Peripheral arterial disease: Epidemiology, natural history, diagnosis and treatment

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Lower extremity peripheral arterial disease (PAD) affects approximately 10% of the American population, with 30% to 40% of these patients presenting with claudication symptoms. The prevalence of PAD increases with age and the number of vascular risk factors. More importantly, it is a marker of atherosclerotic disease burden, and is associated with increased mortality from cardiovascular and cerebrovascular causes. There have been recent advances in noninvasive imaging, endovascular approaches for revascularization, and aggressive risk factor management for prevention of cardiac and cerebrovascular complications in PAD. There is now a trend toward aggressive risk factor modification and endovascular revascularization for most patients, with surgical interventions reserved for certain situations only. In the present article, a systematic review is presented, focusing on the key aspects of the disease epidemiology, presentation, natural history, diagnosis and available management options.

Key Words: *Ankle-brachial index; Claudication; Peripheral arterial disease; Vascular disease*

PREVALENCE

Approximately 50% of patients with peripheral arterial disease (PAD) are asymptomatic, making it difficult to estimate its true prevalence. Available data from population-based studies, using noninvasive diagnostic tools, suggest a progressive increase in prevalence in patients older than 40 years of age, and an association with cardiovascular risk factors such as smoking, diabetes, hypertension, hypercholesterolemia and impaired kidney function (1). An American survey of 2174 patients older than 40 years of age used the ankle-brachial index (ABI) as a screening tool, and showed a PAD prevalence of 0.9% between the ages of 40 and 49 years, 2.5% between the ages of 50 and 59 years, 4.7% between the ages of 60 and 69 years, and 14.5% for the ages of 70 years and older (1). More than 95% of patients with PAD had one or more cardiovascular disease risk factors.

Another study (2) looked at different epidemiological aspects of large-vessel versus small-vessel PAD, and found that large-vessel PAD increased dramatically with age, and was slightly more common in men and in subjects with hyperlipidemia. Isolated small-vessel PAD was unrelated to sex, hyperlipidemia or age, although it was somewhat less common before the age of 60 years. This study (2) also found that assessment of large-vessel PAD prevalence by history of intermittent claudication (IC) significantly underestimated the true prevalence, and assessment by peripheral pulse examination overestimated the true prevalence. Many patients with PAD are asymptomatic, and physical examination alone may not be a very accurate tool for diagnosis of PAD.

NATURAL HISTORY

The natural history of PAD is characterized by an increased risk of coronary and cerebrovascular ischemic events. The mortality and morbidity from these events are significantly higher than the mortality and morbidity from lower extremity complications in patients with PAD. Of the patients with known PAD, approximately 30% to 50% have evidence of coronary artery disease (3,4) and approximately 15% to 25% have significant carotid stenosis (5,6). Of the patients who present with claudication, most have stable disease requiring lifestyle modifications and medical management of risk factors. A small fraction of these patients have critical limb ischemia (CLI) or lifestyle-limiting symptoms requiring revascularization of the lower extremity arteries.

CLINICAL PRESENTATION

The diagnosis of PAD is often confounded by the increased prevalence of comorbidities causing lower extremity pain, and by the fact that a large proportion of patients may not have symptoms, or may have atypical symptoms. Thus, there has to be a high degree of clinical suspicion by the provider based on a patient's risk factors and age. The major considerations in the differential diagnosis are various causes of lumbosacral radiculopathy, such as degenerative joint disease, herniated discs and spinal stenosis. Arthritis of the hip and knees can also present with vague pain on exertion. Other vascular causes, such as vasculitis and extravascular compression, and venous diseases such as thrombosis and venous insufficiency, can also present with similar symptoms. All of these diseases are more common in elderly people and can coexist with atherosclerotic PAD, making the diagnosis more challenging. Patients with PAD can be divided into various categories based on their clinical presentation. The clinical presentation is related to the severity of the underlying disease and comorbidities.

Asymptomatic

These patients do not have typical symptoms of claudication, despite atherosclerotic PAD based on noninvasive testing. Asymptomatic PAD is much more common than symptomatic PAD (2,7,8), stressing the need for appropriate evaluation of high-risk individuals. Most studies have shown that the bulk of patients with PAD diagnosed by noninvasive testing do not

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have classic claudication symptoms. Approximately 20% of the elderly population in these survey studies (2,7,8) had objective evidence of PAD with noninvasive testing, while approximately 2% to 5% of the patients had claudication symptoms.

Atypical pain syndromes

These patients may have other comorbidities such as neuropathy or arthritis, may be physically inactive or may have an altered perception of pain along with coexisting PAD. These patients present with pain that differs from typical exertional claudication pain. Atypical pain includes pain not requiring cessation of physical activity, pain lasting longer than 10 min after cessation of physical activity, and pain that occurs both at rest and exertion (9). These atypical symptoms were the clinical presentation in 60% of the patients in a study of 460 patients with known PAD (9). In another study (8), 6417 patients at high risk for PAD were observed. It was found that approximately 47% of patients with known PAD, as well as 61% of patients newly diagnosed with PAD, had atypical symptoms.

Claudication

Claudication is defined as fatigue, discomfort or pain that occurs due to exercise-induced ischemia in specific limb muscle groups. As mentioned previously, most of the data suggest that classic claudication is present in only a small percentage of patients with PAD. These symptoms may involve different muscle groups based on disease distribution.

- Buttock and hip – aortoiliac artery disease
- Impotence – bilateral aortoiliac artery disease
- Thigh – common femoral or aortoiliac artery disease
- Upper two-thirds of the calf – superficial femoral artery disease
- Lower one-third of the calf – popliteal artery disease
- Foot claudication – tibial or peroneal artery disease

CLI and acute limb ischemia

CLI refers to a chronic, severely compromised arterial blood supply in the affected extremity that manifests as rest ischemic pain, ulcers or gangrene in various combinations. Acute limb ischemia refers to a rapid decrease of perfusion in the affected extremity that requires urgent revascularization to preserve tissue viability. Complications include rhabdomyolysis and renal failure. Other conditions can also present with limb-threatening ischemia, such as embolic disease (thromboembolism, fat embolism), vasculitides and thromboangiitis obliterans. These conditions need to be considered when determining appropriate management.

DIAGNOSIS

ABI

This is a simple, noninvasive, objective and highly reproducible test. The blood pressure is measured in the arteries supplying the legs, and is used to detect evidence of blockages. It is calculated by dividing the systolic blood pressure in the ankle (either the dorsalis pedis or the posterior tibial artery, whichever is higher) by the higher of the two systolic blood pressures in the brachial arteries. Pulse wave reflection in healthy individuals causes the ankle pressure to be 10 mmHg to 15 mmHg higher than the brachial arterial systolic pressure, and thus, the normal ABI systolic blood pressure ratio is equal to or just greater than 1.00. Generally, an ABI higher than 0.9 is considered normal, and an ABI lower than 0.9 indicates PAD with 95% sensitivity and 100% specificity compared with angiography (10). An ABI between 0.4 and 0.9 reflects mild to moderate PAD (claudication), and an ABI lower than 0.4 suggests severe lower extremity arterial disease (rest pain). If the arm blood pressures are not equal, then the presence of subclavian or axillary arterial stenosis is presumed, and the higher blood pressure is used for subsequent blood pressure ratio calculations. The ABI also serves as a surrogate marker of the overall atherosclerotic burden. Multiple studies have confirmed that patients with ABI values lower than 0.9 have a higher overall all-cause mortality rate, greater cardiovascular disease burden and more atherosclerotic risk factors (11-14). Therefore, having an ABI lower than 0.9 should raise concerns for atherosclerotic disease elsewhere.

Although ABI testing is simple and provides important diagnostic information, it has some limitations. It has poor sensitivity in patients with 'thickened arteries' secondary to arterial calcification (diabetic patients, end-stage renal disease patients, elderly patients). ABI testing in these individuals may give results in the normal (1 to 1.3) or supernormal (above 1.3) range, suggesting noncompressible, thickened vessels (15). In such cases, a toe-brachial index (TBI) measurement may be of value, because digital arteries are much less susceptible to medial calcification. Digital arterial pressures are normally lower than brachial pressures; a normal TBI is 0.7. A TBI of less than 0.7 is consistent with claudication, and a TBI of less than 0.2 correlates with rest pain (16-18). The ABI also does not give any information about the location of arterial disease. This can be overcome using segmental pressure measurements. Using this method, the blood pressure is measured with serial sphygmomanometer cuffs to locate the arterial segment with the the maximum pressure drop (19,20). Because it uses the same principle, the results of segmental pressure measurement are also subject to false elevation in patients with 'thickened arteries'. The results of ABI testing may also be falsely normal in patients with aortoiliac artery disease and in patients with extensive collaterals. Therefore, in patients with symptoms highly suggestive of lower extremity PAD, the presence of a normal or high ABI may not rule out PAD. The ABI results must be confirmed with alternative diagnostic tests (ie, TBI, exercise ABI test, Doppler waveform analysis, pulse volume recording or duplex ultrasound).

Exercise ABI testing is useful in patients with claudication symptoms who have normal ABI values. It is based on a principle similar to the exercise cardiac stress test, which assesses functional blood flow limitations. Exercise normally decreases vascular resistance and enhances blood flow to the exercising extremities. An arterial stenosis of less than 70% may not be severe enough to significantly decrease blood flow at rest, or to produce a systolic pressure gradient. Exercise in such patients can induce a systolic pressure gradient across the stenosis or, in patients with a more severe extent of disease, increase the systolic pressure gradient. Exercise testing also allows simultaneous evaluation for the presence of coronary artery disease (21). Pulse volume recording, which uses plethysmographic cuffs to measure decreases in the pulse volume, and Doppler waveform

analysis, which interprets changes in the shape of arterial waveforms with increasing arterial stenosis, are other simple, noninvasive, qualitative measures of PAD that can be used in conjunction with ABI to increase the diagnostic yield (19,22).

Arterial duplex ultrasonography

This technique is one of the most common noninvasive approaches used by vascular laboratories to define anatomy, hemodynamics and lesion morphology. This technique uses B-mode imaging, pulse wave Doppler, continuous wave Doppler and colour Doppler display. The sensitivites of duplex ultrasonography in detecting occlusions and stenoses have been reported to be 95% and 92%, respectively, with specificities of 99% and 97%, respectively (23). Some limitations of Doppler imaging include evaluation of tandem stenoses (24) and tibial vessel imaging (25).

Lower extremity examinations using the duplex Doppler begin at the common femoral artery and proceed distally to the popliteal artery. An area of stenosis is localized with colour Doppler and assessed by measuring Doppler velocities at several arterial sites. The normal peripheral arterial velocity waveform is triphasic. It consists of a forward flow systolic peak, then a reversal of flow in early diastole and finally, forward flow in late diastole. With progressive PAD, the reverse flow is eliminated, the systolic peak decreases and the flow in diastole increases.

Another important use of duplex ultrasound is in graft surveillance, especially in patients with saphenous vein grafts, which are at an increased risk of developing stenosis (26) and, thus, graft failure. Once the graft thromboses, secondary patency rates are very poor. If the stenosis is detected and repaired before graft thrombosis, it is estimated that 80% of grafts would be salvaged (27,28). A well-organized graft surveillance program is crucial to preserve the patency of bypass grafts. If graft stenosis is detected noninvasively using duplex ultrasonography, it is recommended to pursue further definitive studies, such as arteriography or magnetic resonance angiography (MRA), for graft salvage.

Modalities to define arterial anatomy

Imaging modalities are required when either conservative measures to control IC fail, or the patient presents with CLI or acute limb ischemia, and when interventions (endovascular or surgical) are required to relieve symptoms or salvage the limb. Because management involves specific interventions based on the site of arterial stenosis, the purpose of these imaging modalities is to provide the operator with a 'road map' that defines the location, distribution and severity of the disease. Conventional catheter angiography has traditionally been the gold standard, and the only method that defines the anatomy to the extent required by surgeons and interventionalists, which helps in choosing the best therapeutic options for patients with PAD; its usefulness has been validated by years of experience (29). However, with advances in MRA and multidetector computed tomography (MDCT) in the past decade, similar results can be achieved in centres with extensive experience in performing and interpreting these studies. Both of these techniques have unique advantages and applications. Gadolinium-enhanced MRA offers excellent images and has been developed to provide a noninvasive alternative to diagnostic intra-arterial digital subtraction angiography (DSA) in the evaluation of atherosclerotic PAD (30-33). Magnetic resonance techniques offer unique advantages compared with conventional DSA. It does not require the use of nephrotoxic contrast, which is beneficial to patients with PAD, who often have renal insufficiency and/or renal artery stenosis. It is noninvasive, other than a simple intravenous gadolinium injection, compared with DSA, which requires selective catheterization of the diseased vessels, with the associated risks. Neither the patient nor the operator are exposed to harmful ionizing radiation, and MRA also offers great detail about the associated surrounding structures (bone, soft tissue). A limitation that occurs in all magnetic resonance imaging modalities is that MRA cannot be applied when metal clips or stents are present because they can mimic vessel occlusions. Patients with pacemakers and defibrillators, as well as some cerebral aneurysm clips, may not be able to be scanned safely (34). MRA performed with gadolinium has, on rare occasion, been associated with renal toxicity in patients with elevated creatinine levels (35). It also tends to overestimate the degree of stenosis because of turbulence. MDCT requires the use of contrast and exposure to damaging radiation, and is less sensitive and specific than MRA, but it offers some unique advantages over MRA. It can be performed in patients with metallic foreign bodies such as metal stents and pacemakers, and it has a relatively simple protocol with short time requirements. The technology of MDCT is evolving very rapidly, and image quality continues to improve.

A meta-analysis of MRA compared with catheter angiography demonstrated that the sensitivity and specificity of MRA were both in the range of 90% to 100% for the detection of stenoses larger than 50%, with the greatest accuracy occuring when gadolinium enhancement was used (36). The most current studies report similar results (37), with agreement between MRA and catheter angiography of 91% to 97%. In another meta-analysis (38) comparing 34 studies with a total of 1090 patients, three-dimensional, gadolinium-enhanced MRA was highly accurate for assessment of all lower extremity arteries. However, for such results to be achieved in actual practice, a lot of expertise in performing and interpreting these studies is required. Therefore, DSA continues to be performed because of the ease of availability and physician preference.

MANAGEMENT

PAD management involves risk factor modification to decrease overall cardiovascular risk and improve the symptoms of IC.

Coronary risk factor modification

The primary aim of the physician, considering the natural history of PAD, should be to identify individuals at risk for PAD, because the majority of patients are asymptomatic. These patients are at risk for adverse cardiovascular events unless PAD is recognized. The overall goals of medical therapy for patients with PAD are to prevent progression of atherosclerotic disease, minimize the occurrence of cardiovascular events, improve functional status in patients with claudication and prevent limb loss.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for PAD, which were produced in collaboration with major vascular medicine, vascular surgery and interventional radiology societies, identified the following groups at risk for lower extremity PAD (39): all patients older than 70 years of age, irrespective of

risk factors or presence of symptoms; patients 50 to 69 years of age, with a history of smoking and/or diabetes; and patients 40 to 49 years of age, with diabetes and at least one other risk factor for atherosclerosis, leg symptoms suggestive of claudication with exertion, ischemic pain at rest, abnormal lower extremity pulse examination or known atherosclerosis at other sites (coronary, carotid or renal arterial disease). In such patients, the standard review of symptoms should include questions related to a history of walking impairment, symptoms of claudication, ischemic rest pain or nonhealing wounds (39). Resting ABI should be measured in patients with one or more of these findings.

Various studies looking at the natural history of PAD have shown that the bulk of mortality and morbidity is secondary to cardiovascular and cerebrovascular causes, with stable symptomatic PAD progressing to worsening claudication in only about 20% of symptomatic patients. The majority of patients are therefore stable, and management involves recognizing the fact that PAD is a marker of atherosclerotic disease burden that needs to be reduced. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (40) considered PAD to be a coronary heart disease risk equivalent, thereby requiring aggressive risk factor modification similar to patients with known coronary artery disease. The following sections address individual modifiable risk factors.

Cigarette smoking: Smoking cessation has been shown to reduce progression of PAD and improve graft patency rates compared with patients who continue smoking (41,42). Smoking cessation is also the most major and modifiable risk factor for coronary and cerebrovascular atherosclerosis. Whether smoking cessation helps in reducing symptoms in patients with claudication is still not clear (43). However, many observational studies have shown that the risk of myocardial infarction (MI), stroke and limb loss are higher in individuals with PAD who continue smoking than in individuals who quit (44,45). Patients should be made aware of the role of smoking in contributing to the progression of atherosclerosis, including the risks associated with coronary disease, cerebrovascular disease and PAD, as well as increased likelihood of failure of interventions should they continue smoking. Regular physician follow-up and support, combined with pharmacological support (nicotine patch, bupropion), can achieve success rates as high as 16% to 30%, compared with 0.1% in individuals who try to quit on their own (46,47).

Hyperlipidemia: The emerging use of statins for preventing the progression of coronary and cerebrovascular atherosclerotic disease also applies to PAD. Currently, the ACC/AHA recommends a goal low-density lipoprotein (LDL) level of less than 100 mg/dL in all patients with PAD, and a goal LDL level of less than 70 mg/dL for individuals at 'very high risk' for PAD. Patients at 'very high risk' are described by the ACC/AHA guidelines (40) as having established PAD, plus multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking) or multiple risk factors of the metabolic syndrome. The metabolic syndrome is defined by a triglyceride level of 150 mg/dL or greater, a high-density lipoprotein (HDL) cholesterol level lower than 40 mg/dL, blood pressure 130/85 mmHg or greater, a fasting plasma glucose level of 6.1 mmol/L (110 mg/dL) or greater, and abdominal obesity. Statins have also been shown to prevent new onset of claudication and slow the progression of worsening claudication in several studies (48-51).

Diabetes: Diabetes is a well-recognized risk factor for microvascular disease that can lead to nephropathy, retinopathy and neuropathy (52,53). The role of diabetes in PAD was shown to be related to increased glycosylated hemoglobin (HbA1c) levels in a recently finished study (54) in which 1894 individuals were evaluated for complications and prevalence of PAD by comparing different HbA1c values. This study showed that there was a positive, graded, independent association between HbA1c levels and PAD risk in diabetic adults.

Based on these observations and the important role of glycemic control in patients with coronary disease, it seems reasonable to follow an aggressive approach toward treating diabetes. A goal HBA1c level of less than 7% is recommended; 6% is preferrable. This is in agreement with the current recommendations of the American Diabetic Association and the ACC/AHA. Also important for diabetic patients is meticulous and regular foot care, because patients with PAD and diabetes have a very high risk of foot complications secondary to neuropathy and small- or large-vessel arterial disease.

Hypertension: The goals for management of hypertension are similar to other patient groups. Systolic and diastolic blood pressures should be reduced below 140 mmHg systolic and 90 mmHg diastolic in nondiabetic patients, and below 130 mmHg systolic and 80 mmHg diastolic in diabetic and chronic renal insufficiency patients (55). There have been some concerns that beta-blockers worsen PAD symptoms, secondary to a beta-2 blockade; however, most of the available data do not support this theory (56). Beta-blockers can, therefore, be used in patients with mild to moderate PAD without any significant adverse effects; they are important in the management of patients with concomitant hypertension, coronary artery disease and heart failure. Angiotensin-converting enzyme inhibitors reduce the risk of death and nonfatal cardiovascular events in patients with coronary artery disease and left ventricular dysfunction (57,58). These drugs are a good choice for patients with hypertension accompanied by heart failure, structural heart disease or renal disease along with PAD. Their primary role is to decrease the morbidity and mortality related to the hypertension and extensive atherosclerotic burden in these patients. The Heart Outcomes Prevention Evaluation (HOPE) study (59) showed that angiotensin-converting enzyme inhibitors given to patients with PAD only, compared with patients with known coronary disease, provided a similar reduction in cardiovascular mortality, reinforcing the concept that PAD is a coronary artery disease risk equivalent and indicates increased overall atherosclerotic burden in the body.

Antiplatelet agents: The major role of this class of drugs is to prevent MI, stroke or vascular death in patients with PAD. Based on the current data, it is recommended that all patients with PAD take acetylsalicylic acid in doses ranging from 75 mg to 325 mg per day, or clopidogrel 75 mg daily, for patients who are allergic to acetylsalicylic acid (39). The Antithrombotic Trialists' Collaboration meta-analysis (60), published in 2002, reviewed 287 studies involving 135,000 patients to determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events. Overall, among 9214 patients with PAD in 42 trials, there was a proportional reduction of 23% in 'serious vascular events' – that is, nonfatal MI, nonfatal stroke or death from a vascular cause, including any death

from an unknown cause, because most deaths in high-risk patients are likely due to vascular causes. Similar benefits were found among patients with IC, peripheral grafting and peripheral angioplasty. One study, Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) (61), compared clopidogrel (75 mg) with acetylsalicylic acid (325 mg) for cardiovascular risk reduction. The study showed a relative risk reduction of 8.7% clopidogrel compared with acetylsalicylic acid, with a similar safety profile. However, acetylsalicylic acid, because of its low cost, extensive history and associated cardiovascular disease benefits, continues to be the most commonly used antiplatelet drug in patients with PAD. There is currently no indication for combination therapy with acetylsalicylic acid and clopidogrel in patients with PAD alone for primary prevention of ischemic events. Antiplatelet therapy has also been shown to decrease the risk of arterial occlusion and the need for revascularization when used over an extended period of time (62,63). Its use, however, has not been shown to prevent the development of symptoms of claudication (64,65).

Symptomatic therapy

Exercise regimen: Structured exercise programs should be the initial approach to the management of claudication symptoms in patients with lifestyle-limiting PAD. Exercise rehabilitation has been shown to lead to an increase in the walking distance travelled before the onset of claudication symptoms, improvement in quality of life and improvement in functional status in multiple trials (66). The benefits achieved from exercise programs may be as good as the results achieved from a bypass procedure or angioplasty, and better than medical therapy for claudication. However, the exercise programs must be performed at least three to four times a week, under the supervision of a physical therapist, for a duration of at least 30 min to 45 min. They must be maintained for at least 12 weeks, and the exercise level should be adjusted (increased) to the patient's functional improvement. Exercise performed without supervision does not achieve the same level of benefit as a supervised exercise program (67). The exercise regimen is maintained until the patients experience leg pain, which is followed by a period of rest; exercise resumes after the symptoms resolve. The exact mechanism that leads to improvement is not clear at present; however, it is most likely secondary to changes in the muscle metabolism (better oxygen delivery, increased oxygen extraction, alternative methods of ATP generation), rather than formation of collaterals as previously thought.

In addition to improving symptoms, exercise training also helps to control cardiovascular risk factors by improving blood pressure and serum lipid profile; it increases HDL values, decreases triglyceride values and improves glycemic control. Exercise programs can also be used with other medical therapies, and in patients who have undergone bypass or endovascular procedures. Individuals with concomitant coronary disease may have exacerbation of underlying ischemic symptoms with initiation of this program. However, such events are relatively rare, and there is currently no indication for a routine cardiac stress test before beginning an exercise program. If individuals have symptoms of angina during exercise, appropriate evaluation would be indicated.

Pharmacological therapy for claudication

Cilostazol: Cilostazol is a quinolinone derivative and a phosphodiesterase type 3 inhibitor that increases intracellular cyclic AMP. It has been shown to improve symptoms in patients with moderate to severe claudication, with improvements in walking distances of 40% to 60% compared with placebo. It was approved by the Food and Drug Administration (FDA) for the treatment of IC in 1999. Its effects include inhibition of platelet aggregation (68), direct arterial vasodilation (modest improvement in ABI) (69), mild elevation of HDL, decrease in triglyceride levels (70) and inhibition of vascular smooth muscle proliferation (71). The modest improvement in ABI is not sufficient to explain the significant improvement in the patients' symptoms. Therefore, the exact mechanism of how cilostazol improves symptoms in these patients is still unclear. The efficacy of cilostazol has been demonstrated in several studies (72-76) and in a meta-analysis (77) of eight randomized, placebo-controlled trials that included 2702 patients with stable moderate to severe claudication. In the meta-analysis (77), treatment with 100 mg of cilostazol twice daily for 12 to 24 weeks increased maximal and pain-free walking distances by 50% and 67%, respectively. Doses of 100 mg twice a day were more effective than 50 mg twice a day.

Cilostazol appears to be more effective than pentoxifylline. This was illustrated in a trial of 698 patients randomly assigned to cilostazol (100 mg twice daily), pentoxifylline (400 mg three times daily) or placebo for 24 weeks (76). The increase in mean maximal walking distance over baseline with pentoxifylline and placebo was the same (30% and 34%, respectively), but the increase with cilostazol was significantly greater (54%). Various reported side effects in clinical studies include headache (approximately 34% of patients taking 100 mg twice daily), loose and soft stools, diarrhea, dizziness and palpitations (73,75). Because other phosphodiesterase type 3 inhibitors (milrinone) have been shown to increase mortality in chronic stages 3 and 4 heart failure, the FDA currently has a black box warning on the medication package for patients with heart failure.

Based on the evidence of benefit, a therapeutic trial of cilostazol (100 mg orally twice daily) is recommended, in the absence of heart failure, for improving symptoms and increasing walking distance in patients with lifestyle-limiting claudication, particularly if antiplatelet agents and exercise rehabilitation are ineffective, and revascularization cannot be offered or is declined by the patient (39,78).

Cilostazol should be taken 30 min before or 2 h after eating, because high-fat meals markedly increase absorption. Several drugs, such as diltiazem and omeprazole, as well as grapefruit juice, can increase serum concentrations of cilostazol if taken concurrently. Cilostazol can be taken safely with acetylsalicylic acid and/or clopidogrel without an additional increase in bleeding time (79).

Pentoxyfylline: Pentoxyfylline is a methylxanthine derivative that was approved by the FDA in 1984, before cilostazol. It is a rheological modifier and decreases blood viscosity by improving erythrocyte flexibility, decreasing fibrinogen levels and inhibiting platelet aggregation. Pentoxifylline also reduces the development of atherosclerosis (80). While some studies have shown marginal benefits in walking distance (43,80-83), a randomized, controlled trial comparing pentoxyfylline with placebo and cilostazol found no difference in pain-free or maximal walking distance between the placebo and pentoxifylline treatment groups, whereas cilostazol improved both pain-free and maximal walking distances (76). Pentoxifylline is generally

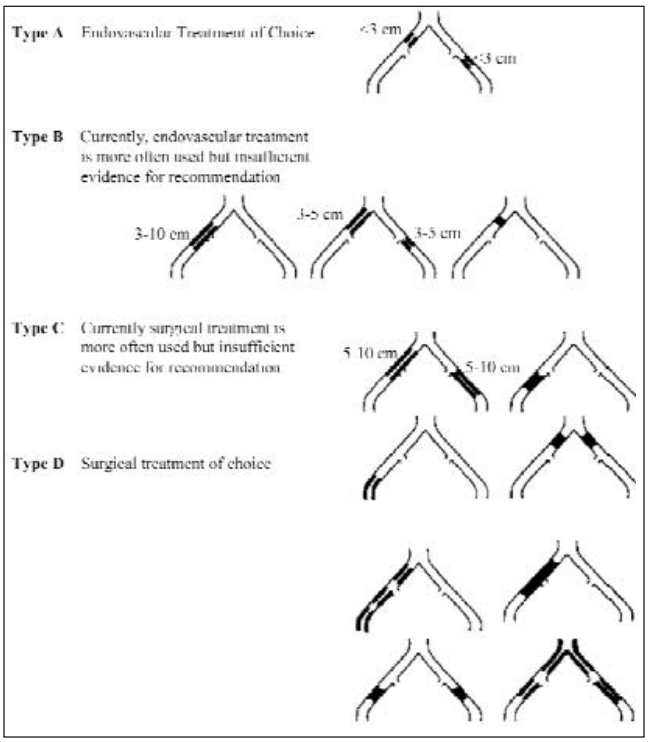

Figure 1) *Summary of preferred options for interventional management of iliac lesions. Reprinted with permission from reference 93. Copyright 2000, Elsevier BV*

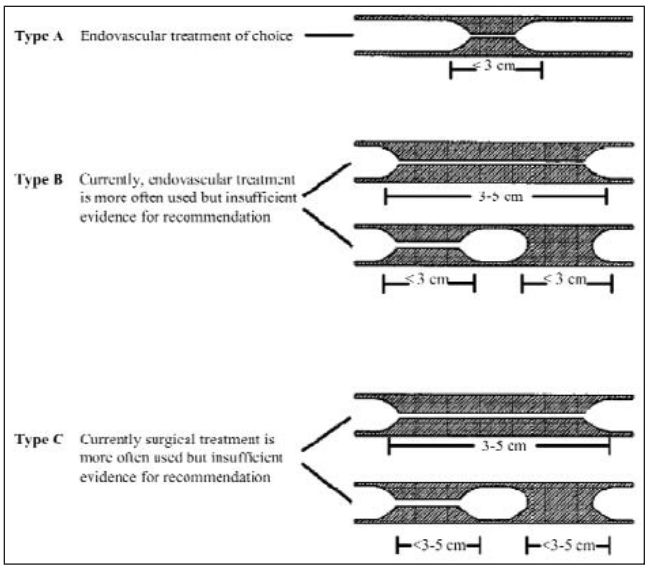

Figure 2) *Summary of preferred options for interventional treatment of femoropopliteal lesions. Reprinted with permission from reference 93. Copyright 2000, Elsevier BV*

very well tolerated, with a low incidence of side effects. It is, however, not recommended in patients with recent cerebral or retinal hemorrhage, or with a history of sensitivity to methylxanthines, such as caffeine, theophylline and theobromine. Although pentoxifylline is recommended for the treatment of IC, a meaningful response is seen only in a minority of patients.

The ACC/AHA currently recommends that pentoxyfylline (400 mg three times per day) be considered a second-line agent to cilostazol to improve walking distance, whereas the Seventh American College of Chest Physicians Consensus Conference does not recommend the use of pentoxyfylline (84).

REVASCULARIZATION

Patients with lifestyle-limiting claudication after aggressive medical management, rest pain or limb-threatening ischemia are candidates for revascularization. Revascularization may be surgical or endovascular, with percutaneous balloon angioplasty, and with or without stenting, based on the lesion characteristics. For management purposes, lower extremity PAD can be subdivided into three categories based on similar prognosis and approach to management – aortoiliac, femoropopliteal and infrapopliteal disease.

Aortoiliac artery disease

There has been a shift over the past decade regarding the best revascularization approach in patients with disease in the inflow vessels. The aorta and the common iliac artery are called the inflow vessels, and patients with atherosclerotic occlusive disease of the inflow vessels are also likely to have distal disease involving the femoral and tibial arteries. In such patients with extensive disease, correction of the inflow lesions is initially performed in a staged procedure because it can lead to improvement in distal lesions without additional procedures.

The less invasive nature and comparable success rates of endovascular approaches, such as percutaneous transluminal angioplasty, with or without stenting, have prompted them to become the standard first approach for patients requiring revascularization of the aortoiliac vessels, over more invasive surgical bypass procedures (85,86). Also, 'primary stenting' is better than 'provisional stenting' for patients who require repeat procedures after balloon angioplasty for restenosed vessels (85). There are various types of stents that can be used; the common ones are self-expandable nitinol stents and balloon-expanded stainless steel stents. There is some indication that nitinol stents may work better in the long term (87); however, more data are required before this idea can be applied. The most serious complications from percutaneous transluminal angioplasty include distal embolization in approximately 4% to 7% of patients (88) and, very rarely, arterial rupture. Surgical bypass procedures are usually reserved for patients with extensively diseased arterial segments and lesions not amenable to endovascular approach (Figure 1).

Femoropopliteal artery disease

Atherosclerotic occlusive disease in these arterial segments is more common and there is no strong evidence for or against an endovascular approach versus surgical bypass. Lesions in this territory initially respond well to recanalization procedures by the endovascular approach; however, the rate of restenosis is higher compared with the aortoiliac area. Even so, stenting in these segments is associated with a significant risk of restenosis. Various approaches to prevent restenosis, such as debulking devices, directional atherectomy, excimer lasers and rotational atherectomy, have been tried but have not been shown to significantly reduce the rate of restenosis. With the advent of drug-eluting stents, which have been useful in decreasing the

rate of restenosis in coronary artery stenting, there may be better results. This was shown in a series of patients with long-segment superficial femoral artery disease; those receiving rapamycin-coated nitinol self-expanding stents developed much less intimal thickening and restenosis at six months (89). However, these stents had problems with strut fractures that precluded clinical application (Figure 2).

Infrapopliteal artery disease

These include the anterior and posterior tibial arteries, and the peroneal arteries. Disease in these vessels usually has accompanying disease proximally, which should be corrected first, because that may relieve disease symptoms in itself. However, if the patient presents with CLI, revascularization in these and the more proximal vessels is also required. Recently, the approach to infrapopliteal disease has changed from the surgical approach, reserved for patients with severe disease accompanied by gangrene and ulcers, to the endovascular approach, with a low threshold for intervention, because it achieved similar success rates and good long-term rates of arterial patency. Primary success rates are generally 80% to 95%, and cumulative two-year patency rates are about 75% (90-92). This is true even in patients with coexisting microvascular disease (diabetic patients), in whom there are concerns regarding the success of small-vessel interventions (93,94).

CONCLUSIONS

PAD is a significant health problem and is associated with increased cardiovascular morbidity and mortality. The ABI is a simple and effective test for diagnosing PAD. Management of PAD includes therapies to improve symptoms and measures to reduce cardiovascular events. All patients with PAD should receive an antiplatelet agent, statins to lower LDL below 100 mg/dL, and optimal therapy for hypertension and diabetes. Most patients with lifestyle-limiting claudication can be treated with endovascular techniques, with a few individuals requiring vascular bypass surgery.

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