International Heart and Vascular Disease Journal
Volume 3, Number 5, March 2015

Journal of the Cardioprogress Foundation

LEADING ARTICLE

Treatment of lower extremity peripheral arterial disease

Aronow W.S.*

Cardiology Division, Department of Medicine, New York Medical College, Valhalla, New York 10595, USA

Author:

Wilbert S. Aronow, MD, FACC, FAHA, Professor of Medicine, Cardiology Division, New York Medical College, USA

Abstract

Patients with lower extremity peripheral arterial disease (PAD) are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from coronary artery disease (CAD). Smoking should be stopped and hypertension, dyslipidaemia, diabetes mellitus, and hypothyroidism treated. Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in patients with PAD and hypercholesterolaemia. Patients with PAD should be treated with high-dose statins which include atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily. Antiplatelet drugs such as aspirin or clopidogrel, angiotensin-converting enzyme inhibitors, and statins should be given to patients with PAD unless contraindicated. Beta-blockers should be given if CAD, especially prior myocardial infarction (MI), is present unless contraindicated. Vorapaxar is an antiplatelet drug which reduces acute limb ischaemia and peripheral revascularization in patients with PAD but is contraindicated if there is a history of stroke, transient ischaemic attack, or bleeding in the head. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programmes should be used. Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in patients interfering with work or lifestyle; 2) limb salvage in patients with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence.

Keywords

Peripheral arterial disease; intermittent claudication; exercise rehabilitation; revascularization; aspirin; statins

* Corresponding author. Tel: +19144 935311. Fax: +19142 356274. E-mail: wsaronow@aol.com

Introduction

Peripheral arterial disease (PAD) is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication which is pain or weakness with walking that is relieved with rest. The Rutherford classification of PAD includes 7 stages [1]. PAD is classified as stage 0 if the person is asymptomatic, stage 1 if mild intermittent claudication is present, stage 2 if moderate intermittent claudication is present, stage 3 if severe intermittent claudication is present, stage 4 if ischaemic rest pain is present, stage 5 if the person has minor tissue loss, and stage 6 if the person has ulceration or gangrene.

If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischaemia occurs with pain at rest or tissue loss. Critical ischaemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene caused by ischaemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

Risk factors

The prevalence of PAD increases with age. Modifiable risk factors that predispose to PAD include cigarette smoking [2-13], diabetes mellitus [2-12,14], hypertension [2-4,9-12,15,16], dyslipidaemia [2-5,7-12,14,17-19], obesity [20], the metabolic syndrome in women [21], and hypothyroidism [22]. These risk factors contribute to the development of PAD and to the increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events associated with PAD.

Coexistence of other atherosclerotic disorders

PAD coexists with other atherosclerotic disorders [4,12,23-28,29]. In a study of 1,886 men and women, 270 of 468 patients (58%) with PAD had coexistent CAD and 159 of 468 patients (34%) with PAD had prior ischaemic stroke [23]. In a study of 1,802 men and women, 161 of 236 patients (68%) with PAD had coexistent CAD and 100 of 236 patients (42%) with PAD had coexistent prior ischaemic stroke [24]. In 1,006 men and women, if PAD was present, 63% had coexistent CAD, and 43% had prior ischaemic stroke [4]. In 273 patients with CAD, the lower the ankle-brachial index (ABI), the higher the prevalence of 3-vessel or 4-vessel CAD [28]. Patients with PAD and CAD have more extensive and calcified coronary atherosclerosis, constrictive arterial remodelling, and greater disease progression [30]. Patients with PAD also have a higher prevalence of left ventricular systolic dysfunction than patients without PAD [31].

Cardiovascular mortality and morbidity

Patients with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events [7,32-39]. At 10-year follow-up of 565 men and women, PAD significantly increased the risk of all-cause mortality (relative risk = 3.1), of mortality from cardiovascular disease (relative risk = 5.9), and of mortality from CAD (relative risk = 6.6) [32]. At 4-year follow-up of 1,492 women, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors [34]. At 7.5-year follow-up of patients in the Cardiovascular Health study in a propensity-matched study of community dwelling older adults, matched hazard ratios for PAD for all-cause mortality, incident heart failure, and symptomatic PAD were 1.57, 1.32, and 3.92, respectively [37]. In a well-balanced propensity-matched population of 2,689 patients with advanced chronic systolic heart failure, during 4.1 years of follow-up, PAD was significantly associated with increased mortality and hospitalization [38].

At 33-month follow-up of 414 patients with PAD and at 48-month follow-up of 89 patients without PAD followed in a vascular surgery clinic, the incidence of death, new stroke/transient ischaemic attack, new MI, new coronary revascularization, new carotid endarterectomy, or new PAD revascularization was significantly higher in patients with PAD (63%) than in patients without PAD (24%) [39]. PAD was a significant independent risk factor for all-cause mortality with a hazard ratio of 2.2.

Risk factor modification

Smoking cessation

Continuing smoking increases the risk of amputation in patients with intermittent claudication [40]. Patency in lower extremity bypass grafts is also worse in smokers than in non-smokers [41]. Smoking cessation reduces the progression of PAD to critical leg ischaemia and reduces the risk of MI and death from vascular causes [42]. Smoking cessation programmes should be strongly encouraged in persons with PAD (Table 1). Patients should be assisted with counselling and developing a plan for quitting that

may include pharmacotherapy and/or referral to a smoking cessation programme [43,44].

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum, which are available over the counter [45]. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant bupropion should be considered [45,46]. A nicotine inhaler may also be used [47]. The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere [47]. Varenicline is also effective for smoking cessation [48]. Concomitant behavioural therapy may also be needed [49]. Repeated physician advice is very important in the treatment of smoking addiction.

Treatment of hypertension

Hypertension should be adequately controlled to decrease cardiovascular mortality and morbidity in patients with PAD [16,50] (Table 1). The blood pressure should be reduced to less than 140/90 mmHg [16]. In the Heart Outcomes Prevention Evaluation (HOPE) Study, 1,715 patents had symptomatic PAD, and 2,118 persons had asymptomatic PAD with an ABI less than 0.9 [50]. In the HOPE study, compared with placebo, ramipril 10 mg daily significantly reduced cardiovascular events by 25% in patients with symptomatic PAD [50]. In this study, ramipril reduced the absolute incidence of cardiovascular events by 5.9% in patients with asymptomatic PAD and by 2.3% in patients with a normal ABI [50].

Treatment of diabetes mellitus

Patients with diabetes mellitus and PAD and no CAD have a 1.5 times higher incidence of new coronary events than non-diabetics with PAD and prior MI [51]. The higher the haemoglobin A1c levels in patients with diabetes mellitus and PAD, the higher the prevalence of severe PAD [52]. Diabetes mellitus should be treated with the haemoglobin A1c level decreased to less than 7% to decrease the incidence of MI [53] (Table 1). The blood pressure should be reduced to less than 140/90 mmHg in diabetics with PAD [16] Diabetics with PAD should also be treated with high-dose statins which include atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily [54].

Treatment of dyslipidaemia

Treatment of dyslipidaemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in patients with PAD [18,19,54-57]. At 5-year follow-up of 4,444 men and women with CAD and hypercholesterolaemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly decreased the incidence of intermittent claudication by 38% [55]. In a study of 264 men and 396 women with symptomatic PAD and a serum low-density lipoprotein (LDL) cholesterol of 125 mg/dL or higher, 318 of 660 patients (48%) were treated with a statin and 342 of 660 patients (52%) with no lipid-lowering drug [57]. At 39-month follow-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior MI, and of 59% in persons with no prior MI [57].

In the Heart Protection Study, 6,748 of the 20,536 patients (33%) had PAD [55]. At 5-year follow-up, treatment with simvastatin 40 mg daily caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels [55]. These data favour administration of statins to patients with PAD regardless of serum lipids levels.

Patients with PAD should be treated with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [54-57] and to improve exercise time until intermittent claudication [58-60] (Table 1). Statins also reduce perioperative MI and mortality [61,62] and 2-year mortality [62] in patients undergoing non-cardiac vascular surgery.

Other lipid-lowering drugs do not reduce cardiovascular events and mortality in patients with atherosclerotic vascular disease treated with statins [54]. Fenofibrate or fish oils may be used to treat patients with serum triglycerides greater than 500 mg/dL to prevent pancreatitis [54]. Niacin should especially not be administered because it does not reduce cardiovascular events and is associated with serious adverse events [63,64].

Increased plasma homocysteine

Increased plasma homocysteine level is a risk factor for PAD [65-68]. Lowering of increased plasma homocysteine levels can be achieved by a combination of folic acid, vitamin B6, and vitamin B12. However, double-blind, randomized, placebo-controlled data have not shown that reduction of increased plasma homocysteine levels will reduce coronary events and slow progression of PAD.

Hypothyroidism

Hypothyroidism is a risk factor for PAD [22]. However, there is no evidence showing that treatment with l-thyroxine will reduce the development of PAD or improve symptoms in patients with PAD.

Antiplatelet drugs

Antiplatelet drugs that have been demonstrated to decrease the incidence of vascular death, non-fatal MI, and non-fatal stroke in persons with PAD are aspirin, ticlodipine, and clopidogrel [69]. Aspirin plus dipyridamole has not been shown to be more efficacious than aspirin alone in the treatment of patients with PAD [69]. Oral platelet glycoprotein IIb/IIIa inhibitors have been shown to increase mortality in treating patients with CAD and have not been investigated in treating patients with PAD [70]. Adverse hematologic effects associated with ticlodipine limit the use of this drug in the management of PAD [71].

Thromboxane A2 induces platelet aggregation and vasoconstriction. Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and thereby blocking the conversion of arachidonic acid to thromboxane A2 [72]. Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor [73].

The Antithrombotic Trialists' Collaboration Group (ATCG) reported a meta-analysis of 26 randomized studies of 6,263 patients with intermittent claudication due to PAD [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the control group, a significant reduction of 23% caused by antiplatelet therapy with significant reductions for all subgroups.

The ATCG reported a meta-analysis of 12 randomized studies of 2,497 patients with PAD undergoing peripheral arterial grafting [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 5.4% in patients randomized to antiplatelet drugs versus 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

The ATCG also reported a meta-analysis of 4 randomized studies of 946 patients with PAD undergoing peripheral angioplasty [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.

If one combines the 42 randomized studies of 9,706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, non-fatal MI, and non-fatal stroke at follow-up was significantly decreased 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty [69]. These data favour treatment with aspirin in men and women with PAD [69] (Table 1).

Aspirin

In high-risk patients, the incidences of vascular death, non-fatal MI, and non-fatal stroke were 19% with an aspirin dose of 500 to 1500 mg daily, 26% with an aspirin dose of 160 to 325 mg daily, 32% with an aspirin dose of 75 to 150 mg daily, and 13% with an aspirin dose of less than 75 mg daily [69]. Since aspirin doses greater than 150 mg daily do not reduce vascular death, non-fatal MI, and non-fatal stroke more than does an aspirin dose of 75 to 150 mg daily and cause more gastrointestinal bleeding than the lower doses, this author prefers an aspirin dose of 81 mg daily in treating patients with atherosclerotic vascular disease.

Clopidogrel

In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5,795 patients with PAD were randomized to clopidogrel 75 mg daily and 5,797 patients with PAD were randomized to aspirin 325 mg daily [74]. At 1.9-year follow-up, the annual incidence of vascular death, non-fatal MI, and non-fatal stroke was 3.7% in patients randomized to clopidogrel versus 4.9% in persons randomized to aspirin, a 24% significant decrease with the use of clopidogrel [74].

On the basis of the available data, it is reasonable to treat patients with PAD with either aspirin or clopidogrel. Aspirin 75 to 325 mg daily or clopidogrel 76 mg daily are recommended by the 2011 updated *American College of Cardiology Foundation* (ACCF)/*American Heart Association* (AHA) guidelines to reduce the risk of MI, stroke, or vascular death in patients with PAD [43,75]. These guidelines recommend the use of aspirin or clopidogrel in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischaemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischaemia, with a class I indication [43,75]. These guidelines also recommend the use of aspirin or clopidogrel to reduce the risk of MI, or vascular death in asymptomatic patients with an ABI less than or equal to 0.90 with a class IIa indication [43,75].

Vorapaxar

Vorapaxar is a protease-activated receptor-1 antagonist. Of 26,449 patients with atherosclerotic vascular disease randomized to vorapaxar or placebo, 3,787

patients had PAD [76]. At 2.5-year follow-up, patients with PAD randomized to vorapaxar had a 6% insignificant reduction in MI, stroke or cardiovascular death, a significant 42% reduction in hospitalization for acute limb ischaemia from 3.9% to 2.3% (*P*=0.006), a significant 16% reduction in peripheral artery revascularization from 22.2% to 18.4% (*P*=0.017), and a significant 62% increase in bleeding from 4.5% to 7.2% (*P*=0.001) [76]. Vorapaxar has recently been approved by the *US Food and Drug Administration* to treat patients with PAD receiving aspirin or clopidogrel to reduce the need for peripheral artery revascularization. This drug should not be used in patients with a history of stroke or transient ischaemic attack or bleeding in the head.

Oral anticoagulants

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, 2,690 patients were randomized after infrainguinal bypass surgery to aspirin 80 mg daily or to oral anticoagulation with phenprocoumon or acenocoumarol to maintain an INR of 3.0-4.5 [77]. At 21-month follow-up, there was no significant difference between the two treatments in the primary outcome of infrainguinal graft occlusion. There was no significant difference between the two treatments in the secondary outcomes of MI, stroke, amputation, or vascular death. However, persons treated with oral anticoagulant therapy had 1.96 times more major bleeding episodes than persons treated with oral aspirin [77]. The *ACCF/AHA* guidelines state that oral anticoagulant therapy with warfarin should not be given to reduce the risk of adverse cardiovascular ischaemic events in persons with atherosclerotic lower extremity PAD (class III indication with no benefit) [43,75].

Angiotensin-converting enzyme inhibitors

Data from the HOPE Study showed that ramipril 10 mg daily significantly decreased cardiovascular events in patients with symptomatic PAD and in patients with asymptomatic PAD [50]. Angiotensin-converting enzyme inhibitors as well as statins also have many pleiotropic effects to account for their vascular protective properties beyond their primary mode of action including inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential [78]. The *ACC/AHA* guidelines recommend treating patients with PAD with angiotensin-converting enzyme inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity [43,75,79] (Table 1).

Table 1. **Medical treatment of peripheral arterial disease**

1	Smoking cessation programme
2	Treatment of hypertension with blood pressure reduced to less than 140/90 mmHg
3	Control diabetes mellitus with the haemoglobin A1c level reduced to less than 7%
4	Treat dyslipidaemia with high-dose statins
5	Antiplatelet drug therapy with aspirin or clopidogrel to reduce MI, stroke, or cardiovascular death with addition of vorapaxar considered to reduce peripheral artery revascularization
6	Treatment with an angiotensin-converting enzyme inhibitor
7	Treatment with beta-blockers in patients with CAD in the absence of contraindications to these drugs
8	Use of high-dose statins to reduce cardiovascular events and mortality and progression of PAD and to improve exercise time until intermittent claudication
9	Treatment with cilostazol in patients with intermittent claudication
10	Exercise rehabilitation programme
11	Foot care

Beta-blockers

Patients with PAD are at increased risk for developing new coronary events [7,32-39]. Many physicians have been reluctant to use beta-blockers in patients with PAD because of concerns that beta-blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies found that beta-blockers do not adversely effect walking capacity or the symptoms of intermittent claudication in patients with mild-to-moderate PAD [80].

An observational study was performed in 575 men and women with symptomatic PAD and prior MI [81]. Of the 575 patients, 85 patients (15%) had contraindications to the use of beta-blockers. Of the 490 patients without contraindications to the use of beta-blockers, 257 patients (52%) were treated with beta-blockers. Adverse effects causing cessation of beta-blockers occurred in 31 of the 257 patients (12%). At 32-month follow-up, use of beta-blockers caused a 53% significant independent decrease in the incidence of new coronary events in patients with PAD and prior MI [81]. In a vascular surgery clinic, 301 of 364 patients (83%) with PAD and CAD were treated with beta-blockers [82]. Beta-blockers should be used to treat CAD in patients with PAD in the absence of contraindications to these drugs (Table 1). The *ACC/AHA* guidelines state that beta-blockers are not contraindicated in treating patients with PAD [43,75,79].

Statins

On the basis of data from the Heart Protection Study, patients with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels [56] (Table 1). Patients with PAD should be treated

with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [54-57] and to improve exercise time until intermittent claudication [58-60] (Table 1). Statins also reduce perioperative MI and mortality [61,62] and 2-year mortality [62] in patients undergoing non-cardiac vascular surgery.

In a study of 69 patients with intermittent claudication, a mean ABI of 0.63, and a serum LDL cholesterol of 125 mg/dL or higher, 3 of 34 patients (9%) treated with simvastatin and 6 of 35 patients (17%) treated with placebo died before the 1-year study was completed [58]. Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy. In a study of 354 patients with intermittent claudication and hypercholesterolaemia, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity [59]. In a study of 86 patients with intermittent claudication and hypercholesterolaemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication [60].

Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders [83]. The data suggest that non-cholesterol-lowering properties of statins may favourably influence functioning in persons with and without PAD [83].

Despite the data recommending use of statins, aspirin, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for secondary prevention in patients with PAD, millions of adults in the United States with PAD are not receiving these drugs [84]. Use of these drugs in patients with PAD and no other cardiovascular disease was associated with a 65% significant reduction in all-cause mortality [84]. Statins also are associated with reduced amputation rates in patients with PAD [85,86].

Drugs to increase walking distance

Chelation therapy has been demonstrated to be ineffective in the therapy of PAD [87], has a class III indication for treating PAD, and may have harmful effects [75]. Numerous drugs have been shown to be ineffective in improving walking distance in patients with intermittent claudication [88,89]. Beraprost sodium, an orally active prostaglandin I2 analogue, was demonstrated to be no more effective than placebo in persons with intermittent claudication [90]. Oral vasodilator prostaglandins such as beraprost and iloprost have a class III indication for treating PAD [75]. Naftidrofuryl [91] and propionyl levocarnitine [92] have been reported to improve exercise walking distance in patients with intermittent claudication but have not been approved for use in the United States. Use of L-arginine, propionyl levocarnitine, and ginkgo biloba to improve walking distance is not established [75]. Use of vitamin E to treat intermittent claudication has a class III indication [75].

Two drugs, pentoxifylline and cilostazol, have been approved by the *United States Food and Drug Administration* for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo [93,94]. The clinical effectiveness of pentoxifyline to treat intermittent claudication is not established [75].

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been documented in numerous trials to improve exercise capacity in patients with intermittent claudication [89,94-98], and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline [97].

Cilostazol should be administered to patients with PAD to increase walking distance (Table 1) but should not be given to patients with PAD who also have heart failure. Other contraindications to the use of cilostazol include a creatinine clearance <25 mL/min, a known predisposition for bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors such as cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and HIV-1 protease inhibitors. The *ACCF/AHA* guidelines state cilostazol 100 mg orally 2 times daily is indicated to improve symptoms and increase walking distance in patients with intermittent claudication due to lower extremity PAD in the absence of heart failure with a class IA indication [75].

A randomized, placebo-controlled trial showed that in 212 patients with intermittent claudication due to PAD, 24-week treatment with ramipril caused a significant 75 second increase in mean pain-free walking time and a significant 255 second increase in maximum walking time [99]. Ramipril also signifi-

cantly improved the overall SF-36 median Physical Component Summary score by 8.2 [99]. Of 159 patients with intermittent claudication due to PAD, patients were randomized to 4 weeks of therapy with subcutaneous injections 3 times a week of granulocyte-macrophage colony-stimulating factor (GM-CSF) or placebo. At 3-month follow-up, treadmill walking performance was not improved by GM-CSF [100].

Exercise rehabilitation

Exercise rehabilitation programmes have been demonstrated to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function [101,102]. The optimal exercise programme for improving claudication pain distance in patients with PAD uses intermittent walking to near-maximal pain during a programme of at least 6 months [103]. Strength training is less effective than treadmill walking [104]. The *ACC/AHA* guidelines recommend a supervised exercise programme for patients with intermittent claudication [75] (Table 1).

Supervised exercise training is recommended for a minimum of 30-45 minutes in sessions performed at least 3 times per week for a minimum of 12 weeks [75] and preferably for 6 months or longer [103]. Among persons with PAD, self-directed walking exercise performed at least 3 times weekly is associated with significantly less functional decline during the subsequent year [105]. A home-based walking exercise programme significantly improved walking endurance, physical activity, and speed in patients with PAD and should be used in patients unwilling to participate in a supervised exercise training programme [106].

Foot care

Patients with PAD must have proper foot care [75,107] (Table 1). They must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a wound of the foot develops, specialized foot gear, including casts, boots, and ankle foot arthoses may be helpful in unweighting the affected area.

Lower extremity angioplasty and bypass surgery

Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence [108]. Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length [108]. Compared to percutaneous transluminal angioplasty alone, stenting improves 3-year patency by 26%) [109]. After infrainguinal bypass surgery, oral anticoagulant therapy is preferable in persons with venous grafts, whereas aspirin is preferable in persons with non-venous grafts [77].

Percutaneous balloon angioplasty and/or stenting is indicated for short-segment stenoses, whereas multisegment disease and occlusions are most effectively treated with surgical revascularization [110]. Revascularization of PAD is discussed extensively elsewhere [75,107]. In patients presenting with severe limb ischaemia caused by infra-inguinal disease and who are suitable for either surgery or angioplasty, bypass surgery and balloon-angioplasty are associated with similar outcomes in terms of amputation-free survival [111]. Patients with intermittent claudication should be considered for revascularization to improve symptoms only in the absence of other disease that would limit exercise improvement such as angina pectoris, heart failure, chronic pulmonary disease, or orthopaedic limitations [75]. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD (class III indication) [75]. Surgical intervention is not indicated to prevent progression to limb-threatening ischaemia in patients with intermittent claudication due to PAD (class III indication) [75].

However, 6-month outcomes from 111 patients with claudication due to aortoiliac PAD randomized to optimal medical therapy, optimal medical therapy plus supervised exercise, or optimal medical therapy plus stent revascularization showed that the greatest increase in treadmill walking performance occurred in the patients randomized to optimal medical therapy plus supervised exercise [112]. Cilostazol significantly reduced angiographic restenosis after endovascular therapy for femoropopliteal lesions with provisional nitinol stenting of femoropopliteal lesions in 200 patients [113].

Amputation

Non-randomized studies have shown that both immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischaemia [114,115]. However, amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage [107].

Conclusion

In conclusion, patients with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Smoking should be stopped and hypertension, dyslipidaemia, diabetes mellitus, and hypothyroidism treated. Patients with PAD should be treated with atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily. Antiplatelet drugs such as aspirin or clopidogrel and angiotensin-converting enzyme inhibitors should be given. Beta-blockers should be given if CAD, especially prior MI, is present unless contraindicated. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programmes should be used. Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in patients interfering with work or lifestyle; 2) limb salvage in patients with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence.

Conflict of interest: None declared

References

1. Dormandy JA, Rutherford RB, for the TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). Management of peripheral arterial disease (PAD). J Vasc Surg. 2000;31:S1-S296.
2. Schroll M, Munck O. Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population of 60 year old men and women. J Chron Dis. 1981;34:261-269.
3. Ness J, Aronow WS, Ahn C. Risk factors for peripheral arterial disease in an academic hospital-based geriatrics practice. J Am Geriatr Soc. 2000;48:312-314.
4. Ness J, Aronow WS, Newkirk E, McDanel D. Prevalence of symptomatic peripheral arterial disease, modifiable risk factors, and appropriate use of drugs in the treatment of peripheral arterial disease in older persons seen in a university general medicine clinic. J Gerontol: Med Sci. 2005;60A:M255-M257.
5. Hughson WG, Mann JI, Garrod A. Intermittent claudication: prevalence and risk factors. Br Med J. 1978;1:1379-1381.
6. Beach KW, Brunzell JD, Strandness DE Jr. Prevalence of severe arteriosclerosis obliterans in patients with diabetes mellitus: relation to smoking and form of therapy. Arteriosclerosis. 1982;2:275-280.
7. Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand. 1982;211:249-256.
8. Pomrehn P, Duncan B, Weissfeld L, et al. The association of dyslipoproteinemia with symptoms and signs of peripheral arterial disease: the Lipid Research Clinics Program Prevalence Study. Circulation. 1986;73(suppl I):I-100-I-107.
9. Stokes J III, Kannel WB, Wolf PA, et al. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. Circulation. 1987;75(suppl V):V-65-V-73.
10. Aronow WS, Sales FF, Etienne F, Lee NH. Prevalence of peripheral arterial disease and its correlation with risk factors for peripheral arterial disease in elderly patients in a long-term health care facility. Am J Cardiol. 1988;62:644-646.
11. Murabito JM, Evans JC, Nieto K, et al. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143:961-965.
12. Sukhija R, Yalamanchili K, Aronow WS. Prevalence of left main CAD, of 3-vessel or 4-vessel coronary artery disease, and of obstructive coronary artery disease in patients with and without peripheral arterial disease undergoing coronary angiography for suspected coronary artery disease. Am J Cardiol. 2003;92:304-305.
13. Conen D, Everet BM, Kurth T, et al. Smoking, smoking status, and risk for symptomatic peripheral arterial disease in women. A cohort study. Ann Intern Med. 2011;154:719-726.
14. Beach KW, Brunzell JD, Conquest LL, Strandness DE. The correlation of arteriosclerosis obliterans with lipoproteins in insulin-dependent and noninsulin-dependent diabetes. Diabetes. 1979;28:836-840.
15. Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510-515.
16. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly. A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society for Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol. 2011;57:2037-2114.
17. Aronow WS, Ahn C. Correlation of serum lipids with the presence or absence of atherothrombotic brain infarction and pe-

ripheral arterial disease in 1,834 men and women aged ³62 years. Am J Cardiol. 1994;73:995-997.
18. Aronow WS. Treatment of older persons with hypercholesterolemia with and without cardiovascular disease. J Gerontol A Biol Sci Med Sci. 2001;56A:M138-M145.
19. Aronow WS. Should hypercholesterolemia in older persons be treated to reduce cardiovascular events? J Gerontol A Biol Sci Med Sci. 2002;57A:M411-M413.
20. Tison GH, Ndumele CE, Gerstenblith G, et al. Usefulness of baseline obesity to predict development of a high ankle brachial index from the Multi-Ethnic Study of Atherosclerosis. Am J Cardiol 2011;107:1386-1391.
21. Conen D, Rexrode KM, Creager MA, et al. Metabolic syndrome, inflammation, and risk of symptomatic peripheral arterial disease in women. A prospective study. Circulation. 2009;120:1041-1047.
22. Mya MM, Aronow WS. Increased prevalence of peripheral arterial disease in older men and women with subclinical hypothyroidism. J Gerontol A Biol Sci Med Sci. 2003;58A:M68-M69.
23. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women □62 years of age. Am J Cardiol. 1994;74:64-65.
24. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischaemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice J Am Geriatr Soc. 1999;47:1255-1256.
25. Aronow WS, Ahn C, Kronzon I. Association of mitral annular calcium with symptomatic peripheral arterial disease in older persons. Am J Cardiol. 2001;88:333-334.
26. Aronow WS, Ahn C, Kronzon I. Association of valvular aortic stenosis with symptomatic peripheral arterial disease in older persons. Am J Cardiol. 2001;88:1046-1047.
27. Park H, Das M, Aronow WS, et al. Relation of decreased ankle-brachial index to prevalence of atherosclerotic risk factors, coronary artery disease, aortic valve calcium, and mitral annular calcium. Am J Cardiol. 2005;95:1005-1006.
28. Sukhija R, Aronow WS, Yalamanchili K, et al. Association of ankle-brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. Cardiology. 2005;103:158-160.
29. Sheikh MA, Bhatt DL, Li J, et al. Usefulness of postexercise ankle-brachial index to predict all-cause mortality. Am J Cardiol. 2011;107:778-782.
30. Hussein AA, Uno K, Wolski K, et al. Peripheral arterial disease and progression of coronary atherosclerosis. J Am Coll Cardiol. 2011;57:1220-1225.
31. Ward RP, Goonewardena SN, Lammertin G, Lang RM. Comparison of the frequency of abnormal cardiac findings by echocardiography in patients with and without peripheral arterial disease. Am J Cardiol. 2007;99:499-503.
32. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326:381-386.
33. Aronow WS, Ahn C, Mercando AD, Epstein S. Prognostic significance of silent ischemia in elderly patients with peripheral arterial disease with and without previous MI. Am J Cardiol. 1992;69:137-139.
34. Vogt MT, Cauley JA, Newman AB, et al. Decreased ankle/arm blood pressure index and mortality in elderly women. JAMA. 1993;270:465-469.
35. Newman AB, Tyrrell KS, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. J Am Geriatr Soc. 1997;45:1472-1478.
36. Criqui MH, Ninomiya JK, Wingard DL, et al. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol. 2008;52:1736-1742.
37. Aronow WS, Ahmed MI, Ekundayo OJ, et al. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomes in community-dwelling older adults. Am J Cardiol. 2009;103:130-135.
38. Ahmed MI, Aronow WS, Criqui MH, et al. Effect of peripheral arterial disease on outcomes in advanced chronic systolic heart failure. A propensity-matched study. Circ Heart Fail. 2010;3:118-124.
39. Chhabra A, Aronow WS, Ahn C, et al. Incidence of new cardiovascular events in patients with and without peripheral arterial disease seen in a vascular surgery clinic. Med Sci Monit. 2012;18:CR131-CR134.
40. Juergens IL, Barker NW, Hines EA. Arteriosclerosis of veterans: a review of 520ses with special reference to pathogenic and prognostic factors. Circulation. 1960:21:188-199.
41. Myers KA, King RB, Scott DF, et al. The effect of smoking on the late patency of arterial reconstructions in the legs. Br J Surg. 1978;65:267-271.
42. Quick CRG, Cotton LT. The measured effect of stopping smoking on intermittent claudication. Br J Surg. 1982;69(suppl):S24-S26.
43. Rooke TW, Hirsch AT, Misra S, et al. Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline). A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol. 2011;58:2020-2045.
44. Creager MA, Belkin M, Bluth EI, et al. 2012 ACCF/AHA/ACRSCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for

peripheral atherosclerotic vascular disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to develop clinical data standards for peripheral atherosclerotic vascular disease). Developed in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Neurology, American Association of Neurological surgeons, American Diabetes Association, Society of Atherosclerosis Imaging and Prevention, Socioety of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Vascular Disease Foundation. J Am Coll Cardiol. 2012;59:294-357.

45. Benowitz NL. Treating tobacco addiction: nicotine or no nicotine. N Eng J Med. 1997;337: 1230-1231.
46. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Eng J Med. 1997;337:1195-1202.
47. Frishman WH, Ky T, Ismail A. Tobacco smoking, nicotine, and non-nicotine replacement therapies. Heart Dis. 2001;3:365-377.
48. Rigotti NA, Pipe AL, Benowitz NL, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease. A randomized trial. Circulation. 2010;121:221-229.
49. Tonnesen P, Fryd V, Hansen M, et al. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. N Eng J Med. 1988;318:15-18.
50. Ostergren J, Sleight P, Dagenais G, et al. HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J. 2004;25:17-24.
51. Aronow WS, Ahn C. Elderly diabetics with peripheral arterial disease and no coronary artery disease have a higher incidence of new coronary events than elderly nondiabetics with peripheral arterial disease and prior MI treated with statins and with no lipid-lowering drug. J Gerontol A Biol Sci Med Sci. 2003;58:M573-M575.
52. Aronow WS, Ahn C, Weiss MB, Babu S. Relation of increased hemoglobin A1c levels to severity of peripheral arterial disease in patients with diabetes mellitus. Amer J Cardiol. 2007;99:1468-1469.
53. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Brit Med J. 2000;321:405-412.
54. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-2934.
55. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischaemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol. 1998;81:333-335.
56. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
57. Aronow WS, Ahn C. Frequency of new coronary events in older persons with peripheral arterial disease and serum low-density lipoprotein cholesterol ⩾125 mg/dl treated with statins versus no lipid-lowering drug. Am J Cardiol. 2002;90:789-791.
58. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at 6 months and at 1 year after treatment. Am J Cardiol. 2003:92:711-712.
59. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003;108:1481-1486.
60. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med. 2003;114:359-364.
61. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation. 2003;107:1848-1851.
62. Desai H, Aronow WS, Ahn C, et al. Incidence of perioperative MI and of 2-year mortality in 577 elderly patients undergoing noncardiac vascular surgery treated with and without statins. Arch Gerontol Geriatr. 2010;51:149-151.
63. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255-2267.
64. The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371:203-212.
65. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995;274:1049-1057.
66. Malinow MR, Kang SS, Taylor IM, et al. Prevalence of hyperhomocyst(e)inemia in patients with peripheral arterial occlusive disease. Circulation. 1989;79:1180-1188.
67. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med. 1991;324:1149-1155.
68. Aronow WS, Ahn C. Association between plasma homocysteine and peripheral arterial disease in older persons. Coronary Artery Dis. 1998;9:49-50.
69. Antithrombotic Trialists' Collaboration. Collaborative meta-analyis of randomised trials of antiplatelet therapy for pre-

vention of death, MI, and stroke in high risk patients. BMJ. 2002;324,71-86.

70. Chew DP, Bhatt DL, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists. A meta-analysis of phase III multicenter randomized trials. Circulation. 2001;103:201-206.
71. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine; a review of 60 cases. Ann Intern Med. 1998;128:541-544.
72. Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets: I. Acetylation of a particulate fraction protein. J Clin Invest. 1975;56:624-632.
73. Mills DC, Puri R, Hu CJ, et al. Clopidogrel inhibits the binding of ADP analogues to the receptor mediating inhibition of platelet adenylate cyclase. Arterioscler Thromb. 1992;12,430-436.
74. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348,1329-1339.
75. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations). A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:1425-1443.
76. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2 {degree} P-TIMI 50. Circulation. 2013;127:1522-1529.
77. Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomized trial. Lancet. 2000;355:346-351.
78. Faggiotto A, Paoletti R. Statins and blockers of the renin-angiotensin system. Vascular protection beyond their primary mode of action. Hypertension. 1999;34(part 2):987-996.
79. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol. 2001;38:1581-1583.
80. Radack K, Deck C. Beta-aderenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease: meta-analysis of randomized controlled trials. Arch Intern Med. 1991;151:1769-1776.
81. Aronow WS, Ahn C. Effect of beta-blockers on incidence of new coronary events in older persons with prior MI and symptomatic peripheral arterial disease. Am J Cardiol. 2001;87:1284-1286.
82. Sukhija R, Yalamanchili K, Aronow WS, et al. Clinical characteristics, risk factors, and medical treatment of 561 patients with peripheral arterial disease followed in an academic vascular surgery clinic. Cardiol in Rev. 2005;13:108-110.
83. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003;107:757-761.
84. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease. National Health and Nutrition Examination Study, 1999 to 2004. Circulation. 2011;96:1031-1033.
85. Westin GG, Armstrong EJ, Bang H, et al. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. J Am Coll Cardiol. 2014;63:682-690.
86. Vogel TR, Dombrovskiy VY, Galinanes EL, Kruse RL. Preoperative statins and limb salvage after lower extremity revascularization in the Medicare population. Circ Cardiovasc Interv. 2013;6:694-700.
87. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. Circulation. 1997;96:1031-1033.
88. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344:1608-1621.
89. Eberhardt RT, Coffman JD. Drug treatment of peripheral vascular disease. Heart Dis. 2000;2:62-74.
90. Mohler ER III, Hiatt WR, Olin JW, et al. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I2 analogue. A double-blinded, randomized, controlled trial. J Am Coll Cardiol. 2003;41:1679-1686.
91. Lehert P, Comte S, Gamand S, Brown TM. Naftidrofuryl in intermittent claudication:a retrospective analysis. J Cardiovasc Pharmacol. 1994;23(suppl 3):S48-S52.
92. Brevetti G, Perna S, Sabba C, et al. Propionyl-L-carnitine in intermittent claudication: a double-blind, placebo-controlled, dose titration, multicenter study. J Am Coll Cardiol. 1999;26:1411-1416.
93. Radack K, Wyderski RJ. Conservative management of intermittent claudication. Ann Intern Med. 1990;113:135-146.
94. Porter JM, Cutler BS, Lee BY, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. Am Heart J. 1982;104:66-72.
95. Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication. Results from a multicenter, randomized, prospective, double-blind trial. Circulation. 1998;98:678-686.
96. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol. 2002;90:1314-1319.
97. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000;109:523-530.
98. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudi-

cation caused by peripheral vascular disease. J Vasc Surg. 1998;27:267-274.

99. Ahimastos AA, Walker PJ, Askew C, et al. Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication. A randomized controlled trial. JAMA. 2013;309:453-460.
100. Poole J, Mavromatis K, Binongo JN, et al. Effect of progenitor cell mobilization with granulocyte-macrophage colony-stimulating factor in patients with peripheral artery disease. A randomized clinical trial. JAMA. 2013;310:2631-2639.
101. Gardner AW, Katzel LI, Sorkin JD, et al. Improved functional outcomes following exercise rehabilitation in patients with intermittent claudication. J Gerontol A Biol Sci Med Sci. 2000;55A:M570-M577.
102. Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease. Functional impact and mechanisms of benefit. Circulation. 2011;123:87-97.
103. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA. 1995;274:975-980.
104. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. Circulation. 1994;90:1866-1874.
105. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. Ann Intern Med. 2006;144:10-20.
106. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease. A randomized clinical trial. JAMA. 2013;310:57-65.
107. Fujitani RM, Gordon IL, Perera GB, Wilson SE. Peripheral vascular disease in the elderly. In: Aronow WS, Fleg JL, eds. Cardiovascular Disease in the Elderly Patient, 3rd ed. New York City: Marcel Dekker, Inc; 2003. p. 707-763.
108. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996;94:3026-3049.
109. Palmaz JC, Garcia OJ, Schatz RA, et al. Placement of balloon-expandable intraluminal stents in iliac arteries. First 171 procedures. Radiology. 1990;174:969-975.
110. Comerota AJ. Endovascular and surgical revascularization for patients with intermittent claudication. Am J Cardiol. 2001;87(suppl):34D-43D.
111. BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005;366:1925-1934.
112. Murphy TP, Cutlip DE, Regensteiner JG, et al. CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease. Six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Study. Circulation. 2012;125:130-139.
113. Iida O, Yokoi H, Soga Y, et al. STOP-IC Investigators. Cilostazol reduces angiographic restenosis after endovascular therapy for femoropopliteal lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol Study. Circulation. 2013;127:2307-2315.
114. Ouriel K, Fiore WM, Geary JE. Limb-threatening ischemia in the medically compromised patient: amputation or revascularization? Surgery. 1988;104:667-672.
115. DeFrang RD, Taylor LM Jr, Porter JM. Basic data related to amputations. Ann Vasc Surg. 1991;5:202-207.