CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Peripheral Artery Disease

Iftikhar J. Kullo, M.D., and Thom W. Rooke, M.D.

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 authors' clinical recommendations.*

A 61-year-old woman presents with a 3-year history of discomfort in the right thigh on exertion. Her symptoms have recently progressed to involve the right calf. She is able to walk no more than 50 m before having to stop because of leg pain. Her medical history is notable for coronary-artery bypass surgery after a myocardial infarction at 55 years of age and for hyperlipidemia, for which she takes atorvastatin at a dose of 40 mg daily. She has a smoking history of 50 pack-years and currently smokes eight cigarettes per day. On examination, the blood pressure is 126/82 mm Hg, there is a bruit over the right femoral artery, and pulses are diminished in the right leg. How would you evaluate and manage this case?

From the Division of Cardiovascular Diseases and the Gonda Vascular Center, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Kullo at the Division of Cardiovascular Diseases, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at kullo.iftikhar@mayo.edu.

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THE CLINICAL PROBLEM

THE TERM "PERIPHERAL ARTERY DISEASE" CLASSICALLY ENCOMPASSES THE various diseases that affect noncardiac, nonintracranial arteries. The most common cause of peripheral artery disease is atherosclerosis; less common causes include inflammatory disorders of the arterial wall (vasculitis) and noninflammatory arteriopathies, such as fibromuscular dysplasia. This review focuses on the management of stable peripheral artery disease that is due to atherosclerosis affecting the infrarenal aorta and the arteries of the legs. There are two broad subtypes of peripheral artery disease: proximal disease, which involves the aortoiliac and femoropopliteal locations, and distal disease, which involves the infrapopliteal location.[1] Distal disease may be accompanied by calcification of the medial layer, which leads to poorly compressible arteries and is associated with high mortality.[2]

On the basis of the prevalence in cohort studies of an abnormal ankle–brachial index — the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm[3] — it is estimated that at least 8.5 million persons in the United States[4] and more than 200 million people worldwide[5] have peripheral artery disease. The total annual costs associated with the hospitalization of patients with peripheral artery disease in the United States are estimated to be in excess of $21 billion,[6] a number that is projected to rise as the population ages.

The risk factors for peripheral artery disease are similar to those for other atherosclerotic vascular diseases, with smoking and diabetes mellitus being the strongest.[5] Markers of inflammation and thrombosis, elevated lipoprotein(a) and homocysteine levels, and chronic kidney disease are also associated with peripheral artery disease.[7] The prevalence of peripheral artery disease is similar among

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KEY CLINICAL POINTS

PERIPHERAL ARTERY DISEASE

- Atherosclerotic peripheral artery disease affects more than 200 million persons worldwide, including at least 8.5 million persons in the United States, and is associated with high rates of cardiovascular events and death. Smoking and diabetes are the strongest risk factors.
- Noninvasive vascular testing provides information on the presence, severity, and location of peripheral artery disease. Exercise testing can uncover mild disease and quantify functional capacity.
- In the treatment of peripheral artery disease, the main goals are to reduce cardiovascular risk and improve functional capacity. Supervised exercise increases walking distance. Cilostazol can be used as an adjunct to an exercise program.
- Conventional angiography is typically performed when revascularization is being considered. Computed tomography or magnetic resonance angiography can also be useful in planning for revascularization.
- Revascularization, endovascular or surgical, is indicated for symptoms that persist despite medical management or for limb salvage in the context of critical limb ischemia.

men and postmenopausal women, but men are more likely than women to have classic symptoms of claudication. Blacks have a lower ankle–brachial index than whites,[8] even after adjustment for differences in risk factors. This difference may be due to physiologic factors, since it is also present among younger persons without cardiovascular risk factors.[9] Studies involving twins suggest that heritable factors confer a predisposition to peripheral artery disease,[10] and in a case–control study,[11] a family history of peripheral artery disease was associated with a doubling of the odds of the disease. However, relatively few genetic variants that influence the susceptibility to peripheral artery disease have been discovered — in contrast to coronary heart disease, for which multiple genetic variants have been found — possibly because of greater clinical and genetic heterogeneity in peripheral artery disease than in coronary heart disease.[12]

Peripheral artery disease is associated with several comorbid conditions; coronary heart disease, cerebrovascular disease, or both are present in more than half the persons who receive a diagnosis of peripheral artery disease.[13] On the basis of registry data, the 1-year incidence of cardiovascular death, myocardial infarction, and ischemic stroke was higher among persons with peripheral artery disease than among those with coronary heart disease (5.35% vs. 4.52%)[14]; the incidence of adverse limb outcomes, including worsening of symptoms, the need for peripheral revascularization, and amputation, was 26% over a period of 4 years.[15] An ankle–brachial index of 0.9 or less is associated with more than twice the mortality that is associated with an ankle–brachial index of 1.11 to 1.40.[16] In spite of high morbidity and mortality, patients with peripheral artery disease are often underdiagnosed and undertreated.[17]

STRATEGIES AND EVIDENCE

ASSESSMENT

Screening

The U.S. Preventive Services Task Force does not recommend routine screening with ankle–brachial indexes because of a lack of evidence that early detection results in more effective treatment of risk factors or better outcomes.[18] Targeted screening of persons who are at increased risk, such as persons who are older than 65 years of age and those who are older than 50 years of age and are smokers or have diabetes, is recommended by the guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA).[19,20]

Symptoms and Signs at Presentation

Patients with peripheral artery disease may be asymptomatic, may have classic symptoms of claudication (discomfort on exertion in the muscle groups that are distal to the affected artery), or may have leg discomfort that is atypical for claudication.[21] A subgroup of patients may present with acute or chronic critical limb ischemia. Signs of peripheral artery disease include diminished pulses, arterial bruits, decreased capillary refill, pallor on elevation, and trophic changes.[21] Patients with critical limb ischemia often have pain at rest and ulceration or gangrene of the toes on examination.

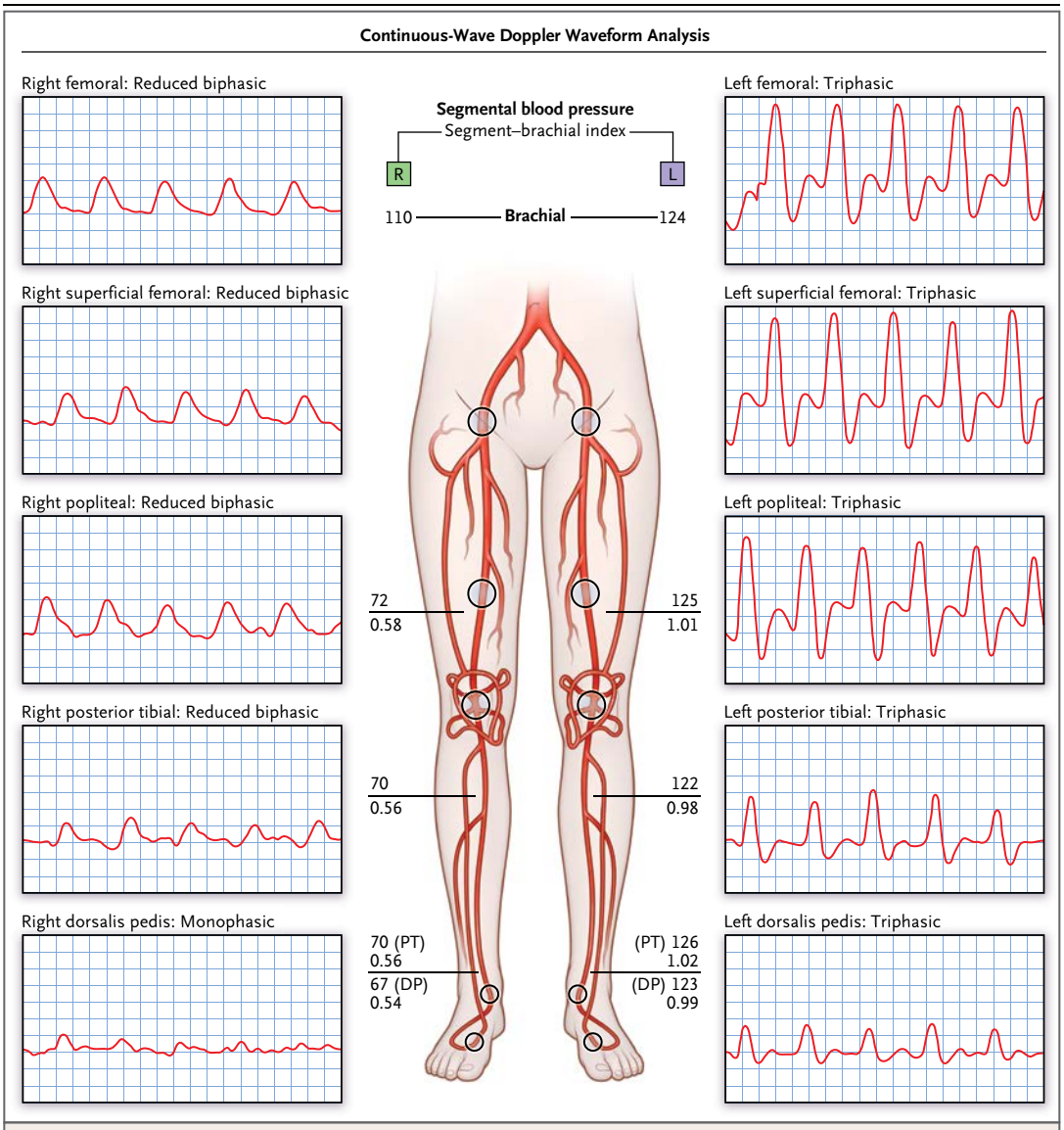

Figure 1. Noninvasive Arterial Testing in the Leg.

Shown are the results of measurement of segmental blood pressures and indexes in the leg and continuous-wave Doppler examination of the patient discussed in the vignette. To obtain segmental blood pressures, cuffs are placed at three or four sites on the legs. The higher of the two arm pressures is used to calculate each segment–brachial index (the ratio of the systolic blood pressure at the segment to the systolic blood pressure in the arm). Peripheral artery disease is considered to be present when the resting ankle–brachial index is 0.90 or less. Generally a drop in the blood pressure of more than 20 mm Hg between two adjacent locations indicates a hemodynamically significant stenosis. Continuous-wave Doppler waveforms can be qualitatively analyzed to assess arterial blood flow (circles indicate sites of Doppler-probe placement). Normally, a triphasic or biphasic response is present, whereas a reduced biphasic or monophasic signal indicates a hemodynamically significant stenosis. DP denotes dorsalis pedis, L left, PT posterior tibial, and R right.

Noninvasive Arterial Testing in the Legs

Noninvasive testing typically includes the measurement of blood pressures at different levels in the legs (segmental blood pressures) and the estimation of corresponding segment–brachial indexes (including the ankle–brachial index), as well as continuous-wave Doppler waveform analysis (Fig. 1 and Table 1).[19,20] Additional testing

Table 1. Noninvasive Evaluation of Peripheral Artery Disease.*

Diagnosis, as assessed on the basis of resting or postexercise ABIs
Peripheral artery disease is considered to be present when the ABI is ≤0.90 (normal range, 1.00 to 1.30; values of 0.91 to 0.99 are considered borderline low) or when the resting ABI is normal but the postexercise ABI is ≤0.90 or there is a ≥20% decrease in ABI after exercise
A high ABI (>1.40) is suggestive of poorly compressible arteries, and an ABI of 1.30 to 1.40 is borderline high; toe–brachial indexes and toe pressures can be used in such a situation
Disease severity, as assessed by resting or postexercise ABIs
Mild: resting or postexercise ABI, ≤0.90
Moderate: resting ABI, ≤0.70, or postexercise ABI, ≤0.50
Severe: resting ABI, ≤0.50, or postexercise ABI, ≤0.15
Disease location, according to continuous-wave Doppler waveforms and segmental blood pressures
Proximal, involving the aortoiliac and femoropopliteal locations
Distal, involving the infrapopliteal location
Proximal and distal (multilevel disease)
Functional capacity, as assessed by the distance walked during exercise on a treadmill
Pain-free walking distance
Maximal walking distance
Tissue oxygenation, as assessed with the use of transcutaneous oximetry, is useful in assessing the healing potential of ischemic wounds and possible amputation sites, as well as in assessing candidacy for hyperbaric oxygen or intermittent pneumatic compression therapy
Concomitant atherosclerotic vascular disease
Coronary heart disease: electrocardiogram positive for ischemia during exercise
Subclavian artery disease: difference of >12 mm Hg in blood pressures in the arm

* The ankle–brachial index (ABI) is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm.[3]

may include exercise testing on a treadmill to detect mild disease and to measure pain-free and maximum walking times, measurement of toe–brachial indexes in patients with poorly compressible arteries, and transcutaneous oximetry to assess tissue oxygenation in the context of severe peripheral artery disease and critical limb ischemia (Fig. 2 and Table 1). Ultrasonography combined with Doppler imaging (duplex scanning) is a relatively inexpensive, readily available technique for imaging atherosclerotic plaque in peripheral arteries and is commonly used to assess stent or graft patency after revascularization.[19,20]

Angiography

Conventional angiography (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) is indicated in symptomatic patients who are being considered for revascularization.[19,20] Computed tomography (CT) or magnetic resonance angiography may also be useful in planning for revascularization. CT angiography is widely available, requires a relatively short scanning time, and provides high-resolution images that can be processed for three-dimensional reconstruction. Drawbacks are that it requires the use of vascular contrast material and may provide poor delineation of heavily calcified or small distal vessels. Magnetic resonance angiography avoids the use of radiation and provides good spatial resolution but is technically more challenging than CT angiography, cannot be used in patients who have certain metallic or electronic implants, and carries a risk of nephrogenic systemic fibrosis when gadolinium that is used for the vascular contrast material is administered to patients with chronic kidney disease.

OVERVIEW OF MANAGEMENT

The main goals in treating patients with peripheral artery disease are to reduce the risks of adverse cardiovascular outcomes, improve functional capacity, and preserve limb viability (Fig. 2). Multiple coexisting conditions are common in patients with peripheral artery disease and present additional challenges in treatment.

TREATMENT OF CARDIOVASCULAR RISK FACTORS

Hyperlipidemia

Recent guidelines recommend high-intensity statin therapy in patients with atherosclerotic vascular disease to lower the low-density lipoprotein (LDL) cholesterol level by 50% or more, but the guidelines do not mandate a specific target level of LDL cholesterol.[22] In the Heart Protection Study,[23] the subgroup of patients with peripheral artery disease who were assigned to simvastatin had a reduction of 25% relative to the reduction among those assigned to placebo, in the risk of cardiovascular events over 5 years of follow-up — a reduction that was similar to that observed in the subgroup of patients without peripheral artery disease. In a large registry

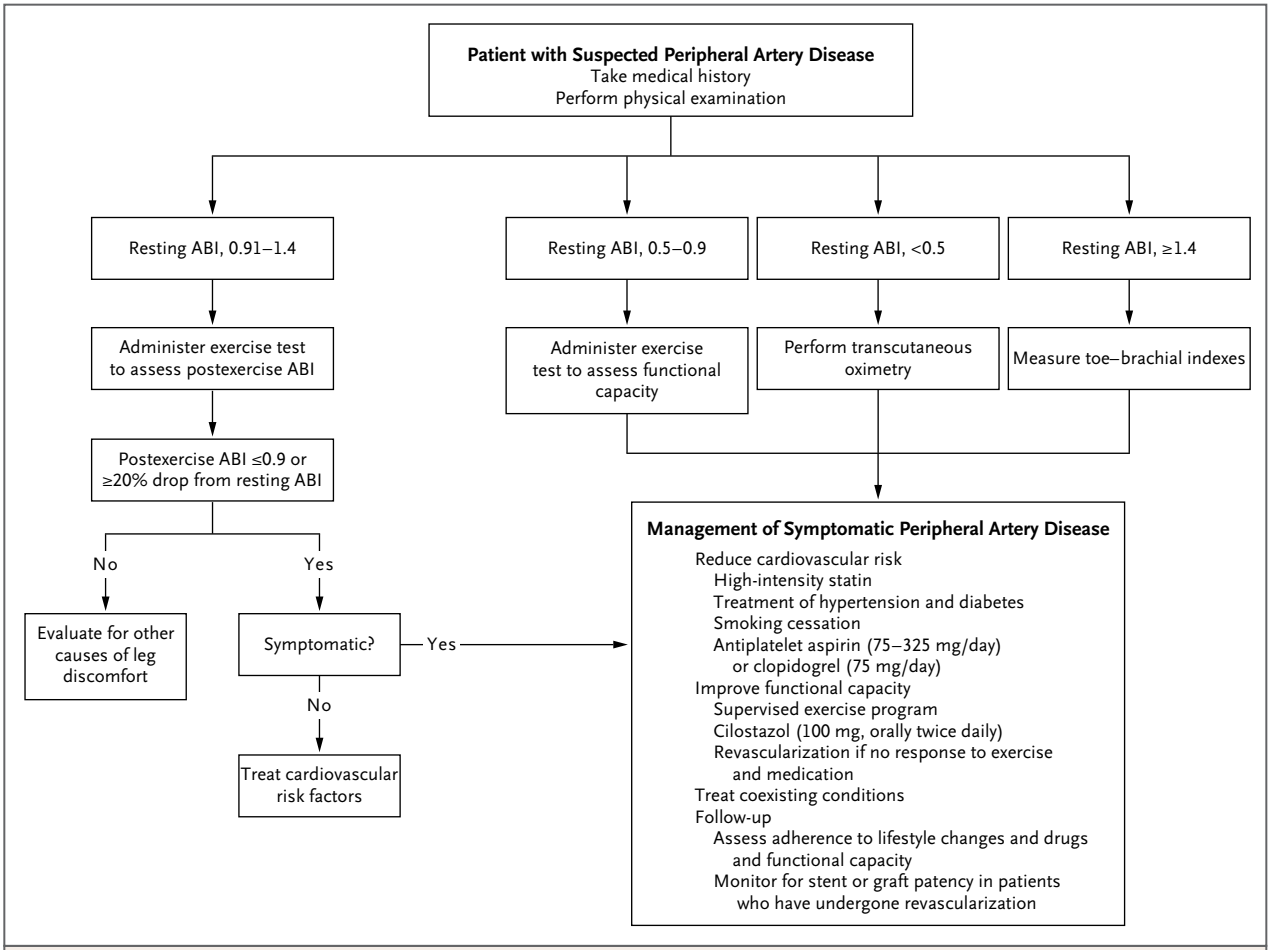

Figure 2. Suggested Approach to the Evaluation and Treatment of Patients with Peripheral Artery Disease.
The ankle–brachial index (ABI) is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm.[3]

study, patients with peripheral artery disease who were taking statins had a rate of adverse limb outcomes (including worsening of symptoms, the need for peripheral revascularization, and amputation) that was 18% lower than the rate among patients who were not taking statins.[15]

Hypertension

There is controversy with regard to blood-pressure targets, with a recent trial suggesting that the systolic blood-pressure goal should be less than 120 mm Hg in patients at high cardiovascular risk.[24] There are no comparative trials to support the use of one particular class of antihypertensive agent over another in patients with peripheral artery disease. However, angiotensin-converting–enzyme inhibitors may be preferred agents to reduce the risk of adverse cardiovascular events in peripheral artery disease.[19,20] In the Heart Outcomes Prevention Evaluation Study[25], which involved 9297 patients with diabetes or vascular disease (including 4051 patients with peripheral artery disease), treatment with ramipril resulted in a lower risk of adverse cardiovascular outcomes than the risk with placebo, over 5 years of follow-up. When indicated, beta-blockers can be safely used in patients with peripheral artery disease.

Diabetes

The treatment of diabetes does not reduce the risk of cardiovascular events but may lower the

risks of microvascular disease and neuropathy.[26] This observation is relevant to patients with peripheral artery disease and diabetes, in whom foot ulceration is a debilitating adverse outcome. Since intensive blood-glucose control may increase mortality among patients with established cardiovascular disease,[27] a target glycated hemoglobin level should be chosen on the basis of the age of the patient, the duration of diabetes, and the presence of coexisting conditions. Proper foot care, daily inspection of the feet, and prompt evaluation of any skin lesion or ulceration are recommended.

Smoking Cessation

Persons with peripheral artery disease who stop smoking have a lower risk of death, progression of disease, critical limb ischemia and amputation, myocardial infarction, stroke, and bypass-graft failure than those who continue to smoke.[28] Referral for counseling, the use of adjunctive pharmacotherapy (varenicline, bupropion, or nicotine-replacement therapy), or both may increase abstinence rates.[20]

Antiplatelet Agents

Patients with symptomatic peripheral artery disease should receive antiplatelet therapy in the form of aspirin (at a dose of 75 to 325 mg daily). A meta-analysis of randomized trials of aspirin use in patients with peripheral artery disease showed no significant reduction in the risk of cardiovascular events but a significant reduction in the risk of nonfatal stroke.[29] Aspirin did not improve outcomes among persons with an ankle–brachial index of 0.95 or less who did not have symptoms.[30] In a randomized trial that included persons with symptomatic peripheral artery disease or other manifestations of atherosclerotic vascular disease, clopidogrel (at a dose of 75 mg daily) was slightly more effective than aspirin in reducing the risk of a composite outcome of ischemic stroke, myocardial infarction, or death from vascular causes.[31] Dual antiplatelet therapy can be considered in patients with symptomatic peripheral artery disease who are not at increased risk for bleeding.[32]

Vorapaxar, a new antiplatelet agent that blocks the thrombin protease-activated receptor 1, reduced the risk of cardiovascular death or ischemic events among patients with atherosclerotic vascular disease but increased the risk of bleeding events, including intracranial hemorrhage.[33] In the subgroup of patients with peripheral artery disease, the drug reduced the risk of acute limb ischemia and peripheral-revascularization events,[34] which led to its approval for use in patients with peripheral artery disease who did not have a history of stroke. Warfarin is not recommended, because the combination of warfarin and aspirin did not result in a greater reduction in the risk of cardiovascular events than aspirin alone and was associated with more bleeding.[35]

IMPROVING FUNCTIONAL CAPACITY

Overview

The association between the ankle–brachial index and functional capacity in patients with peripheral artery disease is modest, and poor functional capacity in patients with peripheral artery disease is often multifactorial, including conditions such as coronary heart disease, pulmonary disease, and degenerative joint disease.[36] Several strategies may improve functional capacity in patients with peripheral artery disease.

Supervised Exercise

A program that incorporates walking at least three times per week (30 to 60 minutes per session) for at least 12 weeks should be the first-line therapy for claudication. In a trial comparing supervised exercise with stenting in patients with aortoiliac disease who were receiving medical therapy, supervised exercise resulted in significantly greater mean peak walking time at 6 months (5.8 vs. 3.7 minutes)[37]; however, quality-of-life indicators were better in the patients who were randomly assigned to stenting. Supervised exercise for peripheral artery disease is not reimbursed by insurers in the United States. A home-based, group-mediated, cognitive behavioral walking intervention that included goal setting, self-monitoring, managing pain during exercise, and walking at least 5 days per week lengthened the 6-minute walking distance by 53 m over the distance walked by the control group that received health education alone.[38]

Medications

Cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilatory properties, increases

the maximal walking distance on a treadmill by approximately 25%, as compared with placebo.[39] Side effects include tachycardia, diarrhea, and increased bleeding tendency; it is contraindicated in patients with heart failure or low ejection fraction. Nafronyl, a 5-hydroxytryptamine–receptor blocker that inhibits platelet aggregation, may be more effective than cilostazol and is approved in Europe for claudication.[39] Atorvastatin (at a dose of 80 mg daily for 12 months) was associated with a modestly longer pain-free walking time, but not a longer maximal walking time, than was placebo.[40]

Revascularization

Revascularization is indicated when there are limiting symptoms in spite of an exercise program and medical therapy and there is a reasonable likelihood that symptoms can be reduced (including absence of other conditions that might limit functional capacity, such as heart failure or lung disease); it is also indicated for limb salvage in the context of critical limb ischemia. Commonly performed revascularization procedures for peripheral artery disease are shown in Figure 3 and Figure S2 in the Supplementary Appendix. An individualized approach should be adopted to select a revascularization strategy for each patient on the basis of the patient's preferences, anatomical factors, the availability of appropriate conduits, and operative risk. Supervised exercise may serve as a useful adjunct to revascularization. In a trial involving 212 patients with claudication, those who were randomly assigned to endovascular revascularization and supervised exercise had a longer maximal walking distance at 12 months than did those who were randomly assigned to exercise alone (1237 vs. 955 m).[41]

Aortoiliac angioplasty and stenting (Fig. S1 in the Supplementary Appendix) have high procedural success rates (approximately 96%) and a 3-year patency rate of approximately 82%.[42] Stent placement is generally avoided in the common femoral artery, owing to the risk of biomechanical stress-related stent fractures and the potential for interference with future arterial access. Endovascular intervention in the superficial femoral artery is associated with high rates of restenosis, and several technologies to limit restenosis, including drug-eluting or covered stents and drug-coated balloons, are being evaluated (Fig. 3). Endovascular therapy of isolated infrapopliteal disease is not recommended for claudication.[19,20] Patients should receive dual antiplatelet therapy for at least 30 days or for a longer period if a drug-eluting stent is placed.[43]

Surgical bypass (Fig. S2 in the Supplementary Appendix) should be considered when an endovascular approach has failed or is not feasible from an anatomical standpoint. Aortofemoral bypass is a durable operation for aortoiliac disease, with patency rates up to 90% at 5 years.[44] In patients who are poor candidates for surgery, cross-clamping of the aorta can be avoided by an axillary–femoral graft, which is often combined with a femoral–femoral graft. Endarterectomy is the procedure of choice for common femoral-artery lesions and is often combined with an endovascular approach. The saphenous vein is the preferred conduit for infrainguinal bypass, but a prosthetic conduit can be used for femoral–popliteal bypass if the above-knee popliteal artery is the target vessel and good runoff is present.[45] Femoral–tibial bypass is an option in patients with critical limb ischemia and infrapopliteal disease.

There is no clear guidance regarding antithrombotic therapy after surgical revascularization; however, in patients undergoing infrainguinal bypass surgery, venous grafts had better patency with warfarin than with aspirin therapy, whereas prosthetic grafts had better patency with aspirin.[46] For below-knee prosthetic grafts, dual antiplatelet therapy is preferred. A cardiac stress imaging study may be indicated preoperatively to assess the presence and severity of coronary heart disease in patients with peripheral artery disease who have poor functional capacity.[47] However, there is no benefit from prophylactic coronary revascularization in patients with peripheral artery disease who are undergoing surgical revascularization.[48]

FOLLOW-UP

Patients should be followed to assess adherence to lifestyle measures and drug therapy and to assess for changes in functional capacity. Patients who have undergone revascularization should be monitored for stent or graft patency.[20] Postsurgical graft stenosis is treated with open or endovascular intervention to prevent graft occlusion.

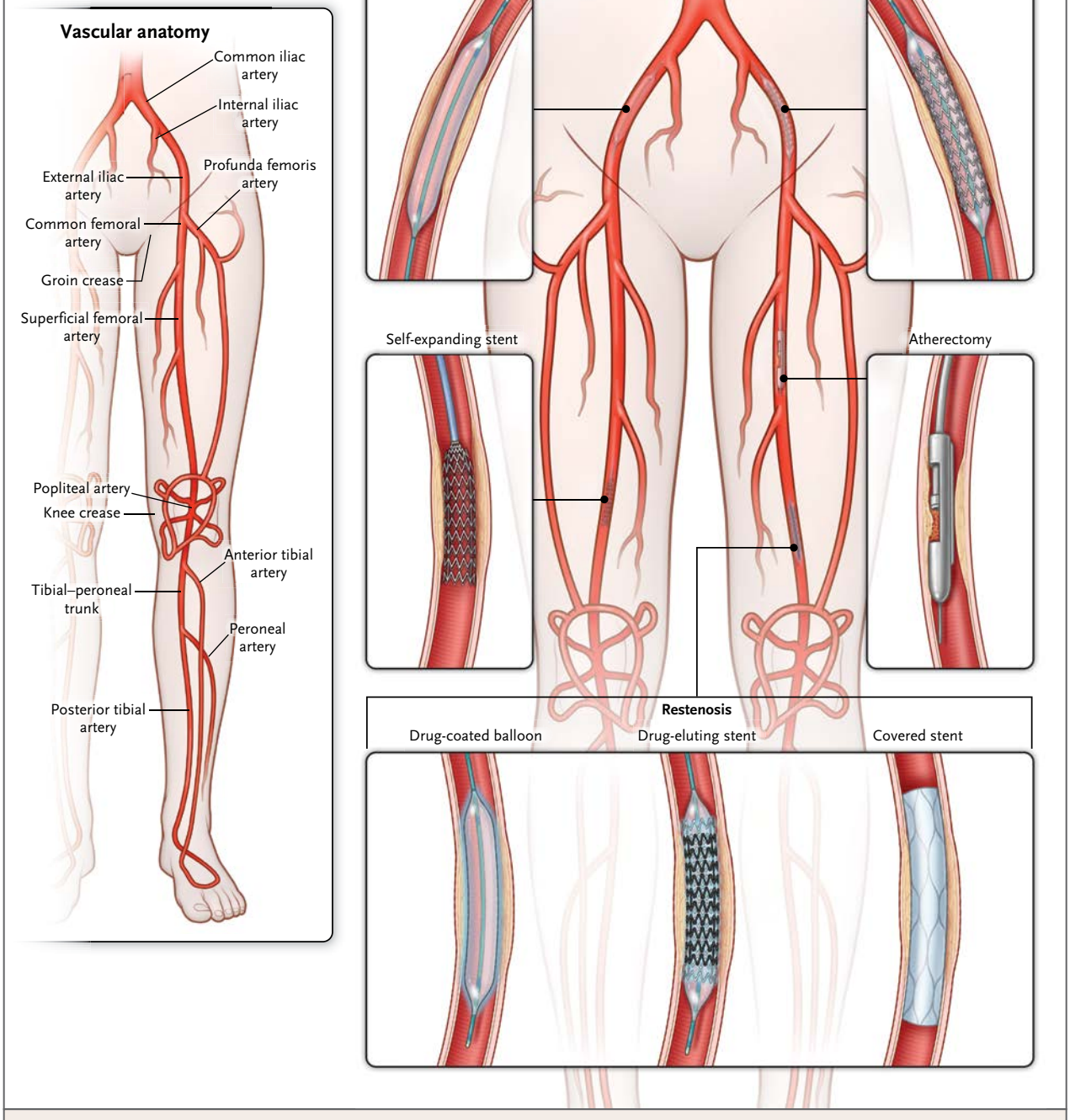

Figure 3. Major Arteries of the Legs and Endovascular Procedures for Treatment of Peripheral Artery Disease.

Balloon angioplasty, stenting (with balloon-expandable or self-expanding stents), and atherectomy are common endovascular procedures. Drug-eluting or covered stents and drug-coated balloons are being evaluated to reduce the rate of restenosis.

AREAS OF UNCERTAINTY

Randomized trials are needed to compare medical therapy and supervised exercise with revascularization and to compare endovascular revascularization with surgical revascularization, particularly in patients with distal (infrapopliteal) peripheral artery disease. Studies are also needed to inform appropriate treatment of patients with peripheral artery disease who are asymptomatic, have concomitant disease in other arterial beds, or have poorly compressible arteries owing to calcification of the medial layer. The role of new antiplatelet or anticoagulant drugs in reducing cardiovascular risk among patients with peripheral artery disease is being assessed in ongoing trials (ClinicalTrials.gov numbers, NCT01732822 and NCT01776424). Additional data are also needed to guide antithrombotic therapy after revascularization. Molecular and regenerative medicine therapies for severe peripheral artery disease are being investigated.[49]

GUIDELINES

The ACC–AHA published updated guidelines for the management of peripheral artery disease in 2011.[20] The TransAtlantic Inter-Society,[42] which represents 16 professional societies from several countries, the Society for Vascular Surgery,[45] and the European Society of Cardiology[50] have also published guidelines for the management of peripheral artery disease. The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has symptoms consistent with claudication. She should undergo a noninvasive arterial evaluation. An ankle–brachial index of 0.9 or less would be consistent with peripheral artery disease, and continuous-wave Doppler waveform analysis and measurement of segmental blood pressures are useful to identify the location of disease. She should be counseled regarding smoking cessation and should start a supervised or a home-based exercise program. We would initiate cilostazol at a dose of 100 mg twice daily and consider increasing the dose of atorvastatin to 80 mg daily. If her symptoms continued to limit her activity despite these interventions, we would recommend angiography and revascularization. An endovascular approach would be considered for proximal disease, whereas surgical revascularization would be considered for distal (infrapopliteal) disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Waves of Snow

Henry Gewirtz, M.D.