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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Peripheral arterial disease: Recognition and medical management

■ ABSTRACT

Peripheral arterial disease (PAD) is common but has a variable presentation and is often unrecognized and undertreated. Patients with PAD have an increased risk of cardiovascular events and death. The ankle-brachial index is a quick, reliable diagnostic tool that also helps assess disease severity and prognosis. Treatment goals for PAD are to improve symptoms, enhance functional performance, prevent limb amputation, and reduce cardiovascular complications.

■ KEY POINTS

Classic claudication consists of predictable leg discomfort induced by walking, relieved with rest, and recurring when walking resumes. Not all patients have symptoms, however, and many patients have atypical leg symptoms.

Angiography and revascularization should be considered for patients with lifestyle-limiting symptoms, pain at rest, or ischemic ulcers that do not heal.

Tightly controlling blood pressure significantly reduces the chance of myocardial infarction, stroke, and death due to vascular disease. Smoking cessation and control of hyperlipidemia and diabetes are mandatory. A supervised walking program is recommended.

A 63-YEAR-OLD MAN comes to the clinic because of fatigue in the right leg: when he walks it feels tired, heavy, and tight. The symptoms improve with rest, then recur when he resumes walking. He has quit golfing as a result.

He has no known atherosclerotic disease or diabetes. He has smoked 1 pack of cigarettes a day for 45 years.

Laboratory values.
- Total cholesterol 280 mg/dL
- Triglycerides 358 mg/dL
- Low-density lipoprotein cholesterol (LDL-C) 127 mg/dL
- High-density lipoprotein cholesterol (HDL-C) 33 mg/dL.

Physical examination. No ulcerations and no varicose veins. Decreased right popliteal, dorsalis pedis, and posterior tibial pulses. Blood pressure 159/97 mm Hg (untreated) in both upper extremities.

What should you do?

■ PREVALENT, BUT OFTEN OVERLOOKED

Peripheral arterial disease (PAD) refers to occlusive atherosclerotic disease of the abdominal aorta and the lower extremities.

The reported prevalence of PAD depends greatly on the demographic factors of the population studied and on the method of diagnosis. For example, it is more common among African Americans than among non-Hispanic whites (odds ratio 2.3). This difference is not completely explained by the higher prevalence of cardiovascular risk factors such as diabetes, hypertension, and obesity in African Americans.[1]

PAD is too often undiagnosed, and only a

Novel risk factors as predictors of peripheral arterial disease
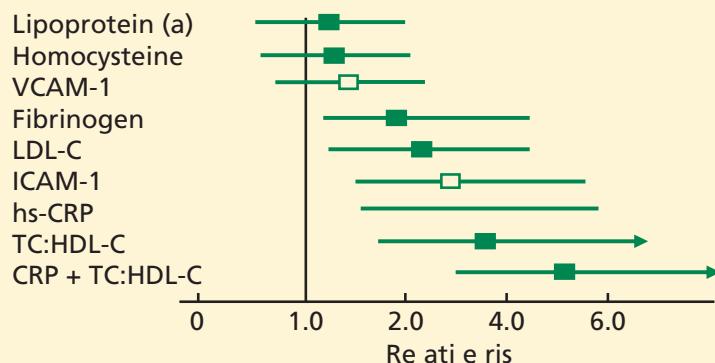
VCAM-1: vascular cell adhesion molecule 1
LDL-C: low-density lipoprotein cholesterol
ICAM-1: intercellular adhesion molecule 1
TC:HDL-C ratio of total cholesterol to high-density lipoprotein cholesterol
CRP: C-reactive protein
hs-CRP: high-sensitivity C-reactive protein

FIGURE 1. Novel risk factors as predictors of peripheral arterial disease (PAD). Relative risk has been adjusted for age, smoking, diabetes, hypertension, family history of PAD, exercise level, and body mass index.

FROM SMITH SC JR, MILANI RV, ARNETT DK, ET AL. ATHEROSCLEROTIC VASCULAR DISEASE CONFERENCE: WRITING GROUP II: RISK FACTORS. CIRCULATION 2004; 109:2613–2616; DATA FROM RIDKER PM, STAMPFER MJ, RIFAI N. NOVEL RISK FACTORS FOR SYSTEMIC ATHEROSCLEROSIS: A COMPARISON OF C-REACTIVE PROTEIN, FIBRINOGEN, HOMOCYSTEINE, LIPOPROTEIN(A), AND STANDARD CHOLESTEROL SCREENING AS PREDICTORS OF PERIPHERAL ARTERIAL DISEASE. JAMA 2001; 285: 2481–2485 AND PRADHAN AD, RIFAI N, RIDKER PM. SOLUBLE INTERCELLULAR ADHESION MOLECULE-1, SOLUBLE VASCULAR ADHESION MOLECULE-1, AND THE DEVELOPMENT OF SYMPTOMATIC PERIPHERAL ARTERIAL DISEASE IN MEN. CIRCULATION 2002; 106:820–825.

minority of patients (approximately 25%) are undergoing proper treatment.[2] This underdiagnosis may be, at least in part, due to the fact that only 10% to 30% of all PAD patients present with the classic symptoms of intermittent claudication.[3] At least 10 million Americans are estimated to have PAD, and 4 million have the classic symptom of intermittent claudication.[4] However, up to 1.3 million people may develop disabling intermittent claudication every 2 years for the next 50 years.[5]

The PARTNERS (Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival) program evaluated nearly 7,000 people at risk (age > 70, or age 50–69 with a history of smoking or diabetes mellitus) attending primary care practices. PAD was detected in 1,865 (29%) of the

patients, but had not been previously diagnosed in more than 800 of them. Patients who had both PAD and cardiovascular disease were more likely to have been diagnosed than patients with PAD alone. Of those with a prior diagnosis of PAD, only 83% were aware of it, and worse, only 49% of their current physicians knew about it.[6,7]

■ PATHOPHYSIOLOGY AND RISK FACTORS

PAD is a manifestation of systemic atherosclerosis that has developed over many years. Along with coronary artery disease and cerebrovascular disease, PAD is one of the three major syndromes of atherothrombosis.

Atherothrombosis is the term currently used to describe the process of thrombus formation on top of a ruptured plaque located at a diseased arterial segment. Such atherosclerotic plaques tend to occur at vessel bifurcations, presumably due to both impaired atheroprotective mechanisms and disturbed blood flow leading to local intimal injury. When clinically significant atherosclerosis is present in multiple vascular beds, it is often referred to as *panvascular disease*.

The risk factors for PAD are similar to those for coronary heart disease. Age, diabetes mellitus, and cigarette smoking are particularly strong risk factors for PAD. The prevalence of PAD increases by up to twofold per decade of life, and both diabetes mellitus and smoking increase the risk independently by threefold to fourfold each. PAD symptoms are seen almost a decade earlier in smokers, and the likelihood of PAD increases by 40% for every 10 cigarettes smoked daily. An analysis of the Framingham study suggested that smoking accounts for approximately 75% of all PAD risk.[8–13]

Other conventional risk factors for PAD include dyslipidemia, hypertension (found in 50%–92% of PAD patients), hyperhomocysteinemia, and chronic kidney disease. A number of novel risk factors for PAD have also been identified (**FIGURE 1**).[14–16]

The pathophysiology of intermittent claudication is not explained simply by the mismatch between oxygen supply and demand. The chronically ischemic skeletal muscle fiber undergoes important metabolic changes (accumulation of metabolic intermediates,

altered control of mitochondrial respiration, increased systemic oxidative stress, and accumulation of somatic mitochondrial DNA mutations) compatible with an "acquired metabolic myopathy" that manifests clinically as muscle weakness, functional impairment, and walking limitation.[17–19]

NATURAL HISTORY OF SYMPTOMATIC PAD

Lower extremity outcomes

Earlier data suggested that most cases of claudication follow a stable course and only a minority of patients have worsening leg symptoms. Nevertheless, when objective functional measures were used, even individuals with PAD who do not report any leg symptoms appear to have impaired lower extremity function, and they often often limit their physical activity to avoid painful symptoms.[20–26]

Cardiovascular morbidity and death

Individuals with PAD are also at risk of atherosclerotic cardiovascular disease. In an angiographic study, Hertzer and coworkers[27] reported that approximately 30% of patients with symptomatic PAD also had coronary artery disease that was severe enough to warrant surgical revascularization.

Both symptomatic and asymptomatic PAD (the latter diagnosed by an abnormal ankle-brachial index—the systolic blood pressure in the foot divided by the pressure in the arm; see below) independently predict adverse outcomes in people presenting with coronary artery disease.

The 5-year death rate in PAD is higher than that in breast cancer. Patients with PAD are four times as likely to have a myocardial infarction, are two to three times more likely to have a stroke, and are at a three times higher risk of death compared with the general population.[27–30]

SYMPTOMS MAY NOT CORRELATE WITH SEVERITY

Leg symptoms

As in coronary artery disease, symptoms of peripheral arterial disease may not correlate with disease severity: vulnerable plaques that may not have caused significant stenosis may

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TABLE 1

Identifying lesion location by symptoms

MUSCLE GROUPS AFFECTED	LOCATION OF OBSTRUCTION
Buttock, hip, thigh	Aorta or iliac artery
Thigh, calf	Femoral arteries or their branches
Calf, ankle, foot	Popliteal or superficial femoral arteries

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unexpectedly rupture and cause a complete occlusion.

One can usually deduce which arteries are involved on the basis of the symptoms (**TABLE 1**), even without angiography and sometimes without a pulse volume recording study (see below). For example, symptoms involving the buttocks, hip, and proximal thighs typically occur with aortoiliac disease, while calf claudication occurs with femoropopliteal involvement, being present in over 60% to 70% of such patients. Resting pain and ischemic leg ulcers are typical with multilevel disease and when the ankle-brachial index is less than 0.4.

Intermittent claudication. The term claudication is a misnomer, as it comes from the Latin word *claudicare*, meaning to limp. The Rose questionnaire, specifically designed to detect claudication secondary to arterial insufficiency, has been used in clinical trials since the 1960s. It defines intermittent claudication as leg pain with a characteristic pattern:
- It does not occur at rest
- It does not resolve with walking
- It prompts the patient to stop walking
- It disappears within 10 minutes of stopping to rest.

However, only a minority of patients with PAD (about 10%) report this classic pattern. About 50% describe a variety of other leg symptoms (fatigue, numbness, tightness, or heaviness), and 40% do not mention leg pain. On the other hand, patients walk more slowly than usual, and typically can walk only one half to four blocks before they must stop to rest. Quality of life is usually affected, with reduced ability to participate in leisure and work activities.

Critical limb ischemia. Chronic limb-threatening ischemia is indicated by pain at rest, ischemic ulcers, or gangrene. Its different

The risk of PAD increases by 40% with every 10 cigarettes smoked daily

TABLE 2

Clinical categories of critical limb ischemia

GRADE	CATEGORY	CLINICAL DESCRIPTION	OBJECTIVE CRITERIA
0	0	Asymptomatic	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise (5 minutes at 2 miles per hour on a 12% incline) Ankle pressure after exercise > 50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and ankle pressure after exercise < 50 mm Hg
II*	4	Ischemic rest pain	Resting ankle pressure < 40 mm Hg Flat or barely pulsatile ankle or metatarsal pulse volume recording Toe pressure < 30 mm Hg
III*	5	Minor tissue loss— nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure < 60 mm Hg Ankle or metatarsal pulse volume recording flat or barely pulsatile Toe pressure < 40 mm Hg
	6	Major tissue loss— extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

*Grades II and III, categories 4, 5, and 6, are embraced by the term chronic critical ischemia

RUTHERFORD RB, BAKER JD, ERNST C, ET AL. RECOMMENDED STANDARDS FOR REPORTS DEALING WITH LOWER EXTREMITY ISCHEMIA: REVISED VERSION. J VASC SURG 1997; 26:517–538.

Features of acute limb ischemia:
- **Pain**
- **Pallor**
- **Paresthesia**
- **Paralysis**
- **Pulselessness**
- **Poikilothermia**

clinical categories are outlined in **TABLE 2**.[31,32] Some patients keep their affected leg dependent to relieve their resting pain, and this occasionally results in secondary edema and rubor of the dependent leg. Elevation pallor should also be sought when evaluating for critical limb ischemia.

The clinical features of **acute limb ischemia** include some or all of the six "P's" (pain, pallor, paresthesia, paralysis, pulselessness, and poikilothermia).[32] Paresthesias and paralysis are the most ominous signs and generally indicate irreversible ischemic injury. In extreme cases, muscle rigidity indicates a nonsalvageable limb.

Ankle-brachial index

Most patients with PAD have no symptoms, and few of those who have symptoms report them to their health care providers. Furthermore, many patients with intermittent claudication have a completely normal physical examination at rest, including peripheral pulses and no bruits. Findings such as thickened nails, poor hair growth, and cold hands and feet are not reliable indicators of arterial insufficiency.

Thus, the use of objective measures to screen patients at risk is essential to establish the diagnosis. Patients at high risk include those with known atherosclerotic disease in other vascular beds, diabetes mellitus, and age greater than 70, or greater than 50 with one or more cardiovascular risk factors such as active or remote smoking history, dyslipidemia, dysglycemia (elevated glucose in a nondiabetic range), hypertension, or a family history of atherosclerotic vascular disease.

The first step in the workup is to measure the resting ankle-brachial index: the ratio of the higher systolic blood pressure measured at the ankle arteries to the highest systolic pressure of the brachial arteries. Normal is greater than 0.90, ie, the pressure in the ankle should be at least 90% of that in the arm (**TABLE 3**). Requiring only a blood pressure cuff and a portable Doppler device, this office test is noninvasive, inexpensive, simple, and reliable and has become the diagnostic test of choice for detecting PAD, having 95% sensitivity and 99% specificity.

If the resting ankle-brachial index is normal but the clinical suspicion for PAD is high, it should also be measured before and during exercise. Patients walk at 2 miles per hour on a graded treadmill for a maximum of 5 minutes; a fall in blood pressure of more than 20 mm in the ankle (with a corresponding drop in the ankle-brachial index) with exercise suggests PAD.

Our patient's ankle-brachial index was 0.72 in his right leg, which indicates mild disease. In his left leg the index was normal at 1.0.

Pulse volume recordings

Pulse volume recordings provide a more detailed physiologic and anatomic evaluation of the arteries of the leg, detecting changes in the volume of blood flow through the limb. Signs of abnormal waveforms include slower upstroke, absence of a dicrotic notch, decreased amplitude, and slower descent. This test is particularly useful when the ankle-brachial index cannot be calculated or is in question due to calcified arteries (as in patients with longstanding diabetes or chronic renal insufficiency and in the very old).

Pulse volume recordings in our patient showed obstruction at the level of the superficial iliac and popliteal arteries of the right leg, with a significant drop in pressure with exercise in the right ankle.

Other useful diagnostic tests include arterial duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, and conventional angiography. Duplex ultrasonography is particularly valuable in patients with noncompressible (ie, calcific) vessels. Standard angiography (see below) remains the gold standard to evaluate

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TABLE 3	
Interpreting the ankle-brachial index	
0.91–1.30	Normal
0.71–0.90	Mild disease
0.41–0.70	Moderate disease
< 0.40	Severe disease

NOTE: A value above 1.0 may not be reliable. Above 1.3 is definitely unreliable and usually indicates inflexibility of vessels due to diabetes, advanced age, or chronic renal insufficiency.

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the anatomy of the peripheral arterial system, but it is invasive and can be nephrotoxic.

Look for atherosclerosis elsewhere

As noted above, patients with documented disease in one vascular bed have significant disease in other vascular beds. Thus, clinicians who identify PAD should consider screening for involvement elsewhere.

■ PREDICTING PROGNOSIS

The more severe the PAD, the lower the survival rate, but even patients without symptoms have lower survival rates than do healthy subjects. After 10 years, about half of symptom-free patients survive, compared with only 25% of age-matched and sex-matched patients with severe symptoms (**FIGURE 2**).[33]

The ankle-brachial index is an excellent predictor of prognosis and survival, and it can be used for risk stratification of PAD patients. Only about 24% of patients who present with severe disease as measured by the ankle-brachial index survive longer than 12 years (**FIGURE 3**).[21,34] A low index also predicts decline in the distance a person can walk in 6 minutes, even if the patient did not report leg symptoms. The lower (worse) the ankle-brachial index, the more the walking distance declines annually.[21]

Failed lower extremity revascularization. Edwards et al[35] report that patients who underwent a lower extremity bypass procedure that failed (eg, the graft clotted, or symptoms recurred) had an 88% death rate at 5 years.

Atherosclerosis in one vascular bed means disease in other beds as well
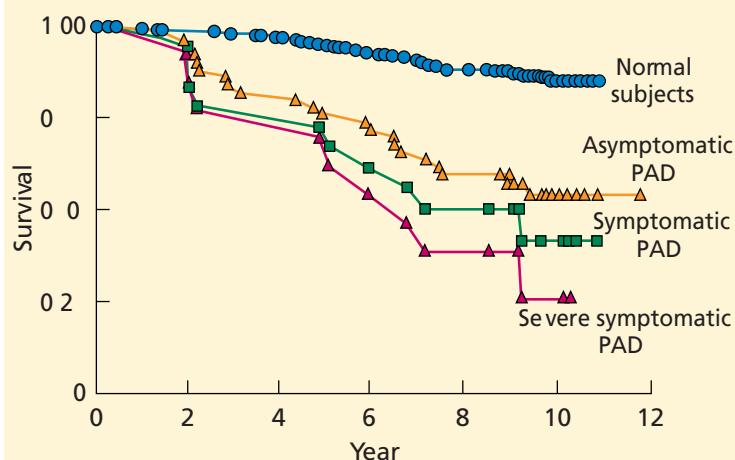
The worse the symptoms, the worse the prognosis

FIGURE 2. Kaplan-Meier survival curve based on death from all causes among normal subjects and subjects with symptomatic or asymptomatic large-vessel peripheral arterial disease (PAD).

CRIQUI MH, LANGER RD, FRONEK A, ET AL. MORTALITY OVER A PERIOD OF 10 YEARS IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE. N ENGL J MED 1992; 326:381–386.

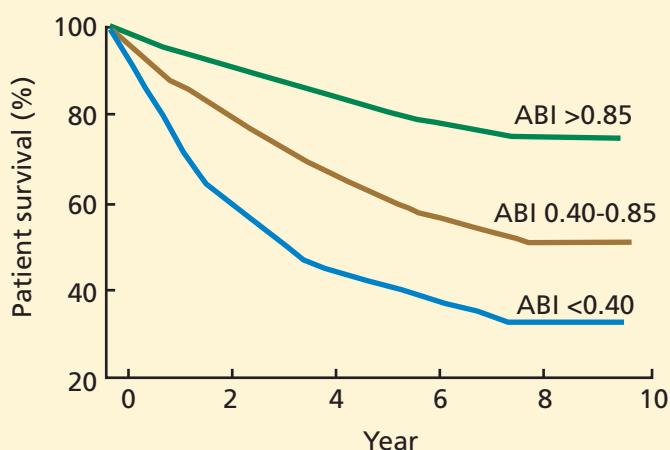## The lower the ankle-brachial index, the worse the prognosis

FIGURE 3. Survival curves for three levels of ankle-brachial index (ABI) measures.

MCKENNA M, WOLFSON S, KULLER L. THE RATIO OF ANKLE AND ARM ARTERIAL PRESSURE AS AN INDEPENDENT PREDICTOR OF MORTALITY. ATHEROSCLEROSIS 1991; 878:119–128.

■ TREATMENT

The goals of treatment in PAD are to:
- Reduce symptoms so that patients can resume activities and have a better quality of life
- Save the limb and avoid revascularization whenever possible
- Prevent the progresion of atherosclerosis with systemic therapy to reduce cardiac and cerebrovascular morbidity and mortality.

Smoking cessation

Smoking is the most important modifiable risk factor in PAD, and smoking cessation favorably changes the natural history of the disease. For example, the prevalence of intermittent claudication among those who stop smoking is equivalent to that for nonsmokers within only 1 year of quitting.[36,37]

Smoking cessation also reduces the severity of limb symptoms and the progression of PAD, including development of critical limb ischemia (which developed in 16% of continuing smokers vs 0% of smokers who stopped smoking over 7 years of follow-up) or major amputation.[38–41]

Furthermore, a recent meta-analysis showed a threefold increased risk of graft failure among patients who continued to smoke after lower-limb bypass surgery regardless of the type of graft used. This study uncovered a strong dose-response relationship: the greater the number of cigarettes smoked, the lower the rate of graft patency.[42]

Smoking cessation also increases the survival rate. Faulkner et al[43] found that patients with symptomatic PAD who quit smoking had almost twice the chance of surviving 5 years compared with those who continued to smoke.

Evidence-based practice guidelines for tobacco cessation have been published elsewhere[44] and contain practical algorithms geared to improve initial success and long-term abstinence rates.

Antiplatelet therapy

Antiplatelet therapy is indicated for all patients with PAD unless it is contraindicated for a compelling reason. I recommend aspirin

75 to 160 mg per day, which reduces vascular events (nonfatal myocardial infarction, stroke, and vascular death) by 22%,[45] and appears to prevent peripheral arterial occlusion after revascularization procedures.[46] Another option is clopidogrel 75 mg per day, which was found to reduce the overall risk of ischemic events by 8.7% compared with aspirin after a mean treatment period of nearly 2 years.[30]

Treating dyslipidemia

The Framingham risk score and the Adult Treatment Panel III[47] classify PAD, whether diagnosed by the ankle-brachial index, lower limb blood flow studies, or clinical symptoms, as a "coronary artery disease equivalent" and recommend the same target lipid levels as for patients with coronary artery disease (LDL-C < 100 mg/dL and triglycerides < 150 mg/dL).

Patients with PAD tend to have a pattern of dyslipidemia similar to that in the metabolic syndrome, including low HDL-C levels and high triglyceride levels (compared with the high LDL-C pattern seen in patients with coronary artery disease).

A recent consensus panel statement proposed more intensive lowering of LDL-C levels with a goal of less than 70 mg/dL (using combination therapy) for high-risk patients and those with other dyslipidemias such as elevated triglycerides or low HDL-C levels.[48]

The Heart Protection Study[49] recently added another paradigm to the use of statin drugs in this population, supporting their routine use regardless of the cholesterol level. In this trial, PAD patients who received simvastatin had a significantly lower rate of cardiovascular ischemic events compared with those who did not (24.7% vs 30.5%, $P < .0001$), irrespective of the presence of coronary artery disease, pretreatment cholesterol or triglycerides concentrations, or the sex or age of the participants.

Unless statins are contraindicated, all patients with peripheral artery disease should be treated with one to meet the guideline recommendations. Not only do statins reduce the relative risk of major vascular events, they also improve leg function (including increasing pain-free and total walking distance, better performance on the 6-minute walking test,

PAD is a coronary artery disease equivalent

faster walking capacity, and enhanced community-based physical activity) independently of their lipid-lowering effect.[50–52] Some of these measures were improved in as little as 3 months in some studies.[51]

Additional treatment (eg, with fibrates or niacin) may be needed to treat low HDL-C or high triglyceride levels, which are becoming therapeutic targets in themselves.

Blood pressure control

The target blood pressure in PAD patients is similar to that for patients with atherosclerosis elsewhere.

Beta-blockers, contrary to once-popular belief, appear to be safe in patients with stable mild to moderate disease, as shown in a rigorous meta-analysis of 11 randomized controlled studies.[53] Furthermore, beta-blocker therapy reduced the incidence of new coronary events in patients with coronary artery disease and concurrent symptomatic PAD by about 50% in one study and should be considered an option for most PAD patients except those presenting with critical limb ischemia.[54]

Angiotensin-converting enzyme (ACE) inhibitors. The benefit of ACE inhibitors for patients with PAD was emphasized by findings from the Heart Outcomes Prevention Evaluation (HOPE) trial.[55,56] Overall, patients who received the ACE inhibitor ramipril had a 22% lower incidence of the composite end point of myocardial infarction, stroke, and cardiovascular death. The improvement in outcomes seen in this trial was independent of blood pressure reduction. The ramipril group also had a lower incidence of diabetes, complications of diabetes, need for revascularization procedures, cardiac arrest, and progression to heart failure. The PAD subgroup in this trial who received ramipril had a similar risk reduction in the composite end points of myocardial infarction, stroke, or cardiovascular death. Further analysis of this trial suggested that the benefits of ramipril extended to patients with both symptomatic and asymptomatic PAD.

ACE inhibitors are the preferred antihypertensive agents in patients with albuminuria, diabetes, congestive heart failure, or chronic renal disease, all of which are common in the PAD population. Therefore, in

most situations the antihypertensive agent of choice should be an ACE inhibitor. If a second agent needs to be added, one can follow the recommendations of the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[57] and use agents in any of the other classes. In patients requiring more than two drugs, a diuretic should be used as one of the antihypertensive agents.[58]

Patients with PAD and hypertension have altered platelet activity and function. It is reasonable to believe that tightly controlling blood pressure significantly reduces the chance of myocardial infarction, stroke, or other vascular death. Survival rates also depend on whether other risk factors are present in addition to hypertension.[59]

■ TREATMENT ISSUES RELATED TO DIABETES

Diabetes increases the risk for PAD, and "prediabetes" (impaired glucose tolerance; see Lee et al[60]) increases the risk to nearly the same level.[60] Women with diabetes are far more likely to develop intermittent claudication than are men with diabetes.[61] Patients with PAD are more likely to develop rest pain and gangrene if they also have diabetes.[62]

The distribution of PAD in people with diabetes may differ from that in people without diabetes: the deep femoral artery and distal vessels (small vessels and tibial and peroneal arteries) are more likely to be involved in patients with diabetes than in those without diabetes. People with diabetes are more prone to develop multilevel disease.

Patients with diabetes tend to have worse arterial disease and a poorer outcome than nondiabetic patients. They are more likely to have diffuse multilevel disease and the blocked vessels tend to be calcified and distal (infrapopliteal and tibial). The presentation of leg symptoms in diabetic patients who have PAD may be compounded by the presence of peripheral neuropathy. In addition, diabetic patients have impaired activation of the compensatory mechanisms such as collateral vessel formation. Consequently, the clinical outcomes (eg, amputation and revascularization rates) are consistently worse among patients with diabetes and PAD.

In successful supervised programs, PAD patients walk 30 minutes three times a week up to near-maximal pain

■ INCREASING WALKING DISTANCE

Exercise

Two meta-analyses[63,64] found that exercise alone led to statistically significant increases in walking distance. In 21 nonrandomized and randomized studies, exercise increased pain-free walking distance in patients with claudication by almost 180% (from 125.9 ± 57.3 m to 351.2 ± 188.7 m) and increased the maximal walking distance by approximately 120% (from 325.8 ± 148.1 m to 723.3 ± 591.5 m).

Another meta-analysis, by Leng et al,[65] included 10 randomized trials and also demonstrated an increase in maximal walking time (of 150%), an improvement that exceeded that of angioplasty and antiplatelet therapy at 6 months and did not differ considerably from that of surgical revascularization.

Successful programs consist of supervised 30-minute walking sessions three times a week for 6 months, with patients walking until near-maximal pain. To date, unsupervised home-based programs have not proven helpful.[66]

Drug treatment

Cilostazol (Pletal) 100 mg twice a day (or 50 mg twice daily for fragile older patients) improves maximum walking distance.[67] The drug is contraindicated in patients with congestive heart failure because of an increased risk of sudden cardiac death. Although one need not obtain an echocardiogram for each patient before starting cilostazol, a thorough and documented history, physical examination, and review of symptoms is essential to rule out signs and symptoms of heart failure.

Improvement can be expected within 2 to 4 weeks after starting the drug; a 3-month trial should be given before deciding if it is ineffective.

Common side effects include headache, diarrhea, gastric upset, palpitations, and dizziness. A temporary reduction in the dose to 50 mg twice per day may alleviate these problems.

Pentoxifylline (Trental) has only a minor effect on improving walking capacity. Two meta-analyses and two systematic reviews have concluded that current data are insufficient to support its widespread use.[68]

■ ANGIOGRAPHY AND REVASCULARIZATION

There has been an explosion in the number of peripheral vascular procedures performed over the past few years. Endovascular procedures are indicated for patients with a vocational or lifestyle-limiting disability due to intermittent claudication if clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and if there has been an inadequate response to exercise or pharmacological therapy, or if there is a very favorable risk-benefit ratio (eg, in focal aortoiliac occlusive disease).

The main indications for angiography and revascularization currently accepted by most practitioners include[69]:

• **Lifestyle-limiting claudication.** We used to define this as "economic-limiting" claudication, that is, symptoms that interfere with a patient's ability to work. Now we define it as lifestyle-limiting, which is determined by what the patient feels is important.

• **Ischemic pain at rest.** Patients typically complain of pain at rest that is worse at night when they lie flat. Some dangle their legs on the edge of the bed, which may relieve pain but results in edema and dependent rubor.

• **Nonhealing ischemic ulcers** are typically seen on the distal portions of the feet and the toes and have a "punched out" appearance with an ischemic base. Despite appropriate conservative measures, including mechanical and topical wound-care protocols, improvement of arterial perfusion is required to heal these ulcers.

Due to differences in structural and anatomic characteristics between the different lower extremity arterial territories, the indications and outcomes of endovascular procedures differ depending on the segment involved. The three distinct anatomic territories of the lower-extremity arterial system are the aortoiliac, femoropopliteal, and infrapopliteal or crural. Percutaneous angioplasty is optimally offered for short-segment stenosis of large-bore vessels (ie, the aortoiliac or femoropopliteal arteries), while surgical methods are best applied to multilevel occlusions involving smaller and more distant vessels. More favorable immediate and long-term outcomes are also achieved with lesions that are concentric and noncalcific, particularly in the presence of a good distal runoff, the absence of postprocedure residual stenosis, and when the indication for the procedure is treatment of intermittent claudication rather than acute or critical limb ischemia.

Catheter-directed thrombolytic therapy is a recommended and beneficial revascularization strategy for acutely ischemic limbs.[69] Best results are obtained if symptoms have been less than 14 days in duration.

■ FUTURE DIRECTIONS

Stimulated angiogenesis (neovascularization) offers hope for the future for patients with PAD, particularly those with no viable revascularization options. So far, studies have not been encouraging, but perhaps more success will be realized with improved methodology and technology.

Hyperhomocysteinemia remains an independent risk factor for PAD, but as yet no prospective trial has evaluated the effect of lowering homocysteine on PAD outcomes.

Screening people at risk may offer an opportunity for early intervention and perhaps may improve the outcomes.

■ WHAT HAPPENED TO OUR PATIENT?

Since our patient presented with lifestyle-limiting leg dysfunction secondary to PAD, the options of conservative management (pharmacotherapy and exercise rehabilitation) as well as revascularization were discussed in detail. He opted to try 6 months of conservative therapy and perhaps proceed with angiography and revascularization if there was no satisfactory improvement.

He was started on a statin with a plan to titrate the dose up to a goal LDL-C of less than 70 mg/dL, with the understanding that once this goal was achieved, additional antilipid medications (fibrates or niacin) would be considered to further improve his lipid profile (increase the HDL-C and decrease his triglyceride levels). He was also started on an ACE inhibitor to achieve a goal blood pressure of less than 140/80 mm Hg. He was prescribed cilostazol 100 mg twice a day and was given an instruction sheet describing the potential food interactions and side effects of this medication. He was also prescribed aspirin 162 mg/day.

PAD patients need:
• **Smoking cessation**
• **Antiplatelet treatment**
• **Lipid treatment**
• **Blood pressure control**
• **Supervised walking**

A comprehensive discussion about smoking cessation was initiated and the importance of this step was emphasized. He asked for help; we referred him to a local smoking cessation program, gave him a prescription for bupropion, and advised him to use a nicotine replacement product (available over the counter).

On follow-up 6 months later, he had quit smoking but continued to have the urge to smoke at least once a week. His walking distance had improved and he was able to finish his golf game with only mild leg discomfort. He had lost 11.8 lb, and his blood pressure was well controlled. His lipid panel showed an LDL-C concentration of 76 mg/dL, HDL-C 46, and triglycerides 165. He did not require a revascularization procedure.

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