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## Research Article

# Lower Extremity Peripherals Arterial Disease Treatment - ②

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## ABSTRACT

In patients with PAD, smoking should be stopped and hypertension, dyslipidemia, and diabetes mellitus 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 coronary artery disease, especially prior myocardial infarction, is present unless contraindicated. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programs 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 ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence.

**KEYWORDS:** Peripheral artery disease; Intermittent claudication; Statins; aspirin; Clopidogrel; Angiotensin-converting enzyme inhibitors; Beta blockers; Cilostazol; Exercise rehabilitation; Revascularization

## RISK FACTOR MODIFICATION

### Smoking cessation

Smoking cessation reduces the progression of peripheral arterial disease (PAD) to critical leg ischemia and reduces the risk of myocardial infarction and death from cardiovascular causes [1-3]. Patients should be assisted with counseling and developing a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program [2-4].

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum available over the counter [5]. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant bupropion should be considered [5, 6]. A nicotine inhaler may also be used. Varenicline is also effective for smoking cessation [7]. Concomitant behavioral therapy may also be used [8]. Repeated physician advice is very important in treatment of smoking cessation.

### Treatment of hypertension

Hypertension should be adequately treated to reduce cardiovascular mortality and morbidity in patients with PAD [9, 10]. The blood pressure should be lowered to less than 140/90 mm Hg [9]. In the Heart Outcomes Prevention Evaluation (HOPE) Study, 1715 patients had symptomatic PAD, and 2118 persons had asymptomatic PAD with an ankle-brachial index (ABI) less than 0.9 [10]. In the HOPE Study, compared with placebo, ramipril 10 mg daily reduced cardiovascular events by 25% in patients with symptomatic PAD [10]. 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 [10]. Angiotensin-converting enzyme inhibitors should be used to treat patients with lower extremity PAD [3, 10].

### Treatment of diabetes mellitus

The higher the hemoglobin A<sub>1c</sub> levels in patients with diabetes mellitus and PAD, the higher the prevalence of severe PAD [11]. Diabetes mellitus should be treated with the hemoglobin A<sub>1c</sub> level lowered to less than 7% to decrease the incidence of myocardial infarction [3, 12]. The blood pressure should be lowered to less than 140/90 mm Hg in diabetics with PAD [9]. Diabetics 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 [13]. Proper foot care is essential in diabetics with lower extremity PAD [3].

### Treatment of dyslipidemia

Treatment of dyslipidemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in patients with PAD [14-16]. At 5-year follow-up of 4,444 men and women with coronary artery disease and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin reduced the incidence of intermittent claudication by 38% [14]. At 5-year follow-up of 6,748 patients with PAD in the Heart Protection Study, treatment with simvastatin 40 mg daily caused a 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels [15]. These data favor treating patients with PAD with statins regardless of serum lipids levels. At 39-month follow-up of 264 men and 396 women with symptomatic PAD and a serum LDL cholesterol of 125 mg/dl or higher, treatment with statins caused a reduction in the incidence of new coronary events of 58% [16].

Patients with PAD should be treated with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [3, 13-16] and to improve exercise time until intermittent claudication [17-19]. Statins also reduce perioperative myocardial infarction and mortality [20, 21] and 2-year mortality [21] in patients undergoing noncardiac vascular surgery.

## ANTIPLATELET DRUGS

Antiplatelet drugs that have been found to reduce the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with PAD are aspirin, ticlopidine, and clopidogrel [22]. Adverse hematologic effects associated with ticlopidine limit the use of this drug in the treatment of PAD [23].

The Antithrombotic Trialists' Collaboration Group (ATCG) reported a meta-analysis of 26 randomized studies of 6,263 patients with intermittent claudication caused by PAD [22]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the control group, a reduction of 23% caused by antiplatelet therapy with reductions for all subgroups.

The ATCG reported a meta-analysis of 12 randomized studies of 2,497 patients with PAD undergoing peripheral arterial grafting [22]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 5.4% in patients randomized to antiplatelet drugs versus 6.5% in the control group, a 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 [22]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a 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, nonfatal myocardial infarction, and nonfatal stroke at follow-up was reduced 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty [22]. These data favor treatment with aspirin in men and women with PAD[22].

## ASPIRIN

In high-risk patients, the incidences of vascular death, nonfatal MI, and nonfatal 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 [22]. Since aspirin doses greater than 150 mg daily do not reduce vascular death, nonfatal myocardial infarction, and nonfatal 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 [24]. At 1.9-year follow-up, the annual incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 3.7% in patients randomized to clopidogrel versus 4.9% in persons randomized to aspirin, a 24% reduction with the use of clopidogrel [24].

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 75 mg daily are recommended by the 2013 updated American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines to reduce the risk of myocardial infarction, stroke, or vascular death in patients with PAD [3]. 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 ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia, with a class I indication [3]. These guidelines also recommend the use of aspirin or clopidogrel to reduce the risk of myocardial infarction, stroke, or vascular death in asymptomatic patients with an ABI less than or equal to 0.90 with a class IIa indication [3].

## VORAPAXAR

Vorapaxar is a protease-activated receptor-1 antagonist. Of 26,449 patients with atherosclerotic vascular disease randomized to vorapaxar or placebo, 3787 patients had PAD [25]. At 2.5-year follow-up, patients with PAD randomized to vorapaxar had no significant reduction in myocardial infarction, stroke or cardiovascular death, a 42% reduction in hospitalization for acute limb ischemia from 3.9% to 2.3%, a 16% reduction in peripheral artery revascularization from

22.2% to 18.4%, and a 62% increase in bleeding from 4.5% to 7.2% [25]. Vorapaxar is 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 ischemic attack or bleeding in the head

## ORAL ANTICOAGULANTS

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, 2690 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 [26]. At 21-month follow-up, there was no significant difference between the two treatments in the primary outcome of infrainguinal graft occlusion or in the secondary outcomes of myocardial infarction, stroke, amputation, or vascular death. However, patients treated with oral anticoagulant therapy had 1.96 times more major bleeding episodes than patients treated with oral aspirin [26]. The 2013 CCF/ AHA guidelines state that oral anticoagulant therapy with warfarin should not be given to reduce the risk of adverse cardiovascular ischemic events in patients with atherosclerotic lower extremity PAD (class III indication with no benefit) [3].

## ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors as well as statins 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 [27]. The 2013 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 [3].

## BETA BLOCKERS

Patients with PAD are at increased risk for developing new coronary events. Many physicians are 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 [28]. At 32-month follow-up of 490 men and women with symptomatic PAD and prior myocardial infarction without contraindications to beta blockers, use of beta blockers caused a 53% reduction in the incidence of new coronary events in patients with PAD and prior myocardial infarction [29]. In a vascular surgery clinic, 301 of 364 patients (83%) with PAD and coronary artery disease were treated with beta blockers [30]. The 2013 ACC/AHA guidelines state that beta blockers are not contraindicated in treating patients with PAD [3].

## STATINS

Patients with PAD should be treated with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [3, 13-16] and to improve exercise time until intermittent claudication [17-19]. Statins also reduce perioperative myocardial infarction and mortality [20, 21] and 2-year mortality [21] in patients undergoing noncardiac vascular surgery.

In a study of 69 patients with intermittent claudication and hypercholesterolemia, compared with placebo, simvastatin increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy [17]. In a study of 354 patients with intermittent claudication and hypercholesterolemia, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily improved pain-free treadmill walking distance by 40% and improved community-based physical activity [18]. In a study of 86 patients with intermittent claudication and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily improved pain-free walking distance and total walking distance on a treadmill, improved the mean ABI at rest and after exercise, and improved symptoms of claudication [19].

Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders [31]. Despite 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 [32]. Use of these drugs in patients with PAD and no other cardiovascular disease was associated with a 65% reduction in all-cause mortality [32]. Statins also are associated with reduced amputation rates in patients with PAD [33, 34].

## DRUGS TO INCREASE WALKING DISTANCE

Chelation therapy has been demonstrated to be ineffective in the therapy of PAD [35], has a class III indication for treating PAD [3], and may have harmful effects [3]. Numerous drugs have been shown to be ineffective in improving walking distance in patients with intermittent claudication [36]. Oral vasodilator prostaglandins such as beraprost and iloprost and vitamin E therapy have a class III indication for treating PAD [3].

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 [37]. The clinical effectiveness of pentoxifylline to treat intermittent claudication is not established [3].

Cilostazol has been demonstrated in numerous trials to improve exercise capacity in patients with intermittent claudication [38, 39], and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline [39]. The 2013 ACCF /AHA guidelines state that 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 I indication [3].

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 [40]. Ramipril also significantly improved the overall SF-36 median Physical Component Summary score by 8.2 [40]. 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 [41].

## EXERCISE REHABILITATION

Exercise rehabilitation programs have been demonstrated to increase walking distance in patients with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function [42]. The optimal exercise program for improving claudication pain distance in patients with PAD uses intermittent walking to near-maximal pain during a program of at least 6 months [43]. Strength training is less effective than treadmill walking [44]. The 2013 ACC/AHA guidelines recommend a supervised exercise program for patients with intermittent claudication with a class I indication [3].

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 [3] and preferably for 6 months or longer [43]. In patients with PAD, self-directed walking exercise performed at least 3 times weekly is associated with less functional decline during the subsequent year [45]. A home-based walking exercise program 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 program [46].

## FOOT CARE

Patients with PAD must have proper foot care [3, 47]. 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 orthoses 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 ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence [48]. The 2013 ACC/AHA guidelines recommend that endovascular procedures are indicated for patients with a vocational or lifestyle-limiting disability due to intermittent claudication when there is an inadequate response to exercise or drug therapy and a very favorable risk-benefit ratio with a class I indication [3]. Revascularization of PAD is discussed extensively elsewhere [3, 47].

Stent placement is indicated in the iliac arteries as salvage therapy for a suboptimal or failed result from balloon dilation, as primary therapy for common iliac artery stenosis and occlusions, and as primary therapy in external iliac artery stenoses and occlusions with a class I indication [3]. Stents, lasers, cutting balloons, atherectomy devices, and thermal devices can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation with a class IIa indication [3].

In patients presenting with severe limb ischemia caused by infra-inguinal disease and who are suitable for either surgery or angioplasty, by-pass surgery and balloon-angioplasty are associated with similar outcomes in terms of amputation-free survival [49]. 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 orthopedic limitations [3]. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD (class III indication) [3]. Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with intermittent claudication due to PAD (class III indication) [3].

Six-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 [50]. Cilostazol significantly reduced angiographic restenosis after endovascular therapy for femoropopliteal lesions with provisional nitinol tenting of femoropopliteal lesions in 200 patients [51].

## AMPUTATION

Nonrandomized studies have shown that both immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischemia [52,53]. 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 [47].

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