Peripheral arterial disease

A systematic management strategy

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Peripheral arterial disease affects over 200 million people worldwide. A proportion of patients are asymptomatic, whereas others experience exertional leg pain or symptoms of critical limb ischaemia. Concomitant atherosclerotic disease progression in other vital vascular territories raises the risk of myocardial infarction and stroke in this patient cohort. A systematic management strategy is crucial and must address risk factors for atherosclerosis while aiming to improve mobility and quality of life and prevent major lower limb amputation.

What is peripheral arterial disease?

Peripheral arterial disease (PAD) commonly refers to atherosclerotic disease with stenosis or occlusions of the lower extremity arterial tree that results in reduced tissue perfusion. PAD encompasses a wide range of symptomatology and disease severity. Although a proportion of individuals with PAD are asymptomatic, other patients experience exertional leg pain (intermittent claudication [IC]) or symptoms of severely advanced PAD (critical limb ischaemia [CLI]).

CARDIOLOGY TODAY 2016; 6(3): 6-12

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The Fontaine and Rutherford classification systems are widely used to describe the severity of PAD (Table 1). The Fontaine classification was first published in 1954 and is based solely on clinical symptoms; the Rutherford classification (published in 1986 and revised in 1997) takes into account clinical findings, Doppler assessment and measurements of ankle brachial index (ABI [see below]).

Intermittent claudication

IC is one of the most common reasons for patients to be referred to a vascular specialist. Patients typically experience calf symptoms while walking, which range from fatigue to aching. These symptoms occur as a result of reduced muscle blood flow, which is unable to meet the increased metabolic requirements of exercise. Pain or discomfort may also occur in the thigh or buttock. The symptoms of IC are alleviated by a brief period of rest, after which the patient can resume walking.

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Critical limb ischaemia

In patients with CLI, tissue perfusion is further reduced and is unable to meet the basal metabolic requirements of the tissue for normal cellular growth, replication and repair. It is associated with rest pain and ischaemic ulceration or gangrene of the forefoot or toes. A clinical diagnosis of CLI is made on the basis of these symptoms in association with reduced ankle pressure (<50 mmHg) or toe pressure (<30 mmHg) or reduced ABI (<0.40).

Rest pain is often described as burning pain, uncomfortable coldness or paraesthesia of the lower limb extremity that interferes with sleep. The discomfort is worsened by leg elevation due to elimination of gravity-assisted tissue perfusion. Rest pain is often lessened by a dependent position, such as hanging a foot over the edge of the bed. Ischaemic ulcers are the result of minor trauma that fails to heal due to poor cellular regenerative capacity from severely compromised perfusion.

Key points

- **Although a proportion of patients with peripheral arterial disease (PAD) are asymptomatic, others experience intermittent claudication (IC) or symptoms of critical limb ischaemia (CLI).**
- **Patients with PAD are at a higher risk of cardiovascular and cerebrovascular morbidity and mortality.**
- **Measurement of the ankle brachial index is a simple, noninvasive test for quantifying vascular compromise to the lower limb extremities.**
- **Management of atherosclerotic risk factors is crucial in all patients with PAD.**
- **In patients with IC, revascularisation should be reserved for those with severe limitation to mobility or who have failed medical management.**
- **In patients with CLI, revascularisation aims to prevent limb loss, resolve rest pain and heal ischaemic ulceration or gangrene.**

Natural history of PAD

After a diagnosis of IC, 25% of patients deteriorate over the course of the first year, whereas 50% of patients remain stable after five years of follow up.[1] Among those who deteriorate, approximately 5% will experience significant deterioration and need to undergo intervention for revascularisation and 1 to 2% may progress to major amputation. Those who remain stable may have had better medical management and risk factor modification. In contrast, observational studies have shown that one year after a diagnosis of CLI, only 50% of affected individuals are alive without a major amputation, and that 25% have required a major amputation and 25% have died.[1] CLI implies advanced atherosclerotic disease with multisegmental involvement of the vasculature and severe compromise to perfusion at the tissue level. A diagnosis of CLI thus indicates a poor long-term prognosis with high rates of mortality and limb loss.

Disease associations

Atherosclerosis in the lower limb arteries is often accompanied by similar disease processes involving the cardiac and cerebral vasculature. Hence, patients with PAD have a higher risk of stroke and myocardial infarction (MI), and the risk has been shown to increase as early symptoms progress to CLI.[2] In patients with PAD, the risk of stroke is increased by up to 40% for stroke and by up to 60% for MI.[2]

Physical examination

In patients presenting with PAD, a comprehensive and systematic approach to physical examination, along with a relevant clinical history, often helps to ascertain the degree of severity of arterial disease. A full physical examination should be undertaken that includes all peripheral pulses. The appearance of the lower extremities provides an indication of the extent and severity of PAD: loss of skin

Table 1. Classification systems for severity of lower limb ischaemia

Fontaine classification	
Stage	**Symptoms and signs**
1	None
2a	Intermittent claudication without pain on resting but with claudication at a walking distance of >200 metres
2b	Intermittent claudication without pain on resting but with claudication at a walking distance of <200 metres
3	Nocturnal and/or resting pain
4	Necrosis and/or gangrene in the limb
Rutherford classification	
Category	**Symptoms and signs**
0	None
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Rest pain
5	Ischaemic ulceration not exceeding ulcer of the digits of the foot
6	Severe ischaemic ulcers or frank gangrene

hair distally, skin thinning and dryness, and nail thickening are all suggestive of chronic ischaemia. Calf, ankle and pedal oedema may indicate a sedentary lifestyle or dependent positioning of the legs to relieve rest pain. Ulcers over the forefoot and toes are a frequent manifestation of severe PAD.

Measurement of the ABI is useful for assessing the degree of arterial disease in the lower limb extremities and to help make informed decisions pertaining to management. The measurement and interpretation of the ABI are described in Figure 1.[3]

Differential diagnosis

Symptoms of PAD can be mimicked by several other clinical conditions. A careful history and detailed clinical examination can often help differentiate PAD from other causes of lower limb pain. Important differential diagnoses of IC are described in Table 2.[4]

Uncommon vascular causes of symptomatic lower extremity arterial disease may also need to be considered. These include arteritis (e.g. giant cell arteritis), popliteal entrapment syndrome, endofibrosis (iliac artery syndrome in cyclists), popliteal aneurysms and Buerger's disease (thromboangiitis obliterans).

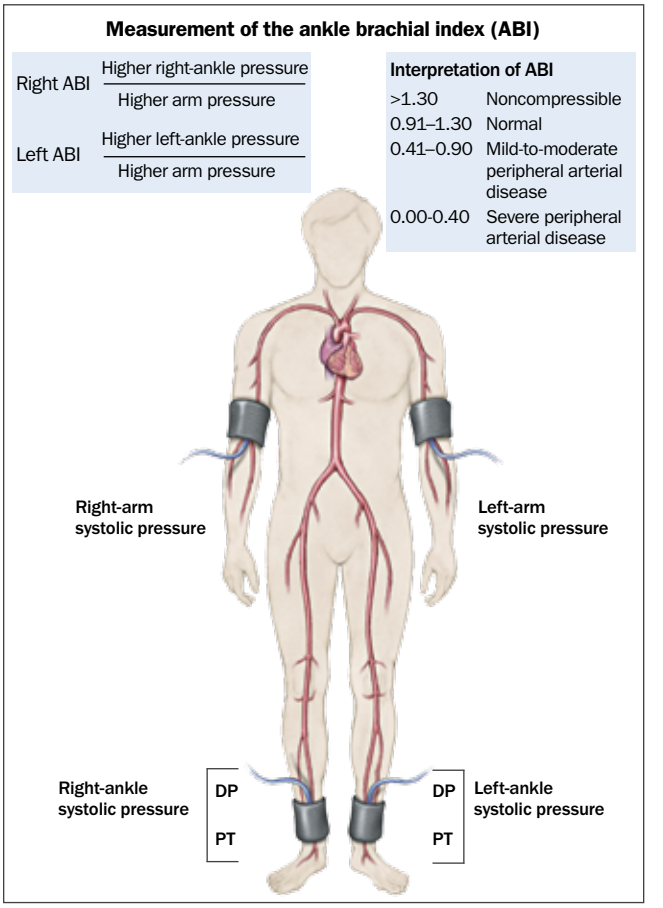


Figure 1. The ankle brachial index (ABI) is used to make an objective assessment of perfusion deficit. Systolic blood pressure is measured in each arm and in the dorsalis pedis (DP) and posterior tibial (PT) arteries. The patient should be supine and resting for at least five minutes before the measurements are made. The right ABI and left ABI are then calculated according to the equations shown above. The higher of the two brachial pressures (left or right arm) and the higher of the two pressures at each ankle (DP or PT) are used for the ABI calculations.

Hiatt WR. N Engl J Med 2001; 344: 1608-1621.[3] © Massachusetts Medical Society. Reprinted with kind permission.

Imaging

Duplex ultrasound

Duplex ultrasound is a noninvasive imaging modality that does not require the use of nephrotoxic contrast agents. Modern duplex ultrasound devices offer significantly improved image quality that can characterise arterial anatomy and detect haemodynamically significant lesions with accuracy similar to that of conventional contrast angiography (Figures 2a and b).

Computed tomographic angiography

Modern multidetector CT scanners are capable of very high-resolution images with 3D reconstructions, enabling clear images of the arterial tree from aorta to calf to be obtained for preinterventional planning (Figure 3). However, computed tomographic angiography poses

Table 2. Differential diagnosis of intermittent claudication[4]*

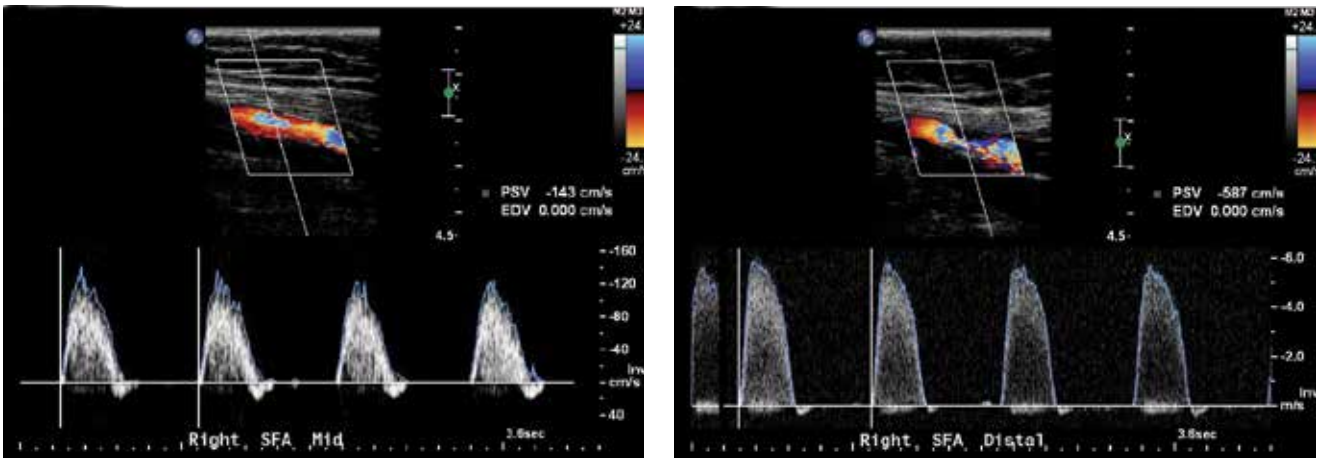
Characteristics	Onset relative to exercise	Effect of rest	Effect of body position
Intermittent claudication			
Cramping, aching, fatigue, weakness or frank pain in the buttock, thigh or calf muscles (and rarely the foot) Symptoms are reproducible	After same amount of exercise	Rapidly relieved	None
Nerve root compression (e.g. herniated disc)			
Sharp lancinating pain that radiates down the leg, usually posteriorly History of back problems is common	Soon, if not immediately, after onset	Not quickly relieved (and often present at rest)	Relief may be aided by adjusting back position
Spinal stenosis			
Motor weakness more prominent than pain Hip, thigh, buttocks may be affected (follows dermatome) History of back problems is common Symptoms provoked by intra-abdominal pressure	After walking or standing for variable lengths of time	Relieved by rest only if position changed	Relief by lumbar spine flexion (sitting or stooping forward)
Arthritic, inflammatory processes			
Aching pain in the foot Symptoms are variable, may relate to activity level	After variable amount of exercise	Not quickly relieved (and may be present at rest)	May be relieved by not bearing weight
Hip arthritis			
Aching discomfort in the hip, thigh, buttocks (usually localised to hip and gluteal regions) Symptoms are variable, may relate to activity level or weather changes	After variable amount of exercise	Not quickly relieved (and may be present at rest)	More comfortable when sitting, weight taken off legs
Symptomatic Baker's cyst			
Swelling, soreness, tenderness behind knee and down calf Symptoms are not intermittent	With exercise	Present at rest	None
Venous claudication			
Tight, bursting pain in the entire leg (usually worse in the thigh and groin) Often history of iliofemoral deep vein thrombosis, signs of venous congestion, oedema	After walking	Subsides slowly	More rapid relief with leg elevation
Chronic compartment syndrome			
Pain in the calf muscles Typically occurs in heavy muscled athletes	After much exercise (e.g. jogging)	Subsides very slowly	More rapid relief with leg elevation

* Adapted from: Norgren L, et al. J Vasc Surg 2007; 45 Suppl: S5-S67.[4]

difficulties with interpreting the patency of arteries with heavily calcified vessel walls, and for this reason it may be of limited use in patients with advanced PAD. In addition, high contrast load limits its use in patients with renal impairment.

Magnetic resonance angiography

The use of gadolinium-enhanced magnetic resonance angiography (MRA) is increasingly gaining acceptance for the evaluation of patients with lower limb ischaemia (Figure 4). It can be used to visualise the entire arterial tree, including pedal vessels, and avoids the need for standard ionic contrast agents. However, MRA may not be a reliable mode of investigating low flow arterial systems because tight stenosis can be misinterpreted as occlusions. In addition, the use of MRA is precluded in patients with pacemakers or newly placed metallic implants and in patients who have severe renal impairment.



Figures 2a and b. Duplex ultrasound of the superficial femoral artery of a patient with symptoms of peripheral arterial disease. a (left). Normal arterial flow pattern with a peak systolic velocity (PSV) of 143 cm/s at the mid-thigh ('SFA mid'). b (right). A blunted waveform with a significantly elevated PSV of 587 cm/s of the distal artery ('SFA distal'), which is suggestive of a tight stenosis.

Digital subtraction angiography

Conventional intra-arterial digital subtraction angiography continues to be an important imaging modality for visualising the lower extremity vasculature (Figure 5). However, angiography is associated with higher morbidity and mortality risks than other (noninvasive) imaging modalities. In contemporary practice, it is generally reserved for cases in which there is an intention to treat a lesion as part of the procedure.

Management guidelines

Comprehensive guidelines on the management of patients with PAD have been published by international associations and are available online. These include the *Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)* (www.jvascsurg.org/article/S0741-5214(06)02296-8/abstract)[4] and the *ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease* (www.jvascsurg.org/article/S0741-5214(11)02076-3/abstract).[5]

Management of risk factors for atherosclerosis

Recommended medical management of cardiovascular risk factors in patients with PAD is essentially consistent with guidelines for risk factor management in ischaemic heart disease. The aims are to reduce the incidence of future cardiovascular events by targeting risk factors and initiating treatment strategies proven to improve outcomes. These strategies are crucial in the management of all patients with PAD, and especially in those with CLI, for whom the overall cardiovascular risk burden is high.

Smoking

There is a close association between smoking and accelerated atherosclerosis, with a large evidence base to demonstrate a dose-dependent correlation between smoking and mortality, cardiovascular events and limb loss from amputation. Current smokers have a two- to fourfold higher risk of PAD than nonsmokers, and smoking cessation has been shown to improve some functional measures in patients with IC and reduce mortality.[6] Clinical trials have validated treatment strategies with nicotine replacement therapy and antidepressants to promote smoking cessation.[7,8]

Hyperlipidaemia

Elevated levels of total serum cholesterol, LDL-cholesterol and triglycerides are major risk factors for PAD and cardiovascular events. The TASC II guidelines recommend an LDL-cholesterol target of less than 2.6 mmol/L for all patients with PAD and a more aggressive target of less than 1.8 mmol/L in those with a concomitant history of atherosclerotic involvement in other vascular beds, such as the heart and brain.[4]

Statins are the first-line treatment for hyperlipidaemia and have been shown to reduce cardiovascular events, stroke and all-cause mortality. This may be largely explained by their pleiotropic effects, which help to improve endothelial dysfunction, reduce cellular inflammation and improve plaque stability. Nevertheless, up to 15% of patients develop intolerance to statin treatment, with symptoms of myalgia and/or deranged liver enzymes, which may require statin withdrawal, at least temporarily. In these situations, therapy can be resumed with the same statin at a lower dose when the blood biochemistry normalises or a switch can be made to a different statin. If symptoms recur, consideration can be given to combination therapy of ezetimibe and a low-dose statin or even to monotherapy with a nonstatin drug that is effective in reducing total serum cholesterol levels, such as nicotinic acid, ezetimibe or fenofibrate.

Hypertension

Hypertension is an independent risk factor for PAD. Current treatment guidelines recommend aggressive management, aiming for a

blood pressure reading of 140/90 mmHg or less in patients with PAD and a tighter range of 130/80 mmHg or less in patients with concomitant diabetes or renal insufficiency.[9] Angiotensin converting enzyme (ACE) inhibitors and beta blockers have been extensively investigated in large clinical trials, with ACE inhibitors in particular showing a significant reduction in stroke, MI and cardiovascular death.[10]

Diabetes

There is a close association between diabetes and PAD, and also patients with PAD and diabetes are at a higher risk of progressing to CLI. Of note is the fact that the limb loss rate in CLI is significantly higher in patients with diabetes than in those without. Although trials have shown that tight glycaemic control is beneficial for reducing microvascular complications, it is unknown whether this translates to improved lower limb perfusion and symptom relief. Patient compliance to glycaemic control measures can be monitored by aiming for glycated haemoglobin (HbA_{1c}) levels of less than 7%.

Antiplatelet therapy

The use of antiplatelet medications is widely accepted among clinicians for the treatment of cardiovascular disease and has been shown to reduce the risk of nonfatal MI, ischaemic stroke and vascular-related death. Major trials have also shown significant survival benefit with antiplatelet therapy in patients with PAD. The Antithrombotic Trialists' Collaboration concluded that the risk of fatal or nonfatal cardiovascular events in a group of patients with cardiovascular disease treated with antiplatelet therapy was superior compared with the untreated control group.[11] In patients who are intolerant of aspirin, the drug of choice is clopidogrel, which prevents platelet aggregation by irreversibly inhibiting an adenosine diphosphate chemoreceptor on the platelet cell membrane. Clopidogrel has been shown to have marginal benefit over aspirin in cardiovascular deaths, MI and stroke but is more expensive.

With the widespread use of endovascular stenting techniques in PAD, the use of dual antiplatelet therapy after insertion of a coronary bare metal stent for at least four weeks and after insertion of a drug-eluting stent for 12 months has become adopted practice. However, the marginal benefit of dual antiplatelet therapy has to be weighed carefully against the considerable risk of major haemorrhage.

Treatment for intermittent claudication

Supervised exercise programs

There is strong evidence to support the use of supervised exercise programs (SEPs) in patients with IC. A recent Cochrane review of 30 trials involving 1816 patients has shown an overall improvement in walking ability ranging from 50% to 200% with SEPs.[12] Exercise training, in the form of walking (performed for a minimum of 30 to 45 minutes per session, three to four times per week for not less than 12 weeks), has been shown to improve walking distance in trial conditions.

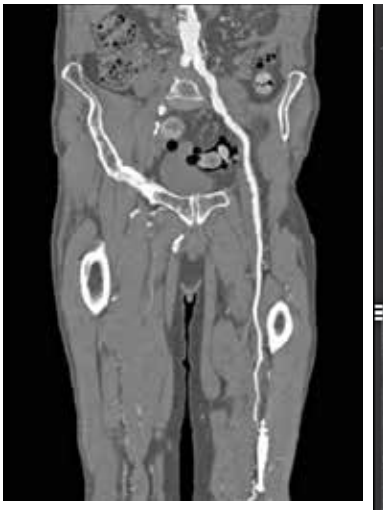


Figure 3 (above). CT angiogram of the left lower limb showing occlusion of the superficial femoral artery origin in the groin with a patent profunda femoris artery and reconstitution of the distal superficial femoral artery above the knee joint.

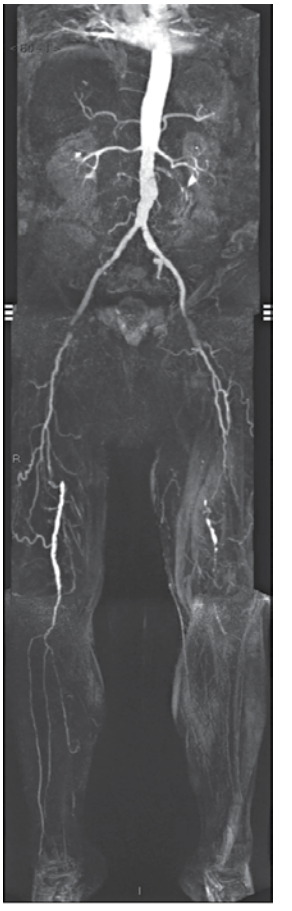


Figure 4 (right). Magnetic resonance angiography of the abdomen and lower limbs showing extensive peripheral arterial disease of the bilateral lower limbs.

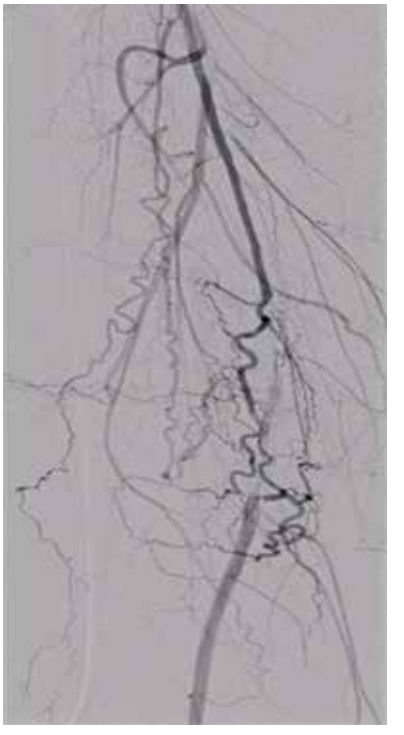


Figure 5 (left). Digital subtraction angiography of the lower limb showing a short occlusion of the superficial femoral artery, with distal refilling of the artery via collateral vessels.

Pharmacotherapy

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor that increases cyclic adenosine monophosphate levels and inhibits smooth muscle cell contraction and platelet aggregation. It also decreases serum triglyceride levels and increases concentrations of the protective HDL-cholesterol component. Several clinical trials and a meta-analysis of cilostazol in patients with IC have shown a significant increase in maximal walking distances and quality of life measures.[13]

Prostaglandins

Prostaglandin therapy has been focused primarily on the treatment of CLI and vasospastic conditions. The effects of prostaglandin analogues on vasodilatation and platelet aggregation are hypothesised to benefit patients with lower extremity ischaemia. Prostaglandins are frequently used for rest pain in individuals who have exhausted all other revascularisation options. Iloprost, a synthetic analogue of prostaglandin I2, is the most frequently used prostaglandin (off-label use). It is administered intravenously over four to six hours as a slow infusion due to its side effect profile. The infusions are continued for three to five days.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that is thought to improve oxygen delivery by its rheolytic effect on red blood cell wall flexibility and deformability, thereby reducing blood viscosity. Early trials of pentoxifylline were promising and showed improved walking distance in patients with IC as compared with placebo. However, more recent studies have given conflicting results and the drug is not widely used in contemporary practice.[14,15]

Revascularisation strategies

Patients who have CLI warrant revascularisation to prevent major lower limb amputation. Persistent lifestyle-limiting claudication despite optimal use of medical therapy and exercise programs is also an indication for intervention. With the advances in endovascular technology and the growing expertise of clinicians, there has been a shift towards an endovascular first approach to revascularisation. In select cases, however, open procedures or combined open and endovascular ('hybrid') procedures may provide optimal results.

In patients with IC, the judicious use of endovascular interventions is acceptable in individuals with a reasonable chance of symptomatic relief and low procedural risk. Most culprit lesions (70%) in IC are located in the femoropopliteal segment, with the remainder being in the aortoiliac segments or below-knee arteries.[16] Stenting of iliac lesions has been shown to be safe with good long-term patency rates. In the femoropopliteal segment, the recommendations are to treat short lesions with angioplasty and to treat longer and calcified lesions with selective stenting using self-expanding stents.

In patients with CLI, endovascular techniques have gained popularity because traditional surgical revascularisation carries significant perioperative risk in this cohort. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial showed equivalent limb salvage rates with both modalities at 36 months, although the patency rate was lower in the endovascular arm and patients required an increased number of secondary interventions.[17] The conclusion of this trial, and other similar trials, was that endovascular interventions are not as durable as open surgery, but facilitate wound healing and limb salvage with lower intervention-related morbidity. Subsequent target vessel restenosis or occlusion, however, does not necessarily lead to limb loss after wound healing has occurred, due to the lower metabolic demands of tissues to maintain homeostasis.

Recent interest in drug-coated stents and balloons for peripheral arterial interventions has been sparked by encouraging results in the coronary arteries. Sirolimus and paclitaxel, the two most widely tested antiproliferative drugs, have antimitotic activity that inhibits myointimal hyperplasia and in-stent restenosis. Trials of these drug-coated stents and balloons show promising early results and long-term results are awaited with interest.

Surgical revascularisation in patients with IC has to be considered carefully, taking into account the relatively benign and non-limb threatening nature of the disease process. Factors that influence the decision include the invasive nature of the intervention and its associated risks, the potential gain in symptom relief, the durability of intervention and freedom from need for re-intervention. Until robust, evidence-based guidelines for the treatment of IC are available, intervention must be customised to the needs of the individual patient. For patients with CLI, however, the guidelines drawn up from outcomes in major trials recommend surgical revascularisation in patients who are suitable surgical and anaesthetic candidates and are expected to live for a further two years.[5]

Future developments

Future developments in the treatment of PAD are aimed at alternative strategies to initiate neovascularisation of ischaemic tissues and prevent intimal hyperplasia. In theory, stem cell transfer and implantation of progenitor bone marrow mononuclear cells could promote neovascularisation, which is particularly relevant in the treatment of CLI in patients who have physiological or anatomical contraindications for revascularisation.

Conclusion

PAD encompasses a wide range of symptomatology and disease severity. Addressing the risk factors for atherosclerosis by optimising medical treatment is key to successful management and improves the overall risk of cardiovascular morbidity and mortality in this patient cohort. Revascularisation strategies for patients with IC improve quality of life and mobility and, more importantly, prevent limb loss in patients with CLI. The modern outlook to revascularisation involves both endovascular and open surgical strategies. **CT**

References

A list of references is included in the website version of this article (www.cardiologytoday.com.au).

COMPETING INTERESTS: None.

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