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How To Assess a Claudication and When To Intervene

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Abstract

Purpose of the Review Peripheral artery disease (PAD) affects close to 200 million people worldwide. Claudication is the most common presenting symptom for patients with PAD. This review summarizes the current diagnostic and treatment options for patients with claudication. Comprehensive history and physical examination in order to differentiate between claudication secondary to vascular disease vs. neurogenic causes is paramount for initial diagnosis. Ankle-brachial index is the most commonly used test for screening and diagnostic purposes. Treatment consists of four different approaches, which are best utilized in combination: non-pharmacological treatment for claudication improvement, pharmacological treatment for claudication improvement, pharmacological treatment for secondary risk reduction, and interventional treatment for claudication improvement.

Recent Findings Cilostazol is the only Food and Drug Administration (FDA)-approved agent for symptomatic treatment of claudication. Supervised exercise programs provide the maximum benefit for claudication improvement, but home-based exercise programs are an alternative. High-intensity statins and an antiplatelet agent should be prescribed to all patients with PAD. Angiotensin-converting-enzyme inhibitors can provide additional risk reduction, especially in patients with diabetes or hypertension. Rivaroxaban of low dosage (2.5 mg twice daily) in combination with aspirin further decreases cardiovascular risk, but this reduction comes at the cost of higher bleeding risk.

Summary Peripheral artery disease (PAD) is a form of atherosclerotic disease that affects hundreds of millions of people worldwide—one of its most common manifestations is intermittent claudication (IC), which results from insufficient blood flow to meet the metabolic demands of an affected extremity. This paper reviews the current literature regarding the workup, diagnosis, diagnostic modalities, treatment options, and management of intermittent claudication.

Keywords Claudication · Peripheral artery disease · Medical management · Peripheral interventions

Introduction

More than 200 million people worldwide and at least eight million in the USA have peripheral artery disease (PAD) [1, 2]. In high-risk populations, the prevalence can be as high as 30% [3]. PAD shares common risk factors with coronary artery disease (CAD), including family history, hypertension (HTN), diabetes mellitus (DM), smoking, and hyperlipidemia (HLD) [1, 2]. Patients with PAD have a 3- to 6-fold increased risk of cardiovascular events, while up to 20% of them will die in a 5-year period [4–6]. The grim prognosis of PAD patients may be associated with the fact that only 30% of PAD patients have typical intermittent claudication symptoms. As a result, a significant percentage remains unrecognized and undertreated [6]. According to the data from the observational NHANES (National Health and Nutrition Examination Survey), 69.5% of PAD patients were not taking statins and 64.2% were not taking aspirin, while use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers was also dramatically low [5]. Interestingly, and in contrast to other fields of cardiovascular medicine, our knowledge for claudication and PAD treatment is largely driven by observational

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data. This is because of the heterogeneity in disease location and also lesion characteristics which makes the PAD population quite heterogeneous and RCTs difficult to be conducted.

History and Physical Examination

History

As the etiology of intermittent claudication can be neurogenic, vascular, or both, obtaining a thorough and comprehensive history is especially important in differentiating between different causes [7]. PAD is the most common cause of vascular claudication and results from inadequate blood flow to meet the metabolic demands of the lower extremity musculature, which is usually secondary to atherosclerotic vascular disease [8, 9]. Important historical features suggestive of a vascular etiology include pain that is relieved by standing alone (even without sitting) and symptoms located mainly below the knee. On the other hand, pain exacerbation even with standing and relieved with sitting and pain located above the knees may suggest a neurogenic etiology. While these symptoms alone often have limited accuracy to differentiate, studies have shown that their combination increases exponentially the diagnostic accuracy for vascular vs. neurogenic causes [7].

Once a vascular etiology is suspected, further history should focus on cardiovascular history and comorbidities detection [10]. The exact pain-free distance that patients can walk is important for classification in different Rutherford classes (Table 1) [11]. Careful history is important for assessment of functional status and quality of life as well. PAD has been shown to worsen the functional status and health related quality of life (HRQOL), especially in elderly patients [12]. HRQOL in PAD can be assessed with either general HRQOL questionnaires or questionnaires specific for HRQOL in PAD populations [13–15].

Physical Examination

Physical examination in the workup of patients presenting with intermittent claudication involves a comprehensive vascular examination as well as focused cardiac, abdominal, and skin examinations. The vascular examination is the most important component as it helps identify both the extent and the severity of PAD [16]. Peripheral pulses of the entire lower extremity arterial system should be assessed, including bilateral femoral, popliteal, posterior tibial, and dorsalis pedis pulses [16]. These pulses should be compared with the opposite side and be graded as normal (2+), diminished (1+), or non-palpable. Physical exam usually is accompanied by an ankle-brachial index (ABI) measurement, for which a value of < 0.9 is considered abnormal [4]. A focused abdominal examination should include abdominal palpation for any abdominal masses concerning for abdominal aortic aneurysm or neoplasm, as well as auscultation for the presence of any bruits concerning for mesenteric or renal arterial stenosis [17]. The skin examination should involve thorough inspection of the limbs with particular attention to the skin color, skin temperature, hair growth pattern, tissue loss, ulcer formation, and nail features [17].

ABI

Given that only 10% of patients with PAD present with typical symptoms of intermittent claudication, early diagnosis in the general population requires a low threshold for testing. The most recent 2016 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines suggest that patients at increased risk of PAD—those > 65 years, patients with risk factors for atherosclerosis such as DM, smoking history, HLD, HTN, or family history of PAD—should be screened with a resting ABI (class IIa recommendation) [18••]. The resting ABI has more than 90% sensitivity and specificity to establish or rule out a diagnosis of PAD [19], and ABI may be also cost-effective for asymptomatic PAD screening as a preliminary analysis [19]. A normal value for ABI ranges from 0.9 to 1.3, while an abnormal value is any number under 0.9, with 0.7 to 0.9 suggestive of mild PAD, 0.4 to 0.69 suggestive of moderate PAD, and < 0.4 suggestive of severe PAD. It is generally accepted that any value of ABI <

Table 1 Fontaine and Rutherford classification systems for grading severity of PAD

Fontaine classification		Rutherford classification		
Stage	Clinical features	Grade	Category	Clinical features
A	Asymptomatic	0	0	Asymptomatic
IIA	Mild claudication	I	1	Mild claudication
IIB	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Rest pain	II	4	Rest pain
IV	Ulcers or gangrene	III	5	Minor tissue loss
		IV	6	Ulcers or gangrene

0.9 meets the criterion of PAD diagnosis and should be followed by prompt referral to a vascular specialist.

It is important to note, however, that ABI values may not necessarily reflect a patient's functional status [20]. Recently, the *Patient-Centered Outcomes Related to Treatment Practices in PAD: Investigating Trajectories* (PORTRAIT) trial studied the correlation of ABI in 1251 patients with claudication with PAD-specific health status as measured by the Peripheral Artery Questionnaire (PAQ). The investigators found that although the ABI was a useful quantitative measure in assessing claudication, it alone was a poor predictor of a patient's functional status, since no correlation was found between ABI and PAQ quality of life and PAQ symptoms score.

After an ABI is obtained, additional supplemental physiological testing studies may be indicated based on the clinical presentation, which include post-exercise ABI testing, measurement of toe-brachial index (TBI), skin perfusion pressure, or transcutaneous oxygen pressure [18••]. In particular, the post-exercise ABI is especially useful in that it may help to differentiate exertional from non-exertional causes of leg pain [21]. Recent studies have also demonstrated that the post-exercise ABI may offer superior prognostic and clinical value in patients with otherwise normal or abnormal resting ABI values, for example in predicting cardiovascular outcomes in asymptomatic patients with normal resting ABIs [21].

Duplex Ultrasound

Other commonly used non-invasive modalities include arterial duplex ultrasound (DUS), computerized tomography (CT), and magnetic resonance imaging (MRI). All of these modalities are important adjuncts in the management and workup of PAD, and each of them has unique benefits and/or limitations. DUS is a non-invasive option that offers the added benefit of localizing the exact level of disease and quantifying the degree of stenosis in the lower extremities with sensitivity and specificity ranging from 80–95% to 89–99% respectively [22]. DUS offers cost-effectiveness and avoidance of radiation exposure or kidney injury when compared to other more advanced imaging modalities such as CT angiography (CTA), MR angiography (MRA), and angiography [22]. Currently, AHA/ACC guidelines give a class I, level of evidence A recommendation for Duplex US to provide an accurate assessment of lower extremity PAD location/severity and for longitudinal surveillance of vessels and flow dynamics following revascularization [18].

CTA/MRA/Angiography

Advanced imaging techniques, including CTA, MRA, and angiography, though noted to have superior diagnostic accuracy than DUS [23], are typically reserved for instances in which revascularization is planned [23]. CTA offers a plethora of information and can characterize many aspects of the vasculature including lesion number, lesion length, stenosis diameter/morphology, and status of distal runoff vessels [24]. CTA is a highly accurate imaging modality, with meta-analysis showing a pooled sensitivity and specificity higher than 95% for detection of more than 50% stenosis or occlusion [25].

MRA also offers excellent diagnostic accuracy through visualization of the arterial tree, tissue characterization, and vessel calcification [26]. MRA also confers the added benefit of not requiring radiation exposure unlike CTA; however, it does have limitations that include the risk of nephrogenic systemic fibrosis related to the contrast material [26]. Similar to CTA, meta-analyses have demonstrated excellent diagnostic accuracy of MRA in detecting lesions of > 50% stenosis or occlusion in patients with claudication, with pooled sensitivity and specificity rates at 95% and 96% respectively [27].

The most recent AHA/ACC 2016 guidelines give a strong recommendation (class I, LOE A) for both MRA and CTA as means for initial angiographic localization for patients with symptomatic PAD [18••]. The final advanced imaging modality, angiography, is widely considered to be the gold standard test in the assessment of PAD [28], as it can directly visualize the circulation pathway and assess for arterial anatomy, stenosis, and calcification [28]. In addition to its diagnostic accuracy, angiography offers the added benefit of allowing for therapeutic intervention at the same time, as endovascular revascularization can be performed if necessary during the test. Limitations of angiography are related to its invasive nature and include the risk of vessel perforation, dissection, hematoma, embolization, and contrast induced kidney injury [29].

Medical Therapy for Claudication Symptoms

Unfortunately, the pharmaceutical options for meaningful improvement in intermittent claudication are limited (Table 2). Cilostazol, pentoxifylline, chelation agents, and naftidrofuryl have shown some benefit in trials, but only cilostazol and pentoxifylline are FDA approved, while cilostazol is the most widely used and well-studied medical therapy option [18••]. Cilostazol is a selective phosphodiesterase inhibitor that accumulates intracellularly, leading to arterial smooth muscle dilatation, increased nitric oxide signaling, and, to a lesser extent, decreased platelet aggregation thereby promoting vasodilation and ultimately improving blood flow through stenotic arteries [30]. Limitations associated with cilostazol use include low adherence because of adverse effects including headache, palpitations, and diarrhea [31]. In the 2016 ACC/AHA guidelines, cilostazol was given a class 1 strength of recommendation (level of evidence: A) for improving symptoms and increasing walking distance in patients with claudication [18••]. Cilostazol has been shown to improve walking performance by 25–40% [32]. A Cochrane review in 2014 studied 15 RCTs

Table 2 Summary of the American Heart Association/American College of Cardiology recommendations for patients with peripheral artery disease

Category	Recommendation(s)	Strength of recommendation	Level of evidence
Smoking cessation	1. Patients who smoke cigarettes or use tobacco should be advised to quit at every visit.	Class I	A
	2. Patients who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy and/ or referral to a smoking cessation program.		
Glycemic control	1. PAD patients with diabetes mellitus should have their care managed and coordinated between members of the healthcare team.	Class I	C-EO
	2. Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.	Class IIa	B-NR
Tissue loss	1. Patients with PAD and diabetes mellitus should be counseled about self-foot exam and healthy foot behaviors.	Class I	C-LD
	2. In patients with PAD, prompt diagnosis and treatment of foot infection are also recommended to avoid amputation.	Class I	C-LD
	3. In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team can be beneficial.	Class IIa	C-LD
Structured exercise therapy	1. In patients with claudication, a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms.	Class I	B-R
Antihypertensive therapy	1. Antihypertensive therapy should be administered to patients with HTN and PAD to reduce the risk of MI, stroke, HF, and cardiovascular death.	Class I	A
	2. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.	Class IIa	A
Antiplatelet therapy	1. Patients with symptomatic PAD should be given antiplatelet therapy with aspirin alone (75–325 mg QD) or clopidogrel alone (75 mg QD) to reduce MI, stroke, and vascular death.	Class I	A
	1. In asymptomatic patients with PAD (ABI < 0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.	Class IIa	C-EO
	2. In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.	Class IIb	-R
	3. The effectiveness of dual antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.	Class IIb	B-R
	4. Dual antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization (127–130).	Class IIb	C-LD
	5. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.	Class IIb	B-R
Oral anticoagulation	1. Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD.	Class III: harm	A
Symptomatic medical therapy for claudication	1. Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication.	Class I	A
	2. Pentoxifylline is not effective for the treatment of claudication.	Class III	BR
Revascularization (general)	1. Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to guideline-directed medical therapy.	Class IIa	A
Endovascular revascularization	1. Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease.	Class I	A
	2. Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease.	Class IIa	B-R
	3. The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown.	Class IIb	C-LD
Surgical revascularization	1. When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material.	Class I	A
	2. Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication with inadequate response to GDMT, acceptable perioperative risk, and technical factors suggesting advantages over endovascular procedures.	Class IIa	B-NR

and a total of 3718 patients with claudication treated with either various dosages of cilostazol (50,100, 150, or 200 mg) or placebo for 6–26 weeks [33]. The investigators found that cilostazol was associated with an improved initial claudication

distance (distance on the treadmill until patients develop claudication symptoms) when compared to placebo both for the 50 mg dose (improvement by 19.9 m, $p < 0002$) and for the 100 mg dose (improvement by 31.4 m, $p < 0.00001$) and improved absolute claudication distance (ACD)—the maximum distance waked on a treadmill (by 43.1 m for the cilostazol 100 mg group, $p = 0.0007$ and 32.1 m for the cilostazol 50 mg group, $p = 0.0004$) compared to the placebo group. Cilostazol 100 mg was also found to be associated with significant improvement in the ABI values, but without a difference in mortality.

Contrary to cilostazol, the data are less positive for the other agents. Pentoxyfylline is a methylxanthine metabolized at the red blood cell membrane level. Pentoxyfylline can increase erythrocytes' flexibility, fibrinogen levels, and decrease blood viscosity [34]. Despite the presence of some positive observational studies for pentoxifylline in the past, there is a lack of quality data [35, 36]. As a result, the AHA/ACC give a class 3 (no benefit) recommendation for its use in symptomatic PAD [18••]. Similarly, no benefit has been shown for chelation agents [37, 38]. Naftidrofuryl, a serotonin receptor antagonist with vasoactive properties in vascular smooth muscle, can inhibit vasoconstriction, reduce platelet aggregation, and decrease cell proliferation [39, 40]. It is the only approved agent for intermittent claudication in the UK (secondary to the favorable safety profile compared to cilostazol) and is used widely in Europe but not in the USA. The dosage is usually 100 to 200 mg three times daily for up to 6 months. There are some comparative data between cilostazol and naftidopuryl which show that naftidopuryl is at least non-inferior [40].

Medical Therapy for Secondary Risk Reduction

PAD is known to be associated with very poor cardiovascular outcomes, including increased incidence of MI, ischemic stroke, and all-cause mortality [41]. Recent studies have demonstrated that both men and women have greater risks of long-term all-cause and cardiovascular mortality, supporting the notion that PAD should be considered a CAD risk equivalent [42]. Thus, aggressive medical therapy (Table 2) to optimize the disease burden and reduce progression is of paramount importance in PAD management [18••, 43].

Non-pharmacological Medical Therapy for Secondary Risk Reduction

Smoking Cessation

Smoking is a well-recognized risk factor for the development of PAD and represents the most important modifiable risk factor for PAD and critical limb ischemia (CLI) [44]. Smoking cessation is probably the most important lifestyle modification a patient with PAD can do. Smoking cessation is associated with decreased likelihood of developing claudication symptoms, improved long-term mortality, improved amputation free survival, and prevention of CLI [44, 45]. Guidelines recommend smoking cessation for all PAD patients [18••]. In order to achieve this, a multidisciplinary approach is needed with patient education, cognitive-behavioral counseling, and even pharmacological aids [46, 47]. Physicians' role in emphasizing smoking cessation importance is considered crucial. However, a preliminary analysis of the Vascular Physician Offer and Report (VAPOR) trial failed to find a significant difference in smoking cessation rates among PAD patients who received provider-delivered smoking cessation model incorporating counseling and nicotine replacement therapy compared to the control group (40.3% quit rate in intervention, 31% quit rate in control; $p = 0.250$) [48].

Weight Loss and Dietary Habits

Weight loss if achieved in a proper way without loss of muscle tissue can help increase walking distance [49, 50]. However, this should happen through an interdisciplinary team with combination of proper nutritional intake, exercise, and muscle strength in order to avoid the risk of sarcopenia and frailty, especially in elderly populations [51]. Imbalanced dietary habits can increase the risk for both development and progression of PAD [52]. A secondary prevention approach by utilizing healthier dietary habits can potentially slow PAD progression [51]. Current knowledge is mainly based on observational data which show that specific dietary habits are associated with higher risk of development and progression of PAD [51]. In the absence of specific recommendations for PAD, clinical practice is largely driven by the general atherosclerosis guidelines [53], an approach that promotes intake of anti-inflammatory and anti-oxidant rich foods and at the same time low in saturated fat, sodium, and red animal protein would be ideal [53].

Antiplatelet and Antithrombotic Agents

Patients with PAD are at increased risk for atherothrombotic events including MI and stroke. Current guidelines include a class I recommendation supporting the use of aspirin or clopidogrel for prevention of atherothrombotic events in all patients with symptomatic PAD [18••]. This recommendation derives in part from a meta-analysis of 9214 patients with symptomatic PAD that showed a 23% relative risk reduction in vascular events in patients prescribed antiplatelet therapy [54]. The "Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events" (CAPRIE) trial compared aspirin vs. clopidogrel for patients with any known vascular disease (CAD, PAD, carotid artery disease), without finding an overall difference [55]. However, in the subgroup analysis for PAD

only, clopidogrel was associated with a decrease in the primary endpoint, which was a composite of ischemic stroke, MI, or cardiovascular death [53].

The "Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease" (EUCLID) trial found that ticagrelor was not superior to clopidogrel in reducing major adverse cardiovascular events or major adverse limb events [56]. Currently, clopidogrel is strongly recommended as an alternative to aspirin in PAD (class 1, LOE B) [18••].

Because of the positive results in CAPRIE, the "Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events" (CHARISMA) trial later compared dual antiplatelet therapy (DAPT) vs. aspirin alone in patients with vascular disease and did not find any difference in the overall analysis [57]. A subgroup analysis of patients with prior MI, stroke, or symptomatic PAD demonstrated that these patients experienced significant decreases in the primary endpoint (the first occurrence of MI, stroke, or death from cardiovascular causes) with DAPT [57]. However, DAPT has a weak recommendation (class IIb, LOE B) and only for cases with low gastrointestinal or central nervous system bleeding risk [18••].

Vorapaxar is a thrombin receptor antagonist that was tested in the "Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction" (TRA2P-TIMI) trial. The primary outcome was the composite 3-year endpoint of cardiovascular death, MI, or stroke and did not differ between the two groups, but vorapaxar improved some of the secondary endpoints, including acute limb ischemia and revascularization rates [58]. However, vorapaxar use was associated with higher risk of moderate or severe bleeding. Currently, vorapaxar is not commercially available in the USA.

The "Cardiovascular Outcomes for People Using Anticoagulation Strategies" (COMPASS) trial compared low-dose rivaroxaban (2.5 mg twice daily) used with or without aspirin vs. aspirin only for the reduction of MACE and MALE in patients with CV disease [59]. In the subgroup analysis of patients with PAD or carotid artery disease, the combination of rivaroxaban and aspirin reduced both the rates of MACE (which was the primary endpoint (5% vs. 7%, HR 0.72; 95% CI 0.57–0.90; $p = 0.0047$) and also the MALE rates (1% vs. 2%, HRL 0.86; 95% CI 0.45–1.00; $p = 0.05$) [57]. However, the combination of rivaroxaban and aspirin vs. aspirin only increased the major bleeding compared to aspirin alone (3% vs. 2%l HR 1.61; 95% CI 1.12–2.31; $p = 0.0089$), mainly driven by gastrointestinal bleeding [59]. Rivaroxaban only was not associated with improved results compared to aspirin alone.

Statins and Lipid-Lowering Agents

There are no PAD-focused RCTs comparing statins vs. placebo for secondary risk reduction. However, evidence from observational studies suggest that statin therapy improves cardiovascular outcomes for these patients [60, 61]. Most of our current knowledge comes from the Heart Protection Study, where simvastatin 40 mg was associated with reduction in cardiovascular events compared to placebo among patients with PAD [62]. Multiple studies have subsequently shown that statins are underused in PAD [63]. Currently AHA/ACC guidelines provide a class I recommendation for use of statins in patients with PAD [18••]. Subgroup analyses from randomized trials and observational studies suggest that high-intensity statin therapy is associated with a reduction in cardiovascular events [63, 64]. Similarly, the current cholesterol guidelines include PAD as a clinical atherosclerotic cardiovascular disease condition and favor either moderate or high-intensity statin therapy for specific subgroups [65]. Interestingly, statins have been also shown—even in the setting of RCTs—to improve the pain-free walk time of claudicants [66–68].

Recently, a PAD-focused post hoc analysis of the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) for the addition of PCSK9 inhibitors (a non-statin lipid-lowering agent) to moderate or high-intensity statins was published [69]. The analysis found that the primary composite endpoint of cardiovascular death, MI, stroke, hospital admission for unstable angina, or coronary revascularization improved in the PCSK9 group (hazard ratio [HR] 0.79; 95% CI 0.66–0.94; $p = 0.0098$) [69]. Also PCSK9 led to a reduction of the MALE rates in all patients (HR, 0.58; 95% CI, 0.38–0.88; $p = 0.0093$) [69].

Blood Pressure Control and ACE Inhibitors

Blood pressure control benefit in PAD has been shown from the UKPDS (UK Prospective Diabetes Study) where a reduction of 10 mmHg in systolic BP was associated with a reduction of 16% in rates of limb amputation or death [70]. Among almost 4000 participants with PAD in the HOPE (Heart Outcomes Prevention Evaluation) trial who were randomized to either ACEI (ramipril 10 mg) or placebo, the primary outcome (composite of myocardial infarction, stroke, cardiovascular death) was reduced in the ramipril group (RR 0.78; 95% CI 0.70–0.86; $p = 0.001$) [71]. The benefit associated with ACEI use was also shown in an observational study of 464 patients, where their use was associated with lower rates of MACE (HR 0.76; 95% CI 0.59–0.99; $p = 0.04$) and overall mortality (HR 0.71; 95% CI 0.53–0.95; $p = 0.02$) [72]. Current ACC/AHA guidelines provide a class IIa, level A recommendation for the use of ACEI or ARB therapy to reduce the risk of cardiovascular ischemic events in patients with PAD [18••]. Of note, a paper that in the past showed that ramipril can improve the pain-free claudication distance was retracted and thus we do not have any evidence supporting this benefit [73, 74].

Glycemic Control

Hyperglycemia enhances atherosclerosis progression. It is known that DM can increase 2–4 times the risk for PAD development while PAD patients with DM have a higher risk for progression to CLI, mainly attributed to the high prevalence of disease in infrapopliteal and small vessel disease [75, 76]. There are no RCTs suggesting stricter glycemic control in patients with PAD. Daily foot inspections and careful footwear selection is also recommended as well as ABI screening for diabetic patients > 50 years old [18••].

Walking and Exercise Programs

Patients with PAD present with a complex array of symptoms, health beliefs, and exercise limitations in their daily lives [77, 78]. Secondary to intermittent claudication symptoms, patients with PAD often avoid walking or slow their walking pace, limiting in this way their quality of life and being a burden for themselves and their families [78]. Supervised exercise training (SET) improves exercise tolerance and HRQOL in patients with heart failure and CAD [79]. Similarly, for PAD, current AHA/ACC guidelines recommend SET as an initial treatment modality for patients with IC (class I, level of evidence A) [18••]. A meta-analysis of a total of 987 patients from 7 RCTs (constituting 9 total comparison arms) showed that the combination of endovascular therapy and SET is associated with an improvement in the walking distance, lowering at the same time the risks for future revascularization or amputations [80•]. No difference was found between endovascular therapy vs. SET alone. The improvement that PAD patients experience with SET is attributed to reduced inflammation and vascular obstruction and improved endothelial and mitochondrial function [79].

However, and despite having a strong recommendation, SET is associated with a number of practical limitations, including high cost when not reimbursed by Centers for Medicare & Medicaid Services (CMS) and patients' reluctance to join SET facilities thrice a week, especially when it comes to elderly or patients with limited mobility [81]. The good news is that now SET is reimbursed by CMS for up to 12 weeks (three sessions weekly, 30–60 min each time) in a hospital or outpatient clinic setting by specialized personnel and under the direct supervision of a physician, which provides optimism regarding potential future coverage of SET by CMS [82]. Unfortunately, a systematic review showed that even when SET is provided without cost to the patients, up to 2/3 of the patients will refuse to participate because of no interest [81].

Home-based walking exercise is the main alternative to SET. Obviously, the benefits of the home-based approach include that patients can avoid the SET-related cost and the need to travel to the facilities three times a week. Before 2010, the data for home-based exercise were very poor and not positive. However, more recent trials have now shown that home-based exercise is definitely more effective compared to no exercise at all and can lead to significant improvement in walking capacity and sometimes even comparable benefit to SET in terms of maximal walking distance [83–87]. Currently, home-based exercise has a class IIA recommendation [18••]. The IRONIC (Invasive Revascularization or Not in Intermittent Claudication) trial randomized claudicants to either revascularization with a home-based walking program or walking program alone. The investigators found that it was the combination arm that had the maximum improvement in the 1-year follow-up [88]. Other less used alternatives to walking exercise include upper and lower extremity ergometry and resistance training [89–92].

Revascularization

Contrary to patients with CLI, revascularization should not be the first treatment of choice for claudicants with PAD. A 3–6-month period of waiting for improvement for patients who undergo exercise therapy and optimal medical management with cilostazol is reasonable before intervening. If despite treatment with cilostazol and SET programs, patients are still symptomatic, an attempt for revascularization is reasonable. This is also mirrored in the 2016 AHA/ACC guidelines especially for iliac disease (class I, level of evidence A) for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease. For FP disease, there is a less strong recommendation (class IIA, level of evidence B), due to the higher rates of restenosis after intervention [18••].

The evolution of endovascular therapy now allows even some of the most challenging cases to be treated with an endovascular approach. Endovascular therapy is considered the standard of care for the majority of cases, because of the less invasive nature and the possibility to decrease the length of stay, while avoiding peri-procedural morbidity and at the same time having comparable patency rates [93, 94]. A notable exception to the above might be lesions in the common femoral artery, where the existing data support a surgical approach in low risk for surgery populations [95]. The Trans-Atlantic Inter-Society Consensus (TASC) is used to describe the angiographic and anatomical findings of arterial disease (Table 3).

Role of Revascularization in Combination with Walking Therapy

The combination of supervised exercise training and revascularization has been studied in three different RCTs. Two of them found a significant improvement in the combination

Table 3 TASC classification for iliac, femoropopliteal, and infrapopliteal disease

Classification	Aortoiliac lesions	Femoropopliteal lesions	Infrapopliteal lesions
TASC A	1. Unilateral/bilateral CIA stenosis 2. Unilateral/bilateral single EIA stenosis < 3 cm	1. Single stenosis < 10 cm in length 2. Single occlusion < 5 cm in length	1. Single stenosis < 5 cm length 2. Similar stenosis or occlusion in other tibial vessels
TASC B	1. Infrarenal aortic stenosis < 3 cm 2. Unilateral CIA occlusion 3. Single/multiple stenosis 3-10 cm involving EIA 4. Unilateral EIA occlusion not involving internal iliac or CFA	1. Multiple lesions (stenoses or occlusions), each < 5 cm 2. Single stenosis or occlusion < 15 cm not involving the infrageniculate popliteal artery 3. Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass 4. Heavily calcified occlusions < 5 cm in length 5. Single popliteal stenosis	1. Multiple stenoses each < 5 cm or total < 10 cm length or single occlusion < 3 cm 2. Similar stenosis or occlusion in other tibial vessels
TASC C	1. Bilateral CIA occlusions 2. Bilateral EIA stenoses 3–10 cm not extending to the CFA 3. Unilateral EIA: stenosis extending to CFA, occlusion involving origins of internal iliac and/or CFA, heavily calcified occlusion with or without involvement of internal iliac or CFA	1. Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification 2. Recurrent stenoses or occlusions that need treatment after two endovascular interventions	1. Multiple stenoses and/or single occlusion >10 cm length 2. Similar stenosis or occlusion in other tibial vessels
TASC D	1. Infrarenal aortoiliac occlusion 2. Diffuse aortic and bilateral iliac disease requiring treatment 3. Diffuse multiple stenoses involving unilateral CIA, EIA, and/or CFA 4. Unilateral occlusions of both CIA and EIA 5. Bilateral occlusions of EIA 6. Iliac stenosis with AAA requiring treatment and not amenable to endograft placement	1. Chronic total occlusions of SFA or CFA (> 20 cm, involving the popliteal artery) 2. Chronic total occlusion of popliteal artery and proximal bifurcation vessels	1. Multiple occlusions > 10 cm length or dense calcification or poor collaterals 2. Other tibial arteries occluded or dense calcification

arm vs. SET only [96, 97], while one of them did not find any differences [98]. A meta-analysis published in 2017 found that the combination can be associated with an improvement in total walking distance, ABI, and lower risk of revascularization or amputation over an intermediate duration of follow-up [80•].

Conclusions and Future Directions

PAD is now recognized broadly as a CAD equivalent but it still remains underdiagnosed and subsequently undertreated. Advancements in pharmacological options both for symptom improvement and secondary risk reduction enable patients with claudication to have a better quality of life and improved life expectancy. Endovascular therapy when offered can improve symptoms in patients where SET and cilostazol did not result in the anticipated symptomatic relief. A multidisciplinary approach with multiple different specialties involved, new medications, and advancements in endovascular technologies enables us to be optimistic about the care of these patients in the future.

Compliance with Ethical Standards

Conflict of Interest Prio Hossain and Damianos G. Kokkinidis declare that they have no conflict of interest.

Ehrin J. Armstrong is a consultant to Abbott Vascular, Boston Scientific, Cardiovascular Systems, Gore, Intact Vascular, Janssen, Medtronic, and Philips.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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