Clinical Assessment of Peripheral Arterial Disease in the Office: What Do the Guidelines Say?

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Semin Intervent Radiol 2018;35:365–377

Abstract

Lower extremity peripheral arterial disease (PAD) is the manifestation of atherosclerotic disease within the lower extremities. The presentation of PAD is diverse ranging from asymptomatic disease to claudication or to debilitating rest pain, nonhealing ulcers, and gangrene. PAD is associated with significant morbidity, mortality, and healthcare costs. Proper diagnosis and management of PAD is important so as to maintain quality of life and reduce the risk of cardiovascular disease and adverse limb events such as amputation. This document provides a comprehensive outpatient approach to the clinical assessment of PAD that includes risk factors, diagnosis, treatment, and follow-up options.

Keywords

- peripheral artery disease
- guidelines
- outpatient
- critical limb ischemia
- claudication
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to list the risk factors; diagnose and determine the category of PAD; determine treatment whether it is risk factor reduction, medical management, an exercise program, or revascularization; and determine the longitudinal follow-up needed in the outpatient setting.

Accreditation: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

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In 2016, the American College of Cardiology (ACC) and American Heart Association (AHA) Task Force published guidelines on the management of patients with lower extremity peripheral arterial disease (PAD). The guidelines were developed in an attempt to improve quality of care by translating scientific evidence into evidence-based clinical practice. The aim of this article is to highlight recommendations of the 2016 ACC/AHA guidelines and integrate additional scientific sources to create an evidence-based approach to the diagnosis and treatment of PAD.

An estimated 8.5 million Americans and more than 200 million people worldwide have PAD.[1,2] In high-income countries, more than 10% of patients older than 65 years live with PAD.[1] Because PAD is often an indication of more widespread atherosclerotic disease, these patients are at increased risk of myocardial infarction and stroke. PAD is regarded as a coronary heart disease risk equivalent.[3] The 5-year mortality rate among patients diagnosed with PAD may be as high as 33.2%, with more than 70% of deaths attributable to cardiovascular events.[4–6] The high disease burden of PAD underpins the importance of identifying and treating these patients.

Clinical Assessment of Peripheral Arterial Disease

Risk Factor Assessment

The AHA/ACC guidelines have identified four groups of patients who are at increased risk of PAD[7]:

1. Patients 65 years of age or older.
2. Patients 50 to 64 years of age with risk factors for atherosclerosis (history of smoking, diabetes

Issue Theme Peripheral Arterial Disease; Guest Editors, Paul Rochon, MD and Parag J. Patel, MD, MS, FSIR

DOI https://doi.org/10.1055/s-0038-1676453.
ISSN 0739-9529.

mellitus, hyperlipidemia, hypertension) or family history of PAD.
3. Patients younger than 50 years with diabetes mellitus and one or more additional risk factors for atherosclerosis.
4. Patients with known atherosclerotic disease in another vascular bed (coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).

The General History for Patients with Peripheral Arterial Disease

A comprehensive medical history and review of symptoms is recommended for patients at increased risk for PAD. History findings suggestive of PAD include claudication, atypical non–joint-related lower extremity symptoms, impaired walking function, ischemic rest pain, and nonhealing wounds (►**Table 1**). The ACC/AHA guidelines recommend that patients with these symptoms should undergo ankle-brachial index (ABI) testing to screen for PAD.[7]

The General Physical Exam for Patients with Peripheral Arterial Disease

Patients at increased risk for PAD should undergo a thorough vascular examination. The femoral, popliteal, dorsalis pedis, and posterior tibial artery pulses should be palpated. The femoral artery should be auscultated for bruits and the lower extremities should be inspected. Physical examination findings suggestive of PAD include abnormal pulses, audible bruits, nonhealing lower extremity wounds, lower extremity gangrene, elevation pallor, dependent rubor, delayed capillary refill, and cool extremities (►**Table 2**). Patients with one or more of these findings should undergo ABI testing.[7]

Table 1 Historical findings suggestive of PAD

History
Claudication
Atypical lower extremity symptoms
Impaired walking function
Ischemic rest pain
Nonhealing wounds

Abbreviation: PAD, peripheral arterial disease.

Table 2 Physical examination findings suggestive of PAD

Physical examination
Abnormal pulses
Audible bruits
Nonhealing lower extremity ulcer
Lower extremity gangrene
Elevation pallor or dependent rubor
Delayed capillary refill
Cool extremities

Abbreviation: PAD, peripheral arterial disease.

Clinical Presentation of Peripheral Arterial Disease

Lower extremity PAD is the condition of compromised arterial circulation of the lower extremities secondary to atherosclerotic disease. Lower extremity PAD may be classified into four distinct categories.

Asymptomatic Peripheral Arterial Disease

Asymptomatic PAD occurs when there is evidence of atherosclerotic occlusive disease in the absence of symptoms.[8] An estimated 20 to 50% of all patients with PAD are asymptomatic. Identifying patients with asymptomatic PAD is of value as these patients are at high risk for cardiovascular disease and stroke and may benefit from cardiovascular risk modification.[9]

The symptoms of PAD may be masked in patients who do not exercise sufficiently or in patients with other comorbid diseases that limit their ability to exercise.[10] Examples of such diseases include severe congestive heart failure, angina, chronic obstructive pulmonary disease, and musculoskeletal disease. Altered pain perception, as seen in diabetics with peripheral neuropathy, may also mask the symptoms of PAD. Although asymptomatic, these patients may have findings on physical exam that are suggestive of PAD. An abnormal ABI is required for the diagnosis of asymptomatic PAD.

Intermittent Claudication and Atypical Leg Pain

Intermittent claudication or simply claudication is atherosclerotic disease resulting in exertional pain or discomfort of the lower extremities. Intermittent claudication typically causes a cramping pain that is reproducible with a predictable level of exercise and is relieved with rest.[10] The discomfort may also be described as aching, numbness, weakness, or fatigue.[11] The pain typically resolves within 10 minutes of rest and does not occur at rest.[12] Claudication most commonly occurs in the calves but may also occur in the buttocks, hips, calves, or feet depending on the level of the arterial disease. Intermittent claudication may be unilateral or bilateral.[8] An estimated 10 to 35% of patients with PAD have classic claudication.[9]

Two types of atypical leg pain symptoms other than claudication have also been described in patients with PAD. The first is "leg pain on exertion and rest" and is defined as exertional leg pain that occurs with exertion but occasionally starts at rest.[13–19] This is distinct from the ischemic rest pain in chronic limb ischemia (CLI).[20] The second is called leg pain/carry on which is exertional leg pain that does not stop the patient from continuing to walk.[13–19] Patients in these leg pain categories tend to have functional impairment and rapid functional decline.[13] Forty percent to 50% of patients with PAD are estimated to have atypical leg pain.[9]

Acute Limb Ischemia

Acute limb ischemia (ALI) is a sudden decrease in lower extremity perfusion that threatens limb viability in patients who present within 2 weeks of the inciting event.[21] The classical symptoms of ALI include pain, pallor, paresthesia,

diminished or absent pulses, paralysis, and poikilothermia. ALI is considered a medical emergency, as delayed treatment may result in permanent disability, amputation, or death. Extensive tissue necrosis can occur in a period of 4 to 6 hours without treatment. ALI is most commonly caused by thrombosis of a preexisting stenotic lesion or by an embolus. It may also result from trauma, arterial dissection, thrombosis of an existing aneurysm, or occlusion of a stent or bypass graft.[22,23]

Chronic Limb Ischemia

Chronic limb ischemia, also referred to as critical limb ischemia, is a condition characterized by the presence of ischemic rest pain, nonhealing ulcers, and gangrene over a period of at least 14 days.[24] Rest pain typically occurs over the forefoot and metatarsal heads. It occurs at rest or with recumbency and is relieved by placing the foot in a dependent position.[22] For a diagnosis of CLI, signs and symptoms must be attributable to objectively proven arterial occlusive disease by ABI, toe-brachial index (TBI), $TcPO_2$, or skin perfusion pressure (SPP).[24]

The Rutherford and Fontaine Classification Systems

Two classification systems are commonly used to grade the severity of walking impairment in chronic PAD. The Rutherford classification system (►**Table 3**) assigns severity based on performance on the 5-minute treadmill test at 2 mph on a 12% incline. The Fontaine classification system assigns severity based entirely on symptoms. The Fontaine classification (►**Table 4**) is used primarily for clinical research and is not routinely used in patient care.[25]

Table 3 Rutherford classification system for PAD

Grade	Category	History
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
III	6	Major tissue loss

Abbreviation: PAD, peripheral arterial disease.

Table 4 Fontaine classification system for PAD

Stage	Clinical findings
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate to severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

Abbreviation: PAD, peripheral arterial disease.

The WIfI (Wound, Ischemia, foot Infection)

The Society for Vascular Surgery (SVS) Lower Extremity Threatened Limb Classification System, or WIfI, is a system that was designed to classify the severity of CLI in a way that more accurately reflects important clinical considerations that affect management and amputation risk. The WIfI system may also be used to stratify patients based on their risk for amputation into four stages (very low, low, moderate, and high), analogous to the tumor-node-metastasis (TNM) staging system for cancer (►**Table 5**).[22,26] Additionally, the WIfI system may be used to estimate the likelihood that a patient will benefit from revascularization (►**Table 6**).[26,27]

Differential Diagnosis of Lower Extremity Pain

There are several disease processes that can cause limb pain and mimic the symptoms of PAD. Neurologic, musculoskeletal, and other vascular causes must be considered in the differential diagnosis.

Neurological Causes of Limb Pain

Neurogenic claudication, also known as spinal claudication or pseudoclaudication, is common in patients with spinal stenosis. Narrowing of the spinal canal causes impingement or irritation of the nerves which results in lower extremity pain or weakness. Neurogenic claudication typically occurs with extension of the spine and is relieved with flexion of the spine. Patients may indicate that the pain is improved when leaning forward to use a shopping cart. The pain may also be relieved when sitting or lying supine.[9,21]

Lower extremity pain from radiculopathy is pain due to nerve root compression and occurs along the distribution of a particular nerve root. It is often described as sharp in character unlike claudication and may be present at rest or induced by sitting, standing, or walking. This pain is often positional.[21] The straight leg raise maneuver may be useful in diagnosis.

Musculoskeletal Causes of Limb Pain

Osteoarthritis may cause lower extremity pain that occurs with exertion. However, unlike PAD, exertional pain from osteoarthritis is not predictable and occurs with varying levels of exercise. Osteoarthritis is relieved by discontinuation of weight-bearing activity and is not relieved as quickly with rest in comparison to claudication.[9,21]

A Baker's cyst or popliteal cyst is a fluid collection (synovial cyst) behind the knee that is often asymptomatic but may cause swelling and pain behind the knee. The pain is typically constant and present both at rest and with exercise.[21] Physical exam, ultrasound (US) of the popliteal fossa, or magnetic resonance imaging of the knee will usually clinch the diagnosis.

Chronic exertional compartment syndrome is an uncommon condition that causes lower extremity pain after moderate-to-high intensity exercise in runners and elite athletes. The pain typically subsides very slowly with rest. Patients often do not have risk factors associated with PAD.[9,21]

Table 5 Estimated risk of amputation at 1 year for each combination

	Ischemia-0				Ischemia-1				Ischemia-2				Ischemia-3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Clinical stage I (very low—VL).
Clinical stage II (low—L).
Clinical stage III (moderate—M).
Clinical stage IV (high—H).
Source: Reprinted with permission from Elsevier (Mills J, Conte M, Armstrong D, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014;59(01)).[27]

Vascular Causes of Limb Pain

Venous claudication is a rare disease that causes lower extremity pain that is provoked by walking and relieved with prolonged rest. Chronic venous disease is associated with limb swelling, varicosities, and increased pain with limb dependency.[9,21]

Thromboangiitis obliterans or Buerger's disease is an inflammatory disease of the small and medium vessels of the hands and feet. The disease may cause claudication, rest pain, ulceration, or gangrene. It is associated with smokers and these patients are typically younger than patients with claudication due to PAD.[9]

Popliteal artery entrapment syndrome occurs in patients with anomalous insertion of the muscles or tendons within the popliteal fossa. Contraction of the muscles during exercise may compress the popliteal artery, causing claudication in a young patient without PAD risk factors.

Types of Ulcers

It is important to be able to distinguish between the different types of ulcers that can be seen in patients with vascular disease.

Arterial Ulcer

Arterial ulcers typically occur over the distal toes, lateral ankle, or pressure points of the foot. The ulcer is described as having a "punched-out" appearance and may be pale or necrotic. The affected extremity will usually have other signs of ischemia and the patient may have dependent rubor or elevation pallor on exam. Arterial ulcers tend to be more painful than other ulcers.[9]

Venous Ulcer

Venous ulcers occur over the posterior calf or medial and lateral malleoli. The ulcers may be large and circumferential. The ulcer is often described as having a red or pink base covered with yellow fibrinous tissue. The limb usually has other signs of chronic venous disease. Pain is usually mild but may be severe in some cases.[9]

Neuropathic Ulcer

Neuropathic ulcers result from peripheral neuropathy and are more common in patients with diabetes. They are found at pressure points including the plantar surface of the foot and at the heel. The ulcer may have a "punched-out" appearance with a red base and a calloused border. Touch, pain,

Table 6 Estimated likelihood of benefit/or requirement for revascularization, assuming infection can be controlled first

	Ischemia-0				Ischemia-1				Ischemia-2				Ischemia-3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Clinical stage I (very low—VL).
Clinical stage II (low—L).
Clinical stage III (moderate—M).
Clinical stage IV (high—H).
Clinical stage V would signify and unsalvageable foot.
Source: Reprinted with permission from Elsevier (Mills J, Conte M, Armstrong D, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014;59(01)).[27]

temperature, and vibratory sensation are often diminished in the foot and reflexes may be absent. The ulcer is usually painless secondary to destruction of the sensory nerves and damage to the motor nerves may cause an imbalance in the opposing forces between the flexor and extensor muscles which can result in deformity of the foot.[9]

Diagnostic Testing for Lower Extremity PAD

Resting Ankle-Brachial Index

The ABI is a diagnostic test used to establish the diagnosis of PAD. First, the systolic blood pressure from both arms and from both the dorsalis pedis and posterior tibial arteries are obtained after the patient has been at rest in the supine position for 10 minutes. The ABI is then calculated by dividing the highest systolic blood pressure in the foot by the highest systolic blood pressure in the arms.[28] An abnormal ABI (<0.90) confirms the diagnosis of PAD (►**Table 7**).

The AHA/ACC guidelines recommend measuring resting ABI, with or without segmental pressures and waveforms, in patients with features of PAD on history or physical exam. The guidelines also indicate that it is reasonable to measure a resting ABI in patients at increased risk for PAD but without features of PAD on history or physical examination. Patients who are not at increased risk for PAD and without features of PAD on history or physical exam should not undergo ABI measurement.[7]

Exercise Treadmill Ankle-Brachial Index

Patients with exertional non–joint-related lower-extremity symptoms but normal or borderline resting ABI (0.90–1.40) should undergo exercise treadmill ABI testing.[7] Exercise testing should occur in a vascular laboratory using a standardized protocol and a motorized treadmill to ensure reproducibility of results.[9] An abnormal treadmill ABI is defined as a decrease in ABI by 20% or greater after exercise, and is diagnostic for PAD. A normal exercise treadmill ABI is defined as no change in ABI or increased ABI after exercise.[8] If treadmill testing is not available, the pedal plantar flexion ABI test is an acceptable alternative with results that correlate well with treadmill testing.[29] In patients with known PAD, it may be reasonable to perform an exercise treadmill ABI test to assess functional status, individualize exercise programs, and monitor response to treatment.[7]

Toe-Brachial Index

The TBI is analogous to the ABI. It is the ratio of the systolic blood pressure of the great toe to the higher of the two arm/brachial artery pressures. TBI less than 0.70 is classified as abnormal. An abnormal TBI is diagnostic of PAD.[7]

Table 7 Resting ankle-brachial index

Abnormal	≤0.90
Borderline	0.91–0.99
Normal	1.00–1.40
Noncompressible	>1.40

In patients with suspected PAD and an ABI which is greater than 1.4 due to noncompressible arteries, TBI should be measured to confirm the diagnosis of PAD (ACC). An abnormally elevated ABI is often due to calcification of the arteries which causes them to become noncompressible. This type of calcification is seen in patients with diabetes mellitus and end-stage renal disease.[30]

Absolute toe pressure is often used to predict wound healing, with greater pressures indicating a higher likelihood for successful healing. An absolute toe pressure above 30 mm Hg is generally favorable for wound healing.[31] However, in diabetic patients, an absolute toe pressure above 45 to 55 mm Hg may be necessary for adequate healing.[32,33]

Segmental Pressure Measurement

Once PAD is confirmed with either an abnormal resting ABI or postexercise ABI, the location and extent of disease can be determined with the use of segmental pressures. The measurement of segmental pressures involves the noninvasive measurement of blood pressure at various anatomical locations in the lower extremity.[30]

Pulse Volume Recording Waveforms, Transcutaneous Oxygen Measurement, and Skin Perfusion Pressure

Obtaining pulse volume recording (PVR) waveforms is useful in identifying the level of disease. PVR waveforms are obtained noninvasively and the appearance of the waveform can be used to determine the severity of disease at each level in the leg. In a normal waveform, there is a steep systolic upstroke with a sharp peak followed by a downstroke with a prominent dicrotic notch. In mild to moderate PAD, there is loss of the systolic peak amplitude, loss of dicrotic notch, and outward bowing of the downstroke. With severe disease, the amplitude of the systolic peak is severely diminished.[30]

The transcutaneous oxygen measurement ($TcPO_2$) and skin perfusion pressure (SPP) are two noninvasive studies that provide information regarding tissue perfusion. Normal $TcPO_2$ in healthy patients at the level of the foot is greater than 50 mm Hg.[34] A $TcPO_2$ greater than 40 mm Hg generally suggests that a wound is likely to heal, although higher oxygen tension may be required for healing a foot ulcer in a diabetic patient. A $TcPO_2$ of less than 20 mm Hg indicates severe ischemia and low probability of wound healing. These patients will likely need revascularization for healing to occur.[30,35] A SPP of less than 30 mm Hg was shown to have 85% sensitivity and 73% specificity in the diagnosis of CLI.[36] A SPP of more than 30 to 50 mm Hg is associated with increased probability of wound healing.[37]

Imaging for Anatomical Assessment

Imaging is not recommended in patients with asymptomatic PAD or in patients who are not candidates for revascularization.[7] Anatomical assessment in these patients is unlikely to change management.

They are needed, however, in patients with symptomatic PAD who are being considered for revascularization. Duplex US, computed tomography angiography (CTA), and magnetic

resonance angiography (MRA) are useful to determine the anatomical location and severity of disease. Information from these studies allows for preprocedural planning whether it should endovascular or surgical.[7] Duplex US has lower spatial resolution but is safe and inexpensive. CTA offers better spatial resolution, but arterial calcification can limit interpretation especially below the knee and there is a risk of contrast-induced nephropathy and anaphylaxis due to needed iodinated contrast.[37,38] CTA also exposes a patient to ionizing radiation which may not be ideal. MRA offers superior spatial resolution and images are not degraded by vessel calcification. Long scanning times may not be ideal in all patients. And gadolinium contrast agents cannot be used in patients with advanced renal disease due to the risk of nephrogenic systemic sclerosis.[39]

In patients with CLI who are being considered for revascularization, digital subtraction angiography (DSA) is indicated. It offers superior detail of arterial anatomy and collateral vessels which allows for true treatment planning for these patients who need timely revascularization to preserve tissue viability. For this reason, DSA with concomitant endovascular revascularization is often performed without prior noninvasive imaging studies so as to avoid delay or unnecessary risk associated with other imaging modalities.[7]

Medical Therapy for Patient with Peripheral Arterial Disease

Because PAD is considered to be a coronary heart disease risk equivalent, the goal of medical therapy is to reduce cardiovascular risk and improve functional status through risk modification. Risk modification can be achieved with smoking cessation, by controlling high blood pressure, high cholesterol, diabetes, and optimizing weight. Antiplatelet therapy and cilostazol are also often needed.

Smoking Cessation

Patients with PAD who use tobacco should be advised at every visit to quit. Patients interested in quitting should be assisted in developing a plan that includes pharmacotherapy and/or referral to a smoking cessation program. Varenicline, bupropion, and nicotine replacement therapy have shown to be beneficial in smoking cessation.[7] Continued smoking limits improvement that might otherwise be gained from exercise and pharmacologic therapy.[40]

Antihypertensive Therapy

Antihypertensive therapy should be prescribed to patients with PAD and hypertension.[7] Studies have shown that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) significantly reduce cardiovascular events in patients with PAD.[41,42] For this reason, it is reasonable to consider ACEIs and ARBs as first-line antihypertensive therapy in patients with PAD.[43] Diuretics, β-blockers, and calcium channel blockers are all suitable alternative antihypertensive medications. The choice of antihypertensive medication is often guided by patient comorbidities.[44] Blood pressure management should follow the most recent multisocietal guidelines.[45]

Statin Therapy

Statin therapy should be prescribed to all patients with PAD.[7] Observational studies and randomized clinical trials have demonstrated that statin therapy reduces cardiovascular events and mortality in patients with PAD.[43,46–48] Statin therapy should follow the most recent ACC/AHA guidelines for cholesterol management.[49]

Glycemic Control

Management of diabetes mellitus in patients with PAD should be coordinated between members of the healthcare team (AHA/ACC). Vascular specialists should maintain regular communication with primary care physicians and endocrinologists to facilitate care.[7] Diet, weight management, and pharmacotherapy for glycemic control are paramount in the management of patients with diabetes. Observational studies have demonstrated that optimized glycemic control is associated with lower rates of amputation and improved patency after revascularization in patients with CLI.[50,51]

Antiplatelet Therapy

Long-term single-antiplatelet therapy with aspirin alone (75–325 mg/day) or clopidogrel alone (75 mg/day) is recommended for patients with symptomatic PAD.[7] Meta-analysis performed by the Antithrombotic Trialists' Collaboration demonstrated a significant reduction in cardiovascular events and vascular death among patients with symptomatic PAD on antiplatelet therapy.[52] A second meta-analysis of trials evaluating aspirin alone or in combination with dipyridamole found a statistically significant reduction in nonfatal strokes with aspirin compared with placebo. Cardiovascular events and vascular death in patients with PAD were also reduced, although the result was not statistically significant.[53] The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed that clopidogrel was superior to aspirin in reducing cardiovascular risk and bleeding events in those with symptomatic atherosclerotic disease, including a subset of patients with symptomatic PAD.[53,54]

Single-antiplatelet therapy is reasonable in patients with asymptomatic PAD (ABI < 0.90). There is no evidence that antiplatelet therapy improves outcomes in these patients. However, because asymptomatic PAD is associated with increased cardiovascular risk, it is possible that antiplatelet therapy could benefit this group of patients.[7]

Dual-antiplatelet therapy in patients with symptomatic PAD after lower extremity revascularization to reduce limb-related adverse events is also a reasonable choice.[7] Two small randomized controlled trials demonstrated that dual-antiplatelet therapy resulted in a reduction in the need for repeat revascularization procedures in patients with PAD who underwent endovascular intervention.[55,56] Another RCT showed a decrease in limb-related adverse events in patients on dual-antiplatelet therapy who underwent below-knee bypass prosthetic grafting.[57]

Cilostazol and Pentoxifylline

Cilostazol, a phosphodiesterase 3 inhibitor, is recommended for the symptomatic treatment of patients with claudication.[7] This recommendation is based on a Cochrane review of 15 randomized controlled trials that found patients with intermittent claudication on cilostazol experienced improvement in symptoms with no change in cardiovascular deaths or quality of life as compared with placebo.[58] Pentoxifylline, another phosphodiesterase inhibitor, is not recommended for the treatment of PAD under current guidelines.[7]

Structured Exercise Therapy

Major multisocietal guidelines recommend supervised exercise as an effective method to improve quality of life, functional status, and provide symptomatic treatment in patients with claudication.[7,43] Regular physical activity reduces cardiovascular risk by improving lipid profile, reducing blood pressure, and facilitating weight loss. Randomized clinical trials have demonstrated that supervised exercise programs produce benefits comparable to intervention with an excellent safety profile (►**Table 8**).[59–62]

Minimizing Tissue Loss in Patients with Peripheral Arterial Disease

Proper wound care for the patient with an active ulcer or gangrene of the lower extremity involves offloading, debridement, perfusion assessment, and evaluation of arterial patency. Debridement is of utmost importance for wound healing and for the prevention of infection.[62] Sharp debridement with a scalpel is preferred over other methods. Debridement should remove all tissue debris and necrotic material. Nonadherent dressings should be applied to the wound at all times. Occlusive dressings may decrease risk of infection.[63] Dressings should be applied so as to prevent excessive pressure, as this may exacerbate ischemia. Assessment of local perfusion may help guide decision making and treatment. Perfusion may be measured using TBI with waveforms, $TcPO_2$, or SPP as described previously. In patients with inadequate perfusion for healing, intervention is necessary. Prompt recognition and treatment of infection is essential to prevent amputation. In patients with suspected foot infection, it may be beneficial to refer the patient to an interdisciplinary care team for management.[7]

Guidelines recommend that physicians educate patients with PAD and diabetes mellitus about healthy foot behaviors such as daily inspection of feet and wearing proper shoes and socks.[7] Footwear should protect the feet from pressure and shearing forces. The shoes must be large enough to protect the margins of the feet. Sandals or tight fitting shoes may delay wound healing. Footwear should fasten with a lace or strip high on the foot.[63] Biannual foot inspection by a physician may be of benefit in patients with PAD and diabetes mellitus.[7]

Table 8 Definition of supervised exercise programs for PAD

Program takes place in a hospital or outpatient facility
Program can be standalone or port of a cardiac rehabilitation program
Program is directly supervised by a qualified health care provider
Program uses intermittent walking as the treatment modality
Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest
Warm-up and cool-down periods precede and follow each session of walking
Training is performed for a minimum of 30–45 min per session; sessions are performed at least 3 times per week for a minimum of 12 wk

Abbreviation: PAD, peripheral arterial disease.
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Revascularization for Claudication

Patients with claudication should initially be managed with risk factor modification, pharmacotherapy, and exercise therapy as described previously. The effectiveness of treatment should be assessed with periodic reevaluation of symptoms. Lifestyle-limiting claudication is defined by the patient rather than by testing, and may include limitation of daily recreational or work-related activities.[7] In those patients with lifestyle-limiting claudication despite guideline-directed management and therapy, endovascular or surgical revascularization can be effective.

Other considerations include extent/complexity of atherosclerotic disease, comorbidities, and the natural history of the disease. The extent of disease should be favorable for intervention with limited risk and high likelihood of initial and long-term success. The natural history of the PAD should be considered as well.[21,64] It has been estimated that less than 15% of patients with claudication will progress to CLI within 5 years.[65–68] Thus, revascularization should not be performed to prevent progression to CLI.[7]

Complications from intervention can occur and may increase the risk for limb-threatening ischemia.[69] Therefore, the risks and benefits of intervention should be discussed at length with the patient.

Management of Acute Limb Ischemia

Classification of Acute Limb Ischemia

Acute limb ischemia is a medical emergency and must be diagnosed and treated rapidly. Extensive tissue necrosis can occur within 4 to 6 hours if untreated. Patients with suspected ALI should be evaluated emergently by a physician with adequate training such as an interventional radiologist, interventional cardiologist, or vascular surgeon.[7] Assessment for limb viability determines the course of management. The limb is assessed for sensory and motor function, as

well as arterial and venous flow with a handheld continuous-wave Doppler. The degree of limb threat is categorized based on the findings (►**Table 9**).[7]

Category I patients have viable limbs that are not immediately threatened. Revascularization should be performed within 6 to 24 hours on an urgent basis.[7,70]

Category II patients are either marginally threatened (IIa) or immediately threatened (IIb). Revascularization should be performed emergently within 6 hours.

Category III patients have irreversible limb damage and therefore amputation should be performed as the primary treatment. Attempts at limb salvage are unlikely to be successful, and the risks associated with reconstruction outweigh the potential benefit.[7,71,72]

Anticoagulation

Heparin should be administered immediately to all patients with ALI, unless contraindicated. Direct thrombin inhibitors may be given to patients with a history of heparin-induced thrombocytopenia (HIT).[7]

Choice of Revascularization

Options for revascularization include catheter-based techniques including thrombolysis as well as surgery. The method of revascularization depends on the available facility and physician's experience. Meta-analysis and randomized clinical trials have found similar limb salvage rates between the two approaches, with better survival for patients who undergo catheter-based therapy.[7,73–80] Patients with significant comorbidities and perioperative risk are better suited for endovascular treatment.

Compartment Syndrome

Compartment syndrome may occur in patients with ALI who have undergone revascularization. Reperfusion to ischemic tissues may cause edema and increase the intracompartmental pressure of the limb, which in turn may result in decreased perfusion. Compartment syndrome should be suspected in patients with a painful, tense muscle compartment. The decision to perform a fasciotomy is based on history, physical exam findings, and/or compartment pressure measurements.[81,82]

Determination of Etiology

The physician should always make an effort to determine the etiology of ALI, as it may affect treatment and prognosis. ALI may be due to an embolic event related to atrial fibrillation, left ventricular thrombus, or endocarditis. Deep vein thrombosis may also result in paradoxical arterial embolism in patients with a patent foramen ovale. Thrombosis of a popliteal artery aneurysm, bypass graft, or arterial stent should also be considered in the appropriate setting. Trauma and aortic dissection are other causes. History should be directed toward identifying prior myocardial infarction, heart failure or left ventricular dysfunction, hypercoagulable state, and family history of thrombosis. Workup may include cardiac monitoring or electrocardiogram to detect atrial fibrillation or myocardial infarction. Cardiac echo may also be performed to identify valvular vegetations, intramural thrombus, or intracardiac shunts when clinically indicated. Determination of the etiology of ALI should not delay treatment.[7,83]

Management of Chronic Limb Ischemia

The natural history of CLI is defined by high morbidity and mortality. One systematic review of 13 studies found that in patients with CLI who did not receive revascularization, all-cause mortality was 22% and major amputation rate was 22% at a median follow-up of 12 months.[84] For this reason, revascularization is of utmost important for treatment of CLI.[62] Performing revascularization for patients with CLI for limb salvage is a class I recommendation under all professional guidelines (ACC/AHA, ECS).[7,21,43] All patients with CLI

Table 9 Categories of acute limb ischemia

Category		Arterial Doppler signal	Venous Doppler signal	Motor function	Sensory function	Capillary refill	Action
I	Viable	Audible	Audible	Normal	Normal	Intact	Urgent revascularization[1] and anticoagulation[2]
IIa	Marginally threatened	Inaudible	Audible	Intact; no muscle weakness	Sensory loss limited to toes if present	Slow-to-intact	Emergent revascularization[3] and anticoagulation[2]
IIb	Immediately threatened	Inaudible	Audible	Impaired; mild-to-moderate muscle weakness	Sensory loss more than toes and with rest pain	Slow-to-absent	Emergent revascularization[3] and anticoagulation[2]
III	Irreversible	Inaudible	Inaudible	Complete loss of motor function	Complete sensory loss	Absent	Primary amputation

Source: Reprinted with permission from Elsevier (Gerhard-Herman M, Gornik H, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease. JACC 2017;69(11):1482).[7]

should undergo an evaluation to assess for the feasibility of revascularization prior to amputation.[7]

The ACC/AHA guidelines outline factors that guide decision making in regard to choosing the most appropriate intervention.[7] Evaluation of the extent of disease, anatomic location, and patient comorbidities are useful in choosing the most appropriate therapy. In patients with increased perioperative surgical risk, an endovascular-first approach should be used regardless of anatomy.[7]

Choice of Conduit for Surgical Bypass

Use of an autogenous vein is recommended for surgical bypass to the popliteal or infrapopliteal arteries. Multiple large randomized controlled trials support the use of reversed or in situ veins for bypass above the knee.[85–88] Single-center trials demonstrate the effectiveness of autogenous vein use in infrapopliteal vessels. A prosthetic graft can be used in patients with CLI who failed endovascular revascularization when no autogenous vein is available.[89–91]

Revascularization for Ischemic Rest Pain

In patients with ischemic rest pain secondary to multilevel disease, it can be beneficial to treat in-flow lesions first when using endovascular or surgical procedures.[7] In-flow lesions are treated first to see if symptoms resolve which is commonly the case. If symptoms persist, then the out-flow lesions are treated at a later date.[92–96]

Revascularization for Nonhealing Wounds and Gangrene

In patients with nonhealing wounds or gangrene, revascularization procedures, whether endovascular or surgical, should be performed to establish in-line blood flow to the foot.[97–101]

Angiosome-Directed Therapy

The angiosome concept was developed to characterize the vascular anatomy of the human body (►**Fig. 1**). The angiosome concept separates the body into three-dimensional sections or angiosomes. Each three-dimensional angiosome is directly supplied by a specific artery. Angiosomes are also indirectly supplied by collateral vessels which can supply blood flow in the absence of direct blood supply.[62,102] Angiosome-directed treatment for nonhealing ulcers involves treatment of the artery that directly supplies the angiosome in which the ulcer is located. Angiosome-directed therapy may result in increased contrast exposure, procedural times, and procedural complexity. While the effectiveness of angiosome-directed therapy is unclear, meta-analyses have found that wound healing and limb salvage are improved with angiosome-guided therapy. However, the evidence is not robust.[7,103,104]

Longitudinal Follow-up

All patients with PAD should be evaluated periodically as an outpatient. Clinic visits should emphasize cardiovascular risk factor reduction to reduce risk of myocardial infarction, stroke, and vascular death. Comprehensive risk factor modification should include smoking cessation, pharmacologic therapy, and exercise as described previously. Patients should be assessed for compliance to therapy and for interval change in functional status at each follow-up appointment.[7]

Patients who have undergone endovascular or surgical revascularization should be assessed for any change in lower extremity symptoms or functional status at periodic intervals. Pulse examination and ABI measurement should be performed at a minimum at 3, 6, and 12 months and annually

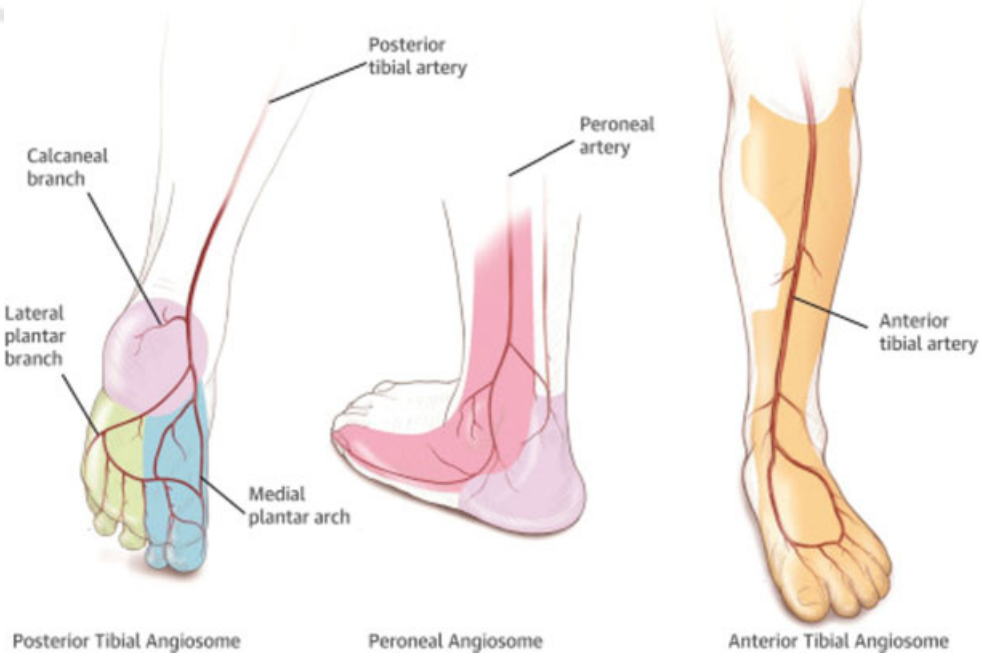

Fig. 1 The infrapopliteal angiosomes. (Reprinted with permission from Elsevier. Shishehbor et al.[62])

thereafter. A change in ABI of 0.15 or greater is regarded as clinically significant.[7,105]

Duplex US may be reasonable for surveillance in patients who have undergone endovascular intervention. Diagnostic criteria have been developed to diagnose restenosis according to the location and specific type of intervention. However, there are limited data comparing surveillance with duplex US to surveillance with ABI and clinical evaluation in this setting.[7,106–108]

Duplex US can be beneficial for routine surveillance in patients who have undergone infrainguinal bypass with autogenous vein graft. The patient may be scheduled for follow-up at a minimum at 4 to 6 weeks, 6 months, and 12 months in the first year and annually thereafter. High-grade stenosis is indicated by a peak systolic velocity above 300 cm/s and peak systolic velocity ratio across the stenosis greater than 3.5. Impending bypass graft failure is suggested by a peak systolic velocity of less than 40 cm/s. Studies comparing surveillance with duplex US to clinical surveillance with ABI have yielded mixed results in terms of patency and clinical outcomes.[7] Studies evaluating the use of duplex surveillance for prosthetic infrainguinal bypass grafts have not shown consistent benefit.[7,109–112]

Conclusion

Peripheral artery disease is growing in prevalence worldwide with devastating consequences such as myocardial infarction, stroke, amputation, and vascular death. A diverse group of healthcare providers are involved in the care of individuals with PAD. Therefore, all providers require familiarity with this disease entity. Hopefully, this article and its content will help the reader gain an understanding of the risk factors, diagnosis, treatment, and follow-up of patients with PAD.

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