

CLINICAL PRACTICE

Peripheral Artery Disease in the Legs

Mary M. McDermott, M.D.^{1,2}

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.

SUMMARY

Peripheral artery disease affects approximately 236 million persons worldwide and is diagnosed with an ankle–brachial index of less than 0.90. Among older persons, 3.3% of those without peripheral artery disease, 18.1% with mild disease, and 52.0% with severe disease could not complete a 6-minute walk test without resting. To prevent cardiovascular events in persons with peripheral artery disease, intensive cholesterol-lowering medications (statins), antiplatelet medications or low-dose aspirin with rivaroxaban, blood-pressure lowering to less than 130/80 mm Hg, and semaglutide are recommended, along with sodium–glucose cotransporter 2 inhibitors in patients with diabetes. Supervised walking exercise and structured home-based walking exercise each improve walking ability in persons with peripheral artery disease. Revascularization in the legs should be reserved for those with persistent disease symptoms that do not respond to exercise.

Author affiliations are listed at the end of the article. Mary M. McDermott can be contacted at mdm608@northwestern.edu or at Northwestern University Feinberg School of Medicine, 750 N. Lake Shore Dr., 10th Fl., Chicago, IL 60611.

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A 62-year-old woman with type 2 diabetes, hypertension, and a history of cigarette smoking presents with exertional leg symptoms consistent with peripheral artery disease. She reports pain in the buttocks and lower legs with walking that resolves within 10 minutes after rest. Walking more than one or two blocks is difficult because of these symptoms. Her blood pressure is 150/70 and pulse is 82 beats per minute. No femoral bruits are audible, the calf muscles are atrophic, and the dorsalis pedis and posterior tibial pulses are grade 1+ bilaterally (range, grade 0 to 3+, with grade 3+ indicating a normal pulse). The ankle–brachial index (ABI; the ratio of the posterior tibial or dorsalis pedis systolic pressure to the brachial systolic pressure) is 0.56 on the right side and 0.64 on the left side. She has no symptoms or history of heart failure. Because of difficulty walking, she no longer engages in activities she enjoys. How would you treat this patient?

THE CLINICAL PROBLEM

PERIPHERAL ARTERY DISEASE IN THE LEGS REFERS TO ATHEROSCLEROTIC blockages of arteries in the legs (Fig. 1). The disease affects approximately 12.5 million persons 40 years of age or older in the United States and approximately 236 million persons worldwide.^{1,2} The term peripheral artery disease is preferred to peripheral vascular disease, which includes both arterial and venous disease. Risk factors for peripheral artery disease include older age, cigarette smoking, diabetes, dyslipidemia (including elevated lipoprotein[a] levels), and hyperten-



Figure 1. Diagnosis and Treatment of Peripheral Artery Disease.

Pathophysiological findings include endothelial damage with reduced activity of endothelial nitric oxide synthase (eNOS) and lower abundance of nitric oxide (NO) (Panel A). This damage results in early atherosclerosis, which progresses and includes a thrombotic component. Inflammation also contributes to the atherosclerosis. Classic symptoms include calf pain during walking activity that increases with greater walking distance and resolves within 10 minutes after rest (Panel B). However, approximately two thirds of patients have exertional leg symptoms other than classic claudication or report no exertional leg symptoms (i.e., are asymptomatic). The ankle–brachial index (ABI) is the ratio of the posterior tibial or dorsalis pedis systolic pressure (or their mean) to the mean of the brachial artery systolic pressures (Panel C). The systolic pressures are measured with Doppler ultrasonography. An ABI of less than 0.90 is consistent with peripheral artery disease (PAD). Treatment of leg symptoms and walking difficulty in peripheral artery disease includes walking exercise (supervised or structured home-based walking exercise), cilostazol, semaglutide, or leg revascularization (or a combination of these therapies) (Panel D). Prevention of cardiovascular events may include a potent statin, blood-pressure treatment (ramipril or telmisartan) to maintain a blood pressure less than 130/80, antiplatelet therapy (aspirin or clopidogrel) or rivaroxaban plus aspirin, and a glucagon-like peptide-1 (GLP-1) receptor agonist, a sodium–glucose cotransporter 2 (SGLT2) inhibitor (for patients with peripheral artery disease and diabetes), or both (Panel E).

sion³ (Table 1). Approximately 10 to 15% of persons older than 65 years and 15 to 20% of those older than 80 years have the condition.⁴ In the United States, peripheral artery disease is approximately twice as common among Black persons as among non-Hispanic White persons.^{3,4} Among persons with peripheral artery disease, those with diabetes have greater walking impairment, higher mortality, a higher prevalence of amputation, and a higher prevalence of atherosclerosis below the knee than those without diabetes.^{3,16}

Peripheral artery disease is associated with an increased incidence of cardiovascular events.^{9,10} Among 13,885 patients with symptomatic disease and either an ABI less than 0.80 or previous revascularization in the legs, 10.7% had a myocardial infarction, ischemic stroke, or death

from cardiovascular causes at a median follow-up of 30 months.¹⁰ The incidence of a major adverse limb event, which is defined as severe ischemia in the legs resulting in revascularization or amputation, among patients with peripheral artery disease ranges from 12.9 to 15.2% over 1.8 to 2.7 years of follow-up.¹¹⁻¹³ Peripheral artery disease is associated with mobility impairment due to leg ischemia during walking.⁵

STRATEGIES AND EVIDENCE

EVALUATION

The most classic peripheral artery disease symptom is claudication, which is characterized by exertional calf pain that does not begin during rest and resolves within 10 minutes after rest.

Table 1. Overview of PAD in the Legs.*

Characteristic	Evidence
No. of persons affected	PAD affects approximately 12.5 million persons in the United States ¹ and approximately 236 million persons worldwide. ²
Prevalence	PAD occurs in approximately 10 to 12% of persons 65 years of age or older ⁴ and in approximately 15 to 20% of those older than 80 years. ⁴
Risk factors	Older age, cigarette smoking, diabetes mellitus, high cholesterol, hypertension, sedentary lifestyle, and elevated lipoprotein(a) levels are risk factors for PAD. ³
Symptoms	Most persons with PAD have difficulty walking long distances, ⁵ most do not have classic symptoms of intermittent claudication, many report no exertional leg symptoms, and others have atypical symptoms such as hip pain or low back pain when walking that resolves with rest. ^{5,6}
Diagnosis	An ABI of less than 0.90 is 69 to 79% sensitive, 83 to 99% specific, and 72 to 89% accurate for diagnosing PAD. ⁷ In a population study, an absent dorsalis pedis pulse was 50% sensitive and 73% specific for diagnosing PAD and an absent posterior tibial pulse was 71% sensitive and 91% specific. ⁸
Adverse outcomes	
Cardiovascular events	The rate of cardiovascular events and death from cardiovascular causes among persons with PAD is 2 to 3 times as high as that among persons without PAD, even after adjustment for potential confounders. ^{3,9,10} Among 48,294 participants in epidemiologic studies, death from cardiovascular causes had occurred in 18.7% of men with PAD and 4.4% of men without PAD ⁹ and in 12.6% of women with PAD and 4.1% of women without PAD at 10-year follow-up. ⁹ Among 13,885 patients with symptomatic PAD and either an ABI of less than 0.80 or previous lower-extremity revascularization, 10.7% had a myocardial infarction, ischemic stroke, or death from cardiovascular causes at a median follow-up of 30 months. ¹⁰
Major adverse limb events	The incidence of major adverse limb events (severe leg ischemia resulting in revascularization or amputation) ranges from 12.9 to 15.2% over 1.8 to 2.7 years of follow-up. ¹¹⁻¹³ Major adverse limb events are more common after leg revascularization. ¹¹⁻¹³
Walking impairment	Persons with PAD have difficulty walking longer distances. For example, among 740 persons 55 years of age or older (460 persons with PAD) who underwent a 6-minute walk test, 29.5% of those with an ABI of less than 0.90 stopped to rest during the test as compared with 3.3% of those with a normal ABI of 1.10 to 1.40, with adjustment for confounders. ⁵ In addition, the distance walked in 6 minutes decreases at a significantly faster rate among persons with PAD than those without PAD. ^{14,15}

* ABI denotes ankle-brachial index, and PAD peripheral artery disease.

Although ischemic leg symptoms typically occur distal to a stenosed artery, approximately 68 to 90% of persons with peripheral artery disease have atypical ischemic symptoms (e.g., hip pain) or report no exertional leg symptoms.^{5,6} Among 6880 patients 65 years of age or older in German primary care practices who underwent ABI testing for a research study, 1429 (21%) had peripheral artery disease. Of these patients, 836 (58.5%) were asymptomatic.¹⁷ Persons with peripheral artery disease often reduce walking activity or speed to avoid ischemic symptoms.^{5,6} The frequent absence of leg symptoms in persons with peripheral artery disease probably contributes to underdiagnosis.

The sensitivity and specificity of pulse palpation for diagnosing peripheral artery disease are modest. In a population study, absence of a dorsalis pedis pulse was 50% sensitive and 73% specific and absence of a posterior tibial pulse was 71% sensitive and 91% specific for diagnosing the condition.⁸ In persons with risk factors for peripheral artery disease and walking difficulty consistent with the disease, the ABI is the recommended initial diagnostic test. The ABI is a ratio of systolic blood pressure in the ankle to systolic pressures in the brachial arteries, as assessed with Doppler ultrasonography.⁷ At the ankle, the higher of the dorsalis pedis and posterior tibial systolic pressures is often used for ABI calculation, because the higher pressure may best reflect leg perfusion.⁷ However, using the lower of the dorsalis pedis and posterior tibial artery pressures for ABI calculation is more sensitive for detecting peripheral artery disease.⁷ Without atherosclerotic obstruction, systolic pressures increase with greater distance from the heart, yielding higher systolic pressures at the ankle than at the brachial artery. Therefore, a normal ABI ranges from more than 1.00 to 1.40. An ABI lower than 0.90 is approximately 69 to 79% sensitive and 83 to 99% specific for diagnosing peripheral artery disease, which is defined as more than 50% angiographic stenosis of a major leg artery.⁷ More severe peripheral artery disease is associated with lower ABI values. Calcium deposits in the medial layer of the arterial wall (medial calcification) reduce artery compressibility, which decreases the sensitivity of the ABI for diagnosing the condition. This phenomenon is particularly common in patients with diabetes or chronic kidney disease. In persons with an ABI of 1.40 or higher or in those with symptoms or signs of peripheral artery dis-

ease and a normal ABI, a toe-brachial index may identify the disease, because the toe artery is less likely to be noncompressible than more proximal arteries.¹⁸ A toe-brachial index of 0.70 or lower is consistent with peripheral artery disease.¹⁸

WALKING IMPAIRMENT IN PERIPHERAL ARTERY DISEASE

Atherosclerotic blockages in leg arteries prevent delivery of oxygen and energy to the legs during walking. Among 740 patients 55 years of age or older who received diagnoses at Chicago medical centers, including 460 patients with peripheral artery disease, 3.3% of those with an ABI of 1.10 to 1.40, 18.1% of those with an ABI of 0.70 to less than 0.90, 31.6% of those with an ABI of 0.50 to less than 0.70, and 52.0% of those with an ABI of less than 0.50 could not complete a 6-minute walk test without resting.⁵ Persons with peripheral artery disease typically have a decrease in walking ability over time.^{14,15} Among 195 trial participants with peripheral artery disease who were randomly assigned to a placebo group or nontreatment control group (53.3% were men and 51.3% were Black), the mean 6-minute walk distance decreased by 10.2 m over a period of 6 months.¹⁴ Among 43 men with the disease, the mean 6-minute walk distance decreased by 34 m over a period of 18 months.¹⁵

TREATMENTS FOR PERIPHERAL ARTERY DISEASE

MEDICATIONS FOR PERIPHERAL ARTERY DISEASE—ASSOCIATED WALKING IMPAIRMENT

Cilostazol, a phosphodiesterase 3 inhibitor, is the only medication recommended by the American Heart Association (AHA) and American College of Cardiology (ACC) joint clinical practice guidelines for walking impairment caused by peripheral artery disease.¹⁹ However, the benefits of cilostazol are modest (Fig. 2). In a meta-analysis of randomized clinical trials, cilostazol was associated with a 40-m increase in maximal treadmill walking distance among participants with peripheral artery disease, as compared with placebo.²¹ In comparison, another meta-analysis of randomized trials showed that supervised walking exercise was associated with a 180-m increase in maximal treadmill walking distance, as compared with control.²⁶ Adverse effects of cilostazol include headache, palpitations, and di-

arrhea (Table 2). Because other phosphodiesterase 3 inhibitors are associated with increased mortality among patients with heart failure, cilostazol should not be prescribed for patients with peripheral artery disease and any heart failure.

A randomized clinical trial involving 792 participants with peripheral artery disease and type 2 diabetes showed that administration of semaglutide, as compared with placebo, for 52 weeks improved the ratio of maximal treadmill walking distance at follow-up to that at baseline (point estimate, 1.13; 95% confidence interval [CI], 1.06 to 1.21; $P < 0.001$).²⁰ In addition, semaglutide increased maximal treadmill walking distance by 39.9 m, as compared with placebo,²⁰ an effect size similar to that of cilostazol. In an open-label clinical trial involving 55 participants with peripheral artery disease and type 2 diabetes, liraglutide increased 6-minute walk distance by 25 m at 6-month follow-up, as compared with usual care (95% CI, 22 to 28; $P < 0.001$).²⁵

SUPERVISED WALKING EXERCISE

Supervised walking exercise for peripheral artery disease consists of treadmill walking performed three times per week in the presence of a nurse or exercise physiologist, with each walk session

designed to elicit maximal ischemic leg symptoms. Supervised walking exercise increases maximal treadmill walking distance by a mean of 180 m and 6-minute walk distance by a mean of 31.8 m (Fig. 2).^{22,26} Medicare covers 36 sessions of supervised exercise (including walking, cycling, or resistance training) during 12 weeks for symptomatic peripheral artery disease (Table 3). However, meaningful benefit begins after approximately 6 weeks of exercise, and gains are lost after exercise ends.^{30,31}

HOME-BASED WALKING EXERCISE

Structured home-based walking exercise consists of unsupervised walking exercise in or around the home, with monitoring by a coach through the telephone or periodic in-person visits (Table 3). Use of behavioral methods is important to help patients adhere to exercise.³²⁻³⁴ Behavioral methods include setting exercise goals, developing strategies to manage walking-induced ischemic leg pain, and monitoring progress relative to exercise goals. In a clinical trial, 305 participants with peripheral artery disease were randomly assigned to home-based walking exercise that induced ischemic leg symptoms (high intensity), home-based walking exercise that did not induce ischemic leg symp-

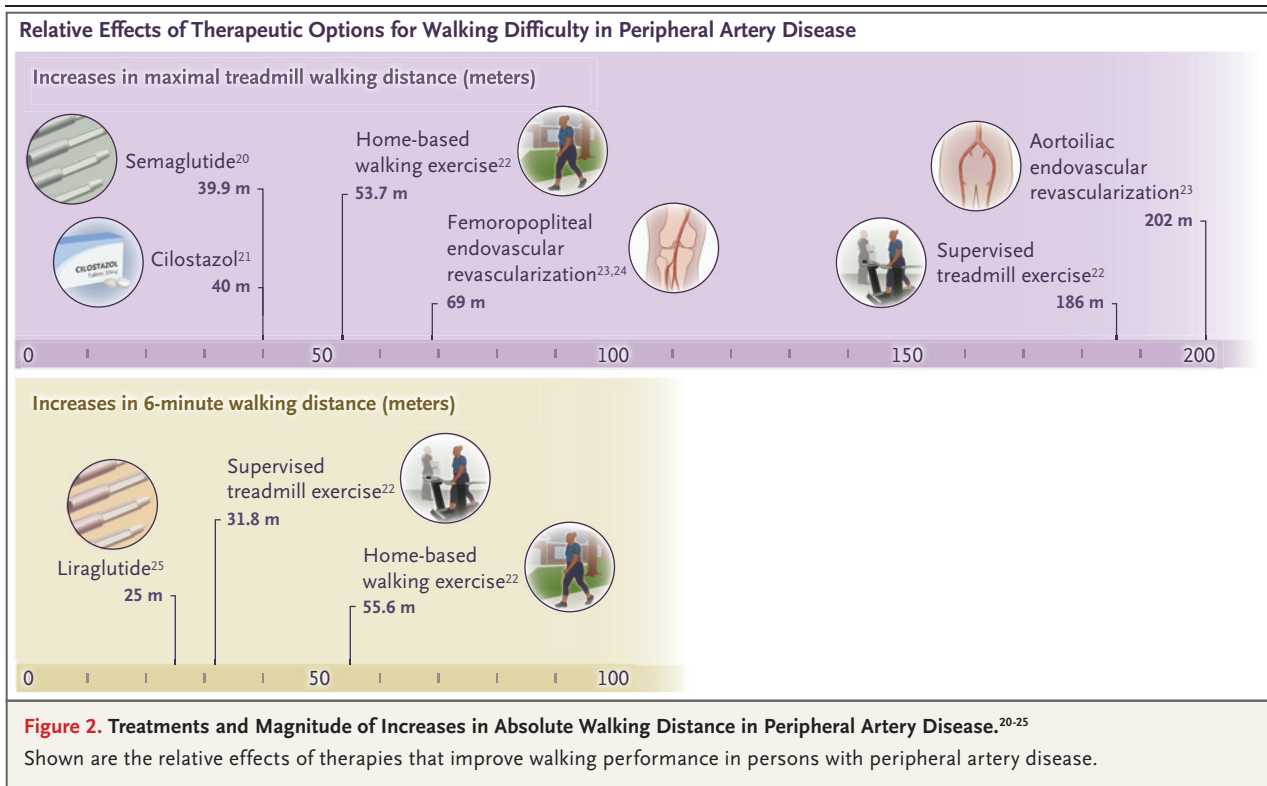


Table 2. First-Line Therapies for Walking Disability in Patients with PAD.*

Variable	Cilostazol ^{19,21}	Leg Revascularization ²⁷⁻²⁹	Supervised Walking Exercise ^{22,30-32}	Home-Based Walking Exercise ^{22,32-34}
Description	Phosphodiesterase 3 inhibitor	Surgical removal of plaque or bypass of occluded artery Nonsurgical catheter-based (endovascular) balloon angioplasty, stent placement, lithotripsy, or atherectomy	Typically performed on a treadmill in the presence of an exercise physiologist, nurse, or coach	Performed in or around the home not in the presence of an exercise physiologist or a nurse but with regular contact with a coach
Indications	Patients with PAD and leg symptoms limiting walking ability; contraindicated in patients with any heart failure	Patients with disabling PAD symptoms that have not responded adequately to exercise therapy	Recommended for all persons with PAD	Recommended for all persons with PAD
Dose or prescription	Begin with 50 mg twice daily and adjust up to 100 mg twice daily	NA	Three times weekly, with a goal of working up to 50 minutes per session if possible	Three to five times weekly for 30 to 50 minutes per session
Efficacy	Resulted in a maximal treadmill walking distance that was approximately 40 m longer than that with placebo	Increase in maximal treadmill walking distance by 110 to 202 m (within-group comparison) with femoropopliteal endovascular angioplasty and by 316 to 685 m (within-group comparison) with aortoiliac endovascular angioplasty	Resulted in a 6-minute walking distance that was 31.8 m longer and a maximal treadmill walking distance that was 180 m longer than that with control	Resulted in a 6-minute walking distance that was 55.6 m longer and a maximal treadmill walking distance that was 50 to 55 m longer than that with control
Adverse effects	Headache, palpitations, or diarrhea	Repeat revascularization, restenosis, or acute limb ischemia	Generally safe, with possibility of a cardiovascular event, fall, or worsening of foot ulcer	Generally safe, with possibility of a cardiovascular event, fall, or worsening of foot ulcer
Other considerations	If a patient does not have improved walking ability after 12 weeks, cilostazol should be discontinued.	Shorter length of stenosis and the absence of diabetes, current smoking, and chronic kidney disease are associated with better outcomes of endovascular procedures.	Supervised walking exercise is covered by CMS for up to 24 weeks in a lifetime. Many patients with PAD do not have access to supervised exercise or find it burdensome to travel for exercise.	Home-based walking exercise is not covered by CMS or insurance. Structured programs with behavioral change interventions are most effective.

* CMS denotes Centers for Medicare and Medicaid Services, and NA not applicable.

toms (low intensity), or a control intervention.³⁴ High-intensity exercise increased 6-minute walk distance as compared with the control intervention (between-group difference, 49.6 m; 95% CI, 24.3 to 74.9; $P < 0.001$), whereas low-intensity exercise did not significantly increase 6-minute walk distance as compared with the control intervention (between-group difference, 8.7 m; 97.5% CI, -17.0 to 34.4; $P = 0.44$).³⁴ Therefore, home-based walking exercise for peripheral artery disease should induce ischemic leg symptoms. Home-based walking exercise that induces ischemic leg symptoms was found to result in a maximal treadmill walking distance that was 53.7 m longer — and a 6-minute walk distance that was 55.6 m longer — than that with the control intervention (Fig. 2).²²

REVASCULARIZATION IN THE LEGS

Endovascular, surgical, or hybrid revascularization should be reserved for patients who continue to have lifestyle-limiting ischemic leg symptoms after treatment with exercise.¹⁹ Surgical revascularization typically removes plaque from occluded arteries (i.e., endarterectomy) or bypasses stenotic or occluded arteries. Endovascular revascularization typically displaces or removes atherosclerotic plaque with a catheter. Definitive endovascular revascularization treatments for peripheral artery disease include uncoated or drug-coated balloon angioplasty and bare-metal or drug-eluting stents. Atherectomy or lithotripsy can alter severely calcified plaque and facilitate balloon procedures or stent expansion.

Table 3. Walking Exercise Therapies for PAD.

	Supervised Walking Exercise	Structured Home-Based Walking Exercise
Definition	Walking for exercise at a health care facility in the presence of a coach (typically an exercise physiologist or nurse)	Walking for exercise in or around the home, without direct supervision but with regular contact with a coach (by telephone or occasional in-person sessions)
Frequency of exercise	Three times weekly ²²	Three to five times weekly ^{32,34}
Characteristics	Repeated bouts of walking exercise to attain maximal ischemic leg pain within 10 minutes after the start of each bout ²²	Walking at a pace that induces ischemic leg symptoms within 10 minutes after the start of exercise ^{33,34}
Coach's role	Provides direct supervision and feedback during exercise	Helps patient adhere to walking exercise using behavioral methods such as setting walking exercise goals, managing ischemic leg symptoms during exercise, monitoring exercise activity relative to goals, and building self-efficacy
Effects as compared with control		
6-Minute walk distance	Increases by 31.8 m ²²	Increases by 55.6 m ²²
Maximal treadmill walking distance	Increases by approximately 180 m ^{22,32}	Increases by approximately 50 to 55 m ^{32,34}
Durability	Benefits are gone by 6 months after exercise ends, and possibly earlier. ³¹	Although benefit wanes when the intervention ends, persistent benefit has been observed at 6 months after completion of the home-based exercise program. ³⁵
Advantages	Presence of a coach during exercise can be motivating and provides immediate assistance with management of ischemic leg symptoms.	Walking in or around the home is convenient and accessible for many patients with PAD.
Disadvantages	Traveling three times weekly for exercise is burdensome. Centers for supervised exercise are not widely available.	Absence of an in-person coach requires more initiative from patients with PAD.
Insurance coverage	Covered by Medicare	Not covered by Medicare
Other	Medicare also covers supervised nonwalking exercise, such as cycling or resistance training.	Structured home-based exercise programs with varying intervention characteristics, such as coach contact by telephone or weekly in-person visits, have been shown to be effective.

The effects of aortoiliac revascularization on walking performance are similar to the effects of supervised treadmill exercise.^{36,37} However, in the CLEVER (Claudication: Exercise versus Endoluminal Revascularization) randomized clinical trial involving 111 patients with aortoiliac peripheral artery disease, improvement in the maximal treadmill walking time (primary outcome) was similar with supervised exercise and with endovascular revascularization, whereas improvement in patient-reported outcomes, such as the Walking Impairment Questionnaire distance score (range, 0 to 100, with higher scores indicating less difficulty walking), was significantly greater with endovascular revascularization than with supervised exercise (mean change in score, 43.8 vs. 25.1; $P=0.03$).³⁷

Benefits of endovascular revascularization in the legs are greatest and most durable in larger

proximal arteries, such as the aortoiliac arteries (Fig. 2). Benefits of endovascular revascularization in the infrapopliteal arteries in patients with claudication are unclear.¹⁹ Definitive randomized clinical trials comparing surgical revascularization with endovascular revascularization for disabling claudication are unavailable. However, in a study comparing 592 patients who underwent endovascular revascularization and 342 patients who underwent open bypass surgery for claudication, a higher percentage of patients underwent repeat revascularization in the endovascular revascularization group than in the open bypass group at 1-year follow-up (12% vs. 5%) and at 3-year follow-up (19% vs. 8%).³⁸ Procedure-related complications within 30 days after the procedure were more common in the open bypass group than in the endovascular revascularization group (30.7% vs. 8.8%).³⁸

CHOLESTEROL-LOWERING THERAPY

Guidelines recommend that patients with peripheral artery disease take a high-intensity statin, such as atorvastatin or rosuvastatin, at the highest dose that does not result in unacceptable adverse events, with the goal of reducing low-density lipoprotein cholesterol by at least 50%.¹⁹ In the Heart Protection Study involving 20,536 persons with cardiovascular disease and a mean cholesterol level of at least 3.5 mmol per liter (135 mg per deciliter), simvastatin at a daily dose of 40 mg, as compared with placebo, reduced the incidence of death from any cause (12.9% vs. 14.7%; $P < 0.001$) and death from coronary heart disease (5.7% vs. 6.9%; $P < 0.001$).³⁹ Results were similar among the 6748 participants with peripheral artery disease.³⁹ Adding a proprotein convertase subtilisin–kexin type 9 inhibitor or ezetimibe to statin therapy in high-risk patients with cardiovascular disease further reduces cardiovascular events and reduces major adverse limb events.^{40,41}

ANTIPLATELET AND ANTITHROMBOTIC THERAPY

A single antiplatelet drug (aspirin at a daily dose of 81 to 325 mg or clopidogrel at a daily dose of 75 mg) or low-dose aspirin plus rivaroxaban at a dose of 2.5 mg twice daily reduces cardiovascular events in patients with peripheral artery disease.^{42,43} In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, 7470 participants with peripheral artery disease or carotid artery disease were randomly assigned to receive oral rivaroxaban at a dose of 2.5 mg twice daily plus aspirin at a dose of 100 mg daily, rivaroxaban alone at a dose of 5.0 mg twice daily, or aspirin alone at a dose of 100 mg daily.⁴² At 21.2 months, fewer participants in the group receiving rivaroxaban plus aspirin than in the group receiving aspirin alone had a cardiovascular event (5% vs. 7%; $P = 0.005$) or a major adverse limb event (1% vs. 2%; $P = 0.004$). The incidence of major bleeding was higher with rivaroxaban plus aspirin than with aspirin alone (3% vs. 2%).⁴² In the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (peripheral artery disease) (VOYAGER PAD) involving 6564 patients with peripheral artery disease who underwent leg revascularization, treatment with rivaroxaban at a dose of 2.5 mg twice daily plus aspirin led to a lower inci-

dence of death from cardiovascular causes, myocardial infarction, stroke, acute limb ischemia, or major amputation (the composite primary outcome) than treatment with aspirin alone at 3-year follow-up (17.3% vs. 19.9%; $P = 0.009$).⁴³ The incidence of major bleeding was higher in the group receiving rivaroxaban plus aspirin.

CESSATION OF CIGARETTE SMOKING

Behavioral interventions and medication (varenicline, bupropion, or nicotine-replacement therapy) should be used to help patients with peripheral artery disease who smoke cigarettes to discontinue smoking. Among 204 patients with peripheral artery disease and claudication or limb-threatening ischemia who smoked cigarettes and underwent leg angiography, the 61 patients who quit smoking during the year after angiography had a lower incidence of death from any cause than the 143 patients who continued smoking (14% vs. 31%), as well as greater amputation-free survival (81% vs. 60%).⁴⁴

BLOOD-PRESSURE TREATMENT

Guidelines recommend lowering blood pressure to less than 130/80 in patients with peripheral artery disease.¹⁹ Large clinical trials of blood-pressure treatments in patients with this disease are unavailable. In the Systolic Blood Pressure Intervention Trial (SPRINT) involving 9361 participants at high risk for cardiovascular disease but without diabetes (5.3% with peripheral artery disease), lowering systolic blood pressure to less than 120 mm Hg led to a significantly reduced rate of cardiovascular events than lowering to less than 140 mm Hg (1.77% per year vs. 2.40% per year).⁴⁵

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular events in persons with cardiovascular disease, including those with peripheral artery disease.^{46,47} In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial involving 17,604 patients with cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but without diabetes mellitus (8.7% with symptomatic peripheral artery disease), treatment with semaglutide resulted in a lower incidence of cardiovascular events than placebo (6.5% vs. 8.0%; $P < 0.001$) at a mean follow-up of 39.8 months.⁴⁶ In

the Semaglutide Cardiovascular Outcomes Trial (SOUL) involving 9650 participants with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both (15.7% with peripheral artery disease), daily oral semaglutide at a dose of 14 mg, as compared with placebo, reduced the incidence of cardiovascular events (12.0% vs. 13.8%; $P=0.006$) at a mean follow-up of 47.5 months.⁴⁷ As described above, semaglutide increased treadmill walking distance among persons with peripheral artery disease in a randomized clinical trial, but the absolute effect was modest.²⁰

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular events in persons with type 2 diabetes, including in those with peripheral artery disease. Among 7020 patients with type 2 diabetes at high risk for cardiovascular events (21% with peripheral artery disease), empagliflozin, as compared with placebo, reduced the incidence of cardiovascular events (10.5% vs. 12.1%; $P=0.04$) at a median observation time of 3.1 years.⁴⁸ In the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program involving 10,142 participants with type 2 diabetes at high risk for cardiovascular events (21% with peripheral vascular disease), canagliflozin, as compared with placebo, reduced the rate of cardiovascular events (in 26.9 participants vs. 31.5 participants per 1000 patient-years; $P=0.02$) at a mean follow-up of 3.6 years, but amputation rates were higher with canagliflozin (in 6.3 participants vs. 3.4 participants per 1000 patient-years).⁴⁹ An association with amputation was not observed for empagliflozin⁵⁰ or dapagliflozin⁵¹, or for canagliflozin in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial involving 4401 patients with type 2 diabetes and chronic kidney disease (23.8% with peripheral vascular disease) (amputation rate, 12.3 per 1000 patient-years with canagliflozin and 11.2 per 1000 patient-years with placebo).⁵²

GUIDELINES

Guidelines recommend intensive cholesterol-lowering therapy, blood-pressure lowering to less than 130/80 mm Hg, and treatment with a single antiplatelet agent or with low-dose rivaroxaban

plus low-dose aspirin to prevent cardiovascular events.¹⁹ Intensive cholesterol-lowering therapy and low-dose rivaroxaban plus aspirin are recommended to prevent major adverse limb events.¹⁹ The AHA and ACC guidelines¹⁹ and the European Society of Cardiology (ESC) guidelines⁵³ recommend supervised walking exercise as first-line therapy. The AHA and ACC guidelines also recommend structured home-based walking exercise as first-line therapy.¹⁹ The ESC considers home-based walking exercise to be “reasonable” but does not consider this method to be a first-line therapy for walking impairment related to peripheral artery disease.⁵³ The recommendations provided here are consistent with the AHA and ACC guidelines and some aspects of the ESC guidelines but differ from the ESC guidelines regarding recommendations for home-based exercise therapy. In addition, the ESC guidelines recommend lowering low-density lipoprotein cholesterol to less than 55 mg per deciliter.

AREAS OF UNCERTAINTY

First, the most effective combinations and the best timing of therapies (i.e., home-based or supervised exercise, cilostazol, GLP-1 receptor agonists, and leg revascularization) to improve walking performance need to be defined. Currently, no single therapy eliminates walking disability in persons with peripheral artery disease. Second, the effects of medications that reduce inflammation, such as canakinumab, and of those that stimulate skeletal muscle growth, such as bimagrumab, on walking in persons with the disease should be studied. Third, the ability of antiinflammatory medications, such as colchicine, to prevent cardiovascular events in persons with peripheral artery disease is unclear.

CONCLUSIONS AND RECOMMENDATIONS

For the patient in the vignette, I would recommend 12 weeks of supervised exercise if the patient can travel for exercise three times weekly and has insurance coverage for supervised exercise. If the patient is not interested in or able to adhere to supervised exercise, or if payment for supervised exercise is difficult, I would recommend structured home-based walking exercise. Cilostazol and semaglutide are reasonable supplemental therapies that can be prescribed for

KEY POINTS

PERIPHERAL ARTERY DISEASE IN THE LEGS

- Up to 90% of persons with peripheral artery disease do not have classic claudication symptoms, and approximately 60% are asymptomatic.
- An ankle–brachial index (the ratio of the systolic blood pressure in the ankle to the systolic blood pressure in the arm) of less than 0.90 is 72 to 89% accurate for diagnosing the disease.
- In population studies, 10-year cardiovascular mortality was greater among persons with peripheral artery disease than among those without the condition for both men (18.7% vs. 4.4%) and women (12.6% vs. 4.1%).
- In a study involving older participants, 3.3% of those without peripheral artery disease, 18.1% of those with mild disease, and 52.0% of those with severe disease could not complete a 6-minute walk test without resting.
- Interventions for preventing cardiovascular events in persons with peripheral artery disease include intensive cholesterol-lowering medications (such as statins), antiplatelet medications or low-dose aspirin with rivaroxaban, blood-pressure lowering to less than 130/80 mm Hg, semaglutide, and sodium–glucose cotransporter 2 inhibitors for persons with diabetes.
- Supervised walking exercise and structured home-based walking exercise can each improve walking ability in persons with peripheral artery disease, cilostazol and semaglutide provide modest benefits, and revascularization in the legs should be reserved for persons with persistent disease symptoms that do not respond to exercise.

walking impairment. If these treatments do not adequately improve peripheral artery disease symptoms, revascularization can be considered. To prevent cardiovascular events, I would prescribe atorvastatin or rosuvastatin at the highest dose that does not cause unacceptable adverse events, prescribe treatment for lowering blood pressure to less than 130/80 mm Hg, and prescribe either rivaroxaban at a dose of 2.5 mg twice daily with low-dose aspirin or clopidogrel

alone. I would consider an SGLT2 inhibitor and semaglutide to reduce cardiovascular events in this patient.

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

AUTHOR INFORMATION

¹Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago; ²Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago.

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