Pharmacology in Peripheral Arterial Disease: What the Interventional Radiologist Needs to Know

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Abstract

Peripheral arterial disease (PAD) is a progressive disease with significant morbidity and mortality. Risk factor control, using diet and lifestyle modification, exercise, and pharmacological methods, improves symptoms and reduces associated cardiovascular events in these patients. Antiplatelet agents and anticoagulants may be used to reduce the incidence of acute events related to thrombosis. The armamentarium available for symptom relief and disease modification is discussed. Novel treatments such as therapeutic angiogenesis are in their evolutionary phase with promising preclinical data.

Keywords

- peripheral arterial disease
- pharmacotherapy
- antiplatelet therapy
- symptom relief
- gene therapy
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to identify the pharmacological options for risk factor modification and symptom control in patients with PAD.

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The primary aim of medical therapy in patients with peripheral arterial disease (PAD) is to reduce the incidence of cardiovascular morbidity and mortality, improve function, limb salvage, and quality of life. PAD patients irrespective of their symptoms are at increased risk of vascular events and mortality.[1] Hence, atherosclerotic risk factors should be identified and aggressively managed in all PAD patients.[2–6]

Risk Factor Management

Smoking Cessation

Smoking is an independent risk factor for PAD, and the magnitude of this association is greater than with coronary heart disease.[7] All types of smoking including cannabis, cigar, pipe, smokeless tobacco, and cigarettes predispose to PAD.[8] There is a dose-dependent relationship and even passive smoking is associated with increased risk of developing PAD.[9,10] The postangioplasty/surgical revascularization patency rates are lower in patients who continue to smoke,[4,11] and smoking cessation reduces postoperative complications with both short-term and long-term benefits.[12]

The effect of smoking, and the importance of smoking cessation, should be explained to all PAD patients. Simple advice is rarely effective and hence patients are usually referred to their primary care physician for active interventions.[13] These include behavioral therapy, nicotine receptor partial agonists, antidepressants, and nicotine replacement

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therapy (NRT). A detailed review of the current pharmacotherapy for smoking cessation is available elsewhere.[14] Varenicline, bupropion, and NRT are first line medications, which achieve high-smoking cessation rates and have good safety profiles. There is no convincing evidence to suggest that these drugs increase the risk of cardiovascular events during the cessation period.[15]

Lipid Control

There is a strong association between elevated low-density lipoprotein (LDL) cholesterol levels and PAD.[16] An aggressive reduction in LDL cholesterol with statins improves walking distance and reduces all-cause mortality, cardiac death, progression to renal failure, and increases amputation-free survival in patients with PAD.[17–20] It also reduces perioperative mortality and improves long-term outcomes in patients undergoing both endovascular and surgical revascularization.[21–25] In spite of these known benefits, effective lipid management remains poor in PVD patients compared with patients with coronary artery disease.[26]

Lipid control can be achieved by dietary and lifestyle changes, exercise, and drugs such as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins), fibrates, bile acid sequestrants, nicotinic acids, and Ezetimibe (cholesterol absorption blocker).[27,28] Along with diet modification, the authors initiate all patients on simvastatin 40 mg, which may be increased up to 80 mg depending upon the response. The goal is to decrease LDL to below 2 mmol/L (77 mg/dL).[28,29] The Heart Protection study has shown that benefits from statin therapy can be obtained in patients with PAD and total cholesterol level greater than 3.5 mmol/L.[30] Ezetimibe is used as an alternative in patients who have contraindications, intolerance or do not respond to statins.[28,31] Aiming for a lower LDL level below 1.8 mmol/L (70 mg/dL) is desirable in higher risk patients with disease in multiple vascular beds, but it can be difficult in practice because of patient compliance.[6]

Hypertension

Hypertension is an independent risk factor for PAD.[16,32] In contrast to coronary artery disease, raised systolic blood pressure (SBP) and a lower pulse pressure are associated with the greatest risk of PAD.[33] In diabetic patients with PAD, reduction of SBP by 10 mm Hg confers a 16% decrease in either lower limb amputation rate or death from PAD over 1,000 person years of follow-up.[34]

The actual choice of antihypertensive drug[35,36] is less relevant as long as the blood pressure should be maintained below 140/90 mm Hg (below 130/80 mm Hg in the presence of diabetes or renal failure).[6,37,38] In the authors practice, thiazide diuretics and angiotensin-converting enzyme (ACE) inhibitors are the initial drugs of choice. In addition to their effect on hypertension, ACE inhibitors reduce cardiovascular events[39] and improve walking distance.[40] Renal function should be checked before and monitored closely following initiation of ACE inhibitors. The results from a nationwide study from Denmark demonstrating that ACE inhibitors may be associated with an increased long-term risk of recurrence after vascular reconstruction need to be confirmed.[41] Similarly, there is no convincing evidence to suggest that β-blockers have a detrimental effect in PAD patients.[42]

Diabetes Control

Diabetes is a major risk factor for PAD. The pattern of PAD in diabetic patients is usually multilevel and predominantly affects the infrapopliteal segments with relative sparing of the pedal vessels.[43] Diabetes affects both the micro- and macro-vessels and increases cardiovascular morbidity and mortality. Diabetes increases perioperative cardiovascular morbidity and mortality, and is an independent risk factor for poor outcome after surgical or endovascular revascularization.[44–46] There is no evidence to suggest that tight glycemic control reduces the progression of PVD or affects the amputation rate.[47] It may however reduce the incidence of myocardial infarction (MI), stroke, and vascular death.[6]

A multidisciplinary approach should be used for diabetic patients with PAD. The aim is to maintain capillary blood glucose levels (Hb A1c) below 7% while avoiding hypoglycemic episodes.[6] Recent trials have shown that there is no significant benefit with intensive glycemic control, especially in long-standing type 2 diabetics (in whom it could increase the mortality risk) and suggest a more tailored approach.[48–50] As with blood pressure control, the choice of intervention (diet control, sulphonylureas or insulin) is less relevant than achieving target glycemic control.

A further consideration with metformin relates to the use of iodinated contrast; guideline recommendations vary significantly.[51] The latest guidance from the Royal College of Radiologists suggests that there is no need to stop metformin after contrast exposure in patients with normal serum creatinine and or eGFR > 60. However, if the serum creatinine is elevated or the eGFR is < 60, then the referring clinician should be involved in the decision of withholding metformin for 48 hours.[52]

Antiplatelet/Anticoagulation

Atherosclerosis is a slowly progressive disease with acute exacerbations due to changes in plaque morphology, ulceration, rupture, and thrombosis. These acute exacerbations lead to vascular events such as MI, stroke, or acute limb ischemia. Antiplatelet and anticoagulant agents reduce the risk of thrombus formation, leading to a reduction in serious vascular events in PAD patients.[5,53] Aspirin therapy leads to a 25% relative risk reduction in ischemic stroke, MI, and vascular death. They also reduce the risk of limb deterioration requiring revascularization in patients with intermittent claudication.[54]

The pharmacology of the inhibition of platelet activation is complex and drugs act on a variety of sites, hence, there is the possibility of synergistic effects when agents are combined. The commonly used medications are cyclooxygenase inhibitors (aspirin), and inhibitors of various platelet surface receptors including P2Y12 (clopidogrel, prasugrel, and ticagrelor), GPIIb/IIIa receptor antagonists (abciximab, tirofiban, and eptifibatide), dipyridamole, phosphodiesterase 3 (PDE3) inhibitor (cilostazol), warfarin, direct thrombin inhibitors (dabigatran and bivalirudin), factor Xa inhibitors

(rivaroxaban and apixaban), and heparin (unfractionated, low-molecular-weight heparin).[55]

The optimal choice and dosage of antiplatelet agents has been long debated. The CAPRIE trial showed that clopidogrel is more effective than a medium dose (325 mg daily) aspirin in reducing serious vascular events and had a similar safety profile.[56] Preoperative use of clopidogrel does not increase the incidence of per-operative bleeding.[57] NICE considers clopidogrel to be cost effective in patients with PAD.[58] In the authors practice, because of historical cost consideration, we use aspirin (75 mg) as first-line antiplatelet for all patients with PAD, with clopidogrel second line in aspirin-sensitive cases. However, current guidance would support a generic clopidogrel-first strategy in all patients with PAD.[58]

Aspirin and clopidogrel resistance are a growing concern with an increased risk of cardiovascular events, including in stent stenosis in patients with antiplatelet resistance.[59,60] Both metabolic and genetic factors are implicated.[60,61] The newer antiplatelet agents such as prasugrel and ticagrelor are more efficient with less incidence of resistance.[62] Although individualized therapy with platelet function testing seems to be the way forward, there are several hurdles to be overcome.[63,64]

A Cochrane systematic review has confirmed that antiplatelet or anticoagulation therapy improves the patency after peripheral endovascular interventions.[65] Aspirin is commonly used for this purpose and is continued life long.[6] Although lacking evidence and guidance,[3,6,66] a second antiplatelet agent such as clopidogrel (dual antiplatelet therapy) is prescribed by some interventionists with variable duration after endovascular procedures.[67] In the authors practice, all patients will be on aspirin even before therapy and continue lifelong. Following SFA stenting or infrapopliteal endovascular interventions, the authors advocate dual therapy for 3 months and for high-risk patients may extend this to 12 months. There is no benefit in continuing dual therapy beyond 12 months.[68,69] Dual therapy is considered better than single therapy, but increases the risk of adverse events related to bleeding.[65] Further randomized trials and consensus guidelines are required to guide this practice.[70]

There is no role for routine usage of warfarin and aspirin in patients with PAD.[66] Similarly, anticoagulants are not routinely recommended after endovascular intervention.[66] In patients who are high risk for bypass occlusion and limb loss, warfarin can be considered after infrainguinal vein bypass.[3,66]

Drug Therapy for Symptomatic Relief

During the initial phases of the disease, patients experience pain only on walking (claudication pain) but with disease progression they also experience pain at rest. There are only five drugs licensed in the United Kingdom for relieving these symptoms,[5] and in the authors' practice naftidrofuryl oxalate is a first choice drug followed by cilostazol.

Naftidrofuryl Oxalate

Naftidrofuryl oxalate is a selective serotonin (5-hydrroxytryptamine 2 [5-HT2]) receptor antagonist acting on endothelial cells and platelets. It inhibits the serotonin-induced contraction in human vessels, increases the efficiency of aerobic metabolism, reduces erythrocyte rigidity, and improves the transcutaneous oxygen pressure in areas of ischemia.[71] It is the authors first choice drug in those patients who have failed to respond to supervised exercise and who are either unsuitable for, or have expressed a desire to avoid intervention. It is prescribed orally at a dose of 100 to 200 mg three times a day for a minimum of 3 months. The adverse effects include skin rash, diarrhea, nausea, and vomiting. Calcium oxalate kidney stones have been reported rarely.

A meta-analysis of randomized controlled trials (RCTs) showed that naftidrofuryl significantly improved the pain-free walking distance compared with placebo. The ratio of relative improvement was 1.37 with an absolute difference of 22.3%.[72] It is more cost effective than other drugs with an estimated cost of £6,070 gained per quality adjusted life year; for these reasons, and hence it is recommended by NICE.[73–76] Intravenous Naftidrofuryl oxalate is no longer used in the treatment of critical limb ischemia.[77]

Cilostazol

Cilostazol is a PDE3 inhibitor with antiplatelet, vasodilator, and antiproliferative activity.[6,78] It is prescribed at 100 mg twice daily, and a meta-analysis of RCTs showed that it improves claudication distance and quality of life.[79] There is emerging interest in its use for critical limb ischemia, and it is shown to have a beneficial effect on preventing and healing arterial leg ulcers.[80] It reduces restenosis and improves long-term patency after infrainguinal endovascular interventions.[81–85] As it is expensive and less cost-effective compared with naftidrofuryl, its routine use in patients with PVD is not recommended in the United Kingdom.[76] It is contraindicated in patients with congestive heart failure.

Other Drugs

Pentoxifylline affects the rheology of blood cells and lowers blood viscosity. It is associated with some improvement in walking distance, but this has limited clinical benefit and cost effectiveness.[73–75,86] Hence, it is not recommended for routine use.[5,6]

Inositol nicotinate has vasodilatory, fibrinolytic, and hypolipidemic effects. Its benefit over placebo is not clear in patients with PAD, and it is not recommended for routine use.[5] Similarly, Cinnarizine, although licensed, has no proven clinical benefit and hence is not recommended for routine use.[5]

Analgesics

In patients with rest pain analgesics play a major role in relieving symptoms before revascularization. In the authors' experience, simple analgesics such as paracetamol and ibuprofen are rarely sufficient and hence opioids (transdermal or oral) remain the drug of choice. Buprenorphine transdermal patches are effective and well tolerated in the outpatient setting. Peridural analgesia is an emerging treatment option, which requires further evidence.[87,88] Neuromodulation using spinal cord simulators improves pain relief and hence limb

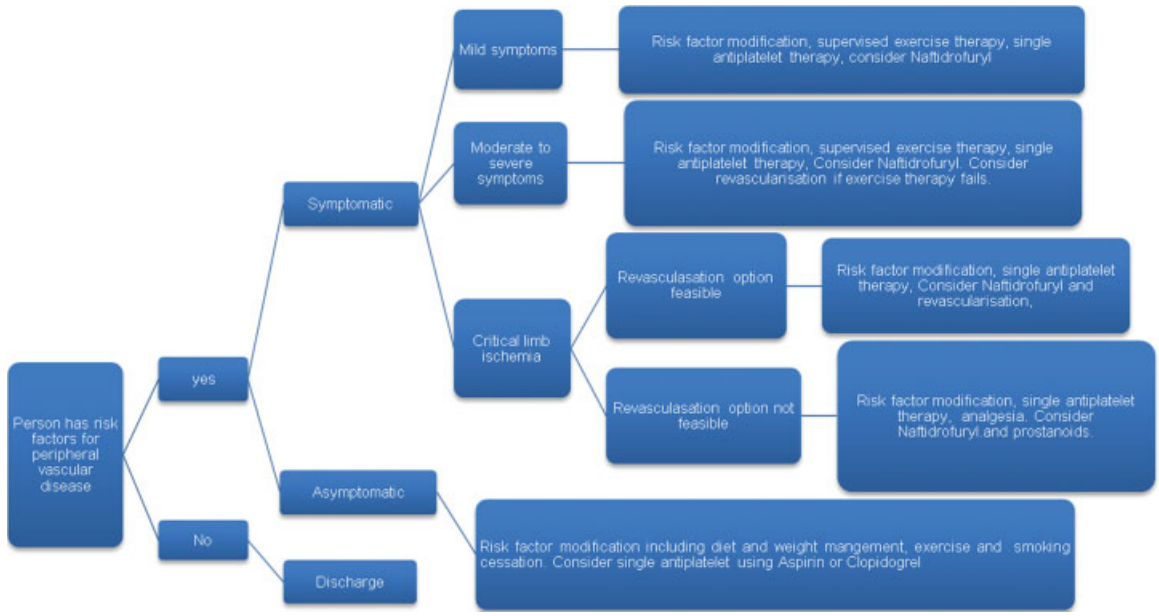

Figure 1 Flow chart showing the management of persons with peripheral arterial disease.

salvage, it should be considered in refractory cases. Spinal cord stimulators are expensive and associated with device specific complications such as infection of leads, which occurs in up to 17% of cases.[89]

Phantom limb pain can be very disabling and several analgesics including IV ketamine, oral or IV morphine, bupivacaine, and gabapentin have been shown to be effective in short- and long-term management.[90,91] However, there is no evidence to support preemptive analgesia in the prevention of phantom pain.[92]

Prostanoids

Prostaglandin and prostacyclin (e.g., iloprost or beraprost), are used in the treatment of critical limb ischemia due to their potent vasodilator, antiplatelet, and antiproliferative properties. They improve the rest pain, rate of ulcer healing and quality of life, and decrease the amputation rate,[93,94] but they are generally reserved for patients not suitable for surgical or endovascular revascularization.[95,96]

Novel Therapies—Therapeutic Angiogenesis

There are currently three therapeutic strategies being investigated for stimulation of collateral vessel formation in patients with PAD.[97]

Growth Factors

Several growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor, and placental growth factor have been shown to induce angiogenesis in PAD experimental models.[97] Only intra-arterial injection of recombinant FGF (bFGF-2) was tested clinically and shown to improve walking time.[98] Because of significant nephrotoxicity and marginal clinical benefit, no further clinical trials were performed.

Gene Therapy

In gene therapy, one or more therapeutic genes are delivered into the somatic cells in the hypoxic tissue (leg) using vectors.[99] *VEGF* gene with the help of adenoviral vector has been extensively investigated in limb ischemia models. Other genes investigated include *bFGF*, hypoxia-inducible factor 1α (*HIF-1α*), and angiopoietin-1 (*Ang-1*).[97] Initial clinical trials used $VEGF_{165}$ gene plasmid, transferred intra-arterially by coating an angioplasty balloon.[100] Later, direct injection into the ischemic muscle was shown to be feasible.[101] These trials, along with placebo-controlled randomized trials, confirmed the efficiency of gene transfer on improving vascularity in ischemic tissues.[102–105] However, significant side effects and a failure to translate into improved ulcer healing or reduced amputation rate means that this remains an experimental treatment.[99,106]

Stem Cell Therapy

The isolation of endothelial progenitor cells in 1997 opened a new chapter in therapeutic angiogenesis.[107] These cells migrate to ischemic tissues and are capable of neovascularization. Several animal model experiments have supported this view.[97] In the therapeutic angiogenesis using cell transplantation study (TACT) in 2002, bone marrow-derived mononuclear cells (BM-MNC) were injected into the gastrocnemius muscle of diabetic patients with PAD and improvement in an ankle brachial index, pain-free walking time, and rest pain was noted.[108] These findings were confirmed in several other small trials.[109,110] In the PROVASA study, there was improved ulcer healing and reduced rest pain within 3 months of intra-arterial administration of BM-MNC.[111] This technology is well tolerated and has good safety profile, but it needs a larger RCTs to practice evidence-based medicine.[112] A summary of the authors current practice is shown in ►**Fig. 1**.

Conclusion

There is good evidence to support therapy to reduce vascular risk factors in patients with peripheral vascular disease. The mainstay of medical therapy for all patients should include lipid lowering, blood pressure control, and an antiplatelet agent. In patients with rest pain, analgesic drugs are essential but revascularization is usually required. Drugs providing symptomatic relief for claudication are usually reserved for patients who fail supervised exercise training. Novel approaches such as angiogenesis may in the future provide an alternative to amputation in patients with critical limb ischemia who lack an option for revascularization.

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