of the pathophysiology of lower extremity PAD. A large proportion of severe vascular occlusions are mediated by thrombotic occlusive disease, even in the absence of major atherosclerotic lesions, reframing PAD as a condition of "athero-thrombo-embolism" and informing the choice of antithrombotics investigated and used clinically.

Lower extremity PAD is continually appreciated as but 1 manifestation of systemic atherosclerosis. As such, the efficacy of antithrombotics in lower extremity PAD are evaluated according to MACE and MALE outcomes. The benefit of antithrombotics in lower extremity PAD in conferring global vascular protection must be weighed against the risk of major and/or fatal bleeding.

2.5.1. Asymptomatic lower extremity PAD

PICO 2.5a: In adult patients with asymptomatic PAD does a single antiplatelet agent compared with placebo affect rates of MACE, MALE, or bleeding?

Patients with a low ABI, but without clinical limb symptoms or previous vascular intervention, are considered to have asymptomatic lower extremity PAD.

RECOMMENDATION

18. We recommend **against** routine antithrombotic therapy (antiplatelet or anticoagulant) for patients with isolated asymptomatic lower extremity PAD (Strong Recommendation; High-Quality Evidence).

Practical tip. Atypical symptoms are common for lower extremity PAD, making a directed history (and consideration for noninvasive imaging when appropriate) essential for PAD classification.

Practical tip. Patients with asymptomatic lower extremity PAD often have atherosclerotic coronary artery or cerebrovascular disease, and might merit antithrombotic therapy for these indications.

2.5.2. Stable symptomatic lower extremity PAD

PICO 2.5b: In adult patients with stable symptomatic lower extremity PAD (no recent or imminent revascularization), what is the optimal antithrombotic therapy considering the outcomes of MACE, MALE, or bleeding?

Patients with intermittent claudication, without recent (< 6 months) endovascular or surgical peripheral artery revascularization, and without acute symptoms of rest pain or tissue loss, are considered to have stable lower extremity PAD. Although single antiplatelet therapy has been the mainstay of antithrombotic therapy for symptomatic PAD patients,[61,62] recent large trials that have tested low-dose DOACs together with aspirin have provided important new evidence.[63,64]

RECOMMENDATION

19. We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for management of patients with symptomatic lower extremity PAD who are at high risk for ischemic events (high-risk comorbidities such as polyvascular disease, diabetes, history of heart failure, or renal insufficiency) and/or high-risk limb presentation post peripheral revascularization, limb amputation, rest pain, ischemic ulcers) and at low bleeding risk (Strong Recommendation; High-Quality Evidence).
20. We recommend combination treatment with rivaroxaban 2.5 mg twice daily and aspirin or single antiplatelet therapy for patients with symptomatic lower extremity PAD and low bleeding risk in the absence of high-risk limb presentation or high-risk comorbidities (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places high value on the overall **C**ardiovascular **O**utco**m**es for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial findings, which showed a significant net clinical benefit with combination low-dose rivaroxaban and aspirin among a heterogenous patient population with PAD. Patients who place a high value on minimizing ischemic risk, such as MI, stroke, acute limb ischemia, or major vascular amputation, might opt for rivaroxaban 2.5 mg twice daily in combination with aspirin. Patients who place a high value on bleeding avoidance and minimizing pill burden might opt for single antiplatelet therapy alone.

Practical tip. Rivaroxaban 2.5 mg twice daily in combination with aspirin should be avoided in patients with strong cytochrome P450 family 3 subfamily A member 4 (CYP3A4) or p-glycoprotein medication interactions, those with recent stroke (< 1 month,) any previous hemorrhagic stroke, and with an estimated glomerular filtration rate < 15 mL/min. Although patients with severe heart failure (New York Heart Association classification III-IV or left ventricular ejection fraction < 30%) were excluded from the COMPASS trial, it might be reasonable to use rivaroxaban 2.5 mg twice daily in combination with aspirin, if otherwise indicated, and alternative etiologies for arterial occlusive disease have been excluded.

Practical tip. At this time, the combination of rivaroxaban 2.5 mg twice daily and aspirin is not considered to be sufficiently equivalent to anticoagulation for management of atrial fibrillation or acute venous thrombosis. Optimal antithrombotic choices for these conditions can be found in the 2020 CCS/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation and the Thrombosis Canada clinical guides, respectively.[65,66]

RECOMMENDATION

21. We recommend single antiplatelet therapy with either aspirin (75-325 mg) or clopidogrel (75 mg) be considered for patients with symptomatic lower extremity PAD at high bleeding risk who remain eligible for antithrombotic therapy (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a high value on the reduction of vascular events despite elevated bleeding risk. Patients at extremely high bleeding risk might not tolerate single antiplatelet therapy alone and might best be served by no antithrombotic therapy, particularly if vascular risk is low.

RECOMMENDATION

22. We suggest that clopidogrel (75 mg daily)[61] should be the preferred agent when single antiplatelet therapy is deemed to be the optimal antithrombotic choice (Weak Recommendation; Moderate-Quality Evidence).
23. We suggest that dual antiplatelet therapy (DAPT; aspirin and clopidogrel or aspirin and ticagrelor) be used for patients with symptomatic lower extremity PAD at high risk for vascular events, at low bleeding risk, and who have contraindications to rivaroxaban (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places greater weight on prevention of ischemic events (particularly coronary events) than on the risk of bleeding. The combination of ticagrelor and aspirin likely has greater ischemic benefit yet higher bleeding risk as contrasted with the combination of clopidogrel and aspirin, with choice of therapy directed by individual patient profile and preferences.

Practical tip. Patients with recent (< 1 year) coronary revascularization and stable lower extremity PAD should have the choice of antithrombotic therapy guided by the 2018 CCS/Canadian Association of Interventional Cardiology focused update on the guidelines for the use of antiplatelet therapy,[67] although patients with symptomatic lower extremity PAD should merit particular consideration for ticagrelor and aspirin in combination.

RECOMMENDATION

24. We recommend **against** the additional use of full-dose anticoagulation with antiplatelet therapy for the purpose of decreasing MACE and MALE events in patients with stable lower extremity PAD (Strong Recommendation; High-Quality Evidence).

Practical tip. Vascular and bleeding risk are not static and should be regularly reevaluated by primary care and vascular care practitioners, with dynamic adjustment of antithrombotic therapy as appropriate.

Practical tip. Patients with stable lower extremity PAD who require full-dose anticoagulation for nonvascular indications might not require antiplatelet therapy. Although not robustly evaluated within the lower extremity PAD literature, analogous patients with stable CAD (no CV events in > 1 year) who required full-dose anticoagulation experienced harm with the additional use of an antiplatelet agent with anticoagulation.[68]

2.5.3. Therapy after elective lower extremity revascularization

2.5.3.1. Endovascular revascularization

PICO 2.5c: In adult patients who undergo elective endovascular revascularization for lower extremity PAD, what is the optimal antithrombotic therapy to prevent MACE, MALE, bleeding, or need for repeat intervention, in the early postoperative period (within 12 months)?

The Antithrombotic Trialists' Collaboration reported a numerical but not statistically significant reduction in MACE associated with single antiplatelet therapy vs placebo (odds reduction, 29%) after peripheral angioplasty.[69] A subsequent Cochrane review identified 2 small trials that compared aspirin and dipyridamole, respectively, vs placebo after endovascular revascularization, with pooled analysis showing a similar nonsignificant result for lesion patency at 6 months.[70]

In the Management of Peripheral Arterial Interventions with Mono or Dual Antiplatelet Therapy (MIRROR) trial, DAPT using aspirin and clopidogrel was compared with aspirin alone in 80 patients after endovascular lower extremity revascularization. DAPT improved target lesion revascularization rates at 6 months (5% vs 8%; $P = 0.04$) but not at 1 year.[25] Despite the lack of robust RCT data, DAPT after endovascular stenting is often extrapolated from the CV literature and mandated in trials investigating varying endovascular options.[71]

Two small trials (n = 160 and n = 167, respectively) that compared full-dose oral anticoagulation with DAPT after endovascular revascularization showed no significant difference in lesion patency with increased bleeding events.[72,73] Both trials were significantly underpowered with respect to their primary end point.

Literature from patients who required full-dose anticoagulation and coronary artery stenting has shown full oral anticoagulant (OAC) in combination with single antiplatelet therapy can be an optimal strategy in select groups of patients.[74-77] Although less robust evidence exists after lower extremity stenting, the pilot **E**doxaban in **P**eripheral **A**rterial **D**isease (ePAD) trial showed no significant difference in restenosis/reocclusion with edoxaban 60 mg compared with clopidogrel, largely on the background of aspirin therapy.[78]

In the **V**ascular **O**utcomes Stud**y** of **A**SA [Acetylsalicylic Acid] Alon**g** with Rivaroxaban in **E**ndovascular or Surgical Limb **R**evascularization for **PAD** (VOYAGER PAD) trial outlined in the following section, two-thirds of the patient

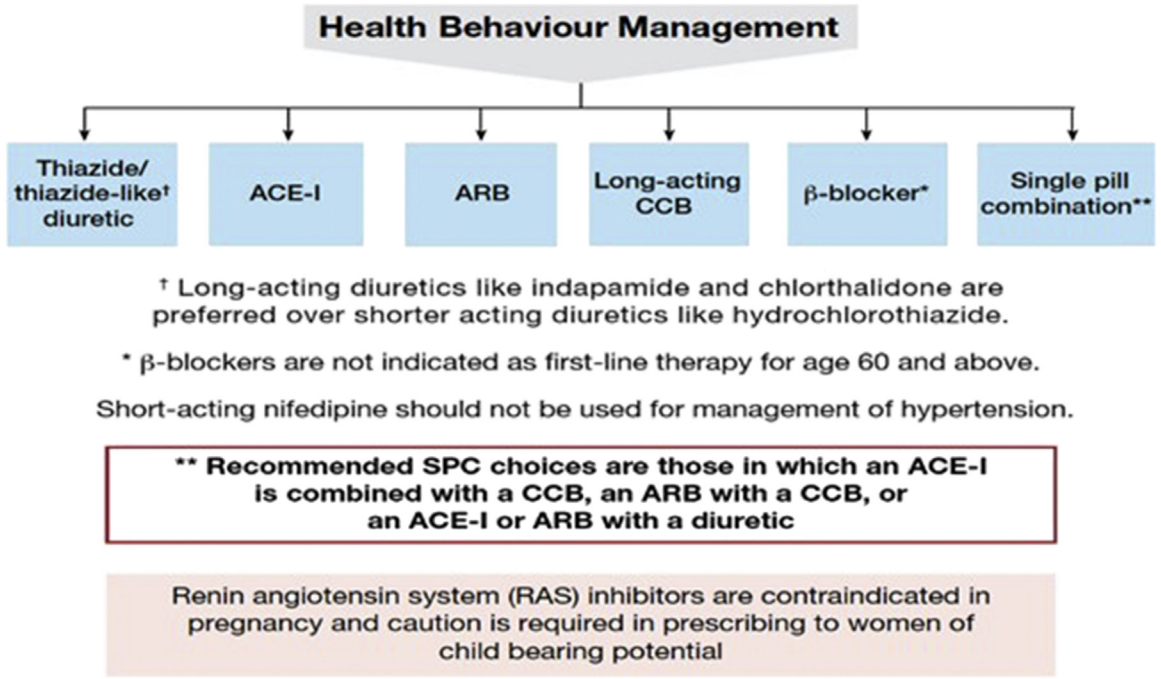

Figure 4. Treatment options for patients with hypertension without a compelling indication for a specific agent as per the Hypertension Canada guidelines.[58] ACE-I, angiotensin-converting enCzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; SPC, single pill combination. Reprinted with permission from Hypertension Canada.

population underwent endovascular intervention, making this the largest such trial conducted to date.[79]

2.5.3.2. Open revascularization

After infrainguinal arterial bypass surgery, a meta-analysis showed improved graft patency with aspirin, with or without dipyridamole (OR, 0.42; 95% CI, 0.22-0.83).[80] Data for alternative antiplatelet regimens are limited. In the **C**lopidogrel and **A**cetylsalicylic Acid in Bypass **S**urgery for **P**eripheral **A**rte**r**ial Disease (CASPAR) trial, clopidogrel and aspirin in combination vs aspirin alone was assessed in patients who underwent infrainguinal bypass surgery, and although no effect on MALE was seen in the overall population, a significant reduction was observed in a subgroup of patients who received prosthetic bypass grafts (hazard ratio [HR], 0.65; 95% CI, 0.45-0.95).[81]

The 2 largest trials in open revascularization include the **Dutch B**ypass, **O**ral Anticoagulants or **A**spirin (Dutch BOA) and VOYAGER PAD trial.[63,82]

Treatment with vitamin K antagonist (VKA) monotherapy (international normalized ratio, 3.0-4.5) compared with aspirin monotherapy did not significantly decrease graft occlusion or MACE, and significantly increased major bleeding (HR, 1.96; 95% CI, 1.42-2.71), in the overall Dutch BOA trial.[82] Subgroup analysis did, however, show improved patency with VKA in venous conduit bypass (HR, 0.69; 95% CI, 0.54-0.88), and with acetylsalicylic acid in nonvenous conduit grafts (HR, 1.26; 95% CI, 1.03-1.55).[82] Multiple smaller trials have assessed oral anticoagulation with single antiplatelet therapy vs single antiplatelet therapy or DAPT and have shown mixed results. The largest of these studies showed increased mortality with the combination of OAC and acetylsalicylic acid without improved graft patency.[83-85]

The VOYAGER PAD trial randomized patients after endovascular or open revascularization to combination therapy with rivaroxaban 2.5 mg twice daily and aspirin or aspirin alone, with the option to additionally use clopidogrel up to a maximum of 6 months at the treating physicians' discretion.[79] Compared with aspirin alone, the combination of rivaroxaban and aspirin reduced composite MACE and MALE events (HR, 0.85; 95% CI, 0.76-0.96), driven largely by a significant reduction in acute limb ischemia (HR, 0.67; 95% CI, 0.55-0.82).[79] Although there was no significant difference in the primary safety outcome of **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) major bleeding, the secondary safety outcome of the International Society on Thrombosis and Haemostasis major bleeding was increased (HR, 1.42; 95% CI, 1.10-1.84), albeit without significant increases in intracranial or fatal bleeding.[79] There was no significant heterogeneity in primary efficacy or bleeding outcomes on the basis of an open or endovascular approach.[79] Notably, most revascularization procedures were performed for the indication of worsening claudication (76.6%), and up to one-third of patients had critical limb ischemia.[79]

Approximately 50% of the VOYAGER trial participants were given clopidogrel. The mean duration of clopidogrel use was 30 days, and the use of concomitant clopidogrel after revascularization did not alter the efficacy of rivaroxaban and aspirin compared with aspirin alone in reducing MACE or MALE events (P for interaction = 0.92), nor rates of acute limb ischemia (P for interaction = 0.93).[86] This was consistent for open and endovascular procedures. However, in those with longer courses of clopidogrel there was a trend toward increased major bleeding. More than 30 days of clopidogrel use came with a 2.71% absolute risk increase of major

bleeding (HR, 3.20; 95% CI, 1.44-7.13), whereas < 30 days of clopidogrel conferred a 0.46% absolute risk increase of major bleeding (HR, 1.30; 95% CI, 0.68-2.47; *P* for interaction = 0.07).[86]

RECOMMENDATION

25. We recommend rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily), with or without short-term clopidogrel use, for patients with lower extremity PAD after elective endovascular revascularization (Strong Recommendation; Moderate-Quality Evidence).
26. We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for patients with lower extremity PAD after elective open revascularization (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places high value on a single large well constructed RCT as opposed to multiple smaller low-quality studies. This recommendation also places high value on minimizing ischemic risk in the setting of acceptable increases to overall bleeding risk.

Practical tip. The additional use of clopidogrel (75 mg daily) with rivaroxaban 2.5 mg twice daily and aspirin (80-100 mg daily) can be considered in patients who undergo complex endovascular stenting. Should clopidogrel be used, it should be continued for a maximum of 30 days in the absence of other indications.

Practical tip. Rivaroxaban 2.5 mg twice daily in combination with aspirin should be avoided in patients with strong CYP3A4 or p-glycoprotein medication interactions, stroke within 1 month, any previous hemorrhagic stroke, or estimated glomerular filtration rate < 15 mL/min.

Practical tip. Patients who start treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin after revascularization should preferably continue this therapy long-term in the absence of bleeding or ischemic manifestations, because previous revascularization represents a high-risk limb presentation for patients with stable lower extremity PAD.

RECOMMENDATION

27. We suggest DAPT with aspirin (75-325 mg) and clopidogrel (75 mg) for at least 1 month in patients with lower extremity PAD after elective endovascular revascularization who are unable to receive low-dose rivaroxaban (Weak Recommendation; Very Low-Quality Evidence).

Values and preferences. This recommendation places high value on expert opinion and indirect extrapolation from the CAD literature. Direct evaluation of DAPT after endovascular revascularization remains limited.

Practical tip. Duration of DAPT might be affected by procedural factors such as use and complexity of stenting, as well as patient factors such as global ischemic and bleeding risk. It should be noted that the effect of stenting complexity or technology of drug-eluting stents (DES) on antithrombotic effect remains minimally studied.

RECOMMENDATION

28. We suggest either a VKA or single antiplatelet therapy for patients with lower extremity PAD after elective open revascularization who are unable to receive low dose rivaroxaban (Weak Recommendation; Very Low-Quality Evidence).

Values and preferences. This recommendation places greater value on overall trial results as opposed to discrepant results within patient subgroups. This recommendation is made acknowledging that robust evidence is not available to guide when VKA or single antiplatelet therapy would be of greater ischemic benefit, yet VKA therapy comes with a notably increased bleeding risk compared with single antiplatelet therapy. Therefore, this recommendation places a high value on expert opinion and intraoperative surgical decision-making for determining the optimal antithrombotic regimen in this scenario.

Practical tip. VKA might be particularly considered for patients who receive infrainguinal bypass using an autologous vein conduit with high-risk features including poor quality conduit, long conduit, disadvantaged distal runoff, or previous failed open revascularization.

Practical tip. Full-dose DOAC therapy has not been studied in the setting of open peripheral revascularization. However, in high-risk patients deemed unsuitable for VKA therapy, full-dose DOAC may be considered as an alternative therapy.

2.5.4. Therapy after urgent/emergent lower extremity revascularization

PICO 2.5d: What is the optimal antithrombotic therapy among adult patients who undergo urgent or emergent revascularization (of any kind) for lower extremity PAD considering the outcomes of MACE, MALE, bleeding, or need for repeat intervention?

Limited comparative data exist to assess antithrombotic regimens in patients who require urgent or emergent revascularization despite their elevated risk of recurrent ischemic events and overall mortality.

RECOMMENDATION

29. We suggest any of: (1) full-dose anticoagulation in combination with single antiplatelet therapy; (2) rivaroxaban 2.5 mg twice daily in combination with

aspirin, with or without short-term use of clopidogrel; or (3) DAPT for patients with lower extremity PAD after urgent or emergent revascularization (Weak Recommendation; Very Low-Quality Evidence).

Values and preferences. This recommendation acknowledges the lack of high-quality data informing antithrombotic treatment after urgent or emergent lower extremity revascularization and the noted heterogeneity in practice.[46]

Practical tip. Evaluation of the risk of re-thrombosis after urgent or emergent lower extremity revascularization should take into consideration the surgical procedure performed (ie, embolectomy or thrombectomy, bypass vs stenting), intraoperative findings (ie, residual distal occlusive disease, length and quality of conduit, infrapopliteal placement of conduit), as well as patient characteristics (ie, previous failed revascularizations, bleeding risk).[87] For patients deemed high-risk for re-thrombosis and low-risk for bleeding, full-dose anticoagulation in combination with single antiplatelet therapy should be particularly considered.

Practical tip. In patients who require urgent or emergent lower extremity revascularization because of acute limb ischemia, care should be taken to rule out non-atherothromboembolic causes of limb ischemia, such as but not limited to cardioembolic cause, to inform the optimal antithrombotic therapy.

2.6. Exercise therapy for intermittent claudication

PICO 2.6: Among patients with PAD who have intermittent claudication, is supervised exercise, home, or community-based exercise therapy more efficacious than usual care, on outcomes of: total walking time and distance, claudication, need for revascularization, and quality of life?

Leg pain during activity is a major determinant of functional capacity among patients with PAD, negatively affecting their ability to perform activities of daily living and their quality of life. Thus, addressing functional impairment is crucial in the management of PAD patients with noncritical leg symptoms. A robust body of data support medical interventions aimed to improve walking and quality of life in patients with PAD. Because cilostazol is not yet available in Canada, and other potential medical interventions such as pentoxifylline, carnitine, propionyl-L carnitine, and chelation therapy have not been recommended in recent US[88] and European[89] guidelines because of lack of benefit or insufficient, potentially biased data, this section focuses on exercise therapy for the management of PAD patients with intermittent claudication.

RECOMMENDATION

30. We recommend supervised exercise programs as first-line therapy for patients with PAD and intermittent claudication, with the objective of improving maximal and pain-free walking distance and time, as well as quality of life (Strong Recommendation; High-Quality Evidence).
31. We recommend that a structured home-based or community exercise program can be offered to improve leg symptoms and quality of life when supervised exercise programs are not available, or not desired by the patient (Strong Recommendation; High-Quality Evidence).
32. We recommend that walking should be the preferred form of exercise in exercise programs for intermittent claudication (Strong Recommendation; High-Quality Evidence).
33. We suggest that, in patients with intermittent claudication who are unable to pursue walking exercise therapy, other forms of exercise such as cycle ergometer, arm ergometer, pole-striding, Nordic walking, or dynamic leg exercises can also be beneficial to improve leg symptoms (Weak Recommendation; Moderate-Quality Evidence).
34. We suggest that resistance training can be used in addition to, but not substitute, walking therapy in exercise programs for patients with intermittent claudication (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. High value is placed on a robust body of evidence that supports exercise therapy as first-line for improvement of walking, claudicant leg symptoms, and quality of life in patients with PAD. Preference is given to supervised exercise therapies that use walking as the primary form of exercise, but emerging evidence also supports home-based or community-based exercise as long as structure and guidance are provided throughout the duration of the program, as well as other forms of exercise when walking cannot be achieved or is not desirable.

Practical tip. Exercise habits should be asked at every visit with a health practitioner.

Practical tip. Every patient with intermittent claudication should be referred to a supervised exercise rehabilitation program tailored to individuals with PAD, when available. When such a program is not locally available, structured guidance for home-based exercise should be provided by clinicians.

Practical tip. Structured exercise guidance, either supervised or home or community-based, should include a minimum of 2 weekly sessions of at least 30 minutes duration, and be pursued for a minimum of 12 weeks of therapy.

Practical tip. The authors acknowledge the lack of uniformity in exercise protocols for intermittent claudication. On the basis of our experience administering exercise therapy for PAD, patients are encouraged to walk on the treadmill or track for 8- to 9-minute bouts, with speed and/or incline sufficient to cause 3-4 of 5 claudicant pain toward the end of the 8- to 9-minute interval. Patients then rest until pain dissipates, and then resume a new bout of walking, repeating the cycles until 3 bouts are complete. Over the course of the program, walking

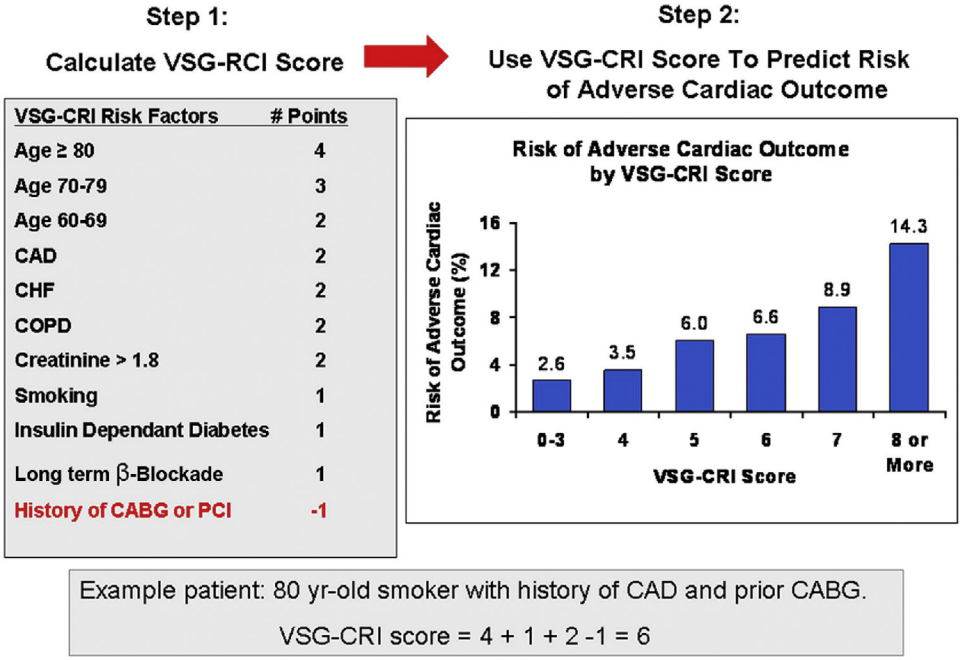

Figure 5. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) score. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention. Reproduced from Bertges et al.[91] with permission from Elsevier.

speed and/or incline is adjusted by the therapist to continue achieving the aforementioned parameters.

Practical tip. After patients complete the exercise program, they should be encouraged to continue walking for at least 30 minutes a day, at least 3 times a week, to maintain the walking and quality of life benefits gained during exercise therapy.

3. Revascularization Procedures for PAD

3.1. Preoperative assessment and risk stratification

3.1.1. Guideline rationale, development, and over-riding principles

Since the publication of the 2017 CCS guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery,[90] new evidence has emerged for evaluating clinical risk indices specific to patients who undergo peripheral vascular surgery. The scope of this section includes the evaluation of available evidence for preoperative assessment and risk stratification of patients who undergo nonurgent vascular surgery for PAD along the following themes: clinical risk indices, cardiac biomarkers, and noninvasive testing.

The recommendations pertain to adult patients, 18 years of age or older, who undergo elective open or endovascular arterial revascularization procedures of the lower extremities.

Patients who require emergency lower extremity arterial revascularization should not have their surgery delayed by a preoperative risk assessment. The risks to life or limb that could result from a delay in surgery are often greater than the risks of not assessing and subsequently optimizing a patient's preoperative cardiac status. However, operative risks must be explained to the patient and their family.

Conversely, patients who undergo scheduled, nonemergency lower extremity arterial revascularization surgery should undergo cardiac risk assessment.

Physicians or surgeons with training and competency in cardiac risk assessment should perform preoperative assessments.

Table 4. Modified Frailty Index (mFI)[97]

Variable	NSQIP categories	Yes = 1; no = 0
Functional and cognitive impairment	• Preoperative functional health status • Impaired sensorium	
Comorbidities	• Diabetes mellitus • History of COPD • Current pneumonia • Congestive heart failure ≤ 30 days before surgery • History of angina ≤ 1 month before surgery • Hypertension requiring medication • History of transient ischemic attacks • Cerebrovascular accident or stroke with neurologic deficit • History of revascularization or amputation for peripheral vascular disease • Rest pain or gangrene	
Total item score		

mFI is calculated as (total item score)/11.

COPD, chronic obstructive pulmonary disease; NSQIP, National Surgical Quality Improvement Program.

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3.1.2. Risk tools

PICO 3.1a: Which risk tool(s) best predict(s) perioperative CV risk and mortality?

Individuals who undergo surgery for PAD have a higher preoperative CV risk compared with other noncardiac surgeries. Various tools have been developed and evaluated to predict the perioperative risk of vascular surgery patients. Tools that included preoperative components only were considered. The following were examined: the **V**ascular **S**tudy **G**roup of New England **C**ardiac **R**isk **I**ndex (VSG-CRI), the **V**ascular **Q**uality **I**nitiative **C**ardiac **R**isk **I**ndex (VQI-CRI), and frailty scores (single domain and multidomain). The evidence for **R**evised **C**ardiac **R**isk **I**ndex (RCRI) was also reassessed with a focus on PAD to determine whether its predictive value differs compared with a heterogenous pool of noncardiac surgeries. The summary of the findings and GRADE Evidence Profile for the 3 clinical risk scores are available on ccs.ca.

RCRI. For vascular surgery, RCRI consistently underestimated the risk of MACE with poor discriminatory ability with the median area under the curve of 0.64 (range, 0.58-0.70; see ccs.ca for table). A number of serious limitations were identified in these studies, and the resulting bias would have been expected to falsely amplify the ability of RCRI to predict MACE. However, despite these limitations, RCRI still had poor prediction even in the largest study with subgroup analysis of lower extremity bypass.

VSG-CRI risk tool. This is a simple scoring algorithm that was derived from a vascular surgery cohort; the Vascular Study Group of New England. It was developed by assigning weighted points to each statistically significant predictor from a multivariate analysis and stratified patients prepared to undergo vascular surgery into 1 of 6 risk categories (0-3, 4, 5, 6, 7, 8) and predicted risk of MACE (2.2%, 3.5%, 6%, 6.6%, 8.9%, 14.3%), respectively. MACE were defined as in-hospital MI, clinically significant arrhythmia, or congestive heart failure (Fig. 5).

INFRA VQI-CRI risk score. This risk score was developed from the Vascular Quality Initiative, the largest vascular surgery-specific database assembled to date representing data from the United States and Canada.[92] An all-procedure model and procedure-specific models were developed (eg, **I**nfrainguinal [INFRA] VQI-CRI for infrainguinal bypass procedures) to predict postoperative MI. The risk tools are freely available online and can be downloaded for offline use through the app, Calculate by QxMD, at https://qxmd.com/calculate/calculator_323/vascular-quality-initiative-vqi-cardiac-risk-index-cri-infra-inguinal-bypass.

Frailty scores. The following tools were examined: single-domain (**m**odified **F**railty **I**ndex [mFI], and the **G**roningen **F**railty **I**ndicator [GFI]).[93-96] Functional dependency is classified as independent if no assistance is needed and dependent if there is some or full dependency for functions. The mFI comprises 11 items, of which 9 are comorbidities, along with measures of functional dependency and cognition variables. The score is calculated by adding 1 point for the presence of each variable, then dividing the sum by 11 (Table 4). Frailty is defined as mFI $\geq$ 0.25.

The GFI includes 16 items organized into 8 different groups. This tool would require further validation studies in peripheral arterial surgery before developing a recommendation regarding its use.

Other prediction tools such as **V**ascular-**P**hysiological and **O**perative **S**everity **S**core for the En**u**meration of **M**ortality and Morbidity (V-POSSUM) (with only preoperative components), **P**re**o**perative **S**core to Predict **P**ost**o**perative **M**ortality (POSPOM), and modified RCRI, were considered but studies of those prediction tools were small, of low quality, and lacked validation using large databases.[98-100]

RECOMMENDATION

35. We recommend **against** using RCRI for preoperative assessment of cardiac risk in peripheral arterial surgery (Strong Recommendation; Moderate-Quality Evidence). Alternate options include the VSG-CRI and INFRA VQI-CRI (see the following recommendations).
36. When evaluating cardiac risk:
    a) We suggest that clinicians use the VSG-CRI to predict MACE in patients who undergo peripheral vascular surgery (Weak Recommendation; Low-Quality Evidence); or
    b) We suggest that clinicians use the INFRA VQI-CRI score to predict postoperative MI in patients who receive peripheral vascular surgery (Weak Recommendation; Low-Quality Evidence).
37. We recommend **against** using the RCRI for preoperative assessment of 30-day mortality in peripheral arterial surgery (Strong Recommendation; Low-Quality Evidence) and alternatively suggest using frailty scores (functional dependency or mFI) over other available risk prediction scores for 30-day mortality assessment (Weak Recommendation; Low-Quality Evidence for functional dependency; Moderate-Quality Evidence for mFI).

Values and preferences. Higher preference and value are given to tools that are readily available and are quick to complete in the context of preoperative care clinics. Preference was also given to tools derived directly from the population of interest (ie, infrainguinal revascularization) because of data that support more reliable prediction than those developed from heterogenous surgical populations.

Practical tip. Although a single risk tool to assess the risk of cardiac events and 30-day mortality would be clinically useful, such a tool was not identified in the current literature search. For 30-day mortality risk assessment, frailty scores are suggested, and for cardiac risk assessment the VSG-CRI or INFRA VQI-CRI are suggested. An online and free calculator is available to assist clinicians with using the INFRA VQI-CRI risk score for postoperative MI prediction.

3.1.3. Cardiac biomarkers

PICO 3.1b: What is the role of preoperative cardiac biomarkers in risk prediction?

Cardiac biomarkers have been shown to help predict MACE in vascular surgery.[101] Brain natriuretic peptide (BNP) and N-terminal fragment pro hormone BNP (NT-proBNP) have shown some promising results (see ccs.ca for evidence tables). The recommendations are largely consistent with the CCS 2017 perioperative guidelines for non-cardiac surgery with a suggested threshold of preoperative NT-proBNP $\geq$ 300 mg/L or BNP $\geq$ 92 mg/L associated with an estimate risk of 21.8% (95% CI, 19.0%-24.8%) for composite of death and nonfatal MI at 30-days postoperatively.[101]

RECOMMENDATION

38. We suggest that clinicians consider measuring BNP or NT-proBNP before peripheral arterial surgery to enhance perioperative cardiac risk estimation (Weak Recommendation; Low-Quality Evidence).

Values and preferences. Cost, accessibility, and reliability of the thresholds were considered for this recommendation. BNP and NT-proBNP are inexpensive and widely available tests. Patients might benefit from further stratification using biomarkers to guide perioperative care and surveillance of cardiac events perioperatively.

Practical tip. Clinicians might consider clinical monitoring postoperatively in individuals with an elevated perioperative troponin level, preoperative NT-proBNP $\geq$ 300 mg/L or BNP $\geq$ 92 mg/L because of the significantly increased risk in these patient groups.[101] Point of care testing is an alternative for obtaining BNP/NT-proBNP levels within minutes in the preoperative setting or where testing is not available through core laboratories.

3.1.4. Noninvasive cardiac testing

PICO 3.1c: What is the role of preoperative noninvasive cardiac testing?

The literature search did not identify new, robust studies that examined the utility of noninvasive cardiac testing for peripheral arterial surgery.

Practical tip. In the absence of new and robust evidence to inform noninvasive testing for peripheral arterial surgery, we suggest referring to the CCS 2017 guidelines for noncardiac surgery.[82] It is essential to continue to apply clinical judgement and current standards of practice for ordering noninvasive testing preoperatively while keeping in mind that the general risk of noncardiac surgery does not reflect the relatively increased cardiac and mortality risk of patients who undergo peripheral arterial surgery.

3.2. Indications for revascularization

PICO 3.2: What are the indications for revascularization procedures in patients with PAD on the basis of their clinical presentation (intermittent claudication, critical limb ischemia, acute limb ischemia, or asymptomatic)?

3.2.1. Intermittent claudication

Symptoms of claudication can manifest as pain, weakness, or numbness in the lower extremity induced with activity, usually walking. Common muscle groups involved include the calf, thigh, or buttock regions depending on the level of atherosclerotic disease (see section 1.1). The natural history of intermittent claudication generally includes a 2%-3% annual risk of progression to chronic limb-threatening ischemia after the first year of diagnosis.[102-104] In addition, the annual risk of amputation is $\leq$ 1% in these patients.[102,103]

Although the management of intermittent claudication is predominantly risk factor modification,[105,106] revascularization can be considered in patients who continue to have lifestyle-limiting symptoms despite best medical management with an acceptable risk profile, reasonable expectation for functional improvement and life expectancy, and in whom a trial of nonoperative therapy with an exercise program on the basis of data from RCTs has failed.

RECOMMENDATION

39. We suggest that revascularization may be considered in patients with intermittent claudication affecting vocational, recreational, or daily living activities who have an acceptable risk profile, reasonable expectation for function and life expectancy, and in whom a trial of nonoperative therapy with an exercise program and optimal medical therapy has failed (Weak Recommendation; Moderate-Quality Evidence).
40. We recommend that the choice of revascularization procedure for intermittent claudication should be individualized, have the expectation of low perioperative morbidity, and have a reasonable likelihood of providing sustained symptomatic benefit (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation emphasizes that early intervention on lesions in individuals with claudication has not been shown to favourably alter the patient's natural history or propensity to develop chronic limb-threatening ischemia.

3.2.2. Chronic limb-threatening ischemia

Unlike claudication, chronic limb-threatening ischemia has a worse natural history with increased propensity for tissue and limb loss.[107] Chronic limb-threatening ischemia is the most advanced form of PAD and patients with chronic limb-threatening ischemia often present with signs of severe arterial insufficiency such as ischemic rest pain, tissue loss, or gangrene.[108] Despite advances in pharmacological risk reduction therapy for PAD over the past 2 decades,[109,110] chronic limb-threatening ischemia patients continue to have high mortality (22% over 1 year) and major amputation (22% over 1 year) rates without revascularization.[111] As such, in addition to CV risk reduction (see sections 2.1-2.6), prompt

revascularization is the cornerstone of management for this condition.[112]

Patients with chronic limb-threatening ischemia should be urgently assessed by vascular specialists who have expertise in endovascular, open, and hybrid surgical techniques for peripheral revascularization. A thoughtful approach to selecting the type of revascularization procedure involves a timely assessment of patient, disease, and procedural factors (see section 3.4).

In addition to revascularization, special attention is required for the management of any associated tissue loss, gangrene, or infection. In patients who present with a deep foot infection or wet gangrene, urgent foot debridement or minor amputation should be considered before revascularization. Close follow-up, appropriate wound care, and frequent reassessment for further debridement are essential in ensuring ischemic and diabetic foot wounds heal after revascularization.

Some chronic limb-threatening ischemia patients might benefit from primary major amputation over a revascularization attempt, such as those with advanced nonreconstructable disease, nonambulatory status, severe sepsis due to progressive limb infection, and those who are unfit for revascularization (often nursing home or bedridden patients).

RECOMMENDATION

41. We recommend that all patients with chronic limb-threatening ischemia should be urgently referred to vascular specialists for consideration of revascularization (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on timely evaluation of chronic limb-threatening ischemia patients by vascular specialists to decrease pain, improve wound healing, and ultimately prevent limb loss.

RECOMMENDATION

42. We recommend that in patients with chronic limb-threatening ischemia, endovascular, open, or hybrid revascularization should be considered on the basis of the anatomical pattern of disease, degree of ischemia, expected durability of the procedure, perioperative risk, and patient life expectancy (Strong Recommendation; Low-Quality Evidence).
43. We recommend wound debridement and/or minor amputation simultaneously with revascularization or in a staged manner depending on the degree of tissue loss, gangrene, and/or infection (Strong Recommendation; Low-Quality Evidence).

Practical tip. Urgent debridement or minor amputation before revascularization is recommended if deep foot infection or wet gangrene is present.

RECOMMENDATION

44. We recommend primary major amputation in chronic limb-threatening ischemia patients with non-reconstructible disease, nonsalvageable limb, non-ambulatory status, severe sepsis, or for palliation for those with a short life expectancy and who are unfit for revascularization (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on primary amputation for chronic limb-threatening ischemia patients who are unlikely to benefit from revascularization.

3.2.3. Acute limb ischemia

Acute limb ischemia, which occurs because of a sudden decrease in limb perfusion (usually within minutes to hours), is distinct from chronic limb-threatening ischemia because there is inadequate collateral circulation present to maintain imminent limb viability. Patients with acute limb ischemia have a poor prognosis, because delays in diagnosis or treatments are associated with high rates of major amputation and mortality.[113] Revascularization options include percutaneous catheter-directed thrombolytic therapy or mechanical thrombus extraction or aspiration, surgical thrombectomy, and surgical reconstruction. Treatment strategies are usually individualized and dependent on the degree and duration of ischemia present, viability of the limb, anatomical factors, patient risk profile, and availably of surgical and endovascular expertise.

3.2.4. Asymptomatic PAD

Often, PAD lesions and/or reduced ABI are identified during screening or as incidental findings. This finding in and of itself is low risk but is a marker for elevated risk of other CV events such as CV death, MI, and stroke.[114] The focus for these patients should be on optimal medical therapy to reduce the risk of MACE; revascularization is generally not indicated unless progression is rapid.

RECOMMENDATION

45. We recommend not offering revascularization to patients with asymptomatic PAD (Strong Recommendation; Low-Quality Evidence).

Practical tip. In patients with asymptomatic PAD, counsel and implement CV risk reduction therapies, in addition to providing education on signs and symptoms of progressive PAD.

3.3. Techniques for revascularization

PICO 3.3a: What are the available revascularization procedures in treating patients with PAD and their outcomes?

3.3.1. Endovascular revascularization

PICO 3.3b: What are the available endovascular revascularization procedures in treating patients with PAD and their outcomes?

3.3.1.1. Overview for endovascular revascularization

Endovascular therapies represent an area of innovation and advancement in the management of patients with PAD. These minimally invasive procedures use variations of balloon dilatation and stent technologies, via small pinhole incisions usually performed as day surgery cases. These procedures have become an especially attractive option for severely comorbid patients with chronic limb-threatening ischemia or claudication, in whom an open surgical revascularization procedure would not have been tolerated, is not feasible as a result of anatomy or conduit availability, or is undesirable because of concomitant morbidity and recovery time. Although less invasive, these endovascular therapies continue to face challenges with respect to limited durability compared with open surgical repair.[115,116]

The objective of endovascular therapy is to target lesions that are hemodynamically significant, usually in the range of 75%-100% occlusion, with the goal of creating inline flow to the affected muscle group or ischemic tissue in the lower extremity. In addition to considering patient factors, anatomical characteristics of lesions considered favourable for endovascular therapy include short lesion length, stenosis (vs chronic total occlusions), proximal lesions (iliac vs femoropopliteal vs tibial), those with minimal calcification, and good distal runoff. Common femoral and profunda artery lesions are generally not considered for standard endovascular therapy.[117-120]

3.3.1.2. Endovascular procedures

See the *3.3.1.2 Endovascular Procedures* section of the Supplementary Material for endovascular procedures.

3.3.1.3. Outcomes of endovascular revascularization

Endovascular revascularization outcomes are heterogeneous and, in many aspects, difficult to quantify. The immediate results of crossing a lesion and providing a treatment resulting in minimal residual stenosis are simple to measure as a procedural success. Other outcome measures such as patient-reported subjective outcomes, hemodynamic improvement, wound healing, and even vessel patency are limited by the inconsistency of definitions. The indication of the procedure, chronic limb-threatening ischemia vs claudication, can also affect outcomes because the severity and natural history of the disease is often worse in the former.

Outcomes are separated into anatomical regions: aortoiliac, infrainguinal, and infrapopliteal. The endovascular treatment of the aortoiliac segment has become the preferred option for the anatomically suitable because of the low incidence of morbidity and mortality compared with open surgical options.[117,121,122]

The common femoral artery area historically has been treated only with open surgery. This practice is currently challenged by studies indicating comparable results with endovascular treatment. The anatomic challenge of a flexible location beneath the inguinal ligament and the potential of covering the profunda femoral artery during possible stent placement must be weighed against the excellent results from a straightforward, open procedure. The consensus remains for operative intervention aside from high-risk anatomy or patient factors.[123]

The superficial femoral artery segment has multiple challenges, including lengthening or shortening, compression, and twisting of the vessel during regular everyday activity. These dynamic challenges have led to stent fractures, which might lead to premature occlusion and restenosis.[124] RCTs have suggested that balloon angioplasty is comparable with bare-metal stents (BMS) for short lesions but for longer disease segments greater than 5-6 cm, nitinol BMS show extended patency.[125,126] BMS, although improved, suffer from recurrent in-stent restenosis in the medium- and long-term, leading to relatively low long-term patency.[127] Covered stents, which prevent tissue ingrowth aside from the proximal and distal edges, might provide some advantage. Nonrandomized industry-sponsored studies showed 1-year primary patency and secondary patency at 73% and 92% percent, respectively.[128] A smaller RCT did not show a benefit compared with BMS for long lesions.[129]

Frequent restenosis of treated lesions has led to randomized trials for drug-eluting technologies, including balloon and stent platforms. Recent data for DES have shown excellent results with 1- and 5-year patency rates at 86% and 66%, respectively. Symptomatic improvement occurred in 92% and 80% of patients during that same period. Registry and single-arm data have also shown dramatic benefits for DES.[71,130]

Drug-eluting balloons have also shown benefits compared with standard balloon angioplasty in randomized trials.[131-133] A meta-analysis of drug-eluting balloons vs balloon angioplasty showed a significant reduction in restenosis rates in the former group. It also showed that higher drug concentrations of paclitaxel were associated with a superior reduction in restenosis than lower doses (3.0 vs 2.0 $\mu g/mm^2$).[134]

A concern about higher mortality rates associated with drug-eluting technologies has led several governing bodies to add warnings to their use.[135,136] However, more recent data have brought these safety concerns into question.[137,138]

A recent network meta-analysis that compared 14 different treatment modalities (ie, atherectomy, brachytherapy, cryoplasty, cutting balloons, drug-coated balloons, bare nitinol stents, DES, covered stents, and combinations), showed DES and covered stents to be the best modalities at 12 months and 24 months, respectively, for restenosis and target lesion revascularization.[139]

Infrapopliteal endovascular treatment has been associated with a high incidence of restenosis of the treated vessel, where primary patency rates range from 22% to 92% at 1 year.[140,141] Although rates of restenosis or occlusion are high, limb salvage can be obtained and maintained despite relatively poor vessel patency rates.

RECOMMENDATION

46. We recommend endovascular therapy in appropriately selected patients with claudication or chronic limb-threatening ischemia (Strong Recommendation; Low-Quality Evidence).
47. We recommend **against** performing endovascular therapy in the common femoral or profunda femoris arteries (Strong Recommendation; Low-Quality Evidence).
48. We recommend **against** performing endovascular therapy for lesions in asymptomatic patients or lesions that are not hemodynamically significant (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on offering a revascularization option in appropriately selected patients that balances the inherent advantages of reduced morbidity, mortality, and faster recovery with the disadvantages of limited durability and increased potential for reinterventions.

Practical tip. Patients with claudication that are selected for endovascular therapy ideally have short stenotic or occlusive lesions in the iliac or superficial femoral artery and reasonable expectation for functional capacity. Endovascular therapy is a reasonable minimally invasive option for limb salvage in patients with chronic limb-threatening ischemia and limited life expectancy, increased number of comorbidities, limited conduit options, or hostile tissue environments including active infection, scarring from multiple repeat surgeries, or radiation.

3.3.2. Open and hybrid surgical revascularization

PICO 3.3c: What are the available open surgical and hybrid (endovascular and open surgical) revascularization procedures in treating patients with PAD and their outcomes?

3.3.2.1. Open surgical revascularization

Despite the increasing use of endovascular interventions, open surgery remains an important therapeutic option in selected patients with PAD. Atherosclerotic disease of the lower extremities is usually described or divided into inflow (aortoiliac) and outflow (infrainguinal) disease.

Endarterectomy is a technique in which the plaque is directly removed from the artery. This is a local open surgical repair and can be used as the sole procedure to treat short segment stenoses or occlusions. The artery can be closed primarily after the endarterectomy but is usually closed with a vein or prosthetic patch angioplasty to increase the diameter of the artery. Endarterectomy can also be used to treat and improve the inflow or outflow vessel(s) in conjunction with surgical bypass procedures. The common femoral artery is the most common lower extremity artery treated with endarterectomy as a sole procedure or at the time of bypass.

Aortoiliac (inflow) disease can be successfully treated surgically with the use of larger-calibre prosthetic bypasses that are associated with good patency rates (aortofemoral 90% at 5 years) and superior to endovascular revascularization in a recent meta-analysis.[121,142] Lower but acceptable 5-year graft patency are noted with less direct inflow from femoral-femoral (60%-80%) or axillo-femoral bypasses (80%).[143-146]

However, all bypasses are associated with a low but significant incidence of operative, wound, and graft complications, which are avoided using the endovascular route. Aortoiliac disease is therefore generally first treated using endovascular techniques (angioplasty with or without stent) but if this is not possible or has failed, then surgical bypass can be considered in selected patients with acceptable risk profiles.

Infrainguinal (outflow) disease can be treated with bypass generally originating from the common femoral artery as inflow and terminating at the above- or below-knee popliteal, or tibial or pedal vessels. Open bypass procedures might be considered for long-segment occlusions that cannot be treated with endovascular techniques or local repairs alone.

Bypass patency is generally highest with the use of autogenous (saphenous or other) vein grafts. These bypasses have patency rates that range from 60% to 80% at 5 years for popliteal vein bypasses.[147] Patency decreases significantly with more distal tibial or pedal artery bypasses, and therefore should only be performed for chronic limb-threatening ischemia. Patency rates are lower with the use of prosthetics at these levels and are avoided if possible.[147]

3.3.2.2. Hybrid procedures

"Hybrid" procedures involve the concurrent use of surgical and endovascular techniques for revascularization. They offer the advantages of less invasive procedures (potential for less local and systemic morbidity, and quicker recovery time) in circumstances in which endovascular treatment alone might be insufficient or is not anatomically feasible. In these procedures, an angioplasty with or without stent is performed proximal or distal to a surgical bypass or endarterectomy during the same sitting to optimize inflow or outflow. This offers a more complete revascularization while limiting surgical exposure and operative time. Recently, these hybrid procedures have been increasingly used as revascularization options for patients.[148] Choosing between exclusively surgical, endovascular, or hybrid revascularization will depend on patient anatomy and condition, and will take into consideration the feasibility, near-term risks, and long-term durability of the procedure(s).

RECOMMENDATION

Surgical revascularization for intermittent claudication

49. We recommend that surgical bypass to the popliteal artery (when indicated) should be performed with an autogenous vein in preference to prosthetic graft material for the treatment of intermittent claudication (Strong Recommendation; High-Quality Evidence).

50. We recommend **against** performing femoral-tibial artery bypasses for the treatment of intermittent claudication (Strong recommendation; Moderate-Quality Evidence).

Surgical revascularization for chronic limb-threatening ischemia

51. We recommend that surgical bypass to the popliteal or infrapopliteal arteries should be performed with an autogenous vein for chronic limb-threatening ischemia (Strong Recommendation; High-Quality Evidence).
52. We suggest that in patients with chronic limb-threatening ischemia for whom endovascular revascularization is not feasible and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries as a last resort in cases of limb salvage (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation emphasizes the use of an autogenous vein as the best conduit for surgical bypass regardless of the indication. The choice of surgical conduit can significantly affect longer-term patency and limb salvage. For example, an autogenous saphenous vein has the best long-term patency rates in open revascularization procedures. The use of arm or composite vein grafts results in decreased but acceptable patency. The use of prosthetic bypasses below the knee generally results in poor long-term patency rates.

RECOMMENDATION

53. We suggest a staged (proximal revascularization of aortic inflow first) approach to surgical procedures is reasonable in patients with ischemic rest pain (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation emphasizes that the extent of revascularization will depend on the severity of presentation. Patients with rest pain, in contrast to patients with significant ulcers or gangrene, might not require all levels of disease to be revascularized to resolve their symptoms. If indicated, and technically or anatomically feasible, endovascular treatment of aorta-iliac disease before, or concurrent with, infrainguinal surgical procedures offers a less invasive approach that can improve inflow and can contribute to the success of revascularization.

3.4. Choosing between open surgical and endovascular procedures

PICO 3.4: How to choose between open surgical and endovascular procedures in patients with PAD who require revascularization procedures?

3.4.1. Evidence for open surgical vs endovascular revascularization

3.4.1.1. Claudication

There are no contemporary trials that have compared surgical with endovascular revascularization in patients with claudication related to aortoiliac and/or infrainguinal artery occlusive disease. Because of the previously discussed recommendation of offering the lowest possible risk intervention when moving forward with revascularization for debilitating claudication, it is unlikely that equipoise needed for a trial will ever exist.

3.4.1.2. Chronic limb-threatening ischemia

Only 1 RCT has been completed on this topic and open surgical bypass was compared with balloon angioplasty in patients with chronic limb-threatening ischemia due to infrainguinal arterial occlusive disease.[149] There were no differences in amputation-free survival at 1 or 5 years. However, post hoc analysis suggested greater amputation-free survival with bypass surgery starting 2 years after randomization.[108] This finding supports the superior durability of surgical bypass relative to balloon angioplasty in patients with chronic limb-threatening ischemia.

There are, however, no trials that have compared open surgical vs endovascular revascularization that include: (1) aortoiliac disease; (2) the full spectrum of open (eg, endarterectomy) and hybrid revascularization (eg, iliac stent and femoral patch angioplasty); or (3) the full spectrum of contemporary endovascular revascularization approaches.

3.4.2. Decision determinants for open vs endovascular

After appropriate imaging is obtained and a decision has been made for revascularization, careful consideration of anatomic, patient, and procedural factors is essential to select the optimal revascularization strategy (Table 5).

RECOMMENDATION

54. We recommend that when selecting endovascular vs open revascularization strategies for PAD, one must consider anatomic, patient, and procedural factors, in addition to operator expertise and resource availability (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on individualizing revascularization strategies for PAD patients.

Practical tip. Hybrid revascularization can be considered in those with common femoral or profunda femoral occlusive disease requiring endarterectomy, in addition to inflow and/or outflow disease amenable to endovascular therapy.

3.4.3. Upcoming trials

Two ongoing clinical trials of endovascular vs open revascularization for patients with PAD have the potential to change practice in the near future. The **B**est **E**ndovascular vs

Table 5. Factors favouring endovascular vs open revascularization in patients with PAD

Favours endovascular
• Focal aortoiliac occlusive disease
• Focal femoropopliteal and/or infrapopliteal disease
• Intermittent claudication indication
• Inadequate vein conduit for bypass
• Prohibitive surgical risk
• Expected survival < 2 years
Favours open
• Diffuse aortoiliac occlusive disease
• Diffuse infrainguinal and/or infrapopliteal disease
• Significant CFA and/or PFA disease
• Adequate vein conduit for bypass
• Failed endovascular revascularization(s)
• Expected survival > 2 years

CFA, common femoral artery; PAD, peripheral arterial disease; PFA, profunda femoris artery.

Best **S**urgical **T**herapy for Patients With **C**ritical **L**imb **I**schemia (BEST-CLI) and **B**ypass vs **A**ngioplasty in **S**evere **I**schemia of the **L**eg (BASIL)-2.[150,151]

Conclusion

In summary, the 2022 CCS guidelines for PAD should provide clinicians with guidance in the following areas: (1) diagnosis and screening of PAD; (2) optimal medical management for patients with PAD; (3) strategies to decrease risk and improve symptoms with smoking cessation therapies, medical therapies, and exercise programs; and (4) decisions regarding indications for interventions, assessing perioperative risk, and choosing between endovascular vs surgical approaches to revascularization. Approximately one-quarter (15/56) of the research questions received a strong recommendation with high-quality evidence, whereas 29% (16/56) were classified as weak recommendation with very low- or low-quality evidence, which illustrates the need for more evidence generation, particularly in preoperative risk assessment and interventional management of PAD patients. A gap in the medical management of patients with PAD has been reported by American and Canadian physicians for 20 years, and we hope that these guidelines will provide primary care, medical specialists, and vascular surgeons with the tools required to help close the treatment gap, and to improve the prognosis of patients with PAD.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.02.029.