Peripheral Vascular Disease: Missed Opportunity for Cardiovascular Intervention

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Key words: peripheral arterial disease, coronary artery disease, diabetes mellitus, outcomes

Introduction

Peripheral arterial disease (PAD) is a common manifestation of atherosclerotic vascular disease; however it is often under-recognized.[1] It affects older patients and disease prevalence is nearly equal among men and women. Intermittent claudication is the most frequent symptom of PAD, although the diagnosis of PAD is often overlooked until the patient presents with limb-threatening ischemia. first diagnosis of PAD is often made at endovascular or surgical treatment of PAD and in nearly half of the patients referred for an amputation.[1] In my own experience, this presentation is especially prevalent in Texas. Importantly, PAD is a marker of generalized atherosclerosis and is closely associated with coronary and cerebrovascular disease.[2] The severity of PAD is associated with an increased risk of myocardial infarction, stroke, and cardiovascular death.[2] The recognition and diagnosis of PAD, combined with its appropriate medical management, is an essential element to its comprehensive care and may well reduce the overall risk of cardiovascular morbidity. When diagnosed early, both exercise and pharmacotherapy can ameliorate symptoms of claudication, augment functional performance, and improve quality of life.

PAD is commonly encountered. It is highly prevalent in general practice setting and should be recognized as an important marker for cardiovascular disease. In the Partners trial,[2] nearly a third of patients with diabetes and hypertension were diagnosed with PAD in a primary care setting. Once recognized, specific therapy directed to the management of PAD manifestations is indicated for most patients.

The Trans-Atlantic Inter-Society Consensus (TASC) document for the first time standardized the evidence-based management approach to PAD. North American and European

vascular professional societies in the fields of cardiology, vascular medicine, radiology, and surgery worked together to develop this consensus document.[3] These recommendations are directed to optimal medical, endovascular and surgical management aspects of PAD. The recommendations also identified many unresolved critical issues, including the uncertain benefits and cost effectiveness of many widely used diagnostic and therapeutic modalities.

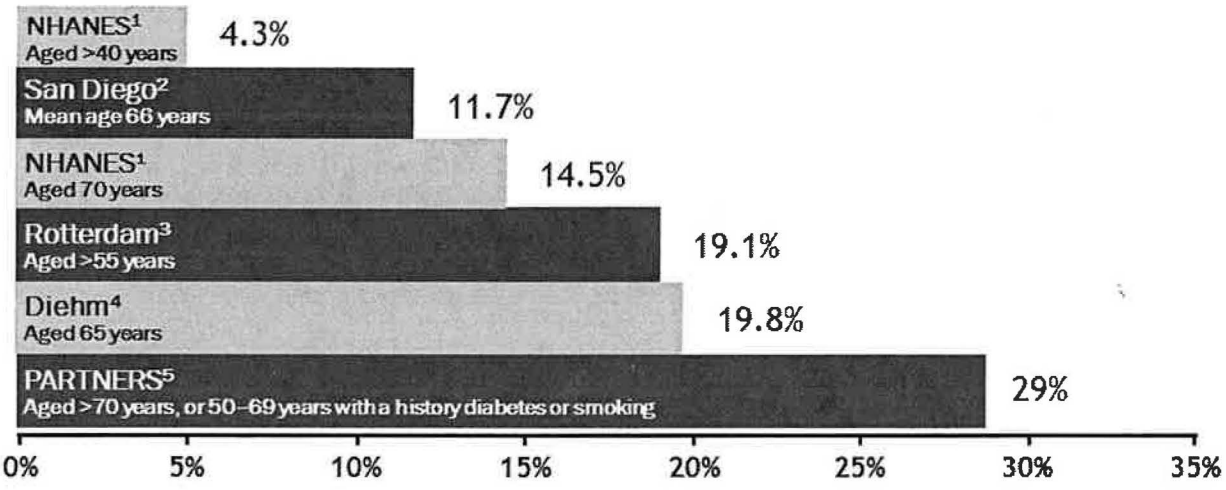
This review is directed to primary care providers, specialists and to a wide spectrum of healthcare providers who may encounter or care for patients with known or occult PAD. This document will primarily address epidemiology, office-based diagnosis, general medical management, and specific minimally invasive therapeutic options for patients with intermittent claudication. The recognition of PAD as part of a system-wide atherosclerotic process is central to its management and therefore a treatment plan that modifies known risk factors for atherosclerosis and its atherothrombotic complications is central to any treatment plan. Select patients with disabling claudication may benefit from surgical therapy or catheter-based interventions. In all, a global PAD management approaches requires a closely functioning team of primary care clinician/family physician, general internist, adult nurse practitioner, physician's assistant, radiologists or cardiologist and vascular surgeons.

Prevalence of PAD

The overall prevalence of PAD is estimated from several population studies that used an objective, noninvasive limb pressure testing (ankle-brachial index) results as the diagnostic criteria.[4-9] **Figure 1** depicts few key epidemiologic studies estimating the prevalence of PAD. The largest and most significant of study was conducted by the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, a multicenter, cross-sectional

study conducted at 27 sites in 25 cities and 350 primary care practices throughout the United States in June-October 1999.

Figure 1: Prevalence of PAD



NHANES=National Health and Nutrition Examination Study;
PARTNERS=PAD Awareness, Risk, and Treatment: New Resources for Survival [program].

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2. Criqui MH, et al. *Circulation*. 1985;71:510-515.
3. Diehm C, et al. *Atherosclerosis*. 2004;172:95-105.
4. Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
5. Hirsch AT, et al. *JAMA*. 2001;286:1317-1324.

A total of 6979 patients aged 70 years or older or aged 50 through 69 years with history of cigarette smoking or diabetes were evaluated by history and by measurement of the ankle-brachial index (ABI). PAD was considered present if the ABI was 0.90 or less, if it was documented in the medical record, or if there was a history of limb revascularization. Cardiovascular disease (CVD) was defined as a history of atherosclerotic coronary, cerebral, or abdominal aortic aneurysmal disease. PAD was detected in 1865 patients (29%); 825 of these (44%) had PAD only, without evidence of CVD. The rest had PAD and CVD. When these rates are generalized to the US population, the overall prevalence of PAD is estimated to be more than

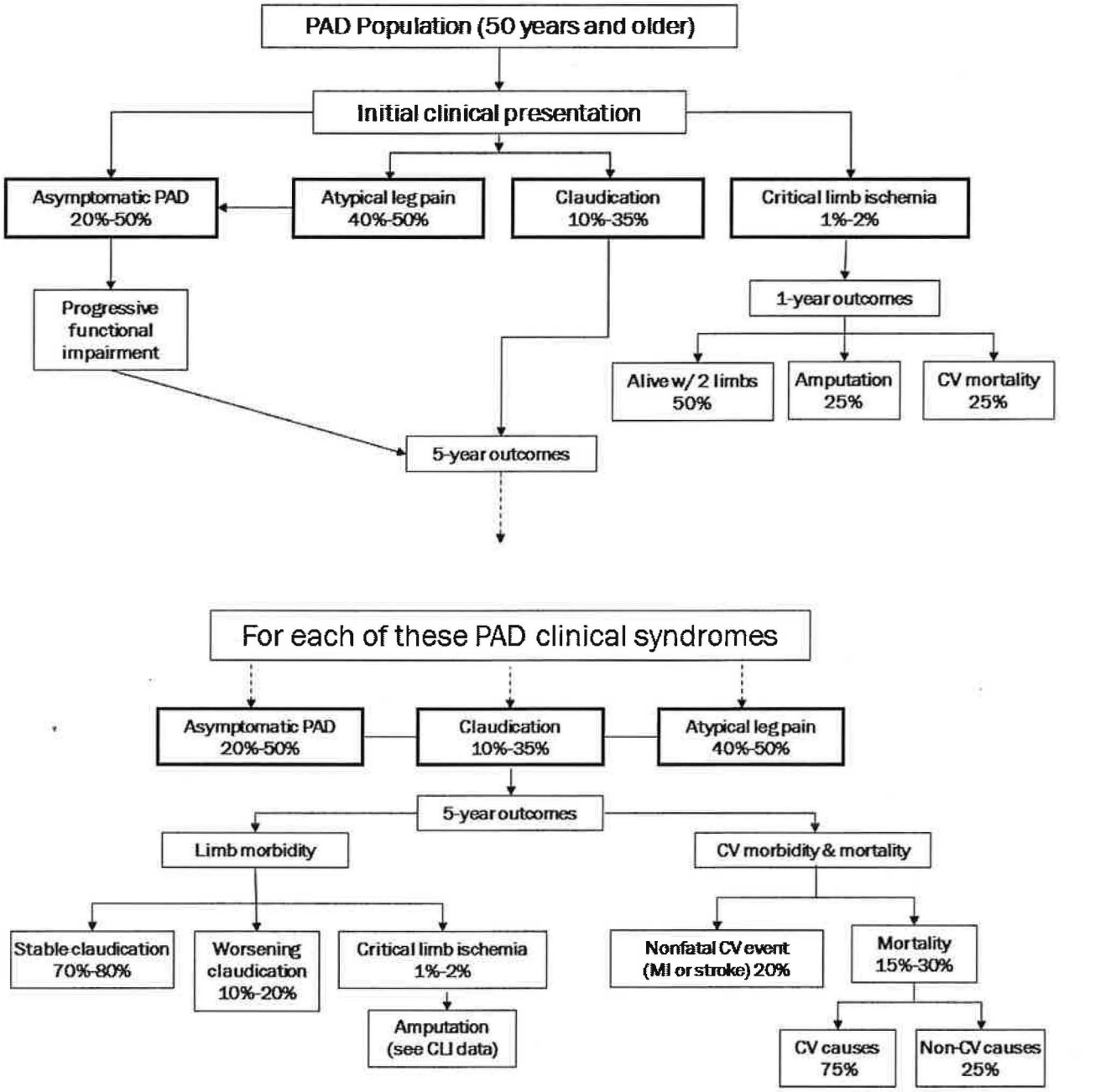
8.4 million individuals.[10] Although these figures represent extrapolations, it is clear that PAD is a highly prevalent disorder and its prevalence increases with age across both sexes.

PAD a Marker of Cardiovascular Risk and a Predictor of Cardiovascular Events

Patients with symptomatic or asymptomatic PAD are at increased risk for cardiovascular morbidity and mortality. All-cause mortality is increased by almost three-fold in men and women with documented PAD compared with age-matched control subjects without PAD.[11] Importantly, this increased mortality was observed even when clinically evident cardiovascular disease was absent at baseline. The diagnosis of PAD was a more important predictor of survival outcome than was a clinical history of coronary disease. Additional analyses correlated PAD severity and relative risk for cardiovascular mortality. Overall, the diagnosis of PAD was associated with a six-fold increase in relative risk for cardiovascular mortality; and it was increased 15-fold in patients with severe symptomatic PAD.[11] Women with PAD have nearly the same risk of mortality as men with PAD[12]. This was independent of whether or not they had claudication or a prior history of cardiovascular disease. The study by Vogt *et al.* [12] showed that the relative risk for all-cause mortality in the study population was increased 3.1-fold at 4 years (after adjustment for age, smoking, and other risk factors). The relative risks for heart disease and cardiovascular disease events were estimated at 3.7 and 4.0, respectively. Leng *et al.*[13] prospectively followed nearly 1600 patients with symptomatic and symptomatic PAD and showed that asymptomatic individuals with PAD have a significantly increased risk of ischemic events. New intermittent claudication symptoms were noted in 1.6% patients per year. Asymptomatic patients appeared to have the same increased risk of cardiovascular events and death as those with claudication.

The overall outcome of patients with PAD is determined primarily by cardiovascular outcomes and to a lesser degree by limb morbidities **(Figure 2).**

Figure 2: Natural History of Atherosclerotic Lower Extremity PAD



CLI=critical limb ischemia; CV=cardiovascular; MI=myocardial infarction

Reprinted with permission from Hirsch AT, et al. *Circulation.* 2006;113:e463-654.

Stroke risk is also increased in patients with PAD. The incidence of ischemic stroke is reported to be as high as 42% in patients with PAD.[14] Further, PAD patients appear to have a poorer prognosis following a stroke than those without PAD. Asymptomatic peripheral arterial disease, a highly prevalent condition in the general older population, is associated with an increased risk of cerebrovascular events because of co-existing clinical or subclinical cerebral atherosclerosis.[15] Patients with asymptomatic PAD show cognitive impairment in a range of psychometric tests, and C-reactive protein (CRP) and D-dimer levels appear to be independent negative predictors of some cognitive performances. These findings suggest the need for screening for PAD among at-risk subjects in order to identify patients to be treated for prevention of functional decline and dementia. This also support the hypothesis that inflammation and hypercoagulability are implicated in the pathophysiology of cognitive dysfunction associated with asymptomatic PAD.[15]

These data clearly indicate that patients with either symptomatic or asymptomatic PAD are at an increased risk of cardiovascular and cerebrovascular events and it is an independent predictor of both all-cause and cardiovascular mortality.

Impact of PAD

Intermittent claudication often presents as leg pain, fatigue or discomfort when walking and is relieved at rest. It is an important symptom associated with PAD and has a significant and measurable impact on overall functioning and quality of life, decrease in functional capacity and correlates well with the severity and extent of PAD.[16] Patients may have impaired walking performance, often without recognizing or reporting classic symptoms and the claudication needs

to be carefully distinguish from a host of conditions listed in **Table 1** that mimic claudication symptoms (pseudoclaudication).[16]

Table 1: Claudication vs. Pseudoclaudication

Pseudoclaudication:		Claudication	Pseudoclaudication
Spinal canal stenosis	**Characteristic of discomfort**	Cramping, tightness, aching, fatigue	Same as claudication plus tingling, burning, numbness
Peripheral neuropathy	**Location of discomfort**	Buttock, hip, thigh, calf, foot	Same as claudication
Peripheral nerve pain	**Exercise-induced**	Yes	Variable
Herniated disc impinging on sciatic nerve	**Distance**	Consistent	Variable
Osteoarthritis of the hip or knee	**Occurs with standing**	No	Yes
Venous claudication	**Action for relief**	Stand	Sit, change position
Symptomatic Baker's cyst	**Time to relief**	<5 minutes	≤30 minutes
Chronic compartment syndrome			
Muscle spasms or cramps			
Restless leg syndrome			

However, careful questioning of such patients may lead to an accurate diagnosis of PAD, because whether or not they report claudication symptoms, they may report a decrement in walking speed and shorter walking distances, both indicative of a positive diagnosis.[17,18] Moderately severe claudication significantly reduces a patient's ability to exercise. Peak oxygen consumption may be reduced by as much as 50%. By comparison, this reduction approximates the decrement in physical performance capability seen with New York Heart Association class III congestive heart failure.[19] Thus, the decrement in physical performance is of a magnitude that warrants definitive medical attention. Further, the physical disability attributable to PAD may further exacerbate long-term cardiovascular risk, as it limits a patient's ability to derive other benefits of aerobic exercise and conditioning of leg skeletal muscles.

Diagnosis of PAD in a Patient with Intermittent Claudication

The diagnosis of PAD is frequently overlooked. Many patients present with concurrent problems, and treatment of intermittent claudication are often not given priority in patients with multiple, coexisting and chronic medical conditions. For sedentary patients, intermittent claudication may not be troublesome and generally goes unreported. Even patients with obvious symptoms may under-report claudication symptoms, accepting "aches and pains" as an inevitable consequence of aging. Additional factors that may contribute to the under-diagnosis of PAD include the limited training that most physicians receive in the management of this disease, some practitioners' lack of ready access to an inexpensive hand-held Doppler device for determination of the ankle-brachial index (ABI), or lack of access to noninvasive vascular laboratory services.[20] Furthermore, PAD is not a prominent diagnosis in established clinical coding systems, and thus its prevalence as an outpatient or discharge diagnosis is likely to be under-reported in many health care systems.

The first step toward making the diagnosis of PAD is the identification of patients at risk for the disease. All patients with symptoms of claudication should undergo a thorough medical evaluation, including a global assessment of atherosclerosis risk factors; if warranted, behavioral and pharmacotherapeutic interventions should be initiated to rapidly achieve optimization of these risk factors. Primary risk factors include advancing age, diabetes, cigarette smoking, hypertension, hyperlipidemia, hyperhomocysteinemia, and postmenopausal status.[21] Of note, a person over the age of 45 years who smokes more than 15 cigarettes a day is nine times more likely to develop intermittent claudication than is a nonsmoker in a similar age group.[22] The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following:

exertional leg symptoms, non-healing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes.[23]

Diagnosis by History and Physical Examination

The diagnosis of PAD in patients with intermittent claudication or critical limb ischemia can typically be made on the basis of a thorough patient history and physical examination. Additional evaluation of PAD is multimodal, and the techniques used vary, depending on the nature and severity of the patient's presenting problem. Most PAD patients can be appropriately managed without specialized diagnostic services or interventions.

Claudication is characteristically described as pain, aching, or muscle fatigue occurring after the onset of exercise (walking) and relieved by rest. The history of PAD is characteristic and consistently reproducible, and may alone be diagnostic for many individuals. A complete physical examination is indicated, however, to evaluate potentially important contributing factors that may have an impact on clinical management. Palpation of pulses at appropriate sites should be correlated with symptom severity; location and auscultation of bruits may also be helpful.

Laboratory Tests and Adjunctive Evaluation

All patients with claudication should be evaluated for atherosclerotic risk factors, including hypertension, lipid abnormalities, and diabetes mellitus. The following blood tests should be performed in new patients presenting with PAD, to screen for common hematologic pathologies, diabetes mellitus, renal insufficiency, and dyslipidemias[3]:

Complete blood count, Platelet count, Fasting blood glucose or hemoglobin A1c, Creatinine, Fasting lipid profile and Urinalysis (for glycosuria/proteinuria).

In addition, the following laboratory investigations are indicated for PAD patients with early-age onset of disease, for those with a personal or family history of thrombotic events, or when there is a lack of common risk factors for atherosclerosis:

Hypercoagulability screening, Homocysteine levels (either fasting or after methionine loading)

Ankle-Brachial Index

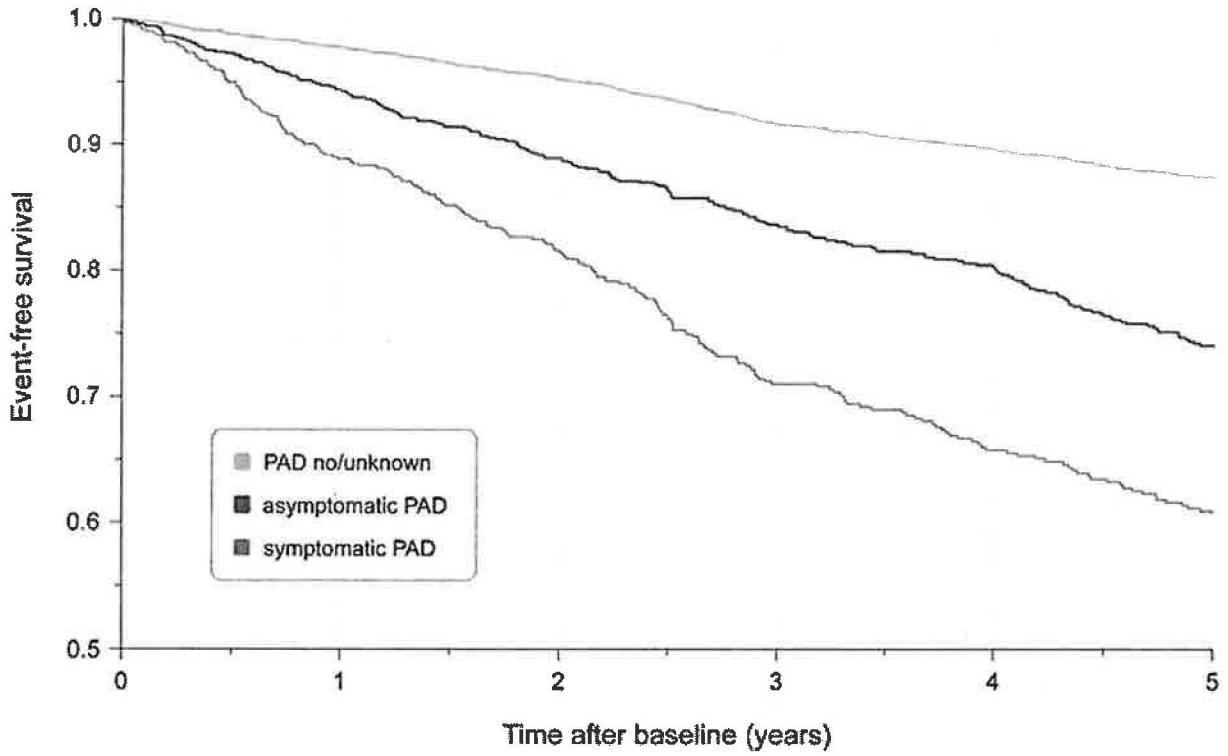
The ABI is a test that is easily performed in any patient care setting and is important in the diagnosis of PAD. Arterial systolic pressure measurements are made with a continuous-wave Doppler ultrasound instrument (5-7 MHz) and conventional blood pressure cuffs. The ABI is determined by dividing the systolic pressure at the ankle (the higher of the tibial artery pressures) by the systolic pressure at the arm (the higher of the brachial artery pressures).

An ABI <0.90 establishes a diagnosis of PAD, with a 95% sensitivity and specificity of nearly 100%.[24] Although ABI values between 0.50 and 0.90 are common in patients with intermittent claudication, the relationship between ABI values and the severity of claudication is difficult to predict. Some individuals may experience moderate to severe symptoms despite a normal or near-normal ABI (as with aortoiliac stenoses), whereas others may experience few symptoms or complain of fewer symptoms, even with a low ABI. The ABI is a useful and objective indicator of disease severity and may also be helpful in identifying patients at increased risk for development of non-healing wounds or progression to amputation. A lower ABI value predicts a higher incidence of atherosclerotic disease elsewhere in the circulation (coronary or cerebral). Thus, the ABI is more than a diagnostic tool for PAD. It can provide an objective indication of the systemic burden of atherosclerosis.

The definitions of normal and abnormal ABI values have been modified based on publication of the results of the Ankle Brachial Index Collaboration. This includes a normal ABI range of 1.00 to 1.40, and abnormal values continue to be defined as those ≤0.90. ABI values of 0.91 to 0.99 are considered "borderline" and values >1.40 indicate non-compressible arteries.[23]

Figure 3, below depicts Kaplan–Meier estimates of all-cause mortality or severe vascular events (myocardial infarction, coronary revascularization, stroke, carotid revascularization, peripheral revascularization, or amputation) during the 5-year follow-up. Patients with an ABI >1.5 were excluded.

Figure 3: Event-free Survival by PAD status at 5 years



Diehm C et al. Circulation 2009;120:2053-2061

Functional Assessments

The Walking Impairment Questionnaire (WIQ) is a PAD-specific instrument used to assess the severity of PAD patients' walking disability. The WIQ is a tool that measures functional status by grading community-based walking ability with questions about walking distance, walking speed, stair climbing, and symptoms of intermittent claudication (pain symptoms). The WIQ can be a useful tool for assessing PAD, particularly in patients without classic claudication symptoms but who nonetheless have walking impairments that may be indicative of PAD. Also, the WIQ is useful to assess changes in walking capacity with treatment. In addition, broader functional status questionnaires, such as the Medical Outcomes Study Short Form-36 (SF-36), may be used for patient evaluation in the office, but these are more commonly used in the setting of clinical trials or outcome studies.

Treadmill testing is the best means to objectively measure a patient's walking performance: the patient walks on a treadmill preset for speed and incline and reports the first onset of pain (giving a measure of pain-free walking distance, PFWD) and the point at which pain becomes severe enough to stop walking (maximal walking distance, MWD). Results from the WIQ have been validated against objective data from treadmill testing.

A treadmill test may be considered to monitor the results of claudication therapies, including exercise training, claudication drugs, angioplasty, and surgery. Treadmill testing may also be useful to distinguish nonvascular causes of leg pain from true intermittent claudication

Management of PAD

Drug therapies for patients with intermittent claudication are directed toward 1) slowing atherosclerotic progression; 2) reducing risk of myocardial infarction, stroke, and cardiovascular

death; and 3) alleviating symptoms. Unless contraindicated, all patients with atherosclerotic disease should receive lifelong antiplatelet therapy.[22,25-50]

Risk Factor Modification

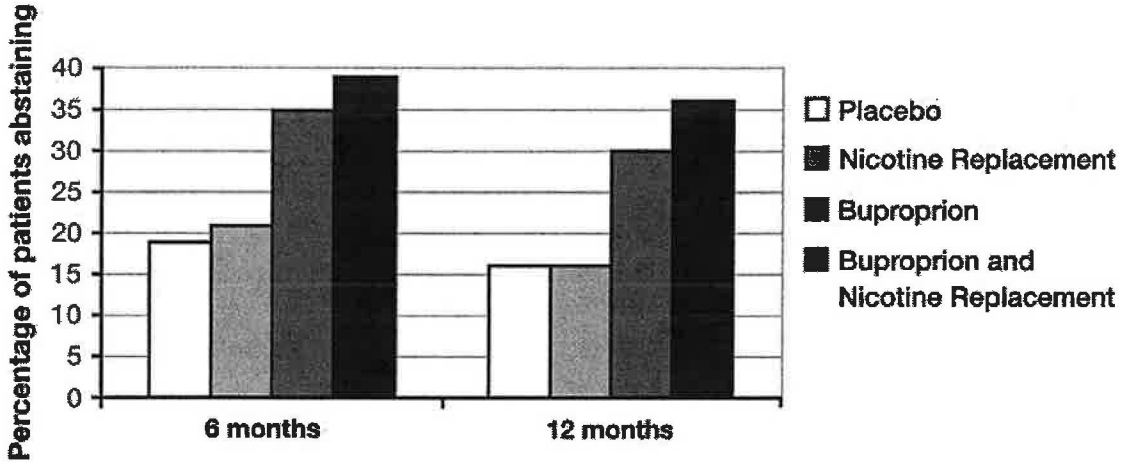
Given that the presence of PAD is indicative of more generalized atherosclerosis, it is important to modify known risk factors that contribute to cardiovascular disease. Such factors include smoking, diabetes mellitus, obesity, hyperlipidemia, hypertension, and homocysteine elevation.[3] The continued use of tobacco products, for example, has been associated with progressive worsening of claudication, an amplified risk of critical-limb ischemia, greatly increased rates of amputation, failure of limb revascularization, increased rates of myocardial infarction and stroke, and heightened mortality.[22] Smoking cessation appears to decrease PAD symptom incidence and severity.[51] Although the magnitude of claudication improvement, if any, is uncertain in individual patients, the promise of decreased cardiovascular ischemic events and the lessened risk of other smoking-related diseases should provide an incentive to quit. Patient education and lifestyle changes to reduce smoking and other risk factors should be implemented as an important first step in any treatment of PAD.

Direct evidence supporting the use of statins to lower LDL cholesterol levels in PAD comes from the Heart Protection Study (HPS).[52] The HPS enrolled over 20,500 subjects at high risk for cardiovascular events including 6748 patients with PAD, many of whom had no prior history of heart disease or stroke. Patients were randomized to simvastatin 40 mg, antioxidant vitamins, a combination of treatments, or placebo using a 2×2 factorial design, with a 5-year follow up. Simvastatin 40 mg was associated with a 12% reduction in total mortality, 17% reduction in vascular mortality, 24% reduction in coronary heart disease events, 27% reduction

in all strokes and a 16% reduction in non-coronary revascularizations. Similar results were obtained in the PAD subgroup, whether they had evidence of coronary disease at baseline or not. Furthermore, there was no threshold cholesterol value below which statin therapy was not associated with benefit. Thus, the HPS demonstrated that in patients with PAD (even in the absence of a prior myocardial infarction or stroke), aggressive LDL lowering was associated with a marked reduction in cardiovascular events (myocardial infarction, stroke and vascular death). A limitation of the HPS was that the evidence in PAD was derived from a subgroup analysis in patients with symptomatic PAD. Despite these limitations, all patients with PAD should have their LDL cholesterol levels lowered to <100 mg/dL. To achieve these lipid levels, diet modification should be the initial approach, however, in most cases, diet alone will be unable to decrease the lipids levels to the values mentioned above; therefore, pharmacological treatment will be necessary.

The role of smoking cessation in treating the symptoms of claudication is not as clear; studies have shown that smoking cessation is associated with improved walking distance in some, but not all patients. Therefore, patients should be encouraged to stop smoking primarily to reduce their risk of cardiovascular events, as well as their risk of progression to amputation and progression of disease, but should not be promised improved symptoms immediately upon cessation. Recent studies have shown a three-fold increased risk of graft failure after bypass surgery with continued smoking with a reduction in that risk to that of non-smokers with smoking cessation.[53] Combining bupropion and nicotine replacement therapy has been shown to be more effective than either therapy alone **(Figure 4)**.[54]

Figure 4: Percent Abstinence from Smoking



Antiplatelet Therapy

Decreases in the rates of fatal and nonfatal myocardial infarction, stroke, and vascular death have been found when antiplatelet therapy is used for secondary prevention of cardiovascular events.[25] In men enrolled in the US Physicians' Health Study,[26] chronic administration of aspirin was found to reduce the need for subsequent peripheral artery surgery. The Antiplatelet Trialists' Collaboration[27] showed that aspirin reduced the risk of cardiovascular events; however, the data suggested that aspirin was less effective for the subgroup of patients with PAD, whereas ticlopidine did show benefit. More recently, the platelet inhibitor clopidogrel was tested in PAD patients at risk for ischemic events and found to be more effective and safer than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, and vascular death.[28,55,56]

Recommendations for Antiplatelet and antithrombotic drugs[23]:

1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with

intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Class I)

2. Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Class I)
3. Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Class I)
4. Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90. (Class IIa)
5. In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding. (Class III)

Exercise Rehabilitation

Exercise therapy - preferably a supervised walking program - should always be considered as part of the initial therapy for patients with intermittent claudication.[3] Regular walking can be expected to result in an increase in the speed, distance, and duration of walking.

The benefits accrue gradually, but are recognized by the patient after a few weeks. The use of formal exercise programs to treat claudication has been studied over the past three decades. In fact, this is perhaps the best studied medical therapy for claudication, with demonstrated efficacy in improving exercise performance, quality of life, and functional capacity. Numerous types of exercise programs have been devised, but the most successful employ a supervised setting.[57,58]

A typical supervised exercise program is 60 minutes in duration, is given three or more times a week, and is monitored by a physical therapist, trained nurse, or experienced technician. Patients should be encouraged to walk on a treadmill, since this most closely reproduces walking in the community setting, is the best studied, and has been shown to be an effective intervention. The initial workload of the treadmill is set to a speed and grade that brings on claudication pain within 3-5 minutes. Patients walk at this work rate until they achieve claudication of moderate severity, then rest until the claudication abates. The exercise-rest cycle is repeated several times during the 1 hour of supervision. Patients should be reassessed clinically on a weekly basis as they become able to walk farther and farther at their chosen workload. This is followed by a regimen of increased speed or grade (or both) to allow patients to successfully walk at harder and harder workloads. The general duration of an exercise program is 3-6 months. Typical benefits include more than 100% improvement in peak exercise performance on the treadmill,[59] significant improvements in walking speed and distance noted with the WIQ, and improvements in physical function and vitality on the SF-36 questionnaire. ***Despite the widespread documentation of efficacy, exercise programs are currently not reimbursed by most health care plans***; however, this is expected to change in the years ahead due to the uniform consensus among vascular professionals and health care payers that supervised exercise is an effective primary therapeutic modality to improve claudication symptoms.

The mechanism of the exercise training benefit has been evaluated in several studies. In general, exercise training is not associated with significant changes in limb blood flow. Further, changes in blood flow have not been correlated with changes in exercise performance. However, it is possible that there may be better distribution of flow to exercising muscle. Several metabolic parameters have been evaluated. Improved extraction of oxygen has been documented with exercise training. Some studies have also shown increases in muscle enzyme activity, but these findings are inconsistent across trials. More important, there is no demonstrated relation between change in any enzyme activity and change in exercise performance. Patients with intermittent claudication accumulate intermediates of oxidative metabolism (acylcarnitines) in their skeletal muscle. Previous studies have shown that patients with the greatest accumulation have the most impaired functional performance. Exercise training has been shown to clear these acyl compounds, and the degree of removal from skeletal muscle is directly correlated with improved performance. Therefore, these data suggest some metabolic improvement as a result of exercise training. Finally, alterations in gait and walking efficiency may contribute to the exercise training response. Several studies have shown that at submaximal workloads, exercise training results in decreased oxygen consumption and therefore improved walking efficiency. This is also associated with the exercise training response. In summary, although exercise training is not associated with significant improvements in skeletal muscle blood flow, changes in skeletal muscle metabolism and walking efficiency may account for much of the observed benefit.

Pharmacotherapy for Intermittent Claudication

Although many drugs have been evaluated for their potential to relieve claudication symptoms, few have actually demonstrated efficacy in adequately designed clinical trials. Of these, cilostazol and pentoxifylline are the only drugs that have US Food and Drug

Administration (FDA) approval for this indication. Other agents in diverse drug classes, such as anticoagulants, vasodilators, growth factors, prostaglandins, ranolazine and prostaglandin analogues, have been suggested for this indication, but treatment outcomes with these agents have been variable and none are currently approved beyond investigational purposes.

Currently Available Options:

Cilostazol, an inhibitor of type III phosphodiesterase, inhibits platelet activation (aggregation and secretion) and relaxes vascular smooth muscle.[60] Other effects of cilostazol include inhibition of vascular smooth muscle cell proliferation, lowering of serum triglyceride levels, and an increase in high-density lipoprotein cholesterol levels.[61] FDA approved this drug in 1999 on the basis of results from eight clinical trials that included 2702 patients with PAD and moderate to severe claudication.[61-65] These studies, 12-24 weeks in duration, showed that cilostazol increased both PFWD and MWD on standardized treadmill testing. The percent mean change from baseline MWD was 28% to 100%, whereas the percent change in the comparable placebo groups was -10% to 30%. A dose-response effect was also observed, with a greater effect seen with cilostazol 100 mg twice daily than with cilostazol 50 mg twice daily.[64] The positive treatment effect with cilostazol was independent of sex, age, race, smoking status, coexisting diabetes, or use of blockers or calcium-channel blockers. The quality-of-life survey instrument, SF-36, was used in six US trials of cilostazol. This widely used general health questionnaire showed that cilostazol improved several patient-reported aspects of well-being. Scores for bodily pain, physical function, role -- physical, physical summary, and vitality were all significantly improved. These data suggested that cilostazol improved the physical (but not the social or emotional) aspects of quality of life for patients with intermittent claudication. Also, in analyses of pooled data, cilostazol-treated patients reported improvements in walking speed

and distance, as assessed by the WIQ. These data confirmed objective evidence obtained from treadmill testing. For example, data from a randomized, placebo-controlled trial[64] with 516 patients demonstrated a significant ($p<0.001$) improvement in PFWD (59% improvement vs. placebo) and MWD (51% vs. placebo) on a treadmill with cilostazol treatment. It should be kept in mind that the mechanism of action of cilostazol, phosphodiesterase type III inhibition, is similar to flosequinan, an older drug originally approved for severe CHF. Flosequinan was abruptly removed from the market due to increases in sudden cardiac death. FDA has made Cilostazol contraindicated in patients with CHF. Lastly, be cautious when prescribing cilostazol PPIs. For example, if prescribed with omeprazole the dose of cilostazol must be halved; alternatively, pantoprazole does not interact with cilostazol. Pentoxifylline, a trisubstituted xanthine derivative classified as a hemorrheologic agent, is the other currently available drug for intermittent claudication therapy. Pentoxifylline, like other xanthine derivatives (Theophylline, Caffeine and chocolate), are also phosphodiesterase type III inhibitors. Although extensively evaluated for claudication therapy, most trials with pentoxifylline have been small, and many were compromised by design shortcomings, such as the lack of an adequate placebo-treated control group or failure to use treadmill testing to objectively assess walking ability. One major pentoxifylline study conducted in the United States[66] enrolled a total of 128 patients in a double-blind, placebo-controlled protocol and found significant differences between the treated and placebo groups in increased initial (PFWD) and absolute claudication distances (MWD). A 59% increase in PFWD and a 36% increase in MWD were noted in the pentoxifylline-treated patients in this study. However, the differences in percent change from baseline values were not significant at the end of the study (24 weeks), reflecting the magnitude of the observed placebo effect (36% increase in PFWD and 25% increase in MWD). Data from the Scandinavian Study

Group[67] indicated an 80% increase in PFWD and a 50% increase in MWD in pentoxifylline-treated patients after 24 weeks of therapy, again with no significant difference between groups, reflecting a large placebo effect.

Hood *et al.*[68] performed a meta-analysis of results from pentoxifylline clinical trials that used treadmill testing as an end point. Evaluating a combined group of 612 patients with moderately severe claudication from 11 randomized, placebo-controlled, double-blind studies, they found that the weighted mean improvement in MWD with pentoxifylline therapy was 48.4 m (95% confidence interval, 18.3-78.6 m), which was significant compared with placebo. These pooled data suggested that pentoxifylline was better than placebo and may be efficacious in improving walking distances. Despite the results of the meta-analysis, however, the lackluster results in broad clinical use and critical reviews of the available data have left many skeptical about pentoxifylline's efficacy.[69,70]

Comparison of Cilostazol and Pentoxifylline: One multicenter, prospective, placebo-controlled trial has directly compared the safety and efficacy of cilostazol and pentoxifylline in the treatment of intermittent claudication and found cilostazol to be superior.[65] This study, with 698 patients randomized to three groups (including placebo), is the largest reported trial of drug therapy for claudication. In addition, with randomization of 232 patients to the pentoxifylline group and 239 patients to the placebo group, the study was the largest placebo-controlled trial of pentoxifylline for claudication, more than three times the size of the largest previous study of pentoxifylline efficacy.

Patients in each active treatment group demonstrated a progressive increase in walking distances over time, with the greatest improvement observed in patients who received

cilostazol.[65] At 24 weeks, the mean improvement in PFWD was 94 m and the increase in MWD averaged 107 m in the cilostazol-treated patients. By comparison, pentoxifylline increased PFWD by 74 m and MWD by 64 m, the same change in walking distance observed in subjects treated with placebo. Both cilostazol and pentoxifylline were generally well tolerated, though fewer patients (15.8%) in the cilostazol-treatment group withdrew due to adverse events than in the pentoxifylline group (18.5%). The most commonly reported side effects after starting cilostazol therapy were headache, diarrhea, and abnormal stools, but these symptoms were generally mild to moderate in severity and self-limited.

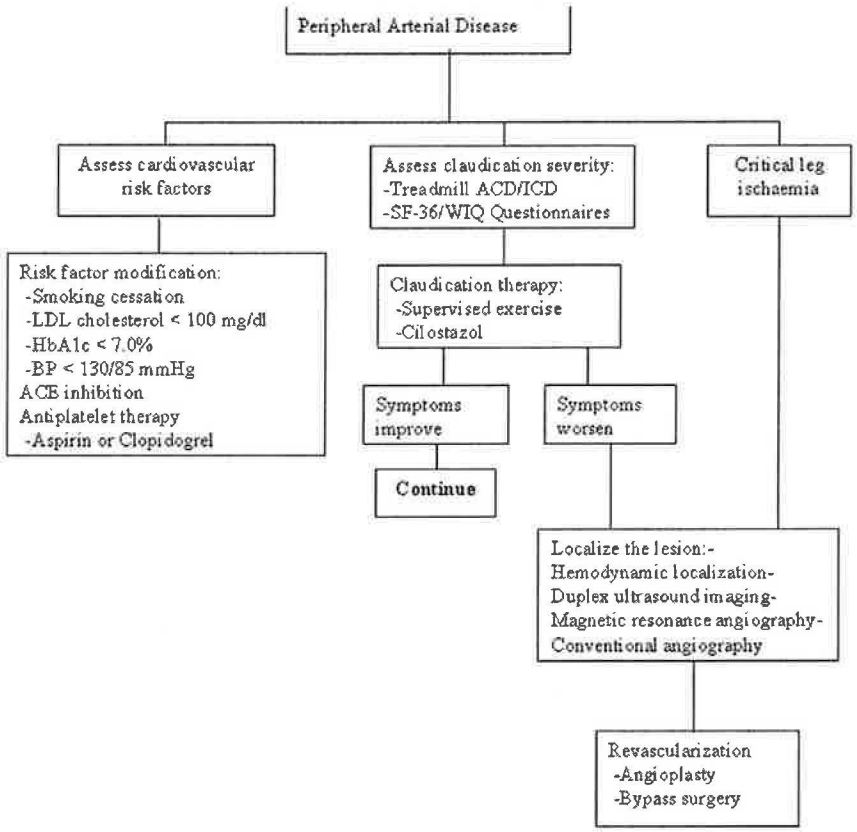
Algorithm for Medical Therapy of PAD

An exercise program should be viewed as a primary treatment modality, with adjunctive drug therapy provided in some cases. For PAD patients who are asymptomatic or who have only mild claudication, exercise alone may be sufficient. Provided there are no contraindications, drug therapy may be added for patients with function-limiting symptoms. There may be a beneficial synergy between drugs and exercise, but supporting data are lacking. Drug therapy may also be used in patients for whom invasive therapy is not indicated. Though drug treatment should complement, not replace, a program of exercise, drug therapy is still an option for those unable or unwilling to exercise regularly.[3]

As with any medical intervention, it is important to provide appropriate patient education and counseling. Common side effects of drugs should be identified, and patients should know that many of the side effects experienced with initiation of drug therapy are self-limited. Drug therapy for claudication treatment generally has a gradual onset of action. Patients should be counseled that they will not recognize immediate benefit and should continue therapy for several

weeks before considering how well the drug is working. Providers should know, however, that not all patients experience meaningful effects on their walking performance, and patients should be periodically evaluated to monitor their response to therapy. This may include use of treadmill tests, walking questionnaires, or consideration of the patient's opinion. In addition, adherence to therapy should be evaluated and possible side effects considered **(Figure 5)**.

Figure 5: Management of a PAD Patient



A trial of medical therapy is a reasonable option for patients with intermittent claudication, even though benefit is not assured. In a single-blind trial of withdrawal of therapy, neither the pentoxifylline- nor cilostazol-treated patients suffered harm by discontinuing therapy, though the benefits of the medication were lost in those who had responded -- as is true for any pharmacotherapeutic intervention.[71] This suggests that clinicians should consider a drug

"holiday" -- a trial withdrawal of chronic pharmacotherapy for claudication if there is uncertainty about the benefits of continuing the medication. The effect of withdrawal should be evident within 6 weeks. Therapy should be restarted only in patients who demonstrated benefit from it. This approach may reduce the number of patients receiving a nontherapeutic, but moderately expensive, drug treatment.

Thus, all patients with peripheral arterial disease, regardless of symptom severity, should undergo risk factor modification to achieve the listed treatment goals and receive antiplatelet drug therapy with aspirin, but clopidogrel is an acceptable alternative drug. Angiotensin-converting enzyme (ACE) inhibitors should be considered because of their potential to prevent ischemic events, which is independent of blood pressure lowering. A treadmill test to define the absolute claudication distance and the initial claudication distance can provide an objective assessment of the severity of claudication and response to therapy. The functional limitations of claudication and response to therapy can also be quantified by the physical function scales of the non-disease-specific Medical Outcomes Short Form 36 questionnaire (SF-36) and the disease-specific Walking Impairment Questionnaire (WIQ). Treatment of claudication should begin with exercise therapy or drugs such as cilostazol. Patients who do not improve and remain disabled, or who have worsening symptoms, should have additional localization of the occlusive lesions to plan endovascular or surgical intervention. Non-invasive disease localization can be done with hemodynamic tests such as segmental limb pressures and/or pulse volume recordings. In addition, duplex ultrasound and magnetic resonance angiography both have a high sensitivity and specificity for localization of lesions, but conventional angiography is still required in most patients before a surgical or angioplasty procedure. Patients with critical leg ischemia typically

have an ankle–brachial index below 0·40 and should initially be considered for localization of their occlusive disease in anticipation of the need for revascularization.

Treatments directed at relieving the symptoms of claudication do not necessarily reduce the risk for ischemic events. Thus, a broad approach is required in the treatment of PAD, recognizing that therapies to prevent mortality do not necessarily treat the symptoms.

Indications for Vascular Specialist Care

Revascularization procedures should be considered for patients who present with critical-limb ischemia, i.e., pain at rest, ulceration, or gangrene. However, before any invasive therapy (catheter-based or surgical) for intermittent claudication is considered, it is important that several criteria be met.[3]

First, the patient should have tried a program of exercise, risk factor modification, and claudication pharmacotherapy.

Second, despite such therapy, there should have remained persistent, functionally disabling symptoms that impair the ability to perform normal work or other activities important to the patient.

Third, the systemic risk of the invasive procedure must outweigh the functional benefit. In this regard, it is important to rule out other causes that may limit walking despite improvement of claudication. Such causes include angina, chronic pulmonary disease, neuropathy, or degenerative joint disease, any of which may result in decreased walking ability.

Fourth, the anticipated natural history and prognosis for each patient should be considered on an individual basis to determine the appropriateness of achieved improvements or lack thereof.

Last, a patient-specific, technically viable option with a high benefit vs. risk ratio should be available. In other words, the proposed intervention should have a low anticipated risk and a high probability of initial and long-term success.

Patients may be referred for vascular laboratory testing. Duplex scanning can often identify arterial lesions amenable to angioplasty. Other essential information can often be identified noninvasively, permitting a realistic risk-benefit discussion to be held with the patient prior to angiography.[72] For example, duplex scanning of the iliac arteries can augment the clinical finding of a normal femoral pulse, thus confirming the suitability of the common femoral artery as a source of inflow to a graft. Preoperative arteriography may not be necessary in all cases, as duplex scanning may provide the necessary information to guide subsequent interventions.[73] Duplex scanning or intraoperative assessment with on-table angiography can identify a suitable target for the distal anastomosis. However, given the time-consuming nature of complete lower extremity arterial mapping with duplex scanning and the extensive nature of lower extremity arterial disease in patients with severe ischemia, preoperative arteriography remains a standard part of most surgeons' evaluation before elective lower extremity bypass procedures.

Definition of Vascular Specialist Care: The vascular specialist may be a vascular surgeon, vascular medicine or cardiovascular physician, or interventional radiologist with experience in the evaluation of PAD patients. Issues of diagnosis, education, pharmacotherapy, and evaluation

are important for all vascular specialists. Few vascular specialists are individually capable of providing the full spectrum of diagnostic and therapeutic services; in most cases a collaborative approach is required. Appropriate care may require angiography or other imaging services, catheter-based interventions (including thrombolytic therapy, angioplasty, or stenting), surgical revascularization, amputations, reconstructive operations, and other procedures. Many revascularization procedures have uncertain long-term benefits. Care should be taken to avoid procedures for patients who do not demonstrate appropriate clinical indications.

Endovascular Treatment of Claudication:

Class I

1. Endovascular procedures are indicated for individuals with a vocational or lifestyle-limiting disability due to intermittent claudication when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (a) there has been an inadequate response to exercise or pharmacological therapy and/or (b) there is a very favorable risk-benefit ratio (e.g., focal aortoiliac occlusive disease). (Level of Evidence: A)
2. Endovascular intervention is recommended as the preferred revascularization technique for Transatlantic Inter-Society Consensus type A iliac and femoropopliteal arterial lesions (refer to appendix 1 and 2). (Level of Evidence: B)
3. Translesional pressure gradients (with and without vasodilation) should be obtained to evaluate the significance of angiographic iliac arterial stenoses of 50% to 75% diameter before intervention. (Level of Evidence: C)

4. Provisional stent placement is indicated for use in the iliac arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). (Level of Evidence: B)
5. Stenting is effective as primary therapy for common iliac artery stenosis and occlusions. (Level of Evidence: B)
6. Stenting is effective as primary therapy in external iliac artery stenoses and occlusions. (Level of Evidence: C)

Class IIa

1. Stents (and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). (Level of Evidence: C)

Class IIb

1. The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well established. (Level of Evidence: A)
2. The effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilation) is not well established. (Level of Evidence: C)

Class III

1. Endovascular intervention is not indicated if there is no significant pressure gradient across a stenosis despite flow augmentation with vasodilators. (Level of Evidence: C)
2. Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries. (Level of Evidence: C)
3. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD. (Level of Evidence: C

Medical Management after Intervention or Surgery

After any interventional procedure, medical management should include continued monitoring of complications, if any, to prevent recurrence. All lifestyle changes to accomplish risk factor reduction should be maintained. Long-term follow-up of these patients is necessary, since many of them will require repeat procedures, for the same reasons that precipitated the intervention in the first place.

Conclusion

The successful management of patients with PAD requires a concerted multidisciplinary approach, with cardiologists, vascular medicine physicians, interventional radiologists, surgeons, and their support staff working in cooperation. Each of these collaborative approaches is also more likely to be effective if performed in concert with a vascular nurse specialist. Excellence in vascular care requires communication and ongoing coordination of multiple care givers, as well as intensive patient education. A vascular nurse can often provide these key functions when physician vascular specialists may not. For all vascular interventionalists, an understanding of the etiology and progression of PAD and knowledge of procedural benefits and limitations are

critical. With a systematic regimen of exercise, lifestyle changes, and pharmacotherapy, most patients with PAD can be successfully managed, with improved limb symptoms and decreased rates of ischemic events. Revascularization, in selected cases, can preserve or restore function and maintain limb viability.

Appendix 1: TASC Lesion Classification (Iliac)

Type A lesions	▪Unilateral or bilateral stenoses of CIA
	▪Unilateral or bilateral single short (≤3 cm) stenosis of EIA
Type B lesions	▪Short (≤3 cm) stenosis of infrarenal aorta
	▪Unilateral CIA occlusion
	▪Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
	▪Unilateral EIA occlusion not involving the origins of internal iliac or CFA
Type C lesions	▪Bilateral CIA occlusions
	▪Bilateral EIA stenoses 3–10 cm long not extending into the CFA
	▪Unilateral EIA stenosis extending into the CFA
	▪Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
	▪Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA
Type D lesions	▪Infra-renal aortoiliac occlusion
	▪Diffuse disease involving the aorta and both iliac arteries requiring treatment
	▪Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA
	▪Unilateral occlusions of both CIA and EIA
	▪Bilateral occlusions of EIA
	▪Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

CIA – common iliac artery; EIA – external iliac artery; CFA – common femoral artery; AAA – abdominal aortic aneurysm.

Appendix 2: TASC Lesion Classification (Femoropopliteal)

Type A lesions

- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length

Type B lesions

- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis

Type C lesions

- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions

Type D lesions

- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

CFA – common femoral artery; SFA – superficial femoral artery.

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