Peripheral arterial diseases of the lower limbs

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Peripheral arterial disease

Introduction

Peripheral arterial disease (PAD) refers to a spectrum of clinical disorders caused by an impairment of blood flow to the extremities secondary to narrowing and/or occlusion of arteries (1). Whilst the true prevalence of asymptomatic PAD remains difficult to determine, a large global study found the overall incidence to be rising and to be more common in older male patients. The prevalence in a younger age group (45-49 years of age) was around 5%, rising to 18% in the over 85 age group (2). The same study also showed that PAD is more prevalent in higher income countries and increasing prevalence in lower income countries indicates an emerging global problem. It is estimated that greater than 10% of individuals over the age of 60 years would have some degree of PAD (3) and accounts for a large proportion of morbidity and mortality in the developed world. Cardiovascular diseases (CVD) including PAD also contribute to significant financial and social burden on any developed nation, with a vast proportion of the healthcare budget being spent to manage the problem (4).

Terminology and classification

Lower limb ischaemia is often classified based on the time of onset: "acute" or "chronic". Acute limb ischaemia refers to sudden disruption of the blood supply to the leg, threatening its viability and hence usually requires urgent revascularisation. The clinical features of acute limb ischaemia are often described as the "6Ps"; namely pain, pallor, pulseless, paraesthesia, paralysis and perishingly cold limb.

Chronic limb ischaemia refers to the gradual reduction of blood supply to the limb, often defined as over 2 weeks. The commonest cause of chronic limb ischaemia is PAD, which is the focus of this review.

Chronic limb ischaemia is often classified based on clinical severity, which reflects the viability of the limb. Intermittent claudication and critical limb ischaemia are the manifestations of peripheral arterial disease of the lower limb. These can be further classified by the Leriche-Fontaine and Rutherford classification systems (Table 1). Intermittent claudication refers to pain in a specific muscle group, brought on by exertion, relieved by rest and is reproducible. Intermittent claudication is caused by the inability of the blood supply to meet the oxygen demand of the muscle group

during exertion although the viability of the affected limb is not under threat. Critical limb ischaemia refers to inability of the blood supply to maintain tissue perfusion that meets the minimum oxygen demand to keep the limb viable. Critical limb ischaemia therefore, manifests as pain at rest despite opiate analgesia and/or tissue loss and a perfusion pressure of less than 50 mmHg for greater than two weeks (5). Patients with critical limb ischaemia will require urgent revascularisation for limb salvage.

Leriche-Fontaine classification		Rutherford clinical classification		
Grade	Clinical Aspects	Grade	Category	Clinical aspects
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Rest pain	II	4	Rest pain
IV	Arterial ulcer or gangrene	III	5	Minor trophic lesion
		III	6	Major trophic lesion

Table 1 – Classification of chronic limb ischaemia symptoms (Fontaine and Rutherford)

Natural history

PAD often has an insidious onset but certain risk factors accelerate symptom and disease progression. The presence of atherosclerotic lesions often predates the onset of symptoms by many years or even decades. The atherosclerotic lesions cause stenosis or even total occlusions, hence reduction of blood supply to the affected limb that may manifest as intermittent claudication or critical limb ischaemia. The effect the lesions have on the symptoms varies from patient to patient, partly depending on the degree of development of collateral blood supply, and their exercise tolerance or overall function. More importantly, the presence of chronic limb ischaemia has been shown to be associated with a higher all cause mortality, cardiovascular mortality and incidence of stroke and myocardial infarction, reflecting the system wide disease process of atherosclerosis (6).

The lower limb outcomes for patients with intermittent claudication are such that the majority do not progress to worsening symptoms, and only a small percentage, about 1 % go on to develop critical limb ischaemia. However, they have significant cardiovascular risk profiles, and their mortality from cardiovascular related disease at five years is about 30% (7). Whilst this is improving with improved risk factor management, it is still significantly higher than the population without PAD or intermittent claudication (7). Risk factor control to reduce major cardiovascular morbidity and mortality is therefore a priority in this patient cohort.

A diagnosis of critical limb ischaemia carries with it significant risk of morbidity and mortality - once diagnosed, about 15% of patients do not survive more than a year while approximately 20% of patients undergo major amputation of the affected limb within a year. The 5-year mortality rate for critical limb ischaemia has been shown to be about 40% (8). The reasons for such poor outcomes reflect the system wide process of atherosclerosis affecting the cardiovascular, renal and cerebrovascular systems causing complications such as myocardial infarction and stroke despite successful limb salvage (8).

Pathophysiology of atherosclerosis

There are many postulated theories on the development of atherosclerotic plaques. The bulk of research has focussed on the intimal injury theory - in which vascular endothelial cells are damaged by shearing forces, particularly so with prolonged periods of hypertension and in areas of increased turbulence within the vascular tree. Intimal injury leads to increased platelet aggregation and Low Density Lipoprotein (LDL) cholesterol deposition, and elevation of the levels of platelet derived growth factor (9). The other well described hypothesis for the development of atherosclerotic plaques is the cholesterol theory (10). In the cholesterol theory, excessive amount of LDL cholesterol deposits in the intimal layer causing an inflammatory response, leading to the formation of fatty streaks, and later plaques. LDL transport is regulated by HMGCoA reductase, which is dysregulated in patients with familial hypercholesterolaemia. Patients with familial hypercholesterolaemia suffer cardiovascular complications from a young age. The Framingham Heart Study (11) and the Japanese migration study (12) showed a strong casual link between cholesterol level and the development of cardiovascular disease.

In reality, it is a combination of factors that results in the build-up of atherosclerotic plaque. The overall pathophysiological process is dynamic in that the atherosclerotic plaques can remodel if risk factors are controlled, or worsen if the conditions allow for it (13).

Other rarer causes of chronic limb ischaemia include vasculitis, fibromuscular dysplasia, endofibrosis, coarctation of aorta, primary vascular tumours, adventitial cyst of artery, popliteal entrapment syndrome and pseudoxanthoma elasticum (1).

Risk factors for PAD

Hypertension

By far the largest risk factor for developing PAD is hypertension, with a greater emphasis on the systolic blood pressure (14). Controlling the systolic blood pressure, keeping this below 140mmHg, has been shown to reduce all cause mortality and morbidity in patients with cardiovascular disease(15). Hypertension is linked to all forms of cardiovascular disease, hence adequate blood pressure control has been shown to reduce mortality from strokes, ischaemic heart disease and PAD (14).

Cholesterol

LDL cholesterol level has been shown to have a linear effect on the development of atherosclerotic plaques and poor outcomes. The National Cholesterol Education Program Adult Treatment Plan III (NCEP ATP III) recommended targeting LDL control according to risk as demonstrated in Table 2 below (16).

Risk Category	LDL Goal	Initiate TLC*	Consider Drug Therapy
High risk: CHD[†]	<100 mg/dL (2.59 mmol/L)	≥100 mg/dL (2.59 mmol/L)	≥100 mg/dL (2.59 mmol/L)
CHD risk equivalents[‡] (10-year risk >20%)	Optional goal <70 mg/dL (1.81 mmol/L)	<100 mg/dL (2.59 mmol/L), consider drug option	
Moderate risk: 2+ risk factors[§] (10-year risk,[ǀ] 10% to 20%)	<130 mg/dL (3.37 mmol/L)	≥130 mg/dL (3.37 mmol/L)	≥130 mg/dL (3.37 mmol/L)
Lower risk	<160 mg/dL (4.14 mmol/L)	≥160 mg/dL (4.14 mmol/L)	≥190 mg/dL (4.92 mmol/L)

Table 2 – LDL targets for different risk groups (17)

(TLC - therapeutic lifestyle changes)

† CHD, coronary heart disease, includes myocardial infarction, unstable angina, stable angina, coronary artery procedures, or clinically significant myocardial ischemia.

‡ CHD risk equivalents include peripheral arterial disease, abdominal aortic aneurysms, carotid artery disease, diabetes, and two or more risk factors.

§ Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or taking antihypertensive medication, low high-density lipoprotein cholesterol (<40 mg/dL) [1.04 mmol/L], family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years)

Diabetes mellitus

Diabetes mellitus is known to accelerate the development of symptomatic PAD via a number of processes. Patients with diabetes mellitus develop endothelial dysfunction, with glycosylation of proteins and down-regulation of the nitric oxide pathway leading to stiffer and non-compliant vessels (18). Calcification of the blood vessels is also accelerated (18). Small vessel disease (microvascular) further complicates and compromises tissue perfusion in addition to large vessel lesions (macrovascular). Tight blood glucose control has been shown to be pivotal in delaying the appearance of PAD symptoms in patients with Type I diabetes mellitus and in reducing the incidence of microvascular complications in Type 2 diabetes mellitus (nephropathy and retinopathy) (19), but has not been shown to reduce the incidence of overall cardiovascular (macrovascular) risks in those with Type II diabetes mellitus (20). Insulin resistance is thought to play a more important role in the development of atherosclerotic lesions in the diabetic populations than previously thought.

Smoking

Tobacco smoking has long been implicated as a major risk factor for the development of CVD and PAD. Tobacco smoke is rich in free radicals that are known to cause endothelial dysfunction, reducing nitric oxide production and therefore vascular smooth muscle reactivity (21). It has been implicated in all stages of the development of PAD from accelerating the stable atherosclerotic plaque build-up, to unstable atheroma ulceration and haemorrhage leading to thrombosis due to its effects on activating the endothelial thrombotic pathways (22).

Age and Gender

Studies such as the Framingham Heart Study have shown an increase prevalence of PAD in men and the elderly populations (11). Women seem to have lower risks for developing PAD, particularly before the menopause, after which, the risks are similar to those in men.

Other risk factors include a positive family history for PAD or coronary artery disease as well as obesity (23).

Modifiable	Non-modifiable
Smoking	Age
Blood glucose control	Gender
Weight	Family History
Dyslipidaemia	Socio-economic background
Physical inactivity	Ethnicity

Table 3- Risk factors for PAD (23)

Clinical presentation and examination

PAD most often presents with symptoms of intermittent claudication; this can be thought of as angina of the calf muscles. History taking is often the key in making a diagnosis. It is often insidious, and the intensity gradually worsens with exertion. Therefore, patients may avoid exertion, limiting their daily function and affecting their quality-of-life. Intermittent claudication often starts in the calf muscles but may progress to the thigh and buttocks depending on the pattern of disease and arteries affected. The important differential diagnoses at this stage and how they can be detected are the following:

- Spinal canal stenosis - most commonly mistaken for PAD. Patients with spinal canal stenosis often complain of a worsening of symptoms when walking downhill, whilst those with PAD find it difficult to walk uphill. The presence of pulses and a pre-existing back condition are often key in differentiating spinal canal stenosis from PAD.

- Heart failure - patients with poor left ventricular function often lack the cardiac output to adequately perfuse the calf muscles when mobilising. The symptoms are identical to those of PAD, and one must be mindful of patients with symptoms in the presence of foot pulses and other symptoms and signs of heart failure. Often these patients will benefit from cardiac risk factors optimisation and a cardiology referral.

- Anaemia - Anaemic patients may sometimes present with worsening of claudication symptoms or claudication may be the presenting symptom of their anaemia. .

Patients with critical limb ischaemia often present with pain at rest, particularly at night, when lying flat which is relieved by sleeping in a chair or by hanging the affected leg out of the bed to overcome this pain. It is often refractory to opioid analgesics. Critical limb ischaemia patients can also present with tissue loss such as ulceration, gangrene and/or non-healing wound (image 1).

Image 1 – Patient with critical limb ischaemia of the left foot, following minor trauma on a background of an occluded superficial femoral artery on the left. Note the dry gangrene and exposed bone at the tip of the hallux and the trophic changes in skin immediately adjacent to the hallux. A mark was drawn upon admission to a specialist unit to monitor the extent of the associated cellulitis.

A general examination to assess the overall state of health of the patient is important for determining the appropriate management plan. Pertinent to patients with PAD, examination of upper and lower limb peripheral pulses by palpation is crucial, comparing the pulses with those of the contralateral limb. Examination of the abdomen to exclude an abdominal aortic aneurysm (felt as a pulsatile and expansile mass) is also routine. Temperature and sensation are useful signs, as is the presence of any tissue loss. Arterial ulcers are often seen on the extremities of the digits; typically they are punched out, with well-defined borders and tend to be deep. The skin surrounding the ulcer may be coo. Necrosis/ gangrene may also be seen over pressure points such as the tips of digits and on the heels.

A thorough history and examination help determine the acuity of each patient and when and where they should be referred for further opinion. In the clinic setting, performing an ankle/brachial pressure index (ABPI) can help confirm the diagnosis and distinguish between other differential diagnoses. ABPI is an index measure obtained by measuring the brachial systolic blood pressure

using a sphygmomanometer and Doppler probe and dividing this by the pressure of either the posterior tibial artery or dorsalis pedis artery in the ankle/ foot of the affected leg. A normal reading should give an index of 1, i.e., no difference between arterial pressure in the upper and lower limb. An index of lower than 0.8 is abnormal and warrants further investigation. One common limitation of the ABPI is that patients with diabetes and/ or chronic kidney disease (particularly end stage renal failure) may have an abnormally high ABPI due to excessive calcification of the lower limb vessels, requiring higher pressures or even inability to compress the vessel. This can mislead the clinician into thinking that blood flow is adequate, when it might not be. Performing ABPI before and after exercise (on a treadmill based on a specific protocol) can reveal a typical drop in the APBI after exercise, often seen in patients with significant PAD.

Image 2 – ABPI being measured at rest and after the patient exercises on a treadmill

All patients with PAD should be referred to vascular specialists / surgeons for assessment and management. In general, patients with suspected acute limb ischaemia should be seen in accident and emergency without delay, while those with critical limb ischaemia and intermittent claudication should be seen and assessed by a vascular specialist as an urgent and routine referral, respectively.

Investigations

Before embarking on any intervention, a clear picture of the pattern of disease is vital. Most vascular units have access to high quality diagnostics within the unit. NICE recommends that the first-line imaging modality should be arterial duplex imaging (24). This combines B-mode ultrasound and colour-flow Doppler to identify any narrowing or occlusions and determine their significance by measuring the velocity change over the lesion. This modality is non-invasive but is time consuming and is highly dependent on specially trained operators.

Cross-sectional imaging, in the form of computed tomography angiography (CTA) or magnetic resonance angiography (MRA) shown in image 3, may provide anatomical information for planning of interventions. NICE recommends MRA as a first choice as this does not involve any ionising radiation and the contrast used is less nephrotoxic (25). This must be taken in the context of the facilities available and the presence of any contraindications to either modality.

Image 3 – MRA of a 72-year-old male patient with disabling right leg claudication, showing multiple stenoses in his iliac and common femoral arteries bilaterally.

Management

Lifestyle and risk factors modification

Lifestyle and risk factor modification form the first-line of treatment for all patients with symptomatic PAD including those requiring operative management.

Smoking cessation
Smoking cessation is important and has been shown to reduce the risk of cardiovascular events and slow down atherosclerotic disease progression (26) (27). Smoking cessation can be achieved using a variety of methods but requires determination from the patient. Nicotine replacement therapy has taken on many forms and most are widely available to purchase over the counter. The use of pharmacotherapy such as Varenicline has seen an increase in successful attempts by patients to stop smoking. Cessation often requires a combined cognitive behavioural therapy and pharmacological approach in order to be successful (28). Patients who continue to smoke have poorer outcomes following revascularisation in terms of limb loss and cardiovascular disease associated complications (29).

Recently, with the advent of e-cigarettes and nicotine replacement therapy, a shift towards harm reduction has taken place, and whilst the safety of some of the newer e-cigarettes available on the market is not proven, a consensus exists that they are less harmful than cigarette smoking (30).

Exercise

Supervised exercise programs (SEP) often involves weekly meetings of groups of patients with PAD facilitated by an allied healthcare professional, normally a physiotherapist who advises on healthy lifestyles and creates a tailored exercise regimen. Patients are seen regularly and progress is tracked over the course of a few months. The NICE recommends that all patients with intermittent claudication should be referred for SEP prior consideration of any arterial revascularisation (24). In units that employ SEP for patients with claudication, intervention rates are lower and patients are often all too keen to have a non-interventional alternative. When compared to home-based exercise and walking advice, a recent Cochrane review (31) found SEP to be superior in increasing the walking distance, making it the preferred treatment option for many patients.

Blood pressure control
Blood pressure control is key in managing patients with PAD, as it is the single largest risk factor for cardiovascular disease. Often patients would need multiple agents to control blood pressure and specialist input may be required (15). The target blood pressure in patients under the age of 80 years is 135/85mmHg and NICE recommends starting with angiotensin converting enzyme inhibitors if tolerated, adding further agents if control is not achieved (32).

Glycaemic control
In recent studies, tight glycaemic control (assessed with HbA1c) has failed to produce a significant reduction in mortality from major cardiovascular events whilst improving microvascular complications (20). Nevertheless, it is important that glycaemic control is achieved, including with the use of newer medications such as DPP-4 inhibitors and glucagon-like peptides. In the context of wounds from critical limb ischaemia, tight glucose control is likely to aid wound healing (33).

Antiplatelet therapy
The use of low dose antiplatelet therapy such as aspirin (75mg *od*) and clopidogrel (75mg *od*) has been shown in a large number of trials to reduce the complication rate of cardiovascular disease. All patients with PAD should be started on an antiplatelet agent, and the most recent NICE guidance (24) favours the use of clopidogrel over aspirin as it is more efficacious in its antiplatelet activity and has lower gastro-intestinal side effects. This was demonstrated by the CAPRIE study, which was a large randomised control trial in patients with atherosclerotic vascular disease to reduce the incidence of complications, when compared to medium dose aspirin (325mg) (34). With the advent of Novel Oral Anti-Coagulants, NOACs, a number of studies have been interrogating their influence on patients with PAD. The COMPASS study was a randomised controlled double-blind study comparing rivaroxaban (5mg twice daily) alone, aspirin (100mg once daily) alone and a combination of rivaroxaban (2.5mg twice daily) and aspirin (100mg once daily), in patients with stable CVD. This study showed superiority with respect to mortality reduction from CVD in the rivaroxaban and aspirin group (35). The Voyager PAD study is currently following up patients with symptomatic PAD, who have been randomised to rivaroxaban (2.5mg twice daily) and aspirin *vs.* aspirin alone. Results from Voyager PAD are expected to be published after October 2019 (36).

Statin therapy
The role of cholesterol in forming atherosclerotic plaques is well established, and with the development of HMGCo-A reductase inhibitors, a marked reduction in cardiovascular events in patients with established coronary artery disease as well improvement in PAD symptoms have been seen (37). One of the first studies to demonstrate this on a large scale was the Scandinavian Simvastatin Survival Study which showed a marked reduction in cardiovascular events and symptoms in patients receiving lipid lowering therapy with simvastatin compared to patients receiving placebo (38). Statins offer benefit almost independent of cholesterol levels, including effects on plaque stabilisation and improved endothelial function. Newer agents such as atorvastatin should be considered for secondary prevention for all patients newly diagnosed with PAD, without the need of a specialist opinion. The 2017 NICE guidance recommends 80 mg of Atorvastatin for secondary prevention and 20mg Atorvastatin for patients in whom primary prevention is considered (Qrisk score Greater than 10%) (39). Patients should be counselled about potential side effects such as muscle ache and liver function tests should be monitored.

Weight loss
Weight loss should be advised where appropriate for patients with PAD, particular in the context of the metabolic syndrome (obesity, hypertensive, dyslipidaemia and diabetes). Weight loss will help improve insulin resistance and hypertension, reducing progression of atherosclerotic disease (20).

Interventional and surgical treatment
Interventional and surgical treatment for patients with PAD is often complex and can be associated with significant risks, including bleeding, infection and limb loss. There are therefore generally reserved for those with critical ischaemic limb.

Critical limb ischaemia - These patients are at risk of losing their limb without intervention, which justifies the risk of procedures to reconstruct the arterial system of the affected limb. There is usually adequate time to plan these interventions which may involve staged procedures.

Intermittent claudication - Most patients with stable intermittent claudication can be managed successfully with modification of risk factors and medical management only. A relatively small group of patients with extremely disabling short distance intermittent claudication despite optimal risk factor and medical management may sometimes be considered for interventional and surgical treatment, provided the benefits outweigh the risks, and patients are fully counselled.

Endovascular treatment
Endovascular treatment relies on the use of digital subtraction angiography to identify and treat arterial lesions. Direct arterial puncture is required followed up contrast injection to visualise the lesions. With the rapid development of adjuncts and techniques, many lesions can now be crossed and angioplastied to improve distal flow, including long occlusions (Image 4) and below-the-knee and even pedal vessels. Some patients can undergo treatment as day case procedures under local anaesthesia, with relatively low peri-procedural complications. However, with the treatment of more complex lesions, particularly in patients with significant co-morbidities, the risk of complications increases. These include systemic complications such as contrast-induced nephropathy and those associated with anaesthesia; puncture site problems such as vessel damage with bleeding and pseudoaneurysm formation; and distal complications such as embolization and target vessel loss. Not all lesions are amenable to endovascular intervention: for example, disease of the common femoral and profunda femoris arteries are more commonly treated by open surgery. Further, lesions that are resistant to endovascular treatment will also require open surgery. Hybrid procedures involving a combination of open surgery and endovascular treatment are also increasing performed in hybrid theatre suites to tackle multi-level disease.

A   B   C

Image 4 – Angiography of a patient with critical limb ischaemia secondary to a superficial femoral artery occlusion (a), with an angioplasty balloon over a wire across the lesion (b), and the end result with good run-off into the popliteal trifurcation (c).

Open revascularisation - This is often achieved by arterial reconstruction such as endarterectomy with or without patch plasty, and/or bypass using a suitable conduit such as autologous great saphenous vein (*in situ* or reversed) or a prosthetic material such as Dacron or polytetraflourethylene (PTFE). Endarterectomy with or without patch plasty is often used to treat short occlusive disease while bypass is required for long occlusions. In order for bypass surgery to be successful, good inflow and outflow vessels, a suitable bypass conduit (e.g. appropriate diameter autologous vein graft), adequately "thinned" blood with anti-platelet and /or anti-coagulation, and sufficient cardiac output are required.

When compared with endovascular revascularisation, open bypass surgery is often thought to be more superior in terms of patency and durability but limited by its invasiveness. For example, for patients with critical limb ischaemia due to femoro-popliteal disease, a large multi-centre randomised controlled trial in the UK (BASIL) demonstrated that there was no significant difference in the amputation-free survival and overall survival between bypass surgery first and balloon angioplasty first strategy in the first two years, with the former being more expensive and associated with higher morbidity. However, after 2 years, there was a trend that bypass surgery first was associated with an increase in overall survival and a trend towards improved amputation free survival (40).

The outcome of revascularisation, in terms of mobility and functional status, is dependant on the pre-morbid condition of the patient. A study found that patients who were non-ambulant prior to

revascularisation did not achieve a significant level of mobility despite successful revascularisation (41). This needs to be taken into account when deciding the optimal treatment option for patients, with lower risk options being preferable for non-ambulant patients despite certain limitations.

Major amputation
Major amputation is the main treatment option for patients with intractable ischaemic rest pain without a viable revascularisation option, excessive tissue loss and worsening infection leading to sepsis. Major amputation at the level of below- and above- the knee carries with it a high cost in terms of morbidity and mortality with up to 40% of patients not surviving more than a year after amputation (42). The socio-economic costs of looking after and rehabilitating patients with major limb amputations is also worth noting. In the UK, major limb amputation is estimated to cost in excess of £10000 in the first year as opposed to £4000-6000 for revascularisation (43). Social isolation and loss of employment are also major issues. It is therefore an option of last resort and performed in an attempt to improve the quality of life of patients whose limb cannot be salvaged.

Others treatment options

Vasodilators such as naftidrofuryl oxalate have a role as an adjunct in patients with claudication together with SEP and risk factor management (24) .

Other than amputation, the options are limited for patients with critical limb ischaemia not amenable to revascularisation. A specialist pain service can help optimise pain control, and they should be involved as early as possible. There is limited evidence that intravenous iloprost (a prostaglandin analogue that causes vasodilatation) can sometimes help alleviate symptoms of rest pain but is not always well tolerated (44). Chemical sympathectomy of the lumbar plexus to alleviate symptoms of rest pain is no longer recommended by the most recent NICE guidance on PAD (24).

Novel therapies aimed at stimulating angiogenesis in patients with critical limb ischaemia using the patients' own stem cells are still in their infancy and so far have only produced mixed results (45). Further studies in this field are being undertaken to develop a better understanding of how patient outcomes can be improved.

Summary
A diagnosis of PAD brings with it additional morbidity and mortality from other cardiovascular diseases such as coronary artery disease and stroke. The system wide presence of atherosclerosis is prompting more vascular surgeons and primary care physicians to focus on risk factor modification and secondary prevention strategies to reduce the overall disease burden.
In patients with intermittent claudication, optimal medical therapy to reduce cardiovascular mortality and SEP to improve walking distance and quality of life are the mainstay of treatment. Arterial reconstruction in this group needs to be considered carefully given the associated risks. Patients with critical limb ischaemia face a poor prognosis in terms of limb loss and overall mortality. However, revascularisation is possible in many patients, with the aim of limb salvage.

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