The Burden of PAD: Diagnosis and contemporary medical management through risk-factor modification

D Fintel

Citation

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Abstract

Introduction: Peripheral arterial disease (PAD) of the lower extremity is primarily the clinical manifestation of systemic atherosclerosis and atherothrombosis. Hence there is a strong correlation between PAD and atherosclerotic disease in other vascular beds and consequently an increased risk of cardiovascular and cerebrovascular morbidity and mortality.
Prevalence: Up to twelve million adults are estimated to have PAD in the US and the prevalence is set to rise with the aging population. Atherosclerosis is the major pathologic process in PAD development, and modifiable atherosclerotic risk factors include cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension.
Diagnosis: The early identification of this at risk population, especially asymptomatic patients with PAD, may be facilitated by the use of the simple and noninvasive ankle-brachial index (ABI) test.
Management: The management of patients with PAD involves cardiovascular risk reduction via atherosclerotic risk factor modification strategies and treatment of claudication symptoms to improve ambulatory activity and quality of life. Cardiovascular risk modification includes implementation of exercise and smoking cessation programs, aggressive control of diabetes, hypertension and hyperlipidemia, and the use of antiplatelet agents, aspirin or clopidogrel, to prevent secondary ischemic events. Recommended therapies for claudication symptoms include cilostazol and pentoxifylline as an alternative. For severe claudication symptoms limiting functional ability, endovascular or surgical revascularization is recommended.
Conclusion: Despite current guidelines, the management of PAD remains suboptimal. Increasing physician awareness and adherence to guideline recommendations may reduce the high rate of cardiovascular morbidity and mortality associated with PAD.

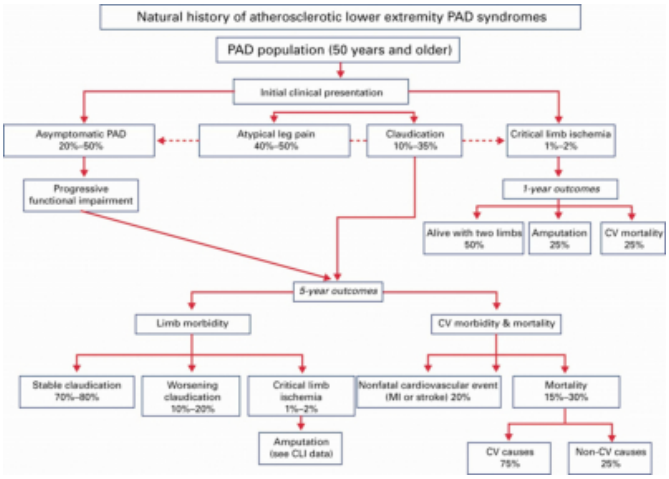
INTRODUCTION

Peripheral arterial disease (PAD) broadly encompasses vascular disease of the aorta, its visceral branch arteries, and arteries of the lower extremity. PAD is by and large a clinical manifestation of systemic atherosclerosis; the presence of atherosclerosis in the peripheral vasculature is often indicative of atherosclerotic disease in other vascular beds such as the coronary and cerebral arteries. Consequently, PAD is associated with increased cardiovascular and cerebrovascular morbidity and mortality [1,2].

Arterial narrowing and obstruction in the lower limbs due to the atherosclerotic lesions reduces blood flow during exercise and a range of symptoms result depending on the severity of the disease [3]. The natural history of lower extremity PAD is depicted in Fig.1.

Figure 1

Figure 1: The natural progression of peripheral arterial disease.



Approximately 20%-50% of patients with PAD may initially have asymptomatic arterial insufficiency, which, if left

undiagnosed, can proceed to a slow decline in lower extremity functioning while increasing the risk for an acute ischemic event [5].

An estimated 10-35% of PAD patients have early symptomatic disease in the legs and generally present with exercise-induced leg discomfort that is relieved with rest, i.e. intermittent claudication [6,7]. A small portion of patients (1%-2%) with lower extremity PAD have the severe form of this disease, critical limb ischemia that is characterized by ischemic leg pain, ulcers or gangrene. For these patients, mobility can be significantly impaired, reducing functional capacity and quality of life, and further complications can develop leading to limb amputation and an increased risk of mortality [8].

This paper is an overview and an educational resource regarding the burden of lower extremity PAD and the available options for the medical management of this debilitating disease.

PREVALENCE OF PAD AND ASSOCIATED RISKS

It is estimated that 8 to 12 million adults have PAD in the US [5,9], with advancing age associated with increased prevalence. Approximately 2.5% of men and women aged 60 years or less are affected, while among those aged 65 years and older the prevalence is much greater at 12%-20% [10,11].

As atherosclerosis is the major pathologic process involved in the development of PAD, risk factors for atherosclerosis that have been associated with increased blood thrombogenicity are also risk factors for PAD [12]. These include cigarette smoking, diabetes mellitus, dyslipidemia, hypertension, and hyperhomocysteinemia [13,14,15,16].

Additionally, patients with PAD have a higher risk of cardiovascular and cerebrovascular morbidity and mortality than those without due to their high incidence of polyvascular disease. In the REduction of Atherothrombosis for Continued Health (REACH) registry investigating patient characteristics, management, and outcomes in more than 67 000 patients with stable atherosclerotic disease across 44 countries, 66% of patients were diagnosed with single arterial bed disease and 16% with polyvascular disease [1]. Only the PAD patients were more likely to have polyvascular disease than single vascular bed disease (i.e. 7.5% of the polyvascular disease patients involved PAD versus only 4.7% of the single bed disease patients). This suggests that patients presenting with symptomatic PAD also likely suffer polyvascular disorders.

In accordance with the high prevalence of polyvascular disease in PAD patients, the Heart Outcomes Prevention Evaluation (HOPE) [17] study showed that clinical PAD was a strong predictor for cardiovascular events, death from cardiovascular causes, myocardial infarction (MI) and stroke. Patients with clinical PAD also had a higher rate of vascular procedures [18]. Similar findings were previously observed by Criqui and others who found that patients with PAD were 3 times more likely to experience all-cause mortality and had a 6-fold greater risk of death from cardiovascular disease than patients without PAD [19]. In addition to PAD being a predictor of death from cardiovascular causes, the risk was seen to increase with the severity of the disease [20].

In general, outcomes for PAD patients are poor and often complicated by severe comorbid conditions. A recent retrospective analysis of medical records of 16 440 patients with PAD in Canada showed annual mortality was higher among patients with PAD (8.2%) than those suffering an MI (6.3%), but lower than in patients following a stroke (11.3%). Patients with comorbid disease (e.g. diabetes) were at highest risk of death and other events [21]. Furthermore, after the first year in the REACH study there was an annual cardiovascular event rate of 4.2% for all patients, 3% for the cohort with PAD alone, increasing to 9.2% for the cohort with polyvascular disease. More than 10% of patients with PAD required peripheral interventions and 1-3% needed amputations [2].

DIAGNOSIS OF PAD

It is increasingly recognized that PAD confers a high risk for fatal and nonfatal cardiovascular ischemic events and that early detection of PAD may be important to reduce this risk. However, results from the large international REACH registry showed that although cardiovascular risk factors are consistent and common worldwide, they are largely underdiagnosed and undertreated in many countries [1]. Specifically, the prevalence of PAD in primary practice is high, yet many cases of PAD are undiagnosed because they are asymptomatic and physician awareness of PAD is relatively low. This was demonstrated in the PAD Awareness Risk and Treatment: New Resources for Survival (PARTNERS) program [9].

Among 6 417 patients screened by history and ankle-

brachial index (ABI) testing at primary care practices throughout the US, 29% were diagnosed with PAD, with or without additional cardiovascular disease. Newly diagnosed PAD was identified in more patients without other evidence of additional cardiovascular disease than those with previous cardiovascular disease history (55% vs 35%; p<0.001). In addition, 83% of patients with prior PAD were aware of their diagnosis, yet only 49% of the physicians knew of this diagnosis at screening [9].

ANKLE-BRACHIAL INDEX

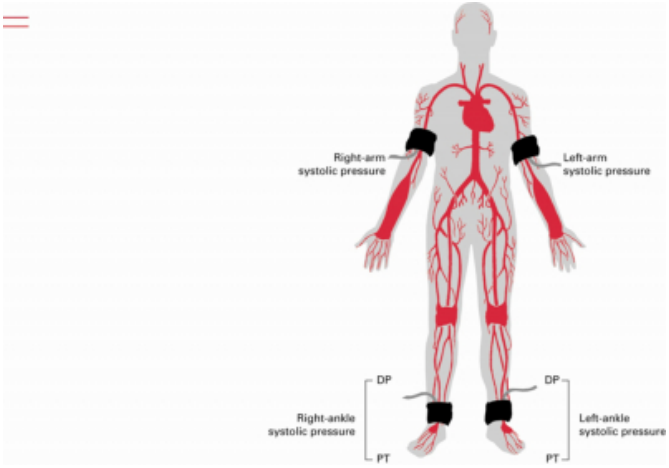
The new American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with PAD emphasize early detection and treatment of the disease [4]. If a patient has no symptoms or atypical symptoms of PAD (only 10%-35% of patients present with classic claudication), then the ABI, also known as the ankle blood pressure index, is a simple, inexpensive and noninvasive method for identifying and monitoring the disease. The ACC/AHA guidelines recommend (Class I/B) that resting ABI should be used to establish diagnosis in patients with suspected PAD (subjects with exertional leg symptoms), with nonhealing wounds and those aged ≥70 years or ≥50 years with a history of smoking or diabetes [4].

As mentioned previously, cardiovascular risk factors in patients with PAD are largely underdiagnosed and undertreated [1,9]; however, the PARTNERS program demonstrated that PAD is highly prevalent in primary practice and is easily identified by ABI examination during routine primary care office visits [9].

The ABI is a simple and reliable test that can be conducted in a primary care setting in approximately 15 minutes to effectively identify undiagnosed PAD [9]. The ABI is determined by measuring systolic blood pressure using Doppler ultrasonography on each arm and ankle from a patient who has been resting in the supine position for 10 minutes(Figure2).

Figure 2

Figure 2: Ankle-Brachial Index (ABI) measurements. DP = dorsalis pedis, PT = posterior tibial artery. This figure has also been used in the ACC/AHA guidelines



Measurements are taken from both arm brachial arteries and from the dorsalis pedis and posterior tibial arteries in both ankles. The higher of the two arm pressures and the higher of the two ankle pressures is selected. The right ABI = higher right ankle pressure/higher arm pressure; the left ABI = higher left ankle pressure/higher arm pressure. A low ABI indicates a high risk of PAD while ABI between 0.91-1.30 is considered normal (Table 1).

Figure 3

Table 1: Ankle-brachial Index (ABI) measurement for diagnosis of peripheral arterial disease (PAD)

ABI	Diagnosis
>1.30	Non-compressible
0.91-1.30	Normal
0.41–0.90	Mild to moderate PAD
0.00–0.40	Severe PAD

Epidemiological studies have shown an inverse relationship between ABI and both cardiovascular disease risk factors and cardiovascular disease among older adults; the lower the ABI, the greater the increase in cardiovascular risk [23,24,25,26]. Furthermore, even modest reductions in ABI (0.8-1.0) appear to increase the risk of cardiovascular disease. A recent study demonstrated the prognostic value of declining ABI in patients with suspected or asymptomatic PAD. Compared with no decline, major decline (>20%) was associated with an increased risk of all-cause mortality, cardiac events, stroke and kidney failure [27].

The HOPE study also found that the ABI, used as a measure

of clinical PAD, was an independent predictor of cardiovascular events and mortality, while Ostergren and others showed that a low ABI was a predictor for the development of diabetic complications and heart failure [17,18]. The sensitivity of the ABI suggests the method may have greater utility than questionnaires and other non-invasive tools for evaluating PAD [28].

Although a survey of the primary care clinicians who participated in the PARTNERS program highlighted that the majority (88%) believed in the utility of incorporating ABI into daily practice [29], the ABI test is not reimbursed by most healthcare payers and is reimbursed by Medicare only for patients with ischemic symptoms [4]. Persuasive data on the cost-benefit of this test as a screening tool for preventing limb amputation are urgently needed to address the lack of reimbursement.

Other available noninvasive vascular diagnostic techniques include pulse volume recordings, duplex ultrasound imaging, Doppler waveform analysis, and exercise testing. Some of these tests may provide anatomical data, and, if required, may be supplemented by the use of MRA, CTA or regular (catheter-based) angiographic techniques [4].

MANAGEMENT OF PAD

The management of patients with PAD is two-fold. First, the risk of an ischemic event must be reduced by modifying the factors driving the progression of atherosclerosis via cardiovascular risk factor modification and antiplatelet therapies. Second, PAD symptoms (claudication) must be managed to improve ambulatory activity and quality of life. A summary of the ACC/AHA guidelines for the management of patients with PAD is presented in Table 2 [4].

Figure 4

Table 2: Management of peripheral arterial disease (PAD)

Cardiovascular risk factor modification (Class/level of evidence)	Claudication treatments (Class/level of evidence)
Smoking cessation support including behavior modification therapy, nicotine replacement or bupropion (I/B)	Supervised exercise program (I/A)
Lipid-lowering agents to achieve target LDL-C: <100 mg/dL (<70 mg/dL in high-risk patients) (I/B) • Statins (IIa/B)	Pharmacotherapy • Cilostazol in the absence of heart failure (I/A) • Pentoxifylline (IIb/A)
Diabetes control: proper foot care (I/B) Target glycosylated hemoglobin (HbA_{1C}): <7.0% (IIa/C)	Revascularization • Endovascular (I/A) • Surgical (I/B)
Antihypertensive therapy to achieve BP <140/90 mmHg; <130/80 mmHg in diabetes and chronic renal failure (I/A) • Beta-blockers (I/A) • ACEI (IIa/B)	
Antiplatelet therapy (I/A) • Aspirin 75–325 mg/day (I/A) • Clopidogrel 75 mg/day (I/B)	

The ACC/AHA recommendations are classified as strong (Class I) or relatively weaker (Class II), where the weight of evidence/opinion is in favor of the usefulness or efficacy of the intervention (Class IIa), or less well established (Class IIb), and weakest (Class III), according to the balance of the benefits, usefulness and effectiveness of the procedure or treatment. In addition, the level of the supporting evidence is classified as either level A, on the basis that the data is derived from multiple randomized clinical trials or meta-analyses, level B if the data is from a single randomized trial or nonrandomized studies, or level C if only consensus opinion of experts, case studies or standard-of-care support the recommendation [4].

CARDIOVASCULAR RISK REDUCTION

The majority of patients with PAD can be treated with lifestyle modifications, pharmacotherapy or both. Lifestyle modifications associated with risk reduction include exercise (walking programs), smoking cessation and control of lipids, diabetes and BP [4].

SMOKING CESSATION

In the absence of evidence from prospective randomized trials investigating the effects of smoking cessation on cardiovascular events in patients with PAD, results from observational studies reported in the ACC/AHA guidelines show that the risk of death, MI and amputation is markedly greater in patients with PAD who continue to smoke compared with those who stop [4]. Based on this evidence, the guidelines recommend (Class I/B) that patients with PAD who smoke cigarettes or use other forms of tobacco should

be advised to stop smoking and should be offered comprehensive smoking cessation interventions including behavior modification therapy, nicotine replacement therapy or bupropion [4]. Varenicline, a nicotinic receptor antagonist, has also recently been approved for smoking cessation although it has not yet been added to the guideline recommendations.

DIABETES CONTROL

Patients with diabetes are at increased risk of developing foot ulcers as a result of preexisting diabetic sensory neuropathy. The Class I recommendation of the ACC/HCC is the encouragement of proper foot care in diabetic patients with PAD, i.e., use of appropriate footwear, chiropody/podiatric medicine, daily foot hygiene and urgent attention to skin lesions and ulcerations to reduce the risk of amputation [4].

Analysis of the Diabetes Control and Complications trial in patients with type I diabetes demonstrated that intensive glucose control including daily insulin therapy with frequent blood glucose monitoring reduced the risk of lower extremity PAD events (claudication, peripheral revascularization or amputation) by 22% compared with conventional therapy; however, this result did not reach statistical significance [30].

Although more intensive glucose-lowering therapy has been shown to significantly reduce diabetes-related complications during long-term follow-up, these effects are predominantly due to significant reductions in microvascular (nephropathy, retinopathy) and not macrovascular events [30,31]. The United Kingdom Prospective Diabetes Study (UKPDS) involving 3867 patients with type 2 diabetes showed that compared with conventional therapy, aggressive therapy with sulfonylureas or insulin over 10 years reduced the risk of MI by 16% (p=0.052), but did not reduce the risk of mortality, stroke or amputation [31].

Based on these findings and in the absence of prospective trials demonstrating evidence of the effect of improved glycemic control on cardiovascular risk in patients with PAD and diabetes, the ACC/HCC recommends (Class II/A) the treatment of diabetes in patients with PAD with glucose-lowering agents to reduce glycosylated hemoglobin (HbA_{1C}) to <7.0% to effectively reduce microvascular complications and potentially improve cardiovascular outcomes [4].

LIPID-LOWERING

Elevated low-density (LDL) cholesterol levels is an established risk factor for cardiovascular events, and a growing body of evidence shows that LDL-lowering therapy reduces this risk [32]. Treatment with hydroxymethyl glutaryl coenzyme-A reductase inhibitors (statins) is recommended for all patients with PAD to achieve a target LDL level of <100 mg/dL. Additionally, when the risk of ischemic events is very high (i.e. in patients with PAD with multiple risk factors, especially diabetes, severe and poorly controlled risk factors such as continued smoking and multiple risk factors of the metabolic syndrome, especially high triglycerides, or acute coronary syndrome) a more stringent LDL-C target is recommended (<70 mg/dL) [4].

In the large UK Heart Protection Study (HPS) consisting of more than 20 000 high-risk patients with coronary disease, other occlusive arterial disease or diabetes, the addition of simvastatin to existing therapy (including aspirin and antihypertensive therapy) significantly reduced the incidence of major cardiovascular events (MI, stroke and revascularization), irrespective of baseline cholesterol levels [33]. Importantly, a similar and significant proportional risk reduction (25%) was seen in the cohort of 2701 patients with PAD over mean follow-up of 5 years ($p<0.0001$) [33]. Similarly, in a recent observational study, there was a lower progression rate of end-stage renal disease and improved cardiovascular outcomes with long-term statin use in patients with PAD followed for 8 years [34].

In addition to the lipid-lowering effect of statins, benefits may also be derived through the modulation of inflammation in atherosclerosis [35]. Schillinger et al. showed that statin therapy was associated with an improved 2-year survival of patients with severe PAD and elevated high-sensitivity C-reactive protein levels, while patients with low inflammatory activity had no additional survival benefit [36].

ANTIHYPERTENSIVE THERAPY

Hypertension is well established as a strong, independent cardiovascular risk factor. As such, the ACC/AHA Class I recommendation for hypertensive patients with PAD is a BP goal of <140/90 mmHg, or <130/80 mmHg for diabetic patients and those with renal failure, to reduce the risk of MI, stroke, congestive heart failure and cardiovascular death [4].

Beta-blockers are the recommended antihypertensives in PAD. As studies have shown, these agents do not worsen walking capacity or symptoms of intermittent claudication [37]. Aronow and Ahn found that beta-blocker therapy in a

cohort of 575 patients with symptomatic PAD and a history of previous MI resulted in a 53% reduction in new coronary events, independent of other confounding variables [38] . This was confirmed recently in a study demonstrating a significant 3-fold reduction in cumulative cardiac mortality in patients with a previous MI and symptomatic PAD following treatment with beta-blocker therapy, compared with patients who did not receive beta-blocker therapy [39] .

There has been some controversy regarding the use of beta-blockers in patients with PAD. Early evidence suggested that treatment with beta-antagonists could precipitate or aggravate the symptoms of arterial insufficiency in patients with PAD [40] . However, a more recent meta-analysis of 11 randomized, controlled trials showed that beta-blockade was not associated with reduced treadmill walking performance in patients with intermittent claudication [37] . Furthermore, a Cochrane systematic review of beta-antagonist use in patients with PAD concluded that given the poor level of evidence, no definite recommendations on use or avoidance could be made [41] .

The use of angiotensin-converting enzyme (ACE) inhibitor therapy for symptomatic patients with PAD is a Class II/A recommendation based on results of the HOPE study, which showed that in patients with symptomatic PAD the ACE inhibitor ramipril reduced the risk of MI, stroke or vascular death by approximately 25%, similar to the reduction seen in the overall study population [17] . However, the majority of patients in the study were normotensive, and the mean fall in systolic blood pressure was only slight (2 mm Hg), suggesting that activation of the renin-angiotensin system may be associated with an increased risk of cardiovascular events independent of a hypertensive state. There is a lack of similar evidence for ACE inhibitor therapy for cardiovascular risk reduction in patients with asymptomatic PAD [4] . Of note, a recent observational study showed there was a lower progression rate of end-stage renal disease and improved cardiovascular outcomes with long-term ACE inhibitor therapy in patients with PAD followed for 8 years [34] . Further large-scale, prospective trials are needed to validate these findings.

ANTIPLATELET AND ANTITHROMBOTIC THERAPY

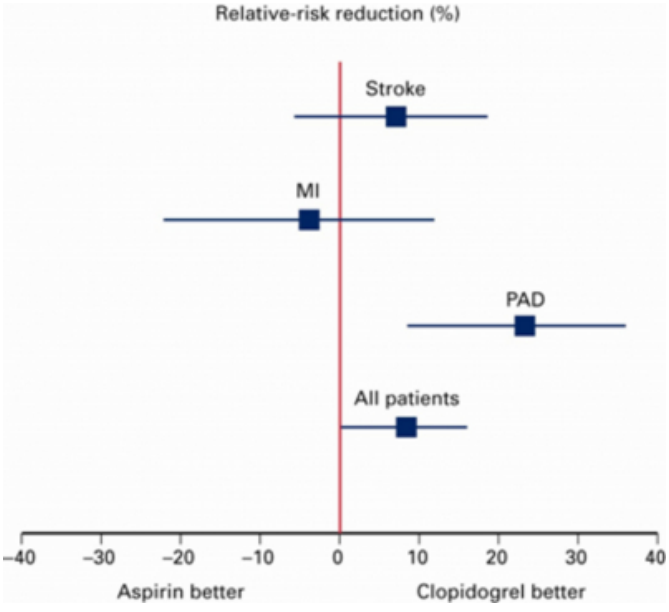
Atherothrombosis is central in the pathophysiology of vascular disease, and the role of platelets in thrombus formation is indicative of the importance of antiplatelet agents for the pharmacologic management of any vascular disease. The ACC/AHA Class I/A recommendation based upon current evidence indicates antiplatelet therapy to reduce the risk of serious vascular events (MI, stroke or vascular death) in individuals with atherosclerotic lower extremity PAD. Aspirin and clopidogrel, as an effective alternative, are currently the only recommended agents [4] .

This recommendation is largely based on the results of the Antithrombotic Trialists' Collaboration (ATC), which demonstrated that among 9214 patients with PAD in 42 trials, there was a 23% proportional reduction in serious vascular events in patients treated with antiplatelet therapy (primarily aspirin) compared with control (p=0.004). These benefits were similar between PAD patients with intermittent claudication, peripheral gaiting and peripheral angioplasty [42] .

Data supporting the effectiveness of clopidogrel in PAD comes from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial in >19 000 patients with a history of recent MI, stroke or established PAD [43] . Compared with aspirin, clopidogrel significantly reduced the risk of MI, stroke or vascular death by 8.7% (p=0.043) in the overall population and 23.8% (p=0.003) in the cohort of 6452 patients with PAD over mean follow-up of 1.9 years (Figure 3).

Figure 5

Figure 3: Relative-risk reduction and 95% confidence interval (CI) by disease subgroup in the CAPRIE study including the cohort of 6452 patients with peripheral arterial disease (PAD); MI = myocardial infarction.



Although the overall tolerability profile was similar between

treatments, the risk of severe gastrointestinal bleeding was significantly greater with aspirin than clopidogrel ($p<0.05$).

Recent evidence has supported the use of dual antiplatelet therapy for secondary prevention of ischemic events in particular patient populations with established cardiovascular disease. The efficacy of short- and long-term therapy with clopidogrel in addition to aspirin therapy was demonstrated in patients with acute coronary syndrome including those undergoing a percutaneous coronary intervention (PCI) in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial [44,45] and in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial [46] . By extension, it was hypothesized that dual antiplatelet therapy may provide benefit to PAD patients as well. An initial evaluation of a cohort of 272 patients with extracardiac vascular disease (either PAD or cerebrovascular disease) in the CREDO trial found that there was a 2-fold greater relative risk reduction with clopidogrel plus aspirin for the primary endpoint compared with patients without extracardiac vascular disease (48% vs 18%) [47] . It was concluded from this trial that the long-term benefits of clopidogrel treatment are not limited to the coronary arteries but rather provide additive protection against thrombotic events throughout the arterial vasculature, suggesting particular benefits for patients with more diffuse atherosclerosis such as PAD.

Data has been limited to date in further demonstrating the translation of marked benefit seen with dual antiplatelet therapy in patients undergoing coronary interventions to patients with PAD. Although clopidogrel plus low-dose aspirin was not significantly more effective than aspirin alone in reducing the rate of major vascular events in patients at high risk for atherothrombotic events in the 28-month Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization (CHARISMA) trial, subgroup analysis showed benefits in specific patient cohorts [48,49] . In a subgroup of 9478 CHARISMA patients with a prior MI, stroke or symptomatic PAD (i.e. a “CAPRIE-like” cohort), the primary event rate was significantly lower with clopidogrel/aspirin than with aspirin monotherapy (7.3% vs 8.8; $p=0.01$) [50] . However, in the cohort of 2838 symptomatic PAD patients, the risk reduction with dual antiplatelet versus monotherapy did not reach statistical significance (7.6% vs 8.7%; $p=0.285$). Furthermore, in the overall population, there was a 25% increase in the rate of severe bleeding with combination therapy compared with aspirin alone (1.7% vs 1.3%; relative risk 1.25, $p=0.09$); the rate of moderate bleeding was 2.1% among clopidogrel/aspirin recipients compared with 1.3% of aspirin recipients (relative risk 1.62, $p<0.001$) [49] . These results suggest that while dual antiplatelet therapy may confer some benefit to patients with symptomatic atherothrombosis, further studies are required to clarify the risk-benefit ratio in this population.

Ticlopidine, another thienopyridine agent similar to clopidogrel, has also been studied in patients with PAD [51] . Although the agent was shown to reduce the risk of MI, stroke and vascular death, the use of ticlopidine is limited by the rate of adverse events such as neutropenia and thrombocytopenia, and is therefore not recommended for use in PAD patients by the AHA/ACC guidelines.

Other available antiplatelet agents (e.g. dipyridamole or the combination of aspirin plus dipyridamole) are not currently advocated in the ACC/AHA guidelines because there is limited evidence for their benefit in PAD. Of note, aspirin/dipyridamole may have some benefit in preventing reocclusion after endovascular intervention [52] .

The ACC/AHA guidelines do not indicate the use of oral anticoagulation therapy with warfarin to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower-extremity PAD, due to an increased risk of bleeding [53,54] . Furthermore, results of the recent Warfarin Antiplatelet Vascular Evaluation (WAVE) trial showed unequivocally that in patients with PAD, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications [55] . In addition, combination therapy was associated with an increased risk in serious bleeding.

Novel antithrombotic therapies are currently under development such as the direct thrombin inhibitor dabigatran etexilate, which is in phase III development with Boehringer Ingelheim, and the novel selective antiplatelet agent TRA-SCH 530348, which is in phase III development with Schering-Plough under Fast Track designation. TRA-SCH 530348 may prove useful in preventing ischemic events in patients with acute coronary syndrome, prior MI or stroke, and in patients with PAD, although no data in this indication are currently available.

CLAUDICATION TREATMENTS

EXERCISE PROGRAM

The ACC/AHA guidelines recommend (Class I/A) a program of supervised exercise training for a minimum of

30-45 minutes, three times per week, for a minimum of 12 weeks as an initial treatment modality for the alleviation of claudication symptoms in all patients with intermittent claudication [4]. Strong evidence supports that regular walking in a supervised claudication exercise program results in an increase in the speed, distance and duration walked, with decreased claudication symptoms at each workload or distance [56].

PHARMACOTHERAPY

Available pharmacotherapies for the improvement of functional capacity in patients with PAD include the phosphodiesterase type-3 inhibitor, cilostazol, and the methylxanthine derivative, pentoxifylline. Cilostazol has been shown to improve maximal walking distance by 40%-60% compared with placebo after 12-24 weeks of therapy [57,58,59,60]. In addition, cilostazol was significantly better than pentoxifylline or placebo for increasing walking distances in 922 patients with moderate to severe claudication but was associated with a greater frequency of minor adverse events [61]. Pentoxifylline improves pain-free and maximal walking distance, albeit marginally, and does not increase ABI at rest or after exercise [62,63].

The ACC/AHA guidelines recommend (Class I/A) cilostazol as an effective therapy to improve symptoms and increase walking distance in patients with PAD and intermittent claudication (in the absence of heart failure as reported in a black box warning); pentoxifylline may be considered (Class IIb/A) as a second-line alternative therapy [4].

Caution is suggested in the use of L-arginine and propionyl-L-carnitine as therapy to improve walking distance in patients with intermittent claudication, as the efficacy of these agents is not well established. In addition, oral vasodilator prostaglandins such as beraprost, iloprost, and chelation therapy are not recommended, as no efficacy has been shown and there is the potential for harmful adverse effects [4].

ENDOVASCULAR OR SURGICAL REVASCULARIZATION

Endovascular (Class I/A) or surgical (Class I/B) revascularization is recommended for patients with claudication symptoms and severe functional disability (that is, vocational or lifestyle limiting) with inadequate response to exercise or pharmacological therapy and/or if there is a favorable risk-benefit ratio [4]. Endovascular procedures are less invasive and carry fewer risks than surgery. These include percutaneous transluminal angioplasty (PTA), also known as balloon angioplasty, with or without stenting to prevent restenosis, atherectomy, laser, cutting balloons, thermal angioplasty and fibrinolysis/fibrinectomy.

Revascularization surgery, endarterectomy, or bypass grafting is recommended in patients in whom the cardiovascular risk of surgical revascularization is low. Patients aged <50 years are generally not suitable candidates for surgery as they may have an aggressive form of atherosclerosis that may recur after surgery. Antithrombotic therapy with antiplatelet or anticoagulant agents is often used post-surgery to prevent graft occlusion.

GUIDELINE ADHERENCE IN CLINICAL PRACTICE

Evidence from observational studies has demonstrated a gap between PAD guideline recommendations and clinical practice [1,9,64,65]. In addition to assessing PAD prevalence and physician awareness, the PARTNERS program also demonstrated that patients with PAD were less intensively treated relative to those with cardiovascular disease [9]. The REACH registry also demonstrated PAD is undertreated [1]. Among the 8273 patients with PAD in the registry, 86% of patients with diabetes or elevated blood glucose received antidiabetic agents and 70% lipid-lowering drugs; antihypertensives were used by 92% of patients with hypertension and antiplatelet therapy was used by 81%. Cilostazol, pentoxifylline, buflomedil or naftidrofuryl were used by 29% of PAD patients.

Similar results were observed among 107 symptomatic PAD patients presenting at a US vascular surgery clinic over a 1-year period [64]. A large proportion of the patients were not treated to guideline recommendations, including 31% who were not receiving antiplatelet therapy, 29% not at target blood pressure, 20% with elevated HbA1c, 19% not at LDL cholesterol goal and 44% who were current smokers.

Moreover, a large Canadian survey showed suboptimal management of cardiovascular risk in high-risk patients (12 106) with diabetes and symptomatic atherosclerosis [65]. Less than 25% of patients received an antiplatelet agent or statin therapy, and less than 50% received an ACE inhibitor. Although patients with coronary artery disease were significantly more likely to receive these therapies than the patients without coronary artery disease, overall use of these agents remained suboptimal and only 11%, 22% and 12% of patients with coronary artery disease, cerebrovascular disease, or PAD, respectively, received all 3 therapies.

A national survey of 1 578 physicians showed that lack of awareness among physicians contributed to lower rates of treatment for atherosclerotic risk factors in patients with PAD compared with those with coronary artery disease [66]. The survey found that physicians were less likely to prescribe antiplatelet agents for patients with PAD than those with coronary artery disease. In addition, the threshold LDL-cholesterol level at which lipid-lowering therapy was 'almost always' initiated was significantly higher among patients with PAD than those with coronary artery disease. Physicians reported that antiplatelet therapy and cholesterol-lowering therapy were extremely important significantly more often for the coronary artery disease patient than for the PAD patient, confirming that perceived importance of risk factor interventions was highly correlated with practice behavior.

Lack of disease awareness, coupled with underdiagnosis of PAD, impedes the effective use of secondary prevention measures for patients with PAD, potentially resulting in adverse cardiovascular outcomes. Education of current fellows and increasing practicing physician awareness and adherence to guideline recommendations may help to significantly reduce the high rates of cardiovascular morbidity and mortality associated with PAD.

CONCLUSIONS

Recent evidence has highlighted the tremendous cumulative risk of PAD patients for additional cardiovascular complications including coronary artery and cerebrovascular disease. Because of this PAD, patients are at increased risk of cardiovascular morbidity and mortality, yet contemporary medical care of PAD patients has fallen short, as this population remains significantly underdiagnosed and undertreated. Early identification of this at risk population in either the primary care setting or at referral is imperative and efforts should be made to use the simple and noninvasive ABI test that accurately identifies patients with PAD. Hopefully, improved reimbursement for this procedure would increase the likelihood of its more frequent utilization by primary care physicians.

Additionally, current evidence strongly supports that aggressive modification of commonly associated PAD risk factors, including smoking, diabetes, hypertension and hyperlipidemia is central to the management of the disease. This is clearly reflected in current evidence-based guidelines, which recommend cardiovascular risk-reduction and symptom alleviation in patients with PAD to reduce microvascular and macrovascular events. The future of PAD management requires a paradigm shift towards recognition of the available clinical evidence that demonstrates the profound global atherothrombotic risk of PAD and the optimal strategies for the treatment of this risk.

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Author Information

Dan J. Fintel, MD
Director, Coronary Care Unit, Feinberg School of Medicine, Northwestern University, Bluhm Cardiovascular Institute