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CLAUDICATION AND IT'S APPROACH TO PRIMARY MANAGEMENT

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Abstract. Peripheral artery disease (PAD) is common and associated with significant morbidity and mortality. PAD occurs in about 18 percent of persons over 70 years of age. Usually, patients who have PAD present with intermittent claudication with pain in the calf, thigh or buttock that is elicited by exertion and relieved with a few minutes of rest. The disease may also present in a subacute or acute fashion. Symptoms of ischemic rest pain, ulceration or gangrene may be present at the most advanced stage of the disease. In caring for these patients, the primary care physician should focus on evaluation, risk factor modification and exercise. Optimal primary medical management of PAD is required for each patient, irrespective of the decision regarding lower extremity revascularization. The goals include reducing cardiovascular morbidity and mortality and improving quality of life. The approach should consist of aggressive and individualized risk factor modification including smoking cessation, antiplatelet therapy, a statin, and an angiotensin-converting enzyme inhibitor. Exercise is critical for cardiovascular health and highly effective for improving claudication symptoms. Cilostazol may be considered for symptomatic treatment in certain patients. Arterial occlusive diseases, such as coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD), are common in the primary care setting. These diseases often coexist in the same patient. Treatment of these diseases, which typically affect older adults, will consume a greater percentage of health care costs as the elderly population in the Russian Federation increases.

Keywords: peripheral arterial disease, atherosclerosis, claudication, primary management

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ХРОМОТА И ПОДХОД К ЕЕ ПЕРВИЧНОМУ ЛЕЧЕНИЮ

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Резюме. Заболевания периферических артерий (ЗПА) широко распространены и связаны со значительной заболеваемостью и смертностью. ЗПА встречается примерно у 18% лиц старше 70 лет. Обычно у пациентов с ЗПА отмечается перемежающаяся хромота с болью в икре, бедре или ягодице, которая возникает при нагрузке и проходит через несколько минут отдыха. Заболевание может протекать как подостро, так и остро. Симптомы ишемической боли в покое, язвы или гангрены могут проявляться на самой поздней стадии заболевания. При уходе за такими пациентами врач первичного звена должен сосредоточиться на оценке, изменении факторов риска и физических упражнениях. Оптимальное первичное медицинское ведение ЗПА необходимо для каждого пациента, независимо от решения о реваскуляризации нижних конечностей. Цели включают снижение сердечно-сосудистой заболеваемости и смертности и улучшение качества жизни. Подход должен включать агрессивную и индивидуальную модификацию факторов риска, в том числе отказ от курения, антитромбоцитарную терапию, статины и ингибиторы ангиотензин-превращающего фермента. Физические упражнения имеют решающее значение для здоровья сердечно-сосудистой системы и высокоэффективны для улучшения симптомов хромоты. Цилостазол может быть рассмотрен для симптоматического лечения у некоторых пациентов. Окклюзионные заболевания артерий, такие как ишемическая болезнь сердца, цереброваскулярные заболевания и ЗПА, часто встречаются в первичном звене медицинской помощи. Эти заболевания часто сосуществуют у одного и того же пациента. Лечение этих заболеваний, которые обычно поражают пожилых людей, будет занимать все большую долю расходов здравоохранения по мере увеличения численности пожилого населения в Российской Федерации.

Ключевые слова: заболевания периферических артерий, атеросклероз, хромота, первичное ведение

INTRODUCTION

Peripheral artery disease (PAD) is a common manifestation of the progressive stenosis of peripheral arteries (Fig. 4). More than 200 million people have PAD worldwide, and the prevalence of PAD is ≥20% in individuals over the age of 80 years [1]. Approximately 30% of patients with PAD experience intermittent claudication, a walking-induced muscle pain primarily affecting the calves that is relieved only by rest [2]. Patients experiencing claudication generally have sedentary lifestyles and poor health-related quality of life [2, 3]. PAD negatively affects the quality and length of life among those affected. The prognosis of the diseased extremity is generally favorable. Without specific therapy, the distance that affected persons are able to walk generally remains stable, worsening in 26 percent of persons and improving in 27 percent [4, 5]. Over five years, approximately 4 to 8 percent of affected persons require arterial reconstruction, and 2 to 4 percent require amputation [4, 6, 7]. The goals of the primary medical management of PAD focus on two areas: helping patients "live longer" by reducing cardiovascular morbidity and mortality and helping patients "feel better" by improving quality of life. However, patients with PAD are at risk for other atherosclerotic diseases. Up to 20 percent of asymptomatic patients may have carotid artery stenosis greater than 50 percent, and 12 to 17 percent have stenosis greater than 75 percent [8, 9]. The cornerstones of the primary medical management of PAD include risk factor modification, medications, such as statins and antiplatelet therapy, and exercise. PAD is associated with a significant increase in mortality [10–14]; a major contributor to this is cardiac death. In the Bypass Angioplasty Revascularization Investigation Trial [13, 14], the five-year survival rate was 77 percent in patients with coronary artery disease and PAD, compared with 90 percent in patients who had isolated coronary disease. Other studies have demonstrated a cumulative mortality of approximately 30 percent at five years and 47 to 61 percent at 10 years [10, 11, 14]. Given these associated risks, it would seem reasonable for asymptomatic patients with PAD to be screened for coronary artery disease and carotid artery stenosis; however, the most appropriate and cost-effective course of action remains unclear. In addition, cilostazol may be considered for treatment of claudication symptoms, although adverse side effects can be limiting.

EVALUATION

It is important to take a complete history that identifies symptoms of and risk factors for systemic atherosclerosis. Patients usually inform physicians of the signs and symptoms of coronary artery disease or cerebrovascular disease, but the presentation of PAD may be subtle, particularly in sedentary patients. The most common complaint is intermittent claudication with pain of the calf, thigh or buttock occurring with exertion and relieved after several minutes of rest. Other conditions that may need to be distinguished from PAD are listed in Table I.

Examination of the patient with PAD may reveal bruits over the abdominal aorta, iliac, femoral, carotid or subclavian arteries, and absent or decreased peripheral pulses. Physical findings that further support the diagnosis of PAD include decreased skin temperature, shiny, hairless skin over the lower extremities, dystrophic toenails, pallor on elevation of the extremity and rubor when the limb is dependent (Fig. 1).

PAD is classified by using the A.V. Pokrovsky, Fontaine Staging System and Rutherford category system (Table 2). The initial claudication distance (distance at which the patient first experiences pain with exertion) and the absolute claudication distance (distance at which the patient can no longer ambulate) are usually constant. With advancing disease or acute ischemia, patients may complain of a sudden decrease in the initial claudication distance, disabling claudication, or rest pain, or on examination may be found to have ulceration or tissue loss. Any of these complaints or findings warrants immediate referral to a vascular subspecialist.

The ankle-brachial index is an effective screening tool. The tools required to obtain an ankle-brachial index include a blood pressure cuff and a continuous wave Doppler. Blood pressure is measured in both upper extremities, and the highest systolic reading — the first return of Doppler sound as the cuff is deflated — is recorded. The ankle systolic pressure is similarly measured using the

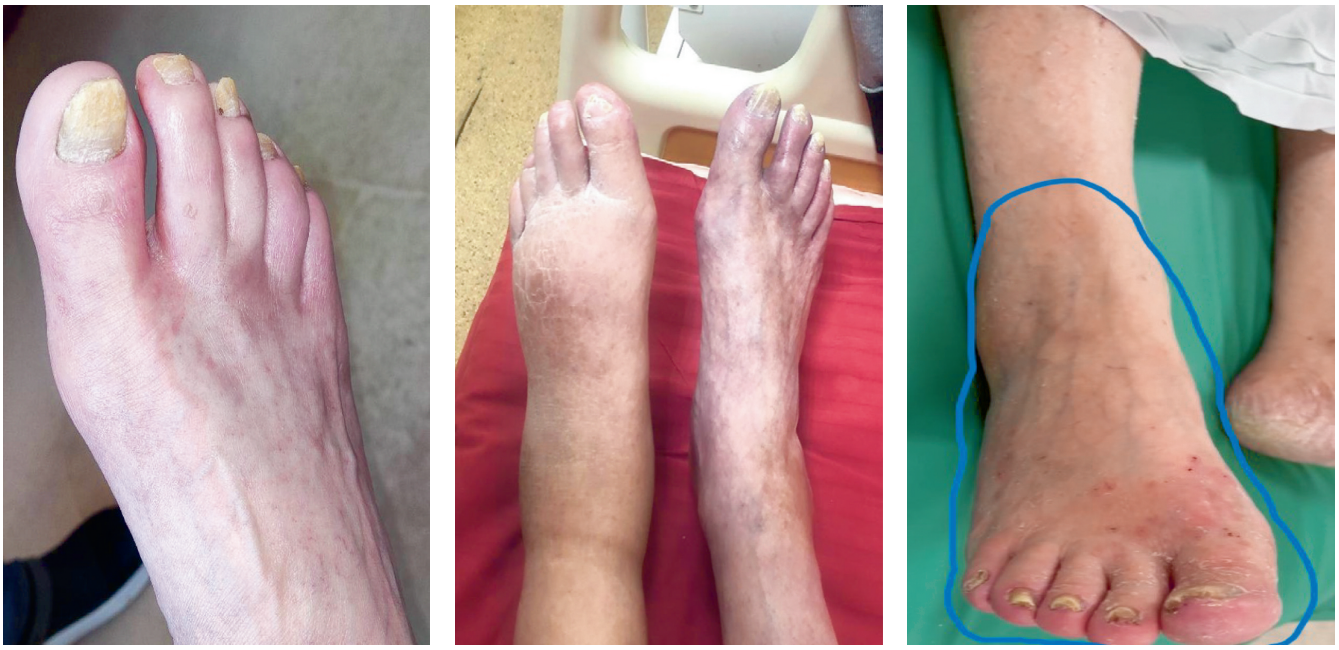
Table 1

Differential diagnosis of lower extremity pain

Таблица 1

Дифференциальная диагностика боли в нижних конечностях

Neurologic	Musculoskeletal	Vascular
• Lumbar canal stenosis (pseudoclaudication). • Radiculopathy/plexopathy. • Peripheral neuropathy	• Baker's cyst. • Muscle strain. • Ligament/tendon injury. • Arthritis/connective tissue disorder	• Intermittent claudication/ischemia. • Arterial thromboembolism. • Cholesterol embolism. • Deep venous thrombosis, vasculitis



а/a *б/b* *в/c*

Fig. 1. Shiny, hairless skin (*a*), dystrophic nail changes (*b*) and dependent rubor associated (*c*) with peripheral arterial occlusive disease of the different patient's right and left foot

Рис. 1. Сияющая, безволосая кожа (*а*), дистрофические изменения ногтей (*б*) и зависимый рубец (*в*), связанные с окклюзионным заболеванием периферических артерий правой и левой стопы у разных пациентов

Table 2

A.V. Pokrovsky, Fontaine and Rutherford peripheral artery disease classification

Таблица 2

Классификация заболеваний периферических артерий по А.В. Покровскому, Фонтейну и Рутерфорду

A.V. Pokrovsky classification	Fontaine classification
• Stage I — Asymptomatic or pain in calf muscles (>1 km). • Stage IIA — Intermittent claudication (>200 meters). • Stage IIB — Intermittent claudication (<200 meters). • Stage III — Intermittent claudication, rest pain. • Stage IV — Ulceration or gangrene	• Stage I — Asymptomatic, decreased pulses, ABI <0.9. • Stage II — Intermittent claudication. • Stage III — Daily rest pain. • Stage IV — Focal tissue necrosis
Rutherford classification	
• Category 0 — Asymptomatic. • Category 1 — Mild claudication (completes treadmill test/ankle pressures >50 mm Hg post treadmill test. • Category 2 — Moderate claudication (between category 1 and 3). • Category 3 — Severe claudication (unable to complete treadmill test/ankle pressures <50 mmHg post treadmill test). • Category 4 — Ischemia rest pain. • Category 5 — Minor tissue loss. • Category 6 — Major tissue loss	

dorsalis pedis or posterior tibial arteries. The ankle-brachial index is calculated by dividing the ankle pressure (the higher of the posterior tibial artery pressures) by the brachial systolic pressure (the higher of the two arm pressures). An ankle-brachial index below 0.95 at rest or following exercise is considered abnormal. An ankle-brachial index between 0.8 and 0.5 is consistent with intermittent claudication, and an index of less than 0.5 indicates severe disease [15]. In patients with an abnormal ankle-brachial index, testing with segmental arterial pressures and a pulse volume recording before and after exercising to the point of absolute claudication are indicated.

Pulse volume recording demonstrating bilateral segmental pressure decrease across the superficial femoral arteries, significantly worse on the left side than on the right side (Fig. 2). Note the mild dampening of the arterial wave form on the left, compared with the right. The ABI is consistent with mild disease on the right and moderate to severe disease on the left. Note the significant decrease following exercise. The resting ABI is calculated

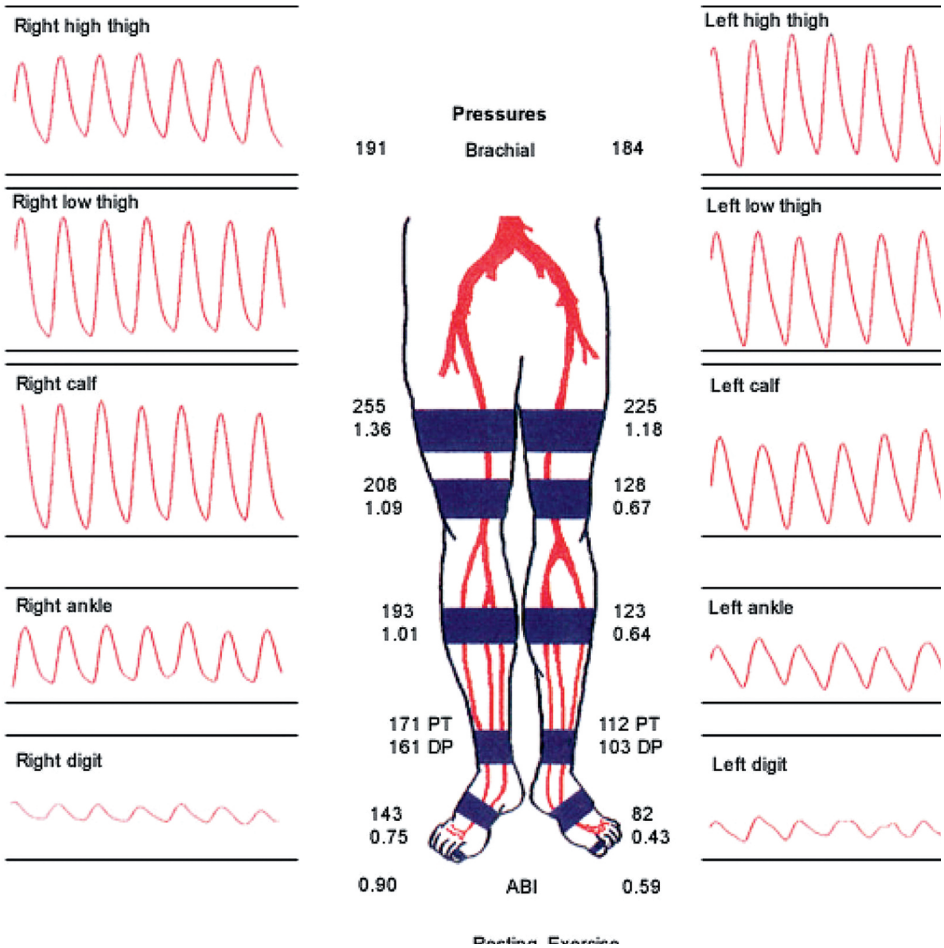


Fig. 2. Pulse Volume Recording (Source: https://doi.org/10.1177/154431671403800306)

Рис. 2. Запись объема пульса (Источник: https://doi.org/10.1177/154431671403800306)

as 171/191=0.90 (right) and 112/191=0.59 (left). All calculations are based on the higher brachial systolic reading, which in this case is 191. The ankle systolic reading is based on the higher of the posterior tibial and dorsalis pedis systolic readings. (ABI=ankle-brachial index; PT=posterior tibial; DP=dorsalis pedis.)

Management. Patients with intermittent claudication should receive conservative treatment. Aggressive risk factor modification, smoking cessation, antiplatelet therapy and a walking program are essential. In addition, medical treatment of the symptoms of claudication may benefit some patients.

RISK FACTOR MODIFICATION

The aim of risk factor modification in patients with PAD are the same as those in patients with coronary artery disease. Unfortunately, many patients with PAD are undertreated [16, 17]. All classes of antihypertensive agents are suitable in the treatment of PAD; the type of therapy is influenced by coexisting disease. Vasodilators provide no symptomatic relief and are not indicated over other agents. Historically, beta blockers have been avoided; however, the literature does not support worsening of symptoms with their use [18]. Many patients may have underlying coronary artery disease and could benefit from treatment with beta blockers.

Lipid abnormalities must be recognized and treated. High levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides are associated with the development and progression of atherosclerosis. Patients should be treated in accordance with the guidelines of the National Cholesterol Education Program [19], which recommend a target LDL cholesterol level of less than 100 mg per dL (2.60 mmol per L) in patients with symptomatic vascular disease.

Tobacco is directly toxic to the vascular endothelium and is implicated in initiating and perpetuating atherosclerosis [20]. All patients must be strongly encouraged to abstain from tobacco use.

Smoking cessation. The effect of smoking in PAD is enormous, both in scope and effect. Up to 80% of patients with PAD

Table 3

Approach to smoking cessation: The 5 A's[a]

Таблица 3

Подход к отказу от курения: 5 A's[a]

The 5 A's	Explanation	Example
Ask	Ask every patient at every single visit if he or she uses any tobacco products (including electronic cigarettes or smokeless tobacco). Implement a system in the office for universal identification.	Do you smoke? Do you use smokeless tobacco like snuff or chew? Do you use electronic cigarettes (vaping)?
Advise	Advise every patient to quit at every visit. Use clear, strong, and personalized advice	You need to quit smoking as soon as possible to help keep your leg arteries open.
Assess	Assess the patient's willingness to quit.	Do you want to quit? Are you ready to quit?
Assist	Assist the patient by helping to set a quit date and providing medication and counseling and resources. For patients who have recently quit, discuss any challenges and the importance of preventing relapse.	What quit date would work for you? (Suggest an upcoming holiday or birthday or anniversary). Prescribe varenicline. Provide hotline information such as 1-800 QUIT NOW and the Smoking Cessation Patient Page from Vascular Medicine [23].
Arrange	Arrange for follow-up contact (office visit or phone call or email), ideally within the first week after the quit date.	Call the patient to check in. Set a delayed message in MyChart reminding the patient of the quit date.

[a] The entire office staff or treatment team can be engaged to help support the smoking cessation efforts [26].

are current or former smokers [21]. The risk of death, myocardial infarction (MI), and amputation is reported to be higher with continued smoking. Smoking cessation in PAD patients may reduce disease progression and may increase walking distance. Smoking after lower extremity bypass increases the risk of graft failure by at least threefold; however, smoking cessation may restore the patency rates to the level of nonsmokers [22]. The patient with claudication is often uniquely motivated to quit smoking after learning that (1) the leg symptoms could improve with smoking cessation, and (2) the disease will worsen with continued smoking. If the symptoms can improve with simply quitting smoking without any further medical or surgical intervention, then smoking cessation should always be the first step [23].

Varenicline is the most effective medication on the market for smoking cessation. It is a partial agonist (it both agonizes and blocks) α-4-β-2 nicotinic acetylcholine receptors, and by doing so, relieves withdrawal symptoms and simultaneously prevents further nicotine binding, which then partially blocks the reinforcing effects of nicotine [24]. Varenicline is more effective than bupropion and more effective than nicotine replacement therapy. Originally, practitioners would tend not to prescribe varenicline until patients were "ready to quit," partly because the medication is to be started ~1 week before the patient's proposed quit date. More recent evidence suggests that perhaps patients should be prescribed varenicline even if they are not immediately ready to quit because it will still increase smoking cessation rates [25]. Table 3 offers a basic approach to smoking cessation in the vascular patient [26]. The five "A's" of smoking cessation are Ask, Advise, Assess, Assist, and Arrange. For providers who prefer not to provide pharmacologic treatment or counseling, another approach is Ask, Advise, and Refer. Partnerships between vascular surgery and vascular medicine can help to achieve this goal. The most important message is that the benefits of smoking cessation greatly exceed any risks associated with pharmacologic treatment [26].

Hypertension. Hypertension should be treated according to current published guidelines to lower the risk of cardiovascular events. Guidelines from the Eighth Joint National Committee advised a target blood pressure of <140/90 mm Hg if the patient has diabetes or chronic kidney disease or is aged <60 years [27]. Otherwise, the target from the Eighth Joint National Committee was <150/90 mm Hg. The more recent SPRINT (Systolic Blood Pressure Intervention Trial) study has led to a more aggressive approach to blood pressure lowering [28]. SPRINT compared the benefit of treatment of systolic blood pressure to a target of <120 mm Hg with treatment of <140 mm Hg among patients at high risk for cardiovascular events but without diabetes. The lower target resulted in lower rates of major cardiovascular events and death from any cause, although with an increased risk of adverse events [28]. The ideal target blood pressure for patients with atherosclerotic vascular disease remains an active topic of debate.

Angiotensin-converting enzyme (ACE) inhibitors are an excellent choice for the treatment of hypertension in the setting of PAD and reduce cardiovascular risk beyond simply lowering blood pressure. The current guidelines support the use of ACE inhibitors or ARBs to reduce the risk of cardiovascular events in patients with lower extremity PAD.

Of note, b-blockers are not contraindicated in PAD patients. A meta-analysis of 11 randomized trials showed that β-blockers do not adversely affect walking capacity or claudication symptoms [29]. However, β-blockers are not first-line for treatment of hypertension but are commonly used for other indications such as heart failure, atrial fibrillation, or secondary prevention after MI.

Diabetes. Diabetes is a major risk factor for PAD and increases the risk of poor outcomes among PAD patients [30]. Patients with diabetes and PAD require a comprehensive and multidisciplinary care plan to include nutrition, weight management, podiatry, ophthalmology, endocrinology, and medications for glycemic control. For many years, the accepted target hemoglobin A_{1c} was <7%. Recently, the trend has shifted to a more individualized approach to glycemic control. For example, a more relaxed goal may be safer in older patients on insulin. Glycemic control has more effect on microvascular complications than on macrovascular complications and is particularly vital among patients with critical limb ischemia.

Body mass index. Body mass index (BMI) is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). The BMI should be calculated at each visit. Being overweight or obese is associated with increased all-cause mortality; all-cause mortality is lowest with a BMI of 20.0 to 24.9 kg/m^2 [31]. The association of obesity as a risk factor for PAD is controversial. However, among patients who already have PAD, weight loss can potentially improve claudication symptoms by reducing workload on the lower extremities. One study found that obesity decreased the time to claudication and delayed postexercise hemodynamic recovery [32]. PAD patients should be encouraged to lose weight if overweight or obese, with the goals of reducing mortality, reducing the risk of developing diabetes and metabolic syndrome, and, potentially, improving claudication symptoms.

MEDICATION

Statin therapy. All patients with PAD should be taking a statin, regardless of cholesterol levels. This recommendation is based on the Heart Protection Study (n 1/4 20,536, of whom 6748 had PAD), which demonstrated a 22% relative risk reduction in the first major vascular event among PAD patients randomized to simvastatin (40 mg) vs placebo [33]. Patients with PAD qualify for high-intensity statin treatment based on current cholesterol guidelines, which means that the goal is lowering the low-density lipoprotein cholesterol (LDL-C) by at least 50% [34]. To achieve this degree of LDL-C lowering, the best options based on clinical trial data are atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg). Atorvastatin and rosuvastatin are similar. One study found that rosuvastatin (40 mg) had a more favorable effect on the lipid profile (with lower LDL-C and higher high-density lipoprotein cholesterol levels) compared with atorvastatin (80 mg), but a similar degree of regression of percent atheroma volume was seen in the coronary arteries [35]. Atorvastatin and rosuvastatin are generic; however, the cost to the patient may differ by formulary or prescription plan. Of note, the maximum daily dose of rosuvastatin is 10 mg if the creatinine clearance is <30 mL/min.

Moderate-intensity statin treatment (lowering the LDL-C by ~30% to <50%) can be considered for patients who are aged >75 years (eg, atorvastatin at 10 mg or 20 mg; rosuvastatin at 5 mg or 10 mg) [34, 35]. Simvastatin (20–40 mg) is another moderate-intensity option, but the FDA has issued restrictions. Simvastatin at 80 mg should be avoided altogether due to the risk of myopathy. Furthermore, the maximum daily dose of simvastatin is 20 mg when combined with amiodarone or with amlodipine, which is commonly prescribed for hypertension. In addition to reducing cardiovascular risk, a few small studies have reported that statins may also improve claudication symptoms. In one study (n 1/4 69), simvastatin (40 mg) increased pain-free treadmill walking time at 6 and 12 months compared with placebo [36]. In a larger study (n 1/4 354), atorvastatin (80 mg) also improved pain-free walking time at 12 months compared with placebo [37]. Statins also improve outcomes in patients with critical limb ischemia [38]. Statins receive considerable attention in the media, with various reports of increased risk of diabetes, muscle issues, and liver toxicity. Much of the current controversy surrounds the use of statins in primary prevention, which is not relevant to PAD patients. Patients with PAD are high risk and have established atherosclerotic vascular disease, in which case there is no debate about the statin benefits, which are enormous regardless of the cholesterol levels.

Given that PAD patients usually already have leg pain, the question of myalgias or statin-induced myopathy often arises among PAD patients. Adverse effects of statins are typically mild and reversible. Efficacy and adverse effects vary among all statins because of their different pharmacokinetic and pharmacodynamics properties [39]. Thus, if a patient reports muscle pains from one statin, then a lower dose of the same statin or an alternative statin should be prescribed. The cardiovascular benefits of statins greatly outweigh any risks in the PAD population.

Antiplatelet therapy. Three antiplatelet agents are available for use in patients with vascular disease. Aspirin should be considered for use in any patient with coronary artery disease, cerebrovascular disease or PAD. In the Physicians' Health Study [40], patients who were randomized to receive aspirin therapy had a relative risk of 0.54 for peripheral arterial surgery when compared with patients who received placebo [40]. The Antiplatelet Trialists' Collaboration Study [41] demonstrated that patients with intermittent

claudication who were treated with antiplatelet therapy had a 17.8 percent relative reduction in the incidence of myocardial infarction, stroke and vascular death.

Treatment with ticlopidine (Ticlid) or clopidogrel (Plavix) should be considered in patients who are intolerant of aspirin therapy. In the Swedish Ticlopidine Multicentre Study [42], the group treated with ticlopidine had an incidence of myocardial infarction, stroke and transient ischemic attack of 13.8 percent versus an incidence of 22.4 percent in the group taking placebo. A lower rate of mortality from all causes was also demonstrated — 18.7 percent of the ticlopidine group compared with 26.1 percent of the placebo group.

The mechanism of action of clopidogrel is similar to that of ticlopidine, with fewer hematologic side effects. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial [43], patients with recent ischemic stroke, recent myocardial infarction or symptomatic PAD were evaluated. Patients who were treated with clopidogrel for the combined end points of ischemic stroke, myocardial infarction and vascular death demonstrated an overall relative risk reduction of 8.7 percent compared with patients who were treated with aspirin without a significant reduction in overall mortality. In the subgroup analysis, patients with PAD had a relative risk reduction of 23.8 percent for the combined end points.

Aspirin (typically 81 mg/d; range, 75–325 mg/d) is recommended for the reduction of the risk of MI, ischemic stroke, and vascular death among patients with symptomatic PAD (Table 4). The data supporting this recommendation are derived from the Antiplatelet Trialists' Collaboration, a meta-analysis of 287 studies of 135,000 patients with cardiovascular disease, including 9214 patients with PAD [44]. In the PAD subgroup, there was a 23% odds reduction for serious vascular events. Subsequent studies have suggested that the benefits of antiplatelet therapy are greater among patients with symptomatic PAD and are somewhat controversial among patients with asymptomatic PAD. In general, aspirin is under prescribed in PAD patients compared with patients with coronary artery disease (CAD). Clopidogrel (75 mg/d) is an alternative to aspirin. It may be marginally more effective than aspirin based on the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, although it is more costly [45].

CAPRIE randomized 19,185 patients with recent MI, ischemic stroke, or symptomatic PAD to clopidogrel vs aspirin (325 mg). In the PAD subgroup (n 1/4 6452), a 23.8% relative risk reduction for vascular events was seen with clopidogrel compared with those treated with aspirin; however, the absolute risk reduction was small (1.15%). Dual antiplatelet therapy (aspirin plus clopidogrel) is generally not needed in PAD patients, although it may be considered in patients who are extremely high risk [46]. For example, dual antiplatelet therapy may be reasonable for a high-risk patient with diabetes who smokes and has PAD with concomitant CAD, particularly for as long as the patient continues to smoke. Ticagrelor is an oral, reversible inhibitor of P2Y12 with faster onset/offset than clopidogrel and more predictable inhibition of adenosine 50-diphosphate-induced platelet aggregation. The recent EUCLID (A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease) trial found that ticagrelor (90 mg twice daily) was not superior to clopidogrel for the reduction of cardiovascular events among patients with symptomatic PAD and that major bleeding rates were similar [47]. In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial, the combination of anticoagulation with warfarin plus antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing cardiovascular events; the combination was associated with an increase in life threatening bleeding [48]. Thus, there is no role for anticoagulation for PAD.

Table 4

Quick reference to assess optimal medical management in patients with peripheral artery disease[a]

Таблица 4

Краткие рекомендации по оценке оптимального медицинского ведения пациентов с заболеваниями периферических артерий[a]

Question to ask	Possible next steps
Is the patient on antiplatelet therapy?	Add aspirin, 81mg daily
Is the patient on a statin?	Add atorvastatin, 40 mg daily (or 10-20 mg if aged >75)
Is the patient currently smoking?	Consider varenicline
Is the blood pressure above goal?	Add ramipril
Is the hemoglobin A_{1c} >7%?	Refer to primary care, nutrition, comprehensive diabetes center, and/or endocrinology
Is BMI >25 kg/m2?	Set appropriate weight loss goals

BMI — Body mass index.
[a]Consider referral to vascular medicine if any of the goals are not met.

EXERCISE

Exercise plays a fundamental role in the treatment of PAD. It has been shown since the 1960s to be an effective treatment for claudication, leading to improvement in both pain-free and maximal walking distance. The CLEVER (Claudication: Exercise Vs Endoluminal Revascularization) trial found that a supervised exercise program improved treadmill walking performance more than endovascular revascularization for patients with aortoiliac disease [49]. A detailed discussion of exercise for PAD is provided in this supplement.

Current guidelines indicate that all patients should achieve 30 minutes of brisk exercise daily for overall cardiovascular health. This recommendation is especially important for PAD patients. Generally, patients should walk until they have moderate pain or discomfort (4 on a scale of 1 to 5), stop and rest until the pain subsides, and then start walking again [49]. Patients should aim to reach this moderate level of pain within the first 5 to 7 minutes of walking. Over time, they will need to walk uphill or more quickly, or both, to bring on the pain within this timeframe. These intermittent bouts of rest and exercise are thought to improve oxygen extraction by the muscles; claudication symptoms improve through a variety of mechanisms [50]. Exercise has tremendous benefits that extend far beyond the improvement in claudication symptoms and functional capacity and include improving endothelial function, blood pressure, cholesterol, glycemic control, and systemic cardiovascular health [50].

Walking improves the symptoms of claudication in several ways. The muscle can better adapt to anaerobic metabolism with repeated exposure to an ischemic environment. Oxidative metabolism and the overall number of available mitochondria increase. A meta-analysis [51] showed an increase of 179 percent in the initial claudication distance and 122 percent in the absolute claudication distance in patients who followed a walking program. Five components of a successful program were also identified. Walking is the preferred mode of exercise. Patients should walk at least three times per week for at least 30 minutes at each session. Near-maximal claudication pain (absolute claudication distance) should be the resting point, and the patients should follow the program for at least six months [51]. A supervised program is superior to a home-based exercise program [52]. A walking program can increase the objective distance that the patient with claudication can ambulate. This may result in subjective improvement and lead to an enhanced quality of life.

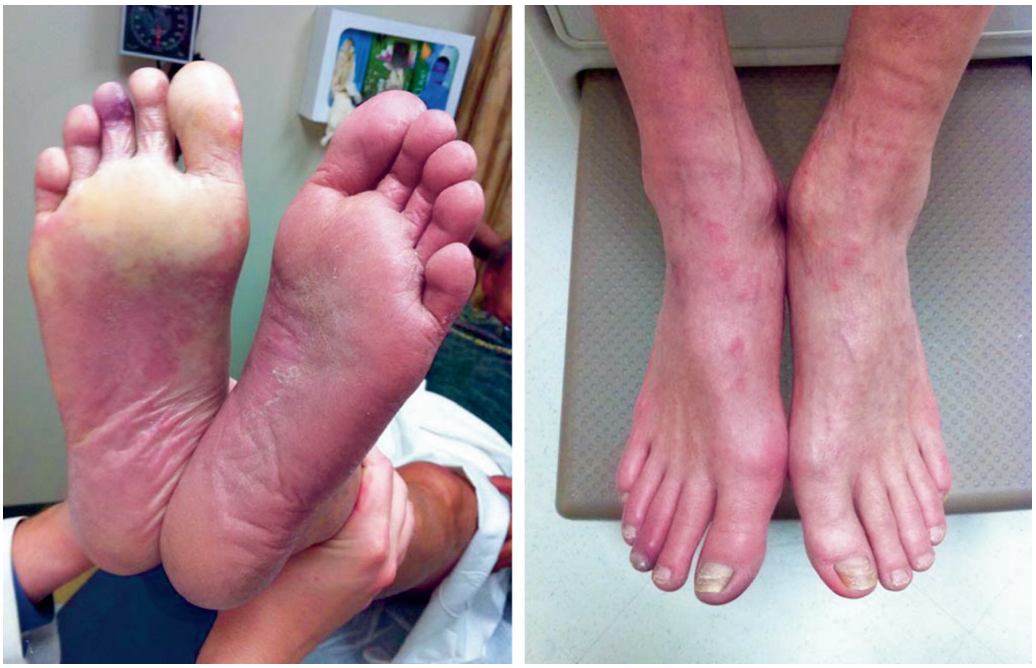
PHARMACOLOGIC TREATMENT OF CLAUDICATION SYMPTOMS

Options are limited in the medications directed at ameliorating claudication symptoms. The first such medication was Pentoxifylline (Trental) (400 mg thrice daily with meals), which was approved by the FDA in 1984 based on small studies. Pentoxifylline is thought to reduce viscosity and improve erythrocyte flexibility; unfortunately, subsequent studies have shown that it is no different from placebo in treating claudication [53]. While the overall efficacy of pentoxifylline has been questioned [54], a recent meta-analysis [55] of patients treated with pentoxifylline demonstrated small improvements in the initial claudication distance and absolute claudication distance. Pentoxifylline is thus not recommended for PAD patients.

The newest agent for treating intermittent claudication is cilostazol. Cilostazol is a phosphodiesterase III inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator [56–58], inhibitor and is more effective than pentoxifylline. In one study [58], the patients who received cilostazol had a 35 percent increase in the distance they could walk before claudication and a 41 percent increase in absolute claudication distance when compared with the subjects who received placebo. One half of the patients treated with cilostazol judged their walking to be “better” or “much better”; 84 percent of patients taking placebo felt that their symptoms were unchanged or worse [58]. Other patients taking cilostazol documented improvement in the absolute claudication distance and ankle-brachial index, along with similar subjective improvements in quality of life and walking ability [59].

A Cochrane review of 15 double-blind, randomized controlled trials (n 1/4 3718) concluded that cilostazol improves walking distance among patients with claudication. Cilostazol is a vasodilator that inhibits vascular smooth muscle cell proliferation and prevents platelet aggregation. Its mechanism for improving claudication symptoms is not clear and is probably multifactorial. The dose is 100 mg twice daily and should be taken at least 30 minutes before or 2 hours after breakfast and dinner. Adverse effects can be limiting and include headache, palpitations, dizziness, and gastrointestinal complaints. Cilostazol is contraindicated in heart failure. The dose should be reduced to 50 mg twice daily in patients with hepatic dysfunction or when given with cytochrome P450 enzyme inhibitors, such as azole antifungals, macrolide antibiotics, or proton pump inhibitors; grapefruit juice should be avoided. The dose may also be reduced if adverse effects are an issue.

In clinical practice, patients with PAD are often taking many medications. For example, a typical ideal regimen may include aspirin (81 mg/d), atorvastatin (40 mg/d), and ramipril (10 mg/d). These three medications are aimed at reducing cardiovascular morbidity and mortality, or to achieve the “live longer” goal. Given the high prevalence of diabetes and hypertension, the same PAD patient may also take other medications such as metformin, gabapentin, amlodipine, or hydrochlorothiazide. With this extensive medication list, the patient and the practitioner may be hesitant to add cilostazol



a/a *б/b*

Fig. 3. Critical limb ischemia: *a* — elevation pallor; *b* — dependent rubor

Рис. 3. Критическая ишемия конечностей: *а* — бледность при подъеме; *б* — зависимый рубец

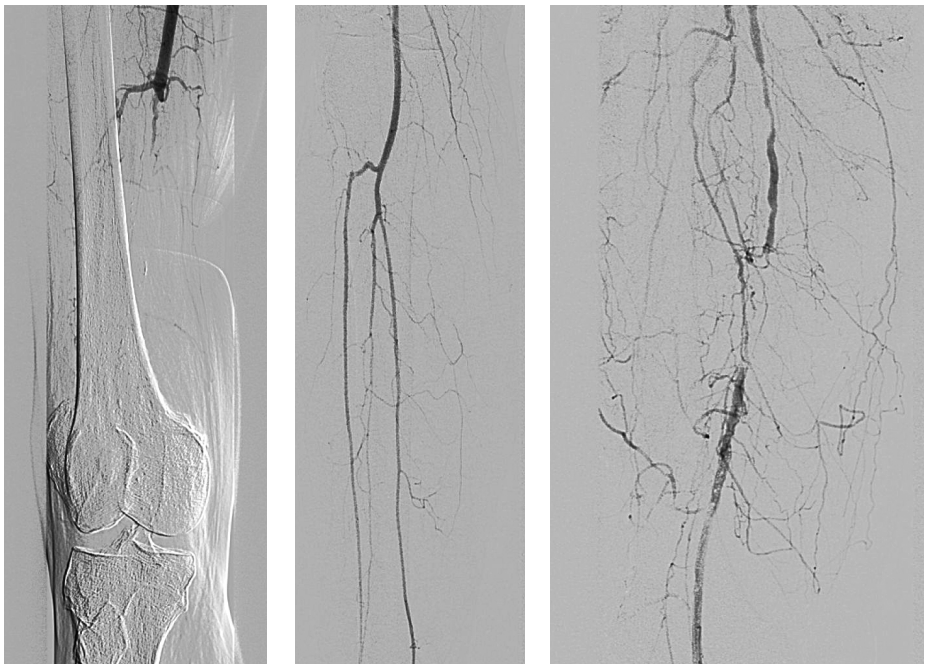


Fig. 4. Angiograms of atherosclerosis in lower limb arteries (peripheral artery disease)

Рис. 4. Ангиограммы атеросклероза артерий нижних конечностей (заболевания периферических артерий)

considering its adverse effect profile and suboptimal efficacy. A 3-month course of medical management, including an exercise program, is a reasonable approach before adding cilostazol, which can be seen as an intermediate step before endovascular or surgical revascularization.

Clinical Presentation. Intermittent claudication is the hallmark of PAD and is defined as fatigue, discomfort, cramping, or pain of vascular origin in the calf muscles of the lower extremities that is consistently induced by exercise and consistently relieved within 10 minutes by rest. In the

general population, only about 10% of persons with known PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg symptoms at all, and 50% have a variety of leg symptoms different from classic claudication, such as exertional pain that does not stop the individual from walking, does not involve the calves, or does not resolve within 10 minutes of rest [60–71]. The 2016 American Heart Association/American College of Cardiology (AHA/ACC) guideline on the management of patients with lower extremity PAD recommends patients at increased risk of PAD should be assessed for exertional leg symptoms, ischemic rest pain, and nonhealing wounds. Other common lower extremity findings include hair loss, shiny skin, and muscle atrophy. Arterial ulcerations are characterized by well-demarcated, "punched-out" lesions. Dependent rubor and elevation pallor may be present in advanced disease and result from impaired autoregulation in the dermal arterioles and capillaries (Fig. 3, 4).

CONCLUSIONS

The primary medical management of PAD clearly demonstrates the benefits of cholesterol lowering statin therapy, smoking cessation, antiplatelet therapy and physical exercises, safely producing highly significant reductions in cardiovascular morbidity and mortality. The medical management is aimed at the two goals of feeling better and living longer. For the "live longer" goal, compulsory medications include antiplatelet therapy, a statin, and an ACE inhibitor, as summarized in Table 4. For the "feel better" goal, the main pharmacologic treatment is cilostazol. Fortunately, smoking cessation, exercise are safe and low-cost treatment option's that achieves both aims.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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