Peripheral arterial disease: more than just a pain in the leg

By Professor Gregory Peterson

The 5-year survival of a patient with intermittent claudication is only around 70%, with three-quarters of the deaths being attributable to cardiovascular events. Whenever a diagnosis of peripheral arterial disease is made the patient should have a full cardiovascular risk factor assessment performed.

Case study

Mr DG is a 68-year-old man with a medical history of diabetes, hypertension, and dyslipidaemia. He has visited his GP because of a 4-month history of muscle pain in his right calf after walking two blocks. The pain is relieved by rest, and he reports no other symptoms. The GP notes that all findings are normal except for reduced pulses in the right popliteal and posterior tibial arteries. Mr DG’s right ankle-brachial index (ABI) is subsequently measured and found to be 0.65, while the left ABI is 0.94. His current medications include aspirin 100 mg daily, lercanidipine 10 mg daily, indapamide 2.5 mg daily, isophane insulin 20 units nocte, metformin 500 mg tds, and atorvastatin 10 mg daily. Mr. DG smoked two packs of cigarettes daily for 40 years, but he quit smoking 10 years ago. He doesn’t drink alcohol. His blood pressure recently averages 160/95 mmHg, HbA1c 7.1% and his BMI is 28.5 kg/m².

Peripheral arterial disease (PAD) in the legs, also known as peripheral vascular disease, is caused by atheromatous deposits in the walls of the arteries leading to insufficient blood flow to the muscles and other tissues. The classic symptom, intermittent claudication, is characterised by leg pain, cramping or weakness brought on by walking or climbing stairs, with disappearance of the symptoms following rest. Symptoms may affect the calves, thighs, hips, or feet. A somewhat surprising finding in population screening studies is that up to 50% of patients with intermittent claudication have never consulted a doctor about their symptoms.

The prevalence of PAD increases with age, with 15% to 20% of persons over 70 years having the condition. However, only about one-third of these people have symptoms (Figure 1); that is, for every patient with symptomatic PAD there are another three to four people with PAD who do not have intermittent claudication. The most widely used diagnostic test for PAD is the measurement of the ankle-brachial systolic pressure index (ABI), the ratio of the blood pressure in the lower legs to the blood pressure in the arms. ABI is calculated by measuring the maximum systolic pressure at the ankle (taking the highest value of either dorsalis pedis or posterior tibial arteries) with a handheld Doppler device and then dividing it by the systolic pressure in the arm (brachial artery). In healthy individuals an ABI of between 0.97 and 1.1 indicates the absence of organic disease. Most patients with symptoms of intermittent claudication will have an ABI between 0.5 and 0.8.

A patient with severe PAD may not have symptoms because some other condition, such as pulmonary disease or arthritis, limits exercise or they are sedentary. In contrast, some patients with very mild PAD may develop symptoms only when they become very physically active. Patients with intermittent claudication can have a markedly reduced quality of life due to their restricted mobility. On the other hand, only 25% of patients with intermittent claudication will ever significantly deteriorate and
major amputation is a relatively rare outcome, with only 1% to 3% of patients with intermittent claudication needing major amputation over a 5-year period.

In much the same manner as impotence, a major concern with PAD is the underlying pathological association with coronary artery disease. PAD is considered a strong marker for systemic atherosclerotic disease. Approximately 50% of patients with PAD also have coronary artery disease or cerebral artery disease. The risk factors for the development of PAD are similar to those for atherosclerosis elsewhere, and include cigarette smoking, diabetes mellitus, dyslipidaemia and hypertension, with cigarette smoking and diabetes conferring the greatest risk. Increasing age, male gender and non-Caucasian race are non-modifiable risk factors. Patients with PAD have a three times greater risk of myocardial infarction, stroke, or death from cardiovascular causes compared to age-matched individuals without PAD.

PAD is a marker for coronary and cerebral arterial events. Coronary artery disease is the cause of death in 75% of patients with PAD. The 5-year rate of non-fatal myocardial infarction and stroke is 20%, and of vascular death, 15%. These high rates of vascular events are similar in PAD patients with typical intermittent claudication, as well as in those who are asymptomatic.

Not surprisingly, the management of PAD should focus on the prevention of cardiovascular events (Box 1). Both lifestyle changes and therapeutic interventions (e.g. smoking cessation, blood pressure and serum lipid control) to reduce cardiovascular risk need to be considered. Symptoms of intermittent claudication, walking distance, and quality of life can be improved by risk factor modification, which includes stopping smoking and a structured exercise program. Further cardiovascular risk modification includes treatment for hypertension, diabetes and high cholesterol.

However, it has been suggested that the importance of risk factor management is less well appreciated in those with PAD than those with coronary artery disease, with a number of studies indicating that risk factor management in practice is less aggressive for those patients with PAD.

Aggressive modification of vascular risk factors to reduce the likelihood of myocardial infarction and stroke is an essential part of the management of peripheral arterial disease.

Exercise is an essential aspect of management of patients with PAD to improve both walking endurance and quality of life. A graduated walking program often increases the claudication distance and should be recommended. The catch-22 here is that walking is likely to induce the symptoms of intermittent claudication, which can clearly pose a barrier to adherence with an exercise program.

Figure 1. Weighted average prevalence of symptomatic peripheral arterial disease (intermittent claudication) from large studies.

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<th>Age-group</th>
<th>Prevalence (%)</th>
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Box 1. Principles of the management of peripheral arterial disease

- Smoking cessation
- Exercise rehabilitation program
- Control blood pressure to <140/90 mm Hg (<130/80 mm Hg in patients with diabetes or chronic kidney disease)
- Control dyslipidaemia
- Reduce HbA1c to <7.0% in diabetic patients
- Antiplatelet therapy with aspirin (or clopidogrel)
- Angiotensin-converting enzyme inhibitors
- Foot care
- Cilostazol in patients with moderate to severe intermittent claudication who have tried and failed an exercise program and are not candidates for vascular surgical or endovascular procedures
- Revascularisation surgery for incapacitating claudication or limb-threatening ischaemia.

Supervised hospital- or clinic-based programs, which ensure that patients receive a standardised exercise stimulus in a safe environment, are therefore preferred. In addition, proper foot care and podiatry supervision are essential.

Some of the components of management guidelines for patients with PAD have been informed by the results of large trials into the prevention of coronary artery disease, which have included sub-analyses of patients with PAD. For instance, in the Heart Outcomes Prevention Evaluation (HOPE) Study, a low ABI was a strong predictor of morbidity and mortality during the follow-up, even in patients with no clinical symptoms of PAD. Ramipril reduced the risk of clinical outcomes in those with a clinical history of PAD, as well as in the patients with subclinical PAD. Compared with placebo, ramipril significantly reduced cardiovascular events by 25% in patients with symptomatic PAD.

It has been consistently shown that treatment of dyslipidaemia with statins reduces mortality, cardiovascular events and stroke in...
patients with PAD, with and without coronary artery disease. In the Heart Protection Study, one-third of the patients had PAD. At 5-year follow-up in these individuals, simvastatin caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independently of age, gender, or serum lipids levels.

In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5796 patients with PAD were randomised to clopidogrel and 5797 patients were randomised to aspirin. At 1.9-year follow-up, the annual incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke was 3.7% in patients receiving clopidogrel versus 4.9% in patients receiving aspirin, a 24% significant decrease with clopidogrel. However, when the available trial data are incorporated into cost-effectiveness models, along with reasonable extrapolations, results suggest that long-term prevention with clopidogrel therapy in PAD does not have sufficient value to support a case for cost-effectiveness.

Antiplatelet agents should be given to reduce the incidence of vascular events. Aspirin is first-line therapy. Clopidogrel is slightly more effective than aspirin in reducing vascular events in patients with PAD, but is not available through the Pharmaceutical Benefits Scheme (PBS) for this indication.

Interestingly, readers might recall that beta-blockers can reduce peripheral blood flow and their use has been traditionally contraindicated or cautioned in with patients with peripheral vascular disease. However, a meta-analysis of 11 randomised controlled studies found that beta-blockers do not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild-to-moderate PAD.

Invasive options (lower-extremity percutaneous transluminal angioplasty or bypass surgery) are indicated for incapacitating claudication interfering with work or lifestyle, or limb salvage in patients with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, infection, or gangrene.

Cilostazol (Pletal) is a phosphodiesterase type-3 inhibitor with antiplatelet and vasodilating activity. It is used in the management of PAD (approved by TGA in January 2009 for intermittent claudication in patients without rest pain or peripheral tissue necrosis) and has been tried as an adjunct to coronary stenting in ischaemic heart disease. Cilostazol (50 to 100 mg twice daily) has been shown to improve walking distance compared with placebo. It is probably the drug of choice for the subset of patients with intermittent claudication where conservative or interventional treatments have failed to alleviate sufficiently their symptoms. The drug is generally well tolerated; the most common side effects reported have been headaches, nausea, diarrhoea, pain, infection, upper respiratory symptoms and peripheral oedema.

While the drug has logical appeal in terms of increasing the patient’s walking distance and capacity for exercise, and therefore ability to fully participate in a structured exercise program, there are no long-term data on whether treatment with cilostazol results in a reduction of cardiovascular events. Without this data, PBS listing is unlikely.

Similarly, it is unknown whether the improvement in walking distance with cilostazol is sustained. It is also unclear from the current evidence as to which patient subgroups gain maximum benefit. Finally, there is also debate about whether there is additional improvement with cilostazol once patients are already on an established exercise program.

Because of the cost of cilostazol therapy, and the safety and efficacy of an exercise program, we recommend cilostazol treatment be reserved for patients with moderate to severe claudication who have tried and failed an exercise program and are not candidates for vascular surgical or endovascular procedures.

Most guidelines now recommend against the use of oxpentifylline (pentoxifylline). In essence, its clinical effectiveness as therapy for claudication is marginal and not well established. To return to our case, one possibility to bear in mind was that Mr. DG’s statin therapy was causing myopathy. The measurement of the ABI has effectively ruled out that possibility. In terms of management, the control of diabetes, hypertension, and dyslipidaemia in Mr DG are all critical as part of the overall management of his PAD. Given the information provided, it appears that his blood pressure control may not be optimal. The addition of an ACE inhibitor would be extremely useful in assisting with blood pressure control, PAD and protecting against diabetic nephropathy. Further information is needed on the control of his dyslipidaemia and whether a larger dosage of atorvastatin is warranted. Mr DG should be encouraged to participate in a structured walking program, both for improving his PAD and for the benefit of his diabetes and cardiovascular risk factors. Essentially, because his PAD does not yet warrant consideration for revascularisation, aggressive medical management accompanied by lifestyle changes is appropriate for Mr DG.

References