CLINICAL PRACTICE

Intermittent Claudication

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 58-year-old, previously healthy mail carrier reports cramping pain in his right calf when he walks. The discomfort has progressively worsened over the past 6 months and now forces him to rest after walking half a block on level ground at a normal pace. The pain is interfering with his ability to perform his job. He has a normal right femoral pulse and a diminished right popliteal pulse; the right ankle and foot pulses are absent. How should this patient be evaluated and treated? Should he undergo revascularization?

THE CLINICAL PROBLEM

Peripheral arterial disease is a common manifestation of atherosclerosis, and its prevalence increases with age and the presence of cardiovascular risk factors.[1,2] Cigarette smoking and diabetes mellitus are the strongest risk factors; more than 80% of patients with peripheral arterial disease are current or former smokers. Hypertension, dyslipidemia, and hyperhomocysteinemia also significantly increase the risk of peripheral arterial disease.

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Most persons with this disease are asymptomatic, and the condition is detected during routine physical examination of abnormal pulses, vascular bruits, or an abnormal value for the ankle–brachial index.[3,4] Less than 20% of patients with peripheral arterial disease report the typical symptom of intermittent claudication — leg-muscle discomfort on exertion that is relieved with rest.[5] Many patients present with atypical symptoms, including leg fatigue, difficulty walking, and leg pain that is not typical of claudication.

Studies of the natural history of intermittent claudication indicate that the risk of limb loss for patients who do not have diabetes is low (2% or less).[6] However, the risk of progression to limb-threatening ischemia is increased by a factor of three among patients with diabetes who require oral or insulin therapy as compared with patients without diabetes, and the risk increases by 20 to 25% for each 0.1-unit decrease in the ankle–brachial index.[7,8]

Cardiovascular disease is the major cause of death in patients with intermittent claudication; the annual rate of cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) is 5 to 7%.[9] Thus, the treatment of claudication is directed not only at improving walking distance but also, and more important, at reducing cardiovascular risk.

STRATEGIES AND EVIDENCE

EVALUATION

A careful history taking and examination will generally distinguish intermittent claudication from nonvascular causes that may mimic claudication (pseudoclaudi-

Table 1. Differentiation of True Claudication from Pseudoclaudication (Nonvascular Causes).

Characteristic	Intermittent Claudication	Spinal Stenosis	Arthritis	Venous Congestion	Compartment Syndrome
Character of discomfort	Cramping, tightness, or tiredness	Same symptoms as with claudication or tingling, weakness, or clumsiness	Aching	Tightness, bursting pain	Tightness, bursting pain
Location of discomfort	Buttock, hip, thigh, calf, foot	Buttock, hip, thigh	Hip, knee	Groin or thigh	Calf
Exercise-induced discomfort	Yes	Variable	Variable	After walking	After excessive exercise
Walking distance	Reproducible	Variable	Variable	Variable	Variable
Discomfort with standing	No	Yes	Yes, changes with shift in position	Yes, changes with shift in position	Yes, changes with shift in position
Relief of discomfort	Rapid relief with rest	Relief with sitting or otherwise changing position	Slow relief with avoidance of bearing weight	Slow relief with leg elevation	Slow relief with leg elevation
Other	Associated with atherosclerosis and decreased pulses	History of lower-back problems	Discomfort at joint spaces	History of deep venous thrombosis, signs of venous congestion	May occur in athletes after strenuous exercise

* Information is from the American Heart Association and the American College of Cardiology (Hirsch et al.[9]) and from Schmieder and Comerota.[10]

cation) (Table 1).[9,10] The patient's lower legs and feet should be examined with shoes and socks off, with attention to pulses, hair loss, skin color, and trophic skin changes.

Calculation of the ankle–brachial index (Fig. 1) is recommended as the initial screening test. An abnormal result (0.9 or less) is sufficient to make the diagnosis of peripheral arterial disease in a clinically appropriate setting. When the disease is suspected on the basis of clinical observations but the resting ankle–brachial index is normal, the index should also be calculated after exercise — after the patient has performed toe raises (standing flat-footed and raising the heels off the ground repeatedly) or has walked on a treadmill. Patients with large-vessel "inflow" disease of the distal aorta or iliac arteries may have normal resting blood flow, but in the setting of exercise and associated vasodilatation, pressure gradients develop across the proximal stenoses, leading to symptoms and an abnormally low value for the ankle–brachial index.

If the diagnosis of peripheral arterial disease is uncertain, or if revascularization is being planned, further imaging with duplex ultrasound, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) may be useful. Segmental pressure recording and pulse-volume recording are used in some cases to assess the location and severity of the lesion. In patients with noncompressible vessels (usually patients with diabetes or renal failure), the diagnosis can be confirmed by measuring the toe–brachial index (determined according to the return of pulsatile flow on deflation of a small blood-pressure cuff on the great or second toe with a plethysmographic device).

Both CTA and MRA produce images of vascular structures in cross-sectional slices that can be reformatted into three-dimensional angiographic images (Fig. 2). In a randomized trial comparing MRA with CTA for initial imaging in peripheral arterial disease, the two techniques were similar in ease of use and clinical outcome, but total diagnostic costs were lower for CTA.[11]

The gold standard for diagnosis and evaluation of peripheral arterial disease is invasive digital-subtraction angiography, which is used if endovascular intervention is planned (Fig. 3). Serious complications of this procedure, which are infrequent, include reactions to the contrast material (in 4% of patients or less), bleeding (2% or less), nephropathy due to contrast material (0.2 to 1.4%), and cholesterol embolization (0.1% or less).[12,13]

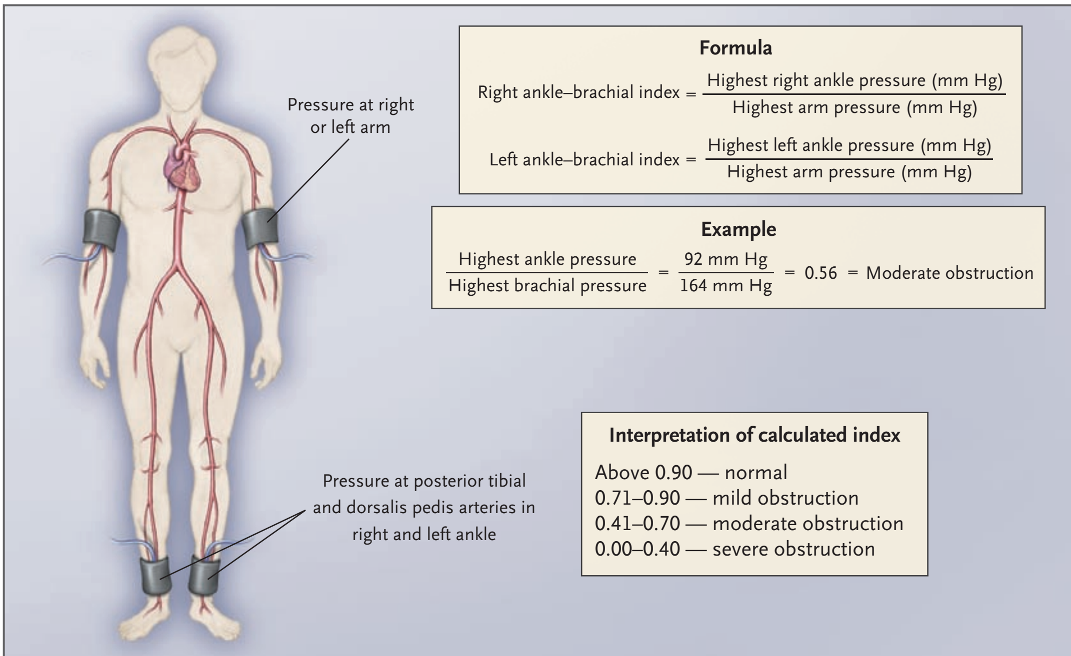

Figure 1. Performing Pressure Measurements and Calculating the Ankle–Brachial Index.
To calculate the ankle–brachial index, systolic pressures are determined in both arms and both ankles with the use of a hand-held Doppler instrument. The highest readings for the dorsalis pedis and posterior tibial arteries are used to calculate the index.

The advantages and disadvantages of digital-subtraction angiography, CTA, MRA, and duplex ultrasound are listed in Table 2.

TREATMENT

The mainstays of treatment for peripheral arterial disease include risk-factor modification, an exercise program, antiplatelet therapy, and, if warranted for symptomatic relief, additional pharmacologic therapy, and revascularization. Revascularization (endovascular or surgical) therapy is reserved for patients whose job performance or lifestyle is compromised by claudication, patients who do not have a response to exercise and pharmacotherapy, and patients for whom the risk–benefit ratio with revascularization is favorable.[9]

Risk-Factor Modification

Since cardiovascular events are the major cause of death in patients with peripheral arterial disease, modification of atherosclerotic risk factors is routinely warranted, with a particular emphasis on smoking cessation and regular exercise. Pharmacologic therapy and dietary modification should be tailored to meet current guidelines for risk factors: low-density lipoprotein cholesterol, less than 100 mg per deciliter (2.6 mmol per liter) or, for those at very high risk for ischemic events, less than 70 mg per deciliter (1.8 mmol per liter); blood pressure, less than 140 mm Hg systolic and 90 mm Hg diastolic or, for patients with diabetes or renal disease, less than 130 mm Hg systolic and 80 mm Hg diastolic; and glycated hemoglobin, less than 7% in patients with diabetes.[14,15]

Beta-blockers are effective as antihypertensive therapy and are not contraindicated in patients with peripheral arterial disease. In the Heart Outcomes Prevention Evaluation study, the risk of heart attack, stroke, and death from vascular causes was reduced by 22% for patients given an angiotensin-converting–enzyme inhibitor (ramipril).[16]

Antiplatelet and Other Pharmacologic Therapy

Antiplatelet therapy with aspirin (75 mg to 325 mg daily) reduces the risk of death from vascular causes, myocardial infarction, and stroke in patients with vascular diseases by 25% and is recommended for patients with peripheral arterial disease.[17] A large, randomized, 3-year trial involv-

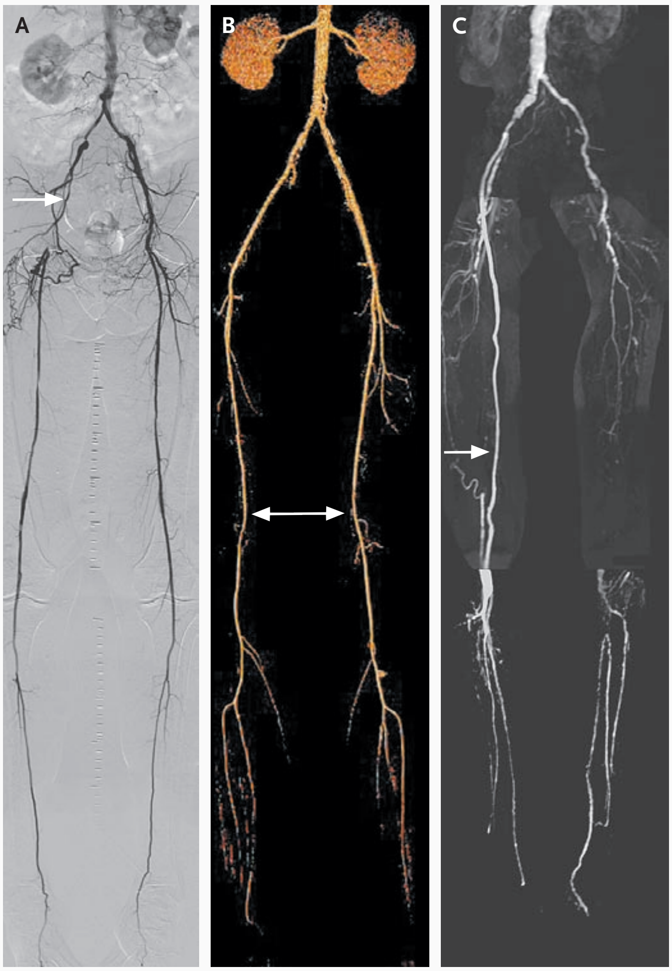

Figure 2. Aortograms with Runoff Images in Three Patients.

The digital-subtraction angiogram in Panel A shows occlusion of the right external iliac artery (arrow), bilateral narrowing of the superficial femoral arteries, and single-vessel runoff below the knees. The CTA in Panel B is a three-dimensional reconstruction showing very mild narrowing of the bilateral superficial femoral arteries (double-headed arrow). The MRA in Panel C, with enhancement from contrast material, shows bilateral occlusions of the superficial femoral arteries with a patent femoral–popliteal graft (arrow) on the right.

ing high-risk patients, including patients with peripheral vascular disease, showed that rates of death from vascular causes, myocardial infarction, and stroke were significantly, albeit modestly, lower with clopidogrel than with aspirin; the rates of bleeding complications were similar.[18] Thus, the more expensive thienopyridines (ticlopidine and clopidogrel) may be considered as alternatives to aspirin, particularly in patients who cannot tolerate aspirin. Current data do not show an advantage of dual antiplatelet therapy (aspirin and clopidogrel) over single-agent therapy in patients with peripheral arterial disease.[9]

Cilostazol is a phosphodiesterase type 3 inhibitor with vasodilator and mild antiplatelet properties. Several randomized trials have shown that walking distance is increased by about 50% with cilostazol (100 mg twice a day), as compared with placebo, after 3 to 6 months of therapy.[19] The most common side effects include headache, diarrhea, palpitations, and dizziness. Cilostazol is contraindicated in patients with heart failure, because similar drugs, such as milrinone, are associated with increased mortality in this group. In a trial comparing cilostazol, pentoxifylline (a derivative of methylxanthine), and placebo, pentoxifylline was inferior to cilostazol and no better than placebo for relief from claudication.[20] Oral vasodilator prostaglandins, vitamin E, and chelation therapy with EDTA have not proved to be effective in reducing symptoms or increasing walking distance.[9] Table 3 summarizes the pharmacologic treatments for peripheral arterial disease and indicates the nature of the evidence supporting their use.

Exercise

A Cochrane review of three randomized trials showed that exercise increased maximal walking distance by 150% over a period of 3 to 12 months, as compared with usual care.[21] A meta-analysis of eight randomized trials showed a greater symptomatic benefit with a supervised (as opposed to unsupervised) exercise program.[22] Supervised exercise commonly involves walking on a treadmill, with the initial workload set to elicit symptoms within 3 to 5 minutes of walking. The patient is permitted to rest until the symptoms resolve and then resumes exercise. In a meta-analysis of 18 randomized and nonrandomized trials, the greatest benefit (assessed according to the distance walked before claudication developed) was associated with continued walking until pain was nearly maximal and with sessions that lasted longer than 30 minutes, took place three or more times per week, and continued for more than 6 months.[23] Typically, it takes 1 to 2 months for the patient to begin to notice benefits, which gradually increase over a period of several months.

Revascularization

Superficial femoral-artery stenosis or occlusion is the most common lesion associated with claudication. Revascularization (surgery or percutane-

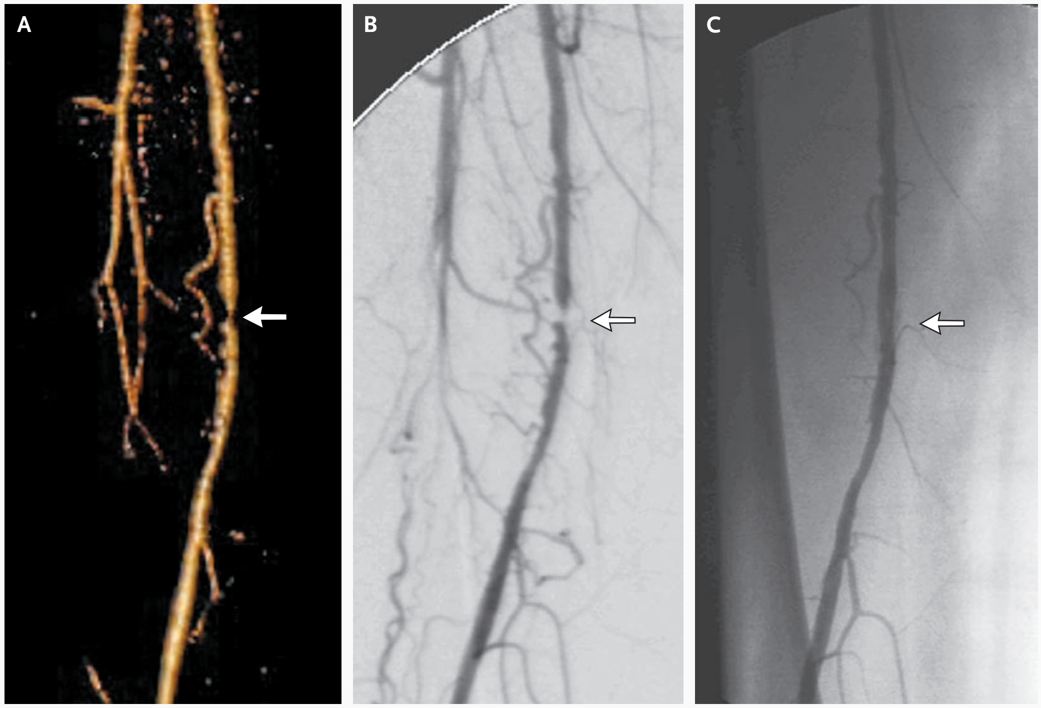

Figure 3. Angiograms of the Right Superficial Femoral Artery before and after Treatment.
The CTA in Panel A shows discrete stenosis of the right superficial femoral artery (arrow). The corresponding digital-subtraction angiogram in Panel B shows stenosis of 99% of the artery (arrow). Endovascular intervention to treat such a stenosis has a high likelihood of success with a low procedural risk. Panel C shows the result of treatment with percutaneous transluminal angioplasty (arrow).

ous transluminal angioplasty [PTA]) is indicated for relief in patients with claudication that limits their lifestyle or ability to perform their job and that has proved to be unresponsive to exercise and pharmacologic therapy.[9,24,25] PTA is preferred when possible in patients who are 50 years of age or younger, because they have a higher risk of graft failure after surgical therapy than do older patients.[9] Data from two randomized trials indicate that surgery and angioplasty result in similar mortality and amputation rates and in similar patency rates at 4 years among patients with ischemia of the legs or feet.[26] However, because PTA is associated with lower estimated rates of both short-term mortality and major complications (0 to 2.9% and 2 to 10%, respectively) than is surgery (1.3 to 6.3% and 10 to 15%, respectively), PTA is preferred for lesions with favorable anatomical features, such as discrete stenoses or occlusions (those less than 15 cm long) (Table 4). Cost-effectiveness analyses suggest that PTA is preferable to surgery as long as the expected 5-year patency rate for the treated vessel is 30% or higher.[28] Outcomes after femoral popliteal PTA have improved over time; patency rates of 87%, 69%, and 55% have been reported at 1, 3, and 5 years, respectively.[26]

A single randomized trial comparing the effectiveness of surgery and exercise therapy showed no significant difference in outcomes — specifically, maximal walking distance and the need for further revascularization — at 8 to 9 months.[28] A large prospective, matched cohort study of 526 patients with intermittent claudication showed that revascularization (surgery or PTA) was associated with improved walking distance and reduced pain as compared with medical therapy, but therapy was not optimized in the nonintervention group (e.g., only 40% of the patients in this group reported engaging in regular exercise, and cilostazol was not used).[29] Outcomes of revascularization were better in patients with higher postprocedure ankle–brachial indexes, suggesting that the effectiveness of the limb revascularization procedure is directly related to the degree of symptomatic improvement.

Table 2. Characteristics of Imaging Methods Used to Diagnose Peripheral Arterial Disease.

Characteristic	Duplex Ultrasound	Digital-Subtraction Angiography	Magnetic Resonance Angiography	Computed Tomographic Angiography
Advantages	Noninvasive, can be used to visualize and quantitate severity of lesion	Gold standard, high resolution, can be used to guide intervention	Noninvasive, no radiation or iodinated contrast material used, three-dimensional	Noninvasive, higher spatial resolution than with magnetic resonance angiography, three-dimensional
Disadvantages	Operator-dependent, imaging limited by dense calcification	Invasive, ionizing radiation and iodinated contrast material used, two-dimensional	Lower spatial resolution than with computed tomographic angiography, contraindicated if patient has claustrophobia, image artifact if stent present	Ionizing radiation (25% of dose with digital-subtraction angiography) and iodinated contrast material used, imaging limited by dense calcification
Charge (Medicare)*	$252.14	$474.07	$973.75	$530.45

* The charges shown represent the allowable total charge by Medicare in the New Orleans area.

Data from studies directly comparing exercise therapy and PTA are scarce. In one small trial, walking distance at 6 years was better for patients treated with exercise therapy than for those treated with PTA.[30] A randomized trial comparing the effects of exercise and PTA (with both groups receiving pharmacologic therapy) demonstrated similar quality-of-life outcomes, similar maximal walking distances, and similar ankle–brachial indexes, but fewer patients in the PTA group had occluded arteries (P=0.004).[31] An analysis of combined data from seven studies that compared exercise with PTA in patients with claudication showed that PTA resulted in a greater increase in the ankle–brachial index but with no significant difference in quality of life.[32] However, none of the studies included in the analysis compared the two interventions directly. A decision-analysis model comparing the costs and quality of life associated with PTA, bypass surgery, and exercise therapy showed that PTA, when feasible, was more effective than exercise therapy alone and was more cost-effective than bypass surgery ($38,000 vs. $311,000 per quality-adjusted year of life gained),[33] but this conclusion, too, was not based on data from comparative clinical trials.

AREAS OF UNCERTAINTY

STENTS

The role of primary stent placement in revascularization of the superficial femoral artery remains controversial. In contrast to the coronary arteries, for which stent placement has largely replaced angioplasty for revascularization, the superficial femoral artery is subject to longitudinal stretching, external compression, torsion, and flexion; these stresses may lead to stent fractures, which have been linked to restenosis.[34] In early randomized trials comparing PTA with stent placement for the treatment of lesions in the superficial femoral artery, stent placement showed no advantage over angioplasty with bail-out stent placement.[35,36]

Technology has improved, however, and a recent randomized trial involving 104 patients with severe claudication showed significantly higher patency rates at 1 year for lesions in the superficial femoral artery that were treated with stent placement than for lesions treated with PTA and bail-out stent placement (63% vs. 37%); the maximal walking distance and the ankle–brachial index were also significantly better in the stent group at 1 year. There were no major complications in either group.[37]

A randomized trial of drug-coated (sirolimus) stents in the superficial femoral artery failed to show a reduction in the risk of restenosis as compared with the risk associated with bare-metal stents.[38] Use of stents covered with polytetrafluoroethylene (PTFE), developed to seal arterial perforations or to exclude aneurysmal segments, was compared with the use of PTA alone in a randomized trial, and there was no significant difference in 1-year patency rates (50% and 45%, respectively); however, major adverse events were more frequent in the group that received PTFE-covered stents (8.2% vs. 4.0%).[39]

Table 3. AHA–ACC Guidelines for Pharmacologic Management of Claudication.*

Medication and Class of Evidence	Level of Evidence	Dose	Side Effects
Class I			
Cilostazol	A	100 mg two times/day	Contraindicated in heart failure; headache, diarrhea, palpitations, dizziness
Class IIb			
Pentoxifylline	A	400 mg three times/day	Sore throat, dyspepsia, nausea, diarrhea
Arginine	B	3 g three times/day	Gastrointestinal distress, drop in hematocrit
Propionyl levocarnitine	B	1–2 g two times/ day	None or mild
Ginkgo biloba	B	120–160 mg/day	None or mild
Class III			
Prostaglandins	A	Beraprost: 40 μg three times/day	Headache, flushing gastrointestinal distress
Vitamin E	C	50 mg/day	None or mild
Chelation EDTA	A	1.5–3 g intravenously two times/wk	Hypocalcemia, renal failure, proteinuria, gastrointestinal distress

* Information is from the American Heart Association and the American College of Cardiology (Hirsch et al.[9]). Class I evidence is defined as evidence, general agreement, or both that the treatment is beneficial, useful, and effective; class IIb as conflicting evidence or divergence of opinion about efficacy or usefulness (or efficacy that is less well established by evidence or opinion); and class III as evidence, general agreement, or both that the treatment is not beneficial, useful, and effective. Levels of evidence are classified as follows: level A, data derived from multiple randomized trials or meta-analyses; level B, data derived from a single randomized trial or from nonrandomized studies, and level C, the consensus opinion of experts, data from case studies, or the standard of care.

ADJUNCTIVE ANGIOPLASTY

Adjunctive angioplasty techniques such as atherectomy, cryotherapy, and the use of a cutting balloon (a balloon with microtomes attached to its surface, which make shallow incisions in the surface of the lesion when the balloon is inflated) have not been tested in meaningful comparative trials in patients with femoral artery disease; the only available data that show the benefit of these approaches is from single-center studies and uncontrolled registries.[40-42] Laser angioplasty has not been shown to be superior to conventional PTA or stent placement.[43-45] Given the substantial additional expense of these approaches, more evidence of their efficacy is needed before widespread adoption can be justified.

Trials of brachytherapy (use of a catheter to deliver radiation to the lesion) for preventing restenosis in the superficial femoral artery after percutaneous PTA have had inconsistent results.[46,47] In one trial, the use of external-beam radiation (at a dose of 14 Gy) after PTA significantly reduced the rate of restenosis at 1 year after PTA,[48] but these results require confirmation. The use of gene or cellular therapies in peripheral arterial disease has not resulted in a clear clinical benefit in small studies[49]; larger, controlled clinical trials are needed to establish whether there is any role for these therapies in patients with claudication.

FOLLOW-UP AFTER PERCUTANEOUS INTERVENTIONS

It is common to measure the ankle–brachial index within a week after a percutaneous intervention has been performed in order to establish a new baseline. Patients are often reevaluated at 3-month intervals for the first year (when the risk of restenosis is highest); these assessments include a detailed history taking, examination, and ankle–brachial index measurements; the value of a walking program and risk-factor modification should be reinforced during these visits. However, data on the optimal approach to follow-up are lacking.

GUIDELINES

Comprehensive guidelines for the management of peripheral arterial disease have recently been published by an expert multidisciplinary committee organized by the American College of Cardiology (ACC) and the American Heart Asso-

Table 4. TransAtlantic Inter-Society Consensus on Classification of Femoral Lesions and Recommended Approaches When Revascularization Is Planned.*

Lesion Type	Characteristics	Recommended Treatment
A	Single stenosis ≤10 cm long Single occlusion ≤5 cm long	Percutaneous transluminal angioplasty strongly preferred
B	Multiple lesions, each ≤5 cm in length Single lesion ≤15 cm long, not involving the popliteal artery below the knee Single or multiple lesions in the absence of continuous tibial vessels for distal bypass Heavily calcified occlusion ≤5 cm long Single popliteal stenosis	Percutaneous transluminal angioplasty generally preferred
C	Multiple lesions >15 cm long Recurrent lesions after two endovascular interventions	Percutaneous transluminal angioplasty or surgery, depending on risk–benefit ratio
D	Occlusion >20 cm long Occlusion of the popliteal or tibial–peroneal vessels	Surgery generally preferred

* Information is from Norgren et al.[27]

ciation (AHA).[9] The TransAtlantic Inter-Society Consensus, representing multiple international specialty societies, has also published guidelines for the management of peripheral arterial disease that are in general agreement with the ACC–AHA document (Table 4).[27]

The ACC–AHA guidelines recommend endovascular therapy for patients whose condition interferes with their job performance or lifestyle and who have had an inadequate response to exercise or pharmacologic therapy, as long as the clinical features suggest a reasonable likelihood of symptomatic improvement and the risk–benefit ratio is very high.[9] The recommendations in this article are in agreement with the ACC–AHA guidelines.

SUMMARY AND RECOMMENDATIONS

The mail carrier described in the vignette has right-calf claudication that interferes with his ability to perform his job, and physical examination shows that his condition is consistent with stenosis or occlusion of the superficial femoral artery. The initial assessment should include measurement of his ankle–brachial index. Risk factors for atherosclerosis should be assessed, and appropriate modification instituted, including smoking cessation, dietary adjustment, and pharmacotherapy as warranted for dyslipidemia, hypertension, or hyperglycemia. He also should be treated with aspirin (75 mg to 325 mg per day).

Management in this case should include a supervised exercise program and a trial of cilostazol for claudication, an approach that is consistent with the AHA–ACC guidelines. Revascularization is warranted if the condition does not improve with conservative therapy and if the lesion has anatomical features that are associated with a good outcome of revascularization. PTA is preferred over surgery and may be considered up front if there is a high probability of success and a low procedural risk (Table 4).[9] An imaging study (duplex ultrasonography, CTA, or MRA, with the choice guided by the physician's preference and the availability of local expertise) is indicated in patients who are candidates for revascularization in order to determine the location and morphologic characteristics of the obstructive lesion (or lesions). If a percutaneous intervention is considered to be likely, one can proceed directly to digital-subtraction angiography, with a plan to perform the percutaneous intervention immediately if the angiographic anatomy is suitable. Regardless of the initial therapy for this patient's claudication, follow-up care should involve ongoing attention to control of atherosclerotic risk factors, antiplatelet therapy with aspirin, and encouragement of the patient to engage in regular exercise.

No potential conflict of interest relevant to this article was reported.

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