Management of Cardiovascular Disease Risk Factors among Older Adults with Peripheral Arterial Disease

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Peripheral arterial disease (PAD) is a common but frequently undetected and undertreated condition among older adults. Untreated PAD and cardiovascular disease (CVD) risk factors results in functional impairment, poor quality of life and increased risk for cardiovascular disease morbidity and mortality. The increased risk for CVD events associated with PAD necessitates raising public awareness of PAD and the potential impact on health, and placing greater emphasis by providers on detection and management of PAD to maximize survival and life quality. This article briefly describes the detection and medical management of PAD, with greater emphasis on lifestyle modification among older adults with PAD.

Key words: vascular disease, cardiovascular disease, risk factor reduction, lifestyle modification

Introduction

Peripheral arterial disease (PAD) is a manifestation of aggressive systemic atherosclerosis that is most prevalent among older adults and is associated with an increased risk for cardiovascular disease (CVD) morbidity and mortality resulting from untreated CVD risk factors.[1–4] In addition to the increased risk of CVD events, individuals with PAD experience substantial walking impairment due to symptoms of limb ischemia; this eventually leads to physical disability and poor quality of life.[5–9] Despite the devastating consequences of PAD, recent studies have shown that PAD is largely undetected and CVD risk factors are undertreated in this patient population.[10,11] The increased risk associated with PAD and the lack of treatment of CVD risk factors underscores the importance of increasing public awareness and implementing more aggressive screening and management programs for these individuals. This article reviews the current evidence for the detection and management of patients with PAD. In particular, we focus on nonpharmacological strategies to reduce atherosclerotic risk factors.

Prevalence of PAD and Associated CVD Risk Factors

The prevalence of PAD is higher than that of other vascular diseases, including myocardial infarction (MI) and stroke. The prevalence of PAD is age dependent, increasing from 9% in ages 55–65 years to as high as 47–57% in those over the age of 70 years.[3,12–14] By 2050, approximately 9.6–16 million adults ages 65 years and older will be diagnosed with PAD.[15] Peripheral arterial disease has a threefold higher CVD morbidity rate and a 40% greater mortality rate if associated with symptomatic cerebrovascular disease.[4] Most persons with PAD (some 68%) have concomitant coronary artery disease,[16,17] which contributes to the high rate of nonfatal cardiovascular events.[16,18–20] A majority of patients with PAD have multiple modifiable CVD risk factors including cigarette smoking,[1,21,22] type 2 diabetes,[1,23,24] hypertension,[1,24,25] dyslipidemia,[1,24,26,27] obesity,[28,29] and a sedentary lifestyle.[30,31] Additionally, 57% of individuals with PAD have at least three of five factors that classify them with metabolic syndrome, according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), placing these individuals at even greater risk for future CVD events and mortality.[32,33] The significance of multiple risk factors in PAD is their additive effect on overall risk.[34] Despite the known detrimental effects of CVD risk factors and the proven efficacy of individual risk factor modification in other patient populations, recent studies suggest that persons with PAD are untreated or receive inadequate treatment for CVD risk factors in a variety of practice settings, ranging from general primary care clinics to specialty clinics in vascular surgery.[1,10,11,35–41] Undertreatment of atherothrombotic risk factors among individuals with PAD is attributed to deficiencies in provider knowledge and attitudes,[42] glucocentric treatment goals,[43] and a lack of public awareness of CVD risks associated with PAD.[44]

Table 1: Clinical Symptoms and Differential Diagnosis of Lower Limb Ischemia

Symptom Assessment	Intermittent Claudication	Arthritis in the Hip or Knee	Spinal Stenosis	Venous Congestion
Location of discomfort?	Calf, hip, thigh, buttock, or foot (rarely)	Hip or knee joint	Buttock, hip, or thigh	Groin or thigh; entire leg possible
Characteristics of the discomfort?	Pain, cramping, tightness, and tiredness	Aching	Tingling, weakness, numbness, or symptoms or peripheral arterial disease	Tightness or throbbing pain
Exercise-induced discomfort?	Yes, and reproducible onset	Yes, but mostly related to bearing weight	Yes, after some time; but weight bearing alone may cause	Yes, after walking; variable
Relief of discomfort?	Discontinue exertion	Discontinue weight-bearing activity	Discontinue weight bearing or change position	Discontinue walking; elevate leg

Diagnosis

Symptoms of Lower Extremity Ischemia

The hallmark of PAD is intermittent claudication, defined as exercise-induced lower limb ischemia distal to the site of arterial occlusion that is relieved within 10 minutes of rest.[5] Claudication symptoms are often described as pain, cramping, fatigue, numbness, or weakness in the hips, buttocks, thighs, or calves that is alleviated with rest[45] (Table 1). While claudication is associated with PAD, recent studies suggest that symptoms of leg ischemia vary and, in fact, only 30–50% of older adults with documented PAD report classic or typical claudication symptoms.[5,9] One study suggests that individuals who are older, male, diabetic, or screened with ankle-brachial index (ABI) in primary care settings are more likely to be asymptomatic or have exertional leg symptoms other than intermittent claudication.[46] The range of leg symptoms associated with PAD may be attributed to a number comorbid conditions, including arthritis or pulmonary disease. However, given the age of persons who have PAD, another likely factor is the lack of physical activity of sufficient intensity to induce lower-extremity ischemic symptoms.[46] Further, some individuals may be able to compensate for an increased oxygen demand during exertion because of increased collateral arterial channels.[47]

Other factors such as gender and mood state may also have an effect on symptom presentation. There is preliminary evidence for gender differences in symptom presentation. Based on a limited number of trials, women report a higher prevalence of leg pain at rest or with exertion, lower functional capacity, impaired walking ability, and worse self-reported quality of life and physical functioning compared with men who have PAD.[5,46,48–51] Mood state or depression also has an impact on a patient's awareness of or description of leg pain.[5] We recently found that women reported lower physical functioning and impaired mood state compared with men of similar age and with equivalent severity of PAD.[50] These studies demonstrate the importance of increasing the awareness of the full spectrum of symptoms associated with a broad range of patients with PAD. Importantly, these findings suggest that clinicians who use the classic symptom description of claudication in lieu of objective assessment of limb blood flow via ABI testing may miss an opportunity to accurately diagnose PAD.[11]

Accordingly, the PAD guidelines set forth by the American College of Cardiology/American Heart Association (ACC/AHA) taskforce recommends ABI screening for all individuals at risk for PAD, namely men or women with exertional leg pain, adults ages 50 years and above with associated risk factors (smoking, diabetes, high cholesterol, high blood pressure), those with a 20-year history of diabetes, and all individuals age 70 years and older.[52,53]

Ankle Brachial Index

The ABI is a simple, noninvasive test used to diagnose PAD (Figure 1).[54] The ABI determines the ratio between the systolic blood pressures of the legs and the arms and is calculated by dividing the higher of the two systolic blood pressures at each ankle (dorsalis pedis or tibialis posterior) by the higher of the two systolic blood pressures in each arm. An ABI ≤0.90 is indicative of PAD (Table 2).[11] An ABI ≥1.30 may reflect medial calcification, often seen in patients with diabetes or chronic renal failure. In these individuals, it is recommended to take toe pressures using photoplethysmography or pulse-volume recordings to assess the severity of PAD.[52] Occasionally, an individual with PAD may present with typical limb ischemic symptoms (claudication) but normal resting pedal pulses and ABI. For these individuals, exercise testing is recommended to provoke symptoms of limb ischemia and to determine walking time using a graded exercise test such as the Skinner-Gardner exercise protocol.[55] Persons with typical

limb ischemic symptoms will exhibit a decrease in ankle pressure of at least 20 mm Hg within 1 minute postexercise. If a treadmill test is not an option, active pedal plantar flexion may be performed instead.[52]

Lifestyle Modification in the Treatment of PAD

According to the NCEP ATP III guidelines, PAD is a coronary heart disease equivalent, in the highest risk category, and thus warrants intensive CVD risk factor management with optimal medication management and therapeutic lifestyle modification. The latter includes exercise, weight management and changes in diet, and smoking cessation.[56]

Exercise

The cornerstone of PAD treatment is exercise. Exercise has demonstrated efficacy in improving peripheral circulation, walking economy, cardiopulmonary function, and functional capacity.[57] Supervised exercise programs result in an increase in the pain-free walking distance, absolute walking distance, and walking speed, with decreased claudication symptoms at each workload or distance.[58–60] The length of the program influences the magnitude of increase in maximal walking distance.[61]

In a meta-analysis of 21 studies, pain-free walking time was shown to increase by 120% in patients with claudication who underwent exercise training.[57] Comparatively, pharmacotherapies including pentoxifylline and cilostazol have been less effective in increasing maximal walking ability (20–25% and 40–60%, respectively) than supervised exercise in persons with PAD.[62,63]

While the time course of the response to a program of exercise has not been fully established, exercise-induced functional benefits (increased walking speed, distance, and duration and decreased symptoms) can be appreciated within 4–8 weeks; but, as expected, greater benefit is conferred with programs of 6 months or longer.[64–67] Improvements in walking distance have been shown to include more than 100% increase in peak exercise performance and self-reported physical function. Therefore, exercise is a critical component of optimal management for this patient population.

Exercise-induced functional benefits are attributed to alterations in the skeletal muscle metabolism, muscle hypertrophy, and improvements in endothelial function.[68] Though the development of collateral circulation is an attractive mechanism to explain clinical improvement associated with exercise, currently, there is inadequate evidence to attribute any functional benefits of exercise to the growth of collateral blood vessels.[47]

Exercise studies of patients with PAD have primarily been conducted in a laboratory setting; therefore, current recommendations include referral to an exercise program.[69] Although a Current Procedural Terminology code (93668) is available for this referral, the overall effectiveness is restricted because of the lack of insurance reimbursement for exercise programs. Exercise recommendations from clinical trials in patients with PAD indicate that walking is the most effective mode of exercise.[47] Although resistance training does confer some benefit, it has been shown to be less effective than walking in improving walking distance in persons with PAD.[70] Another form of exercise that has been shown to be effective is pole striding, which has been demonstrated to increase cardiovascular fitness and improve symptoms and quality of life in a small group of individuals with PAD.[71,72]

ACC/AHA PAD guidelines suggest the key elements of a therapeutic claudication exercise training program; these are presented in Table 3.[68]

Weight Control and Diet

There is little evidence to address specific dietary recommendations for persons with PAD. Accordingly, recommendations are similar to those for established CVD.[56] Recent findings suggest that diets high in fruits, vegetables, and whole grains; with limited dairy and salt intake; plus reduced saturated fat, total fat, and cholesterol improve CVD risk factors (cholesterol, blood pressure, and weight) and fatal and nonfatal CVD events.[73–75] Most notable of these diets are the Dietary Approaches to Stop Hypertension (or DASH) and the Mediterranean diet.[73–75] Research is needed to determine the underlying mechanisms responsible for improvement from adherence to various types of diet as well as the extent of improvement resulting from multiple risk factor reduction programs that integrate dietary modification.[76] Weight reduction to prevent diabetes is critical in preventing PAD since diabetes represents a major risk factor for atherosclerosis and PAD.

Table 2: Interpretation of Ankle-Brachial Index

Ankle-Brachial Index (ABI)	Interpretation
>1.30	Noncompressible (further testing required)
0.91–1.30	Normal
0.71–0.90	Mild obstruction
0.41–0.70	Moderate obstruction
0.00–0.40	Severe obstruction

Smoking Cessation

Smoking is one of the greatest risk factors for PAD. More than 80% of persons with PAD are current or former smokers.[77] ACC/AHA PAD guidelines recommend that individuals with PAD who smoke cigarettes or use other forms of tobacco should be advised by their physician to stop smoking and should be offered comprehensive smoking cessation interventions, including behaviour modification therapy, nicotine replacement therapy, or bupropion.[52,53] While no prospective randomized trials have examined the effects of smoking cessation on cardiovascular events in patients with lower-extremity PAD, observational studies have found that the risks of death, MI, and amputation are substantially greater in those individuals with PAD who continue to smoke than in those who stop smoking.[26,78–80] Physician advice coupled with

frequent follow-up achieves 1-year smoking cessation rates of approximately 5% compared with only 0.1% in those attempting to quit without a physician's intervention.[22,81]

Pharmacotherapy

As described earlier, PAD is most common in older adults, particularly men over the age of 70 years. Because of the increased incidence of CVD morbidity and mortality in addition to the increased disease burden, aggressive risk factor modification is recommended to reduce adverse events. Treatment goals for PAD include symptom relief with exercise and medical therapy, and secondary prevention to prolong life by medical management, smoking cessation, and lifestyle modification with diet and exercise. PAD is a coronary heart disease equivalent by the NCEP ATP III guidelines and warrants aggressive management of risk factors.[56] Risk factor management is described in detail in the ACC/AHA PAD guidelines that integrate current treatment guidelines for individual risk factors.[52,53]

Secondary analyses of large longitudinal prospective randomized clinical trials, including the Heart Protection Outcome Evaluation[82] study and the Scandinavian Simvastatin Survival Study,[83,84] have demonstrated the efficacy of pharmacotherapy in reducing nonfatal cardiovascular events, including MI and death, and microvascular events, such as neuropathy and retinopathy, in person with PAD. These studies found that treatment of hyperlipidemia with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) and niacin; hypertension with angiotensin-converting enzyme inhibitors; type II diabetes with sulfonylureas and insulin; along with antiplatelet therapy with acetylsalicylic acid effectively reduced adverse CVD events. Further investigation is needed to examine the provocative findings that statins, independent of their lipid-lowering effects, improved symptoms and pain-free walking distance in patients with PAD.[85]

Antiplatelet therapy is a highly effective means of altering the natural history of PAD and coronary artery disease by interfering with platelet function and thrombus formation, and reducing subsequent ischemic events.[86] Therefore, treatment of PAD necessitates lifelong antiplatelet therapy. Based on the evidence from the Antiplatelet Trialists' Collaboration, which demonstrated a 23% relative risk reduction in favour of antiplatelet therapy, acetylsalicylic acid (75–150 mg/d) is currently recommended.[87] The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial suggests that clopidogrel (75 mg/d) may be superior to acetylsalicylic acid (325 mg/d) in improving walking distance and reducing mortality.[88] However, because of the higher cost and nonformulary status of clopidogrel, acetylsalicylic acid is still the most widely prescribed antiplatelet agent. The efficacy of combining the agents clopidogrel and acetylsalicylic acid has not been substantiated, and studies are currently under way to examine the safety and efficacy of this antiplatelet regimen.[89,90]

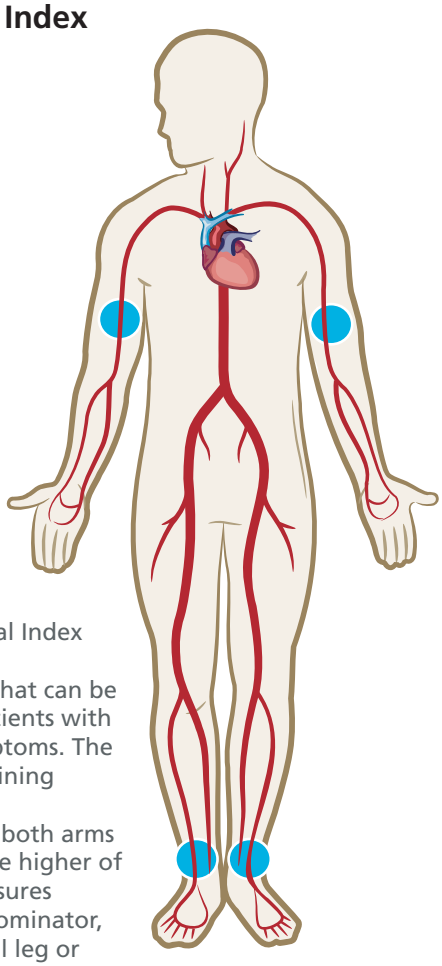
To date, pharmacotherapy for treatment of claudication is limited. Currently, pentoxifylline, a xanthine derivative with rheological properties causing red blood cell deformability, is available. However, its efficacy has not been fully demonstrated in patients with PAD. Another alternative for claudication is cilostazol, a type 3 phosphodiesterase inhibitor that acts to inhibit platelet aggregation and also induces vasoldilation.[89–92] Although a meta-analysis of eight randomized clinical trials demonstrated the benefit of cilostazol in improving pain-free and maximal walking

Table 3: ACC/AHA PAD Guidelines for a Therapeutic Claudication Exercise Training Program

Aspect	Details
Modality	Treadmill and track walking are the most effective types of exercise for reducing claudication symptoms and improving functional benefit. While resistance training has been shown to benefit individuals with other forms of cardiovascular disease, it should only be used to complement walking exercise.
Intensity	Exercise intensity is based on the workload that elicits claudication pain within 3–5 minutes of walking during a treadmill test. Exercise is progressively increased until this workload is achieved and then continued until the onset of claudication, at which point exercise is discontinued (rest period) until pain dissipates and the exercise bout is resumed. This exercise-rest-exercise pattern should be repeated for the entire duration of the exercise session.
Duration	The initial duration recommended is 35 minutes of intervals of walking and rest. If possible, the duration should be increased by 5 minutes each session until 50 minutes of intermittent walking can be performed. The stimulus of initial claudication pain should always be achieved during the workout, so, as the patient's walking ability improves, the workload should be augmented by increasing the treadmill grade, speed, or both.
Frequency	The patient should exercise with a frequency of three to five times per week for a minimum of 12 weeks, although 6+ months of supervised exercise would be much more beneficial to the patient.

Source: Data from Hirsch et al., 2006.[68]

Figure 1:
Ankle-Brachial Index



The Ankle-Brachial Index (ABI) is a simple, noninvasive test that can be used to assess patients with claudication symptoms. The ABI involves obtaining blood pressure measurements in both arms and both legs. The higher of the two arm pressures becomes the denominator, and the individual leg or ankle pressures serve as the numerator in calculating the ABI for each leg. Thus, the ABI is a ratio that roughly compares the blood flow in the arms with that in the legs, and can help screen for arterial insufficiency as a source of the claudication symptoms.

distances, it is contraindicated for persons with PAD and heart failure because of the increased cardiac mortality seen with other drugs in this class.

Due to the limited medical treatments available to individuals with PAD for the management of claudication symptoms, research has been directed to alternative therapies. One such agent is l-arginine, a semiessential amino acid that is the precursor of endothelium-derived nitric oxide, a potent vasodilator with antiatherogenic properties.[93] While initially promising, recent evidence supporting the beneficial effects is controversial. In preclinical studies, short-term administration of l-arginine was shown to improve vasodilation and increase vascular nitric oxide synthesis.[94] However, the Nitric Oxide in Peripheral Arterial Insufficiency (NO-PAIN) study showed that long-term administration of l-arginine does not increase nitric oxide synthesis or improve vascular reactivity. In fact, the expected placebo effect observed in studies of functional capacity was attenuated in the l-arginine treated group.[95] Further investigation is currently under way.

Another alternative therapy that is being examined is gingko biloba. This agent has been used in Europe to treat PAD but is under current investigation in the U.S. The efficacy of this agent has primarily been attributed to its antioxidant effects, endothelium-dependent relaxing effects, and inhibition of platelet-activating factors. While promising, the mechanism of action and efficacy have yet to be determined in this population.[96]

Conclusion

Peripheral arterial disease is a common and often neglected chronic disease of older adults that is associated with increased CVD morbidity and mortality and eventual physical disability and poor quality of life. Groups at high risk for PAD requiring screening include individuals with exertional leg pain, older adults with CVD risk factors, persons with diabetes of >20 years' duration, and all persons over the age of 70 years.

A major challenge that exists is the lack of public and clinical awareness of this condition. Although PAD is a common clinical condition and signals systemic atherosclerosis requiring aggressive risk factor management, it is frequently not detected and diagnosed. Population-based surveys indicate a major public knowledge gap regarding this common atherosclerotic syndrome.[44] Moreover, surveys of primary care providers and vascular specialists have indicated that persons with PAD, compared with persons with coronary atherosclerosis, are much less likely to be treated by their physicians to lower rates of MI, stroke, and death.[1,11,35,38–40] Because achieving target risk-reduction goals is known to improve with active patient participation, it is probable that efforts to improve public awareness of PAD could be used to achieve major improvements in cardiovascular outcomes.

Evidence-based practice guidelines are currently available for the detection, diagnosis, and management of PAD. However, when there is a diagnosis of PAD, management of the CVD risk factors does not meet the currently recommended level specified in the ATP III guidelines for a CHDe equivalent. The challenge that currently exists is to increase public and provider awareness of PAD to improve screening and detection of PAD. Once diagnosed, an integrated, preventative approach is needed that

combines pharmacotherapy and lifestyle modifications to address the multiple CVD risk factors commonly found in this population.

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