Chapter e35: Peripheral Arterial Disease

Kristin Watson; Sarah Anderson

KEY CONCEPTS

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1. Peripheral arterial disease (PAD) is a form of atherosclerotic cardiovascular disease (ASCVD) that occurs in the peripheral arteries. Lower extremity PAD is the most common form of PAD.

2. Lower extremity PAD is associated with an increased risk of limb loss and death.

3. The most prevalent PAD risk factors are tobacco smoking, diabetes mellitus (DM), hypertension, and dyslipidemia. The risk of developing PAD increases with age.

4. Symptoms of lower extremity PAD may include cramping or discomfort in the affected lower extremity(ies). A significant portion of those with PAD will be asymptomatic. Signs of lower extremity PAD include, but are not limited to, diminished or absent pedal pulses, nonhealing wounds, brittle and hypertrophic toenails, and/or cool skin. The presence of signs and/or symptoms in those at risk for PAD should prompt further evaluation.

5. The ankle-brachial index (ABI) is the most common test used to diagnose lower extremity PAD. PAD is defined by an ABI score ≤0.9 for one or more of the pedal pulses (ie, dorsalis pedis, posterior tibial). A score >1.4 is indicative of noncompressible arteries which may be present in those with DM and/or chronic kidney disease (CKD).

6. ASCVD risk reduction is prudent to lower the risk of cardiovascular (CV) complications associated with PAD. This includes acheiving good glycemic and blood pressure (BP) control. A high-intensity statin is recommended to reduce the risk of CV and limb-related events. Smoking cessation has been shown to reduce the risk of limb loss and death.

7. Participation in a structured exercise training program has been shown to improve functional status and quality of life and to decrease lower extremity symptoms.

8. Revascularization surgery is a potential therapeutic option for patients who have persistent lower extremity PAD symptoms despite pharmacological therapy, exercise, and smoking cessation.

9. Low-dose aspirin or clopidogrel is recommended for patients with symptomatic lower extremity PAD to lower the risk of CV events and death.

10. An antithrombotic regimen should be prescribed after revascularization surgery to lower the risk of CV events and limb-related events. Options include aspirin or clopidogrel monotherapy, dual antiplatelet therapy with aspirin and clopidogrel, or rivaroxaban 2.5 mg twice daily combined with low-dose aspirin.

11. Cilostazol can be considered in those with lower extremity PAD symptoms despite other pharmacological therapy, exercise, and smoking cessation. This agent is not to be used in those with heart failure due to an increased risk of death.

BEYOND THE BOOK

BEYOND THE BOOK

Readers are encouraged to watch the following videos:

- Overview of the physical examination for peripheral arterial disease (PAD): https://youtu.be/sJ6YkxQeAbo (Duration: 10:08 minutes)
- Overview of Surgical Approaches for Peripheral Arterial Disease (PAD): https://www.youtube.com/watch?v=Y1WK6p0l80A&ab_channel=ColumbiaUniversityDepartmentofSurgery (Duration: 5:38 minutes)

INTRODUCTION

1 Peripheral arterial disease (PAD) is characterized by atherosclerosis of the peripheral arteries. Lower extremity PAD specifically refers to atherosclerotic disease from the aortoiliac segments to the pedal arteries.[1] While PAD can occur in several peripheral arteries, this chapter will focus predominantly on the treatment of lower extremity PAD because it is most common. The atherosclerotic process leads to the accumulation of plaque material within the arterial wall, narrowing the lumen and reducing blood flow to the lower extremities. Risk factors for PAD are similar to those for atherosclerosis in other parts of the body and include age ≥65 years old, tobacco smoking, diabetes mellitus (DM), hypertension (HTN), and dyslipidemia.[2,3] Presence of PAD is associated with a high risk of morbidity and mortality; those with PAD have a threefold increased risk of all-cause mortality compared to those without the disease.[2,3] PAD is a marker for atherosclerotic cardiovascular disease (ASCVD) that requires multiple interventions aimed at lowering risk.[4] The treatment of lower extremity PAD focuses on minimizing and managing risk factors, alleviating symptoms, and reducing cardiovascular disease (CVD) progression through nonpharmacologic and pharmacologic therapy.[3,4]

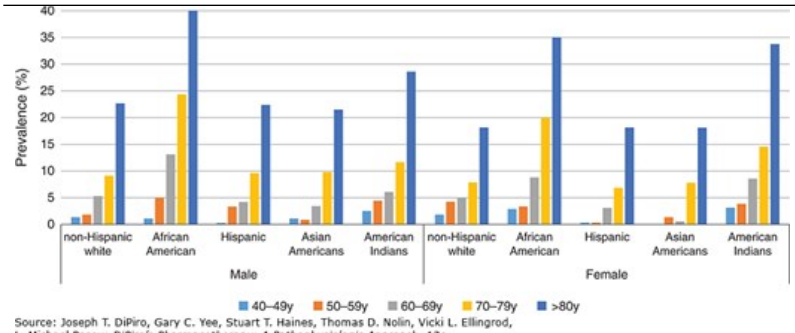
EPIDEMIOLOGY

Lower extremity PAD, defined as an ankle-brachial index (ABI) ≤0.9, is present in as many as 6.5 million US adults ≥ 40 years old.[1,3,4] More than 202 million people worldwide are affected by PAD.[1,4] In the United States, prevalence estimates may be higher as published information does not include recent data obtained during the current DM and obesity epidemics.[1] Between 2000 and 2010, the incidence of PAD increased by 13.1% in high-income countries and by 28.7% in low-income countries.[5] 2 Up to 1.3% of patients with lower extremity PAD experience chronic limb-threatening ischemia (CLTI), which can be attributed to either luminal narrowing or atherothrombosis, often leading to above- and below-the-knee amputations.[4,6,7] CLTI is defined as two or more weeks with ischemic rest pain, non-healing wounds or ulcers, or gangrene.[3] The global mortality rates attributable to PAD are 45.4% for males and 54.6% for females.[4] Taken together, these data represent a global public health concern and burden, given the increasing incidence in all countries and the close link between PAD and CV morbidity and mortality.

3 The incidence of PAD increases with increasing age, with an approximate doubling per decade of life beginning with age 40.[4] Males and females are similarly affected by PAD, with prevalence varying by age and race/ethnicity within each sex category (Fig. e35-1).[4] Prevalence of PAD is greater in Black persons compared to non-Hispanic White persons, particularly after the age of 50 years in males and after the age of 60 years in females.[8] Lower income and lower educational attainment are associated with increased prevalence of PAD while lower socioeconomic status and Black race are associated with greater risk of amputation related to PAD.[9–11]

FIGURE e35-1

Use of ankle-brachial index in the diagnosis and management of patients with leg symptoms and risk factors for peripheral arterial disease.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

With respect to lifestyle choices, being a current or former tobacco smoker is the risk factor most strongly associated with PAD, with current tobacco smokers having the highest risk.[5,12,13] Current or prior tobacco smoking also contributes to disease progression.[4,5,14] Comorbidities also confer risk of PAD. The presence of DM increases the risk of PAD by 30% to 80%.[5,12] HTN is similarly associated with a 50% increase odds of developing PAD; each 20 mm Hg increase in systolic blood pressure (SBP) increases the risk of PAD by up to 32%.[5,12] Dyslipidemia, defined as total cholesterol (TC) > 200 mg/dL (5.17 mmol/L), is less strongly associated with PAD; each 39 mg/dL (1.01 mmol/L) increase in TC increases the risk of PAD by 14%.[5,12] As much as 75% of the risk associated with PAD has been attributed to tobacco smoking, type 2 DM (T2DM), HTN, and dyslipidemia.[15] Patients with PAD risk factors should undergo a comprehensive medical history and physical exam annually in an effort to mitigate risk factors and evaluate for the presence of PAD and other forms of ASCVD.[3]

ETIOLOGY

Risk factors for PAD are like those for other atherosclerotic conditions (Clinical Presentation box).[3,5,13] The risk of PAD increases by 50% with one risk factor and more than 10-fold with three or more.[13] A risk assessment tool was created to predict an individual's lifetime risk of developing PAD. This calculator accounts for the presence of atherosclerotic risk factors, race, and sex, and is available at[12]: http://ckdpcrisk.org/padrisk/

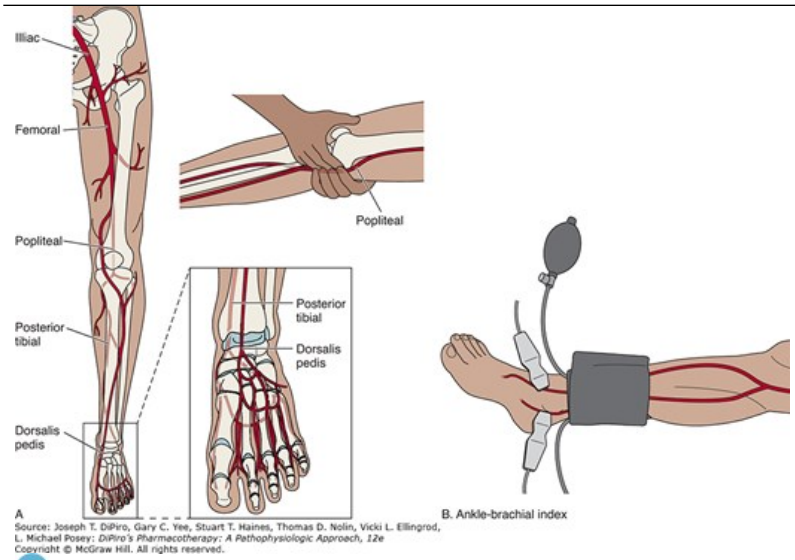
Family history and genetics play a role and are independent of atherosclerotic risk factors.[4,16] Elevated homocysteine levels have been associated with an elevated risk of developing atherosclerosis.[17] HTN during pregnancy and sedentary behavior may also contribute to the development of PAD.[4,18] The presence of chronic kidney disease (CKD) is associated with an increased risk of lower extremity PAD and amputation, a complication of PAD.[19] Other predictors for amputation include the severity of PAD, based on the ABI, the severity of symptoms, and DM.[20,21]

PATHOPHYSIOLOGY

In most cases, PAD in the lower extremities is caused by progressive atherosclerosis and impacts medium and large-sized arteries. The iliac, femoral, popliteal, and/or tibial arteries are most involved (Fig. e35-2A).[20–23] Endothelial injury, often at the artery branches, results in the accumulation of plaque in the vessel intima. DM and smoking are examples of factors that can cause damage to the vessel wall. The atherosclerotic plaque that develops is comprised of cholesterol, inflammatory cells, smooth muscle cells, and connective tissue. Decreased nitric oxide (NO) production and increased oxidative stress impair vasodilatory response and increase arterial stiffness.[22,24] These factors lead to chronic occlusion and stenosis within atherosclerotic arteries.[23,25] PAD can form in one or more arteries of one or both legs. Additionally, disease development and progression can vary between each leg.[26]

FIGURE e35-2

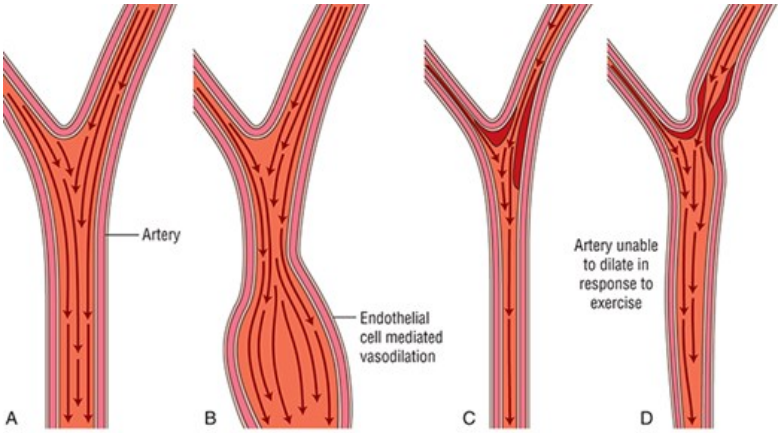
(*A*) Anatomy of the major arteries in the leg. (*B*) Measurement of the ankle systolic pressure.



Ischemic symptoms and complications of the lower extremities are common. Walking and other activities involving the legs increase oxygen demand. In the absence of PAD, vasodilation occurs in response to increased oxygen demand permitting perfusion to the muscles and preserving blood flow.[23] In patients with PAD, the increase in demand cannot be met because the atherosclerotic plaque occludes blood flow and impaired vasodilation causes fixed resistance (Fig. e35-3).[23,25] Impaired perfusion of skeletal muscle contributes to pain or discomfort in the affected portion(s) of the leg(s). For example, intermittent claudication (IC) is a common symptom of limb ischemia causing discomfort or cramping of the lower extremities with exertion. Those with impaired flow in the iliac artery may experience buttock pain with exertion (Fig. e35-2A). Decreased blood flow to the skin and subcutaneous tissues can result in CLTI.[3] Nonhealing wounds and amputation are also potential consequences of impaired blood flow and vascular dysfunction in the lower extremities. Importantly, many patients with lower extremity PAD are asymptomatic, typically a result of a sedentary lifestyle.[3,26]

FIGURE e35-3

Hemodynamic alterations in peripheral arterial disease. (*A*) Perfusion through a lower extremity artery without atherosclerotic disease at rest. (*B*) Perfusion during exercise (increase oxygen demand) through a lower extremity artery without atherosclerotic disease. A compliant blood vessel allows for arterial dilation in response to an increase in oxygen demand. There is a balance of oxygen supply and demand. (*C*) Perfusion of a lower extremity artery with PAD at rest. Narrowing of the arterial lumen occurs in those with PAD. (*D*) Perfusion of a lower extremity artery with PAD during exercise. Arterial dilation is unable to appropriately respond to the increased oxygen demand leading to a mismatch of oxygen supply and demand. This is due to the presence of the atherosclerotic lesion(arrows) and impaired endothelial function. PAD, peripheral arterial disease.



There are several possible nonatherosclerotic causes of PAD, including trauma, vasculitis, and thrombosis, among others, but these are uncommon.[22]

This chapter focuses on the management of PAD due to atherosclerosis.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Peripheral Arterial Disease

General

- Patients with PAD are likely to be male, 40 years of age and older, with hypertension, hypercholesterolemia, DM, impaired renal function, presence of CAD or CVD, and/or current or former tobacco smoking.

Signs and Symptoms

- The clinical presentation of lower extremity PAD is variable and includes symptoms ranging from asymptomatic to lower extremity IC and pain. Patients may also present with CLTI, which appears as nonhealing wounds and/or gangrene of the lower extremities in combination with lower extremity pain at rest. Acute limb ischemia, a potentially life-threatening medical emergency, develops over a short period of time (<2 weeks). Patients with acute limb ischemia will have evidence of severe hypoperfusion potentially leading to major tissue loss. Those with more serious cases may have profound muscle paralysis or significant sensory loss.[3]
- IC is generally regarded as the primary symptom indicator in lower extremity PAD. IC has been described as a discomfort, cramping, pain, or numbness in the affected lower extremity(ies) (typically the buttock, thigh, calf, or foot, either singularly or in combination) during physical activity and resolves within 10 minutes of rest. Patients can present with atypical symptoms. For example, some patients may start to develop pain at rest and the pain intensifies with exertion. Functional impairment has been shown to be similar between those with IC, atypical symptoms, and those who do not report symptoms. Therefore, clinicians cannot rely on the presence of symptoms alone when assessing for the presence of PAD.[3,27]
- Physical examination may reveal nonspecific signs of decreased blood flow to the lower extremities (eg, cool, dry skin; cyanosis; bruits; brittle, hypertrophic toenails; muscle atrophy; lack of hair on the calf, feet, and/or toes). Additionally, posterior tibial and/or dorsalis pedis pulse strength may be diminished or pulses absent.[3]

Diagnostic Tests

- There are no laboratory tests specific to PAD.
- Patients with risk factors for or with symptoms and/or physical examination suggestive of lower extremity PAD should undergo ABI testing.[1,3]
    - Risk Factors for PAD[3,14]
        - Known atherosclerosis in another vascular bed (eg, carotid, coronary, renal)
        - Age 65 or older
        - Age 50 to 64 with atherosclerosis risk factors, including DM, hypertension, dyslipidemia, current or prior tobacco smoking; and/or family history of PAD
        - Age less than 50 with DM and at least one additional risk factor for atherosclerosis
- The ABI is a noninvasive, quantitative test that is highly sensitive and specific (≥90%) for diagnosing lower extremity PAD.

ABI, ankle-brachial index; CAD, coronary artery disease; CLTI, chronic limb-threatening ischemia; CVD, cardiovascular disease; DM, diabetes mellitus; IC, intermittent claudication; PAD, peripheral arterial disease.

An important component of PAD assessment is obtaining a thorough patient history of both symptoms and prior diagnoses of atherosclerosis and/or

known atherosclerotic risk factors (eg, HTN, dyslipidemia, DM, tobacco smoking). However, sole reliance on patient history will miss up to 90% of patients with lower extremity PAD.[28,29] PAD symptoms gradually worsen over time, making it challenging for clinicians and patients to identify changes that may occur.[1] Therefore, a physical examination of the patient is a key component of the assessment process (refer to Beyond the Book for a link to a video describing this in more detail). Evaluation of the lower extremities may reveal nonspecific signs of decreased blood flow to the extremities (eg, cool, dry skin; cyanosis; bruits; brittle, hypertrophic toenails; muscle atrophy; lack of hair on the calf, feet, and/or toes) or, in severe cases, nonhealing ulcers or gangrene may be present.[30] Care should be taken to exclude other conditions (eg, peripheral neuropathy, deep vein thrombosis) that possess similar signs and symptoms. Those with signs and/or symptoms of PAD should undergo diagnostic testing.

5 The ABI is a noninvasive, quantitative test that is a highly sensitive and specific (≥90%) tool in the diagnosis of lower extremity PAD.[3] To perform an ABI measurement, the patient should first rest in the supine position for 15 to 30 minutes. Then, in this position, the SBP is measured at the brachial arteries on both arms and the dorsalis pedis and posterior tibial arteries of the legs with a standard sphygmomanometer and a hand-held doppler (Fig. e35-2B).[3] The higher pressure obtained at the ankle arteries is divided by the higher measurement taken at the brachial arteries; thus, the ABI is the ratio of the higher ankle SBP divided by the higher brachial SBP.[14] An alternative method for screening uses the lower (rather than the higher) of the two ankle pressures as the numerator in the calculation.[31] Interpretation of the results are presented in Table e35-1. The ABI measurement can be a strong predictor of future atherosclerotic CV morbidity and mortality associated with PAD; patients with an ABI < 0.3 are at a significantly high risk of such events.[32]

TABLE e35-1

Ankle-Brachial Index Interpretation

Ankle-Brachial Index Score	Classification
>1.4	Noncompressible arteries may be present in those with diabetes
1-1.4	Normal
0.91-0.99	Borderline
≤0.9	PAD
0.7-0.9	Mild PAD
0.4-0.7	Moderate PAD
<0.4	Severe PAD

PAD, peripheral arterial disease.

Data from Reference 3.

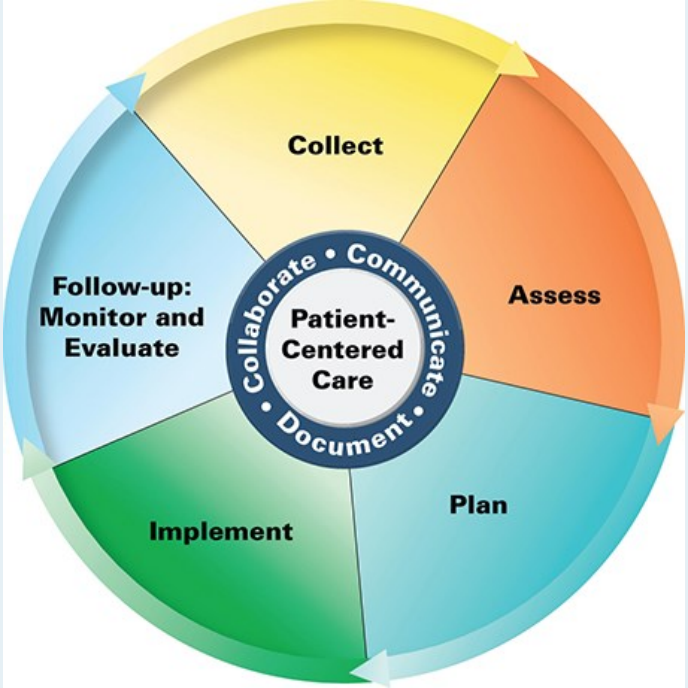
An ABI of >1.40 is consistent with noncompressible arteries, typically observed in those with DM and/or CKD.[1] If PAD is still suspected in a patient with an ABI >1.40, a toe-brachial index (TBI) can be used instead to confirm the diagnosis. This is because toes are rarely affected by calcification.[1] Similarly, in a patient with a normal or borderline ABI (>0.90 to ≤ 1.40) who is experiencing PAD-like symptoms, exercise treadmill ABI testing should be used to determine if PAD is present.[3,33] Patients with lower extremity PAD will demonstrate a significant drop in the ABI after exercise, but their pain remains normal or unchanged unless IC is present. When a patient is not found to have PAD with symptoms suggestive of the disease, alternative diagnoses (eg, nerve root compression) should be considered.[34,35]

Other noninvasive tools are available for the diagnosis of PAD, including duplex ultrasound, magnetic resonance angiography (MRA), and computed

tomographic angiography (CTA). However, an ABI is a sufficient means of diagnosis and arteriography is not necessary or encouraged except in situations such as planned surgical revascularization where it can aid in further visualization of the affected vasculature.[3,36]

PATIENT CARE PROCESS

Patient Care Process for Peripheral Arterial Disease



Collect

- Patient characteristics (eg, age, past medical history)
- Healthcare and prescription insurance status
- Social history (eg, tobacco smoking status, physical activity habits)
- All current prescription medications and over-the-counter products
- Medication intolerances (eg, prior bleeding with antiplatelet) and allergies
- Objective data:
    - Left and right brachial blood pressures
    - Left and right dorsalis pedis blood pressures
    - Left and right posterior tibial blood pressures
    - Physical examination findings of lower extremities (document: strength or absence of peripheral pulses; temperature; presence or absence of bruits, muscle atrophy, pallor, cyanosis, ulcers, non-healing wounds, and/or gangrene)
    - Walking assessment, including pain-free walking and maximum walking distances
    - Baseline laboratory parameters (eg, basic metabolic panel, lipid panel, hemoglobin A1C)

Assess

- ABI for left and right legs (see Table e35-1, Fig. 35-2B)
- Quality of life related to limitations in mobility
- Control of ASCVD risk factors (ie, hypertension, DM, dyslipidemia, and tobacco smoking)
- Physical and financial ability to participate in a supervised or structured exercise program (see Table e35-2)
- Presence of contraindications to antithrombotic and/or anticlaudication therapies (see Table e35-5)

Plan*

- Drug therapy regimen, including antithrombotic therapy and anticlaudication therapy (for each: brand and generic name, dose, route and frequency of administration, and duration of therapy), when appropriate (see Tables e35-3, e35-4, and e35-5)
- Risk factor modification to achieve goals (eg, BP, glucose, lipids) and tobacco smoking cessation (see Table e35-3)
- Monitoring (including self-monitoring) parameters of efficacy (eg, claudication pain, quality of life) and safety (eg, signs and symptoms of bleeding); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, physical activity recommendations)
- Referrals to other providers when appropriate (eg, vascular specialist, physical therapist)

Implement*

- Provide patient education regarding all elements of the pharmacotherapy and nonpharmacotherapy treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, walking assessment) within 1 to 3 months

Follow-up: Monitor and Evaluate*

- Changes of lower extremity PAD symptoms (eg, claudication pain) and improvements in quality of life
- Presence of adverse drug reactions (eg, signs and symptoms of bleeding for those receiving an antiplatelet agent; Table e35-5)
- Walking assessment
- Adherence to pharmacotherapy and nonpharmacotherapy treatment plans using multiple sources of information
- Reevaluate therapy every 3 to 6 months

****Collaborate with patients, caregivers, and other healthcare professionals.***

(ABI, ankle-brachial index; BP, blood pressure; DM, diabetes mellitus; PAD, peripheral arterial disease)

TREATMENT

Desired Outcomes

Overarching treatment principles for patients with lower extremity PAD include an improvement or alleviation of symptoms, reduction of ASCVD risk, and prevention of limb loss. Specific goals related to symptom improvement include increasing maximum walking distance, walking duration, pain-

free walking, and overall quality of life. Specific goals to reducing ASCVD risk include lowering the risk of myocardial infarction (MI), stroke, and death, as well as control of modifiable risk factors (ie, achievement of goal blood pressure [BP], low-density lipoprotein cholesterol (LDL-C), hemoglobin A1C and smoking cessation, as appropriate).[3,37,38]

General Approach to Treatment

Several key risk factors play important roles in the morbidity and mortality of patients with PAD. Many of these risk factors are modifiable using various nonpharmacologic and pharmacologic interventions. Optimization of cardiometabolic risk factors and smoking cessation have demonstrated improvements in morbidity and/or mortality in patients with PAD.[3,9,39] However, there is insufficient evidence that therapies to lower homocysteine concentrations (ie, folic acid, vitamins B6 and B12, and/or betaine) improve lower extremity PAD symptoms or reduce the risk of complications.[17,40] Patients with PAD should be counseled on the importance of receiving an annual influenza vaccine to lower their risk of CV events.[3]

Risk Factor Modification

Tobacco Smoking Cessation

6 Tobacco smoking cessation is key for those with PAD who continue to smoke. Clinicians should assist patients with PAD who are currently smoking tobacco products by connecting them to a tobacco cessation program and/or provision of pharmacotherapy for tobacco smoking cessation. Pharmacotherapeutic options for tobacco smoking cessation include nicotine replacement therapy (NRT; eg, nicotine patches, lozenges, gum), bupropion, and varenicline. All lots of varenicline were recalled in September 2021. Clinicians are encouraged to check the Food and Drug Administration website for updates.[41] These tobacco cessation products are described in detail in Chapter 45 (“Chronic Obstructive Pulmonary Disease”). In all patients with PAD, whether current, former, or nonsmokers, avoidance of second-hand tobacco smoke is also important for reducing their risk of tobacco smoke-related complications.[3]

Cardiometabolic Disease Management

HTN, DM, and dyslipidemia assessment and treatment optimization are key to ASCVD risk reduction in patients with PAD. Current HTN guidelines recommend treating patients with PAD similar to those with ASCVD.[42] In patients with PAD, the BP goal should be < 130/80 mm Hg, and preference should be given to the use of either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) as first-line therapy.[43] While not recommended as a first-line agent to treat hypertension, it is important to note that β-blockers are appropriate in patients with PAD who have a compelling indication for use (eg, heart failure with a reduced ejection fraction, history of MI). β-Blockers do not worsen IC in patients with PAD, a previous concern with this medication class.[44]

Analogous to current HTN guidelines, current lipid guidelines classify PAD as a form of ASCVD. As such, patients with PAD should be treated with high-intensity statin therapy with a goal of ≥50% LDL-C reduction. In patients with PAD who are at very high risk (eg, multiple ASCVD events or 1 ASCVD event with multiple high-risk conditions), adjunctive therapy should be considered if the LDL-C threshold of <70 mg/dL (1.81 mmol/L) is not met with statin therapy alone. Ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be added to statin therapy to optimize LDL-C reduction and overall ASCVD risk.

Guideline recommendations for the treatment of T2DM in patients with PAD are similar to those for patients with other forms of ASCVD.[38] Use of a glucagon-like peptide-1 (GLP-1) receptor agonist and/or sodium-glucose cotransporter 2 (SGLT2) inhibitor is recommended by the American Diabetes Association for those with T2DM and either established ASCVD or indicators of high ASCVD risk (eg, lower extremity artery stenosis >50%) due to the established CVD benefits. Use of an agent with proven benefit from one or both classes is recommended regardless of metformin use, baseline A1C, and target A1C.[38]

Good glycemic control is key to risk mitigation in patients with PAD. The Atherosclerosis Risk in Communities (ARIC) study demonstrated that patients with poor glycemic control (A1C >7.5% [58 mmol/mol]) were five times more likely to develop IC and to be hospitalized for PAD compared with those with an A1C < 6% (42 mmol/mol).[45] Establishment of a patient-specific hemoglobin A1C target and selection of the most appropriate antihyperglycemic regimen are discussed in Chapter 94 (“Diabetes Mellitus”).

Dosing, monitoring guidelines, and contraindications for specific agents used in the treatment of hypertension, DM, and dyslipidemia may be found in Chapters 30 ("Hypertension"), 94 ("Diabetes Mellitus"), and 32 ("Dyslipidemia").

Nonpharmacological

Nonpharmacological treatment options for PAD help improve various outcomes including reducing the risk of limb loss as well as improvement in the quality of life.[3,39,46,47] Both tobacco cessation (discussed above) and exercise programs are recommended for appropriate patients with PAD.

7 There are two types of exercise programs that have been found to be beneficial for those with symptomatic PAD. One is termed a *supervised* program and the other is *structured*. These program types are compared in Table e35-2. Appropriate screening of patients to determine the safety of one of these programs is key to avoiding adverse effects related to exercise.[3] In addition to helping with symptoms of claudication, appropriate exercise can improve other cardiometabolic risk factors by reducing weight, BP, blood glucose, and LDL-C.[48] Limited evidence suggests that participation in an exercise training program may improve walking distance in those with asymptomatic PAD.[49]

TABLE e35-2

Supervised Versus Structured Exercise Training

	Supervised	Structured
Location	Clinical setting (eg, hospital, outpatient facility)	Nonclinical setting preferred by the patient (eg, home)
Guidance	Direct supervision and instruction by a healthcare provider	Self-directed; healthcare provider counsels the patient on an exercise regimen "Coach" to hold patient accountable
Exercise	Walking on a treadmill until moderate-to-maximum claudication symptoms develop, alternating with rest Goal to reach the onset of symptoms within 3-5 minutes of walking; rest period typically lasts 2-5 minutes At least 3 sessions per week, each lasting at least 30-45 minutes	Written how to start and progress through the program by increasing the walking distance or speed Individualized plan; goal to achieve walking for 45-50 minutes, not including rest periods 3-5 times per week
Program duration	At least 12 weeks, ideally 6 months	At least 6 months

Data from References 3,49,50.

For those with DM, self-foot examination and healthy foot behaviors are imperative to minimize the risk of tissue loss or amputation. This includes wearing socks and shoes, selection of appropriate footwear, and daily inspection of the feet.[51] All patients with PAD should rapidly seek medical attention if there is any concern for foot infection (eg, local pain/tenderness, peri-wound edema, discharge, foul odor, visible bone). This will allow prompt assessment and treatment (if an infection is present) to minimize the risk of serious consequences.

8 Lower extremity revascularization is a therapeutic option for those with PAD symptoms when nonpharmacological, including structured exercise, and pharmacological treatment options fail to improve or maintain quality of life and functional status at a level suitable for the patient. Revascularization is necessary for those who develop CTLI or acute limb ischemia. Revascularization can be achieved through an endovascular procedure (eg, angioplasty, stenting) or surgery. Factors to determine which approach is best for an individual are beyond the scope of this Chapter. Readers wishing to learn more about this topic are referred to the 2016 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease.[3]

Herbal remedies and dietary supplements have been promoted and/or investigated in those with PAD. These include vitamin B complex and flaxseed/flaxseed oil.[40,52] There is no evidence to suggest that the use of these or other supplements plays a role in the management of PAD.

Pharmacological

In addition to ASCVD risk reduction strategies previously discussed, pharmacological treatment options for PAD are determined based on several factors including the presence or absence of symptoms. Guideline recommendations for patients with PAD are summarized in Table e35-3 and recommendations for antithrombotic therapy following lower extremity revascularization are detailed in Table e35-4. Dosing recommendations, adverse drug reactions, and practical considerations for the antithrombotic agents and cilostazol which will be discussed in this section and can be found in Table e35-5.

TABLE e35-3

American Heart Association/American College of Cardiology Recommendations for Those with Peripheral Arterial Disease

Treatment Option	Recommendations for Use and Potential Benefit(s)	Class of Recommendation	Level of Evidence
Antithrombotic Therapy[a]			
Aspirin or clopidogrel (Plavix®) monotherapy	Symptomatic PAD: recommended to reduce the risk of vascular death, MI, and stroke Asymptomatic PAD (ABI ≤ 0.9): reasonable to reduce the risk of vascular death, MI, or stroke Asymptomatic PAD (ABI 0.91-0.99): usefulness to reduce the risk of vascular death, MI, or stroke is uncertain	I IIa IIb	A C-EO B-R
Oral anticoagulation[b]	All patients with PAD: oral anticoagulation should not be used to decrease the risk of ischemic events; use increases the risk of bleeding without any clinical benefit	III: Harm	A
Treatment of claudication			
Supervised exercise program	Claudication: recommended to decrease leg symptoms, and improve quality of life and functional status Discuss as a treatment option prior to possible revascularization	I I	A B-R
Structured exercise program (community- or home-based)	Symptomatic PAD: can be beneficial to improve functional status and walking ability	IIa	A
Cilostazol (Pletal®)	Claudication: effective option to improve walking distance	I	A
Risk factor modification			
Antihypertensive therapy	Hypertension and PAD: administer to lower the risk of CV death, MI, heart failure, and stroke	I	A
Glycemic control	Glycemic control can be beneficial for patients with CLTI to lower the risk of limb-related outcomes	IIa	B-NR
High-intensity HMG-CoA-reductase Inhibitor (statin)[c]	All patients with PAD: recommended to reduce the CV and risk of limb-related events (eg, worsening claudication, lower extremity revascularization); improve walking distance in those with intermittent claudication	I	A
Tobacco cessation	All patients with PAD: recommended to decrease the risk of death, ischemic CV events, limb-related events, and amputation	I	A

[a]Refer Table e35-4 for recommendations following lower extremity revascularization.

[b]Guideline preceded the publication of rivaroxaban data in this patient population.

[c]High-intensity statin regimens include atorvastatin 40-80 mg daily or rosuvastatin 20-40 mg daily.

ABI, ankle-brachial index; CLTI, chronic limb-threatening ischemia; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease.

Class of recommendation: I = strong, benefit >>> risk; IIa = moderate, benefit >> risk; IIb = weak, benefit ≥ risk; III: no benefit = moderate, benefit = risk; III: Harm = strong, risk > benefit.

Level of evidence: A = high-quality evidence from more than 1 randomized controlled trial (RCT); meta-analyses of high-quality RCTs; one or more RCTs corroborated by high-quality registry studies; B-R = moderate-quality evidence from one or more RCTs; meta-analyses of moderate-quality RCTs; B-NR = moderate-quality evidence from one more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; C-LD = randomized or nonrandomized observational or registry studies with limitations of design or excretion; meta-analyses of such studies; physiological or mechanistic studies in human studies; C-EO = consensus of expert opinion based on clinical experience.

Data from Reference 3.

TABLE e35-4

Antithrombotic Recommendations Following Lower Extremity Revascularization for Peripheral Arterial Disease

Treatment Option	Recommendations for Use and Potential Benefit(s)	Class of Recommendation	Level of Evidence
Antiplatelet therapy			
Monotherapy: Aspirin 75-100 mg once daily or clopidogrel 75 mg once daily	Recommended to reduce the risk of vascular death, MI, and stroke	I	A
Dual antiplatelet therapy: Aspirin 75-100 mg once daily and clopidogrel 75 mg once daily	Lower extremity revascularization: use may be reasonable to lower the risk of limb-related events (eg, need for repeat revascularization)	IIb	C-LD
Oral anticoagulation			
Rivaroxaban 2.5 mg twice daily in combination with aspirin 81 mg/day[a]	Lower extremity revascularization: may be considered to reduce the risk of CV events or lower extremity ischemic events	NA	NA
Warfarin (adjusted to an INR goal of 2.0-3.0)	Following autogenous vein or prosthetic bypass: usefulness of uncertain	IIb	B-R

CV, cardiovascular; NA, not applicable.

Class of recommendation: I = strong, benefit >>> risk; IIa = moderate, benefit >> risk; IIb = weak, benefit ≥ risk; III: no benefit = moderate, benefit = risk; III: Harm = strong, risk > benefit.

Level of evidence: A = high-quality evidence from more than 1 randomized controlled trial (RCT); meta-analyses of high-quality RCTs; one or more RCTs corroborated by high-quality registry studies; B-R = moderate-quality evidence from one or more RCTs; meta-analyses of moderate-quality RCTs; B-NR = moderate-quality evidence from one more well-designed, well-executed nonrandomized studies, observational studies, or registry studies; C-LD = randomized or nonrandomized observational or registry studies with limitations of design or excretion; meta-analyses of such studies; physiological or mechanistic studies in human studies; C-EO = consensus of expert opinion based on clinical experience.

[a]Guideline preceded the publication of rivaroxaban data in this patient population.

Data from References 3,14,53.

TABLE e35-5

Overview of Select Pharmacotherapeutic Treatment Options for Those with Lower Extremity Peripheral Arterial Disease

Agent	Key Pharmacological Considerations	Dosing and Administration	Drug Interactions	Adverse Drug Reactions	Comments
Aspirin	Platelet binding:	75-100 mg orally	Nonsteroidal anti-inflammatory drugs, other	Bleeding,	Contraindicated

	irreversibly inhibits thromboxane A_2 formation Absorption (oral): immediate release – complete; enteric-coated – erratic Metabolism: rapid, hydrolysis to salicylic acid Duration of antiplatelet effect: 10 days (life of the platelet)	once daily Rectal formulation available	antiplatelets, anticoagulants: may increase bleeding risk	dyspepsia gastrointestinal ulcer, allergic reaction	in those with a hypersensitivity to nonsteroidal anti-inflammatory drug products
Clopidogrel	Platelet binding: irreversibly to the $P2Y_{12}$ receptor Metabolism: converted through a two-step process to the active metabolite; CYP2C19 is mostly involved Maximum inhibition of platelet aggregation: 5-7 days without a loading dose Duration of action: platelet aggregation returns to baseline within 5 days after discontinuation	75 mg orally once daily	CYP2C19 inhibitors[a]: may decrease efficacy of clopidogrel as it prevents formation of the active metabolite; avoid concomitant use of omeprazole and esomeprazole CYP 2C19 inducers (strong)[b]: may increase bleeding risk Non-steroidal anti-inflammatory drugs, other antiplatelets, anticoagulants: may increase bleeding risk	Bleeding, thrombotic thrombocytopenic purpura (rare)	Loading dose of therapy is not necessary Contraindicated in those with an active pathological bleeding (eg, peptic ulcer, intracranial hemorrhage) Role of CYP2C19 genetic testing for this patient population has not been substantiated
Cilostazol	Metabolism: CYP 2C19 and 3A4 (major) Elimination half-life: 11-13 hours Excretion: over 70% excreted in the urine; active metabolite concentrations increase in severe renal disease Onset of action: at least 2-4 weeks until walking distance impacted	100 mg orally twice daily Take 30 minutes prior or 2 hours after meals	CYP3A4 inhibitors (moderate and strong)[c]: can increase cilostazol exposure – decrease cilostazol dose to 50 mg twice daily when used in combination CYP2C19 inhibitors[a]: can increase cilostazol exposure – decrease cilostazol dose to 50 mg twice daily when used in combination Cigarette smoking: may decrease effectiveness of cilostazol	Abnormal stools, diarrhea, dizziness, headache, palpitations	Discontinue if no benefit observed after 12 weeks Contraindicated in those with heart failure as use may increase the risk of death
Rivaroxaban	Absorption: 2.5 mg dose is not affected by food Metabolism: hydrolysis and oxidative degradation	2.5 mg orally twice daily in combination with aspirin 75 -	CYP 3A4 (strong) and P-glycoprotein inducers[d]: avoid combination CYP 3A4 (strong) and P-glycoprotein inhibitors[e]: avoid combination	Bleeding	Take with or without food

	catalyzed by CYP 3A4, CYP3A5, CYP2J2 Elimination half-life: 5-9 hours Excretion: substrate of the P-glycoprotein efflux transporter proteins; about a third of unchanged drug is recovered in the urine	100 mg once daily Creatinine clearance < 30 mL/min (0.5 mL/s): limited data for use	CYP3A4 (moderate) and P-glycoprotein inhibitors[f]: may increase bleeding risk, do not use combination if creatinine clearance 15 to < 80 mL/min (0.25 to 1.33 mL/s) in combination unless benefit outweighs bleeding risk Nonsteroidal anti-inflammatory drugs, antiplatelets, other anticoagulants: may increase bleeding risk		

CYP: cytochrome P.

[a]Fluconazole, omeprazole, ticlopidine.

[b]Rifampin.

[c]**Moderate**: erythromycin, diltiazem, grapefruit juice, etc.; **strong**: ketoconazole.

[d]Carbamazepine, phenytoin, rifampin, St. John's wort, etc.

[e]Ketoconazole, ritonavir, etc.

[f]Erythromycin.

Data from References 3,54–57.

Antithrombotic Agents

Antiplatelets

Platelets play a significant role in the pathogenesis of atherothrombosis. In patients with atherosclerotic disease, including those with PAD, plaque formation occurs within the arterial lumen. In patients with PAD, plaque rupture can occur, which can result in atherothrombosis leading to tissue loss in the lower extremities, MI, stroke, and/or death. Platelets begin to adhere to the vessel wall after an injury occurs (ie, plaque rupture). Platelets then become activated and platelet agonists, including adenosine diphosphate (ADP) and thromboxane A_2, are released and promote platelet aggregation. ADP induces platelet aggregation by binding to the $P2Y_{12}$ receptor on the platelet. These aggregated platelets make up part of the thrombosis that develops in response to vessel injury.[dipipharm12_c035_bib058,dipipharm12_c035_bib059] A more detailed discussion of arterial thrombus formation in response to ruptured atherosclerotic plaques is provided in Chapter 34 ("Acute Coronary Syndrome").

Several antiplatelet therapies have been developed in an attempt to mitigate atherothrombosis formation. Aspirin and clopidogrel are the antiplatelet therapies recommended for use in select patients with PAD. Aspirin is an irreversible thromboxane A_2 inhibitor. Clopidogrel, following metabolism to its active form, prevents ADP from binding to the $P2Y_{12}$ receptor.[60,61]

9 Aspirin has been a mainstay for secondary prevention of CVD for decades due to its antiplatelet properties. A meta-analysis assessing the impact of antiplatelet therapy of ischemic events in those with known vascular disease or at high risk for atherosclerotic disease, including those with PAD (history of IC, peripheral grafting, or angioplasty), demonstrated that antiplatelet therapy was associated with a 23% reduction in vascular events in the PAD subgroup.[60] This analysis also demonstrated that a lower daily dose of aspirin (75-150 mg) is as effective as higher doses (≥ 160 mg daily) in reducing CV events in those with known vascular disease.[60] These observations established the role of aspirin for those with symptomatic PAD. More recent trials sought to identify if there was a benefit of antiplatelet therapy in those without PAD symptoms.

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial compared the use of aspirin (100 mg/day) to placebo in patients with DM and asymptomatic PAD. No differences were observed between groups in the risk of death from coronary heart disease or stroke, nonfatal MI or stroke, or above the ankle amputation for CLTI.[62] The Aspirin for Asymptomatic Atherosclerosis trial randomized patients with an ABI ≤ 0.95 to aspirin (100 mg/day) or placebo and observed no difference in the risk of fatal or nonfatal coronary events or stroke between groups.[62] Aspirin use was associated with an increased risk of the first major hemorrhagic event. These two trials called into question the routine use of aspirin in those with asymptomatic PAD.

Clopidogrel was compared to aspirin in patients with stable atherosclerotic disease in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study. Approximately, one-third of the study population had symptomatic lower extremity PAD, defined as IC with an ABI ≤ 0.85 or less, prior revascularization or amputation. Although the use of clopidogrel was associated with a lower overall risk of the primary composite outcome (MI, stroke, or vascular death) compared to aspirin, subgroup analyses found event rates were significantly lower in the PAD subgroup but not the MI and stroke subgroups.[61] The aspirin dose in this trial was higher (325 mg once daily) than currently recommended.[3] Severe bleeding events were low and comparable between groups. Therefore, it is unlikely that a lower dose of aspirin would have been associated with a lower risk of bleeding compared to clopidogrel. Although this trial was not powered to determine the superiority of clopidogrel over aspirin in patients with symptomatic PAD, it provides evidence that clopidogrel is a suitable alternative to aspirin in this population. The use of clopidogrel has not been evaluated in those with asymptomatic PAD.

The combination of aspirin and clopidogrel (dual antiplatelet therapy or DAPT) in patients with PAD was evaluated in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial to determine if this more potent antiplatelet regimen would result in a lower risk of CV events (MI, stroke, or CV) in those with established ASCVD, including those with symptomatic PAD. The DAPT regimen was associated with an increased risk of bleeding and no difference in CV events when compared to aspirin monotherapy.[63] Therefore, the use of DAPT should not be recommended for an individual with PAD unless another indication for use exists (eg, revascularization, MI).[3]

Ticagrelor, a more potent $P2Y_{12}$ receptor antagonist compared to clopidogrel, was evaluated in patients with symptomatic lower extremity PAD. In the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial, the use of ticagrelor was not associated with a lower risk of CV events when compared to clopidogrel. Bleeding rates were comparable between the two groups.[64] Now, there is no role for ticagrelor or prasugrel, another potent $P2Y_{12}$ receptor antagonist, for patients with PAD.

In the absence of another indication for use, aspirin is typically selected as the antiplatelet therapy for most patients with established ASCVD, including those with symptomatic PAD, given its low cost and availability over-the-counter (OTC). The dose of aspirin should be 75 to 100 mg once daily. Higher doses have not been shown to improve clinical outcomes but are associated with a higher risk of bleeding.[60,65] The enteric-coated formulation of aspirin was developed to minimize the risk of gastrointestinal toxicity associated with the use of this agent. Absorption of the enteric-coated product is variable and influenced by several variables (eg, food, alcohol). Variable absorption could affect the effectiveness of therapy. There is no evidence that enteric-coated formulations of aspirin decrease the risk of gastrointestinal adverse drug reactions.[66–68] Therefore, the noncoated formulation is recommended.

It is reasonable to consider clopidogrel as the first-line antiplatelet agent. Care should be taken to assess for the presence of drug interactions that could alter the metabolism of clopidogrel before initiating therapy. For example, select cytochrome P450 (CYP) 2C19 inhibitors (eg, omeprazole) will decrease the conversion of clopidogrel to its active metabolite, potentially leading to decreased efficacy. Clopidogrel, available by prescription only, should be utilized in those with a hypersensitivity to aspirin. Unlike patients treated with clopidogrel for acute coronary syndrome, loading doses of antiplatelet therapies are not necessary for those with PAD because there is not an urgent need to achieve maximum platelet inhibition.[69,70]

Patients should be counseled to monitor for and informed to report signs or symptoms of bleeding. Clinicians should assess for signs and symptoms of bleeding during each patient visit. Periodic assessment of hemoglobin/hematocrit should be considered in those at a higher risk of bleeding (eg, older patients). When a significant decrease in hemoglobin or hematocrit is identified, the cause for blood loss, including the use of antiplatelet therapies, should be investigated. Patients should be counseled against the use of a nonsteroidal anti-inflammatory agent in combination with aspirin or clopidogrel as there is an additive risk of bleeding.

Oral Anticoagulant Therapy

Despite the use of antiplatelet therapy, CV events and limb loss can occur in those with PAD. In addition to stimulating platelet aggregation, plaque rupture also leads to activation of the coagulation cascade with thrombin and other coagulation proteins being generated. Thrombin plays a critical role in stabilizing the clot that forms following activation of the coagulation system. Thrombin also converts fibrinogen to fibrin, which solidifies the clot. While arterial thrombi are rich in platelets, fibrin becomes the primary component as thrombi extend distally.[71]

Anticoagulants have been studied in the PAD population as an additional treatment option to lower the risk of CV events as well as limb-threatening events. These agents increase clotting time within the blood. Two oral anticoagulants, warfarin and rivaroxaban, have been evaluated in this patient population. Warfarin has a complex mechanism of action but ultimately results in reduced production of clotting factors II, VII, IX, and X. Rivaroxaban, a direct-acting oral anticoagulant, inhibits Factor Xa. Factor Xa is responsible for the formation of active thrombin (Refer to Chapter 38: Venous Thromboembolism for more details on the mechanism of action and the pharmacokinetic and pharmacodynamic properties of these agents).

In patients with PAD, warfarin, adjusted to a target international normalized ratio of 2.0 to 3.0, in combination with an antiplatelet was associated with more than a threefold increased risk of life-threatening bleeding without an incremental benefit in lowering CV risk when compared to antiplatelet therapy alone.[72] Consequently, warfarin is not recommended in those with PAD without another indication for use.[3]

Rivaroxaban has been studied as a secondary prevention strategy in combination with aspirin in patients with stable atherosclerotic disease. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial compared rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg daily; rivaroxaban monotherapy (5 mg twice daily); or aspirin monotherapy (100 mg daily) in patients with stable atherosclerotic disease, including 15% with lower extremity PAD.[73] Overall, combination therapy with low-dose rivaroxaban and aspirin was associated with a 24% lower risk of CV death, MI, or stroke compared to aspirin monotherapy; no differences were observed between the rivaroxaban monotherapy and aspirin groups. The benefit was driven by a reduction in the risk of CV death and stroke. A sub-group analysis of the PAD cohort revealed the combination of rivaroxaban 2.5 mg twice and aspirin was associated with a 43% lower risk of major adverse limb events including amputation and vascular intervention compared to aspirin monotherapy. Major bleeding was 60% higher in the combination group compared to those only receiving aspirin.[74]

10 The Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) study demonstrated that the use of rivaroxaban 2.5 mg twice daily, in combination with aspirin (100 mg/day), was associated with a 15% reduction in the risk of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death compared to aspirin monotherapy in patients with PAD who underwent recent revascularization. This difference was driven by a reduction in acute limb ischemia between groups.[53] Like COMPASS, major bleeding was more common in the rivaroxaban group.

10 The use of aspirin, clopidogrel, or the combination of these two agents is recommended post-revascularization in the AHA/ACC Lower Extremity PAD guideline (Table e35-4.).[2] This guideline has not been updated since the COMPASS and VOYAGER PAD trials were published. While these data are compelling, it is prudent to have more robust evidence exploring the use of this regimen in those with symptomatic lower extremity PAD population that did not undergo revascularization before rivaroxaban can be routinely recommended for this group. There is a role for rivaroxaban 2.5 mg twice daily in combination with low-dose aspirin in those who underwent lower extremity revascularization. Shared decision-making should be employed before prescribing this regimen. The potential benefit and risk of bleeding should be weighed for each person. Clinicians should ensure that the correct dose is used for PAD as various dosing regimens and dosage forms exist for rivaroxaban.[54] Rivaroxaban is renally eliminated; therefore, the potential for increased risk of bleeding exists in patients with CKD stage 4 or 5. Because there is limited data to support the use of low-dose rivaroxaban in those with a creatinine clearance <30 mL/min (0.5 mL/s), it may be prudent to avoid rivaroxaban in this setting until more data is available.

Cilostazol

Cilostazol, a phosphodiesterase-3 inhibitor, improves peripheral vasodilation potentially leading to improved blood flow in the lower extremities.[55] However, the exact mechanism of this agent in those with PAD remains unclear. Cilostazol is considered an add-on therapy for individuals who have persistent PAD symptoms despite smoking cessation, if applicable, and participation in an exercise program.[3,75] Compared to placebo, cilostazol use was associated with a mean increase of 43 m in distance walked on the treadmill before the development of claudication symptoms.[76] A meaningful change is considered 20 to 50 m when using the 6-minute walking test.[49] Therefore, while the magnitude of the effect may be less than that of a

supervised exercise program, the improved walking distance associated with cilostazol may allow a patient with PAD to walk across a room without provoking symptoms, for example.

The presence of drug interactions (Table e35-5) should be assessed prior to initiating and during cilostazol therapy, and dose adjustments made as necessary. Clinicians should assess for the presence of heart failure before implementing therapy. Cilostazol has been associated with an increased risk of death in patients with heart failure and is, therefore, contraindicated in this population.[55]

Improvements in symptoms may begin as early as 4 weeks after initiation of cilostazol but it may take up to 12 weeks for any benefit to occur. This expectation should be clearly communicated to the patient. If symptomatic improvement is observed, there may be a progressive benefit over the first 12 to 24 weeks of therapy. Thereafter, the benefit of therapy will plateau.[77,78] Treatment should be stopped in those who have not experienced symptomatic improvement after 12 weeks since there is no evidence that any benefit will develop after this time if it has not already occurred.[3,55] There is no evidence that increasing the dose above 100 mg twice daily is associated with a greater benefit.

Other Therapies

Protease-activated receptor (PAR)-1 is a receptor for thrombin on the surface of platelets that plays a role in platelet activation. Vorapaxar is a PAR-1 antagonist that has been evaluated in combination with aspirin in patients with stable CVD, including those with PAD.[79] Vorapaxar in combination with aspirin was shown to decrease the risk of revascularization in participants with lower extremity PAD. However, this benefit was outweighed by an increased risk of bleeding. Importantly, vorapaxar increases the risk of intracranial hemorrhage and is contraindicated in those with prior stroke or transient ischemic attack. The AHA/ACC Lower Extremity PAD guideline notes that the overall benefit for this agent is uncertain.[3] Pentoxifylline is not an effective agent for managing claudication symptoms and is not recommended by AHA/ACC.[3] Now, neither vorapaxar nor pentoxifylline should not be considered for any individuals with PAD.

EVALUATION OF THERAPEUTIC OUTCOMES

There are several methods that should be employed for monitoring those with PAD. First, it is imperative to assess and control ASCVD risk factors to lower the patient's overall risk of death and CV events.[3] BP measurements should be taken at each office visit and HTN treatment should be initiated or optimized as necessary. Home BP or ambulatory BP monitoring may be necessary for some patients to determine if their goal is being met.[42] A baseline A1C should be determined at the time of PAD diagnosis to evaluate the presence and control of DM. A repeat A1C should be completed at least every 3 years for a person 45 years of age or older who has not been previously diagnosed with T2DM. Repeat A1C testing can occur sooner based on the clinician's judgment.[80] Refer to Chapters 30, Hypertension , 32, Dyslipidemia, and 94, Diabetes Milletus,for more specific information on the frequency of monitoring and strategies to achieve BP, cholesterol, and glycemic goals, respectively. Tobacco use should be addressed at each patient encounter, even in those who never smoked. Assessment for the risk of relapse should be conducted in former smokers.[81]

Inquiries about new CV events (ie, MI, stroke, sudden cardiac death) should be completed at each visit. A review of symptoms to assess for signs and symptoms of CVD and cerebrovascular disease should be completed at each visit. When present, clinicians should recommend additional strategies to lower one's ASCVD risk, if possible.

Clinicians should assess for changes in functional status and lower extremity symptoms during each patient encounter.[3] The details reported by the patient should be documented (eg, distance walked when pain begins). This can assist providers in determining if symptoms and/or functional limitations change over time. Physical examination findings should be clearly documented for similar reasons. Reports from the exercise training program, when part of the treatment plan, should also be reviewed to allow for a comprehensive assessment of functional status and symptoms.[3]

Recommendations for repeat testing and imaging are presented in the box. There is not a consensus on when follow-up ABI testing should occur in a patient who has not undergone lower extremity revascularization. Clinical decision-making should likely drive this decision, including when there is a significant decline in functional status. It is important that ABI testing be done in both limbs during follow-up even if there was not a prior diagnosis of PAD in both lower extremities. A decrease in an ABI score of >0.15 is considered to be evidence of significant lower extremity PAD progression.[82] Therefore, when this magnitude of change in ABI is detected, more routine follow-up should occur. Imaging is necessary when revascularization will be considered for those with symptomatic PAD despite guideline-directed medical therapy.[3,14] Consultation with a vascular specialist should occur to

determine which test(s) is most appropriate.

A biannual foot examination can be conducted in those who have DM and may assist in reducing the risk of tissue loss as a clinician may be more like to identify a foot infection than a patient. In patients with PAD and DM, peripheral neuropathy can make the signs of this infection more subtle. Thus, further evaluation may not be sought out as quickly if depending solely on patient reports.[3]

Recommendations for Longitudinal Testing and Imaging in Those with PAD[3,14]

- Duplex ultrasound, computerized tomography angiography, or magnetic resonance angiography is useful to determine the anatomic location and severity of stenosis when revascularization is being considered for a patient with symptoms
- Invasive angiography is useful for patients who may undergo revascularization with CLTI and is reasonable when revascularization is being considered for those with life-limiting claudication who do not respond to guideline-directed medical therapy
- Periodic ABI testing should occur for those who have undergone lower extremity revascularization but should not be used alone to monitor these patients
- Surveillance duplex ultrasound can be beneficial for those who have undergone infrainguinal, autogenous bypass grafts
- Surveillance duplex ultrasound is reasonable after endovascular procedures

During each patient encounter, patients should be evaluated for the presence of adverse drug reactions and scenarios that may increase the risk of adverse events. For patients treated with antithrombotic therapy, clinicians should assess for the presence of signs and symptoms of bleeding. Renal function should be evaluated periodically for patients treated with rivaroxaban. Clinicians should screen patients treated with cilostazol for the development of concomitant heart failure. Lastly, clinicians should evaluate for the presence of drug-drug interactions during each patient encounter.

CONCLUSION

PAD is underrecognized despite the known serious consequences of this condition. Assessing for the presence of symptoms and physical examination findings suggestive of PAD should occur in those at risk. Identification of signs and symptoms of PAD should prompt subsequent diagnostic testing. The ABI is the most common diagnostic tool used as it is noninvasive and relatively easy to complete.

Treatment of PAD consists of ASCVD risk reduction strategies including achievement of BP, glycemic, and cholesterol goals. Patients with PAD should receive high-intensity statin therapy unless contraindicated. Antithrombotic therapy with either low-dose aspirin or clopidogrel is recommended in those with symptoms of PAD to lower the risk of death, MI, and stroke.

Both nonpharmacological and pharmacological options exist to manage PAD symptoms. Tobacco smoking cessation is one of the most effective methods to improve symptoms and to prevent complications of PAD including the risk of amputation. Exercise training is an effective nonpharmacological treatment option to decrease symptoms and improve functional capacity. Cilostazol may be considered as a treatment option for those who continue to have PAD symptoms despite smoking cessation and participation in an exercise program.

Lower extremity revascularization is an option for some patients when symptoms are not controlled despite optimization of other treatments. An antithrombotic regimen should be prescribed following revascularization. Treatment options include low-dose aspirin or clopidogrel monotherapy; low-dose aspirin and clopidogrel used in combination; or rivaroxaban 2.5 mg twice daily and low-dose aspirin.

ABBREVIATIONS

ABI	ankle to brachial index

ACC/AHA	American College of Cardiology/American Heart Association
ACE	angiotensin-converting enzyme
ADP	adenosine diphosphate
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BP	blood pressure
CAD	coronary artery disease
CKD	chronic kidney disease
CLTI	chronic limb-threatening ischemia
COR	class of recommendation
CV	cardiovascular
CTA	computed tomography angiography
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DM	diabetes mellitus
GLP	glucagon-like peptide
HTN	hypertension
IC	intermittent claudication
LDL-C	low-density lipoprotein-cholesterol
LOE	level of evidence
MI	myocardial infarction
MRA	magnetic resonance angiography
NO	nitric oxide
NRT	nicotine replacement therapy
PAD	peripheral arterial disease
PAR -1	protease-activated receptor-1

PCSK-9	proprotein convertase subtilisin/kexin type 9 serine protease
SBP	systolic blood pressure
SGLT	sodium-glucose lowering therapy
TC	total cholesterol
T2DM	type 2 diabetes mellitus

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SELF-ASSESSMENT QUESTIONS

1. Which of the following risk factors is most strongly associated with the development of peripheral arterial disease (PAD)?

   A. Current tobacco smoking

   B. Diabetes

   C. Dyslipidemia

   D. Hypertension

2. A 53-year-old male with a medical history notable for hypertension (HTN), dyslipidemia, myocardial infarction (MI) 3 years ago, and a previous 30 pack-year smoking history presents to your clinic for follow-up. Physical exam is notable for bilateral lower leg and foot pain and cramping during daily walks. Vital signs include height 5′11″ (180 cm), weight 91 kg, blood pressure (BP) 138/90 mm Hg, HR 80 bpm, T 37°C. Laboratory values include hemoglobin A1C 6.1% (43 mmol/mol), low-density lipoprotein cholesterol (LDL-C) 100 mg/dL (2.59 mmol/L), high-density lipoprotein cholesterol (HDL-C) 40 mg/dL (1.03 mmol/L), triglycerides (TG) 150 mg/dL (1.70 mmol/L), total cholesterol (TC) 170 mg/dL (4.40 mmol/L). Which of the following patient findings is most indicative of PAD?

   A. Hemoglobin A1C 6.1% (43 mmol/mol)

   B. History of tobacco smoking

   C. LDL-C 100 mg/dL (2.59 mmol/L)

   D. Lower extremity pain and cramping during exertion

3. Which of the following ankle-brachial index (ABI) measurements is consistent with a diagnosis of lower extremity PAD?

   A. 1.4

   B. 1-1.4

   C. 0.91-0.99

   D. ≤0.9

4. Which of the following is a symptom improvement goal when treating lower extremity PAD?

   A. Improved BP control

   B. Pain-free walking

   C. Reduced risk of MI

   D. Smoking cessation

5. Which of the following is TRUE regarding hypertensive management in a patient with lower extremity PAD?

   A. β-Blockers should be used first-line

   B. Calcium channel blockers should be used first-line

   C. BP goal is <130/80 mm Hg

   D. BP goal is <140/90 mm Hg

6. Which of the following statin choices would be best for optimizing cardiovascular risk reduction in a patient with lower extremity PAD?

   A. Atorvastatin 20 mg orally daily

   B. Lovastatin 20 mg orally daily

   C. Rosuvastatin 20 mg orally daily

   D. Simvastatin 20 mg orally daily

7. A 72-year-old patient develops intermittent claudication symptoms after walking 20 feet (6.1 m). Medical history includes coronary artery disease, heart failure with a reduced ejection fraction, and HTN. The patient does not smoke. BP is at goal. Medications, all taken once daily, include aspirin 81 mg, atorvastatin 80 mg, lisinopril 40 mg, and amlodipine 10 mg. Which of the following treatment options could be considered for this patient to improve his claudication symptoms?

   A. Cilostazol

   B. Clopidogrel

   C. Rivaroxaban

   D. Structured exercise program

8. The recommended dose for aspirin in those with symptomatic lower extremity PAD is

   A. 75 to 100 mg once daily.

   B. 75 to 100 mg twice daily.

   C. 100 to 325 mg once daily.

   D. 100 to 325 mg twice daily.

9. Which of the following is the correct antithrombotic regimen for a patient who will be initiated on rivaroxaban following lower extremity revascularization for PAD?

   A. 20 mg once daily with dinner

B. 15 mg twice daily for 21 days then rivaroxaban 20 mg once daily

C. 5 mg twice daily and aspirin 325 mg once daily

D. 2.5 mg twice daily and aspirin 81 mg once daily

10. After how many weeks of therapy should cilostazol should be discontinued if no benefit is observed with use?

A. 6 weeks

B. 12 weeks

C. 24 weeks

D. 48 weeks

11. In a patient with lower extremity PAD, which of the following comorbidities or circumstances would vorapaxar use be contraindicated?

A. Heart failure

B. Type 1 diabetes mellitus

C. Prior lower extremity revascularization

D. Prior stroke or transient ischemic attack

12. What is the American Heart Association/American College of Cardiology recommendation for the use of pentoxifylline for those with lower extremity PAD?

A. Use is not recommended

B. Consider if antiplatelet therapy is contraindicated

C. Initiate treatment when an exercise training program begins

D. Reasonable to use if claudication symptoms persist despite smoking cessation

13. What is the American Heart Association/American College of Cardiology recommendation for the use of warfarin for those with lower extremity PAD who have not undergone revascularization?

A. Use is not recommended

B. Consider if antiplatelet therapy is contraindicated

C. Initiate treatment when an exercise training program begins

D. Reasonable to use if claudication symptoms persist despite smoking cessation

14. A 75-year-old patient with heart failure with reduced ejection fraction is diagnosed with PAD after undergoing ABI testing (ABI = 0.72). This test was recommended based on physical examination findings. The patient denies pain or discomfort in the lower extremities with exertion or at rest. The patient has no functional limitations due to PAD. The patient is currently not receiving any antithrombotic therapy. Which of the following recommendations is best regarding the use of clopidogrel in this patient?

A. Recommended to prevent the development of PAD symptoms in the future

B. Reasonable to lower the risk of cardiovascular events and death

C. Not recommended because of the presence of heart failure

D. Not recommended as risk of bleeding outweighs any potential benefit

15. Which of the following nonpharmacological strategies has been shown to decrease the risk of amputation in patients with lower extremity PAD?

A. 10% reduction in body weight

B. Supervised exercise training

C. Structured exercise training

D. Tobacco cessation

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Current tobacco smoking is the risk factor most strongly associated with PAD. Diabetes (30%-80% increased risk), dyslipidemia (up to 14% increased risk), and hypertension (50% increased odds) each contribute to PAD risk, but to a lesser degree than current tobacco smoking. Refer to Introduction and Epidemiology sections for more information.

2. **D.** Lower extremity pain and cramping during exertion are most indicative of PAD. There is no specific lab test or laboratory value associated with PAD. His history of smoking is a risk factor for PAD, but is not diagnostic for the condition. The patient should undergo further assessment to determine if he has PAD as he has symptoms and risk factors for the condition. See the Clinical Presentation section for more information.

3. **D.** ≤0.9 is diagnostic of PAD (and can be further broken down into mild [0.7-0.9], moderate [0.4-0.7], and severe [<0.4]). The other answer choices indicate noncompressible arteries (>1.4), normal (1-1.4), and borderline risk for PAD (0.91-0.99). Refer to the Clinical Presentation (Diagnostic Tests) section for more information.

4. **B.** Pain-free walking is a treatment goal to improve symptoms for a person with PAD. The other answer choices are goals of treatment for PAD but are related to atherosclerotic cardiovascular disease (ASCVD) risk reduction rather than symptom improvement. Refer to the Treatment section for more information.

5. **C.** The blood pressure goal for those with PAD is <130/80 mm Hg; <140/90 mm Hg is not strict enough given that PAD indicates the presence of ASCVD. An angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) should be used as a first-line agent. β-Blockers are only preferred if compelling indications exist (eg, post-myocardial infarction). Refer to the General Approach to Treatment (Risk Factor Modification, Cardiometabolic Disease Management) section for more information.

6. **C.** Patients with PAD should be treated with at least a high-intensity statin that will reduce their LDL-C levels by ≥50%. Rosuvastatin 20 mg orally daily is the only option that will result in this level of LDL-C reduction; all other options indicate moderate- (or low-) intensity statin therapy. Other high-intensity statin regimens are atorvastatin 40 to 80 mg once daily or rosuvastatin 40 mg once daily. Refer to the General Approach to Treatment (Risk Factor Modification, Cardiometabolic Disease Management) section for more information.

7. **D.** Structured exercise training has been shown to improve symptoms in those with lower extremity PAD. Refer to the Nonpharmacological section and Table e35-3 for more information. Cilostazol may provide improvement in symptoms but cannot be considered for this patient as he has heart failure (see Table e35-5). There is no evidence that the addition of clopidogrel or rivaroxaban improves symptoms in those with PAD. Refer to the Antithrombotic Agents section for more information.

8. **A.** The recommended dose of aspirin to reduce the risk of cardiovascular events and death in those with symptomatic PAD is 75 to 100 mg once daily. Higher doses (and increased dosing frequency) increase the risk of bleeding without improving efficacy. Refer to Table e35-5 and the Antithrombotic Section (Aspirin) for more information.

9. **D.** The regimen of rivaroxaban 2.5 mg twice daily and aspirin 81 mg once daily was found to be effective in lowering the risk of cardiovascular and limb-related events in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. There is no evidence that other rivaroxaban regimens produce similar results. See the Pharmacological (Antithrombotic Agents, Anticoagulation) section for more information.

10. **B.** Cilostazol should be discontinued if no benefit is observed after 12 weeks of use. See Table e35-5 for more information.

11. **D.** Use of vorapaxar is contraindicated in those with a prior history of stroke or transient ischemic attack. Use in this patient population is associated with an increased risk of intracranial hemorrhage. Refer to the Pharmacological (Other Therapies) section for more information.

12. **A.** Pentoxifylline has not been proven effective in those with PAD. Therefore, this agent is not recommended for any patients with PAD by the American Heart Association/American College of Cardiology. Refer to the Pharmacological (Other Therapies) section for more information.

13. **A.** Use of warfarin in combination with antiplatelet therapy in those with PAD is associated with an increased risk of life-threatening bleeding. There was no benefit of this combination therapy observed. Therefore, warfarin is not recommended for patients with PAD, without another indication for use, by the American Heart Association/American College of Cardiology owing to the risk of harm. Refer to the Pharmacological (Antithrombotic Agents, Anticoagulation) section and Table e35-3 for more information.

14. **B.** There is no clear evidence that the use of antiplatelet therapy (ie, aspirin or clopidogrel monotherapy) reduces the risk of cardiovascular events in those without PAD symptoms and an ABI ≤ 0.9. Therefore, the American Heart Association/American College of Cardiology notes that use is "reasonable" in this situation. The risk versus benefit would need to be discussed with the patient before starting antiplatelet therapy. Antiplatelet therapy does not prevent the development or progression of PAD symptoms (A). Cilostazol, not clopidogrel, has been associated with an increased risk of death in patients with heart failure (C). Refer to the Pharmacological (Antithrombotic Agents) section and Table e35-3 for more information.

15. **D.** Of these four potential options, tobacco cessation is the only nonpharmacological treatment strategy that has been shown to reduce the risk of amputation. See the Nonpharmacological section and Table e35-3 for more information.