Peripheral arterial disease: a literature review

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Introduction: Peripheral arterial disease (PAD) is a common vascular condition that affects both quality of life and life expectancy with an increased risk of cardiovascular events.

Sources of data: A literature search was carried out of Pub-Med, MEDLINE, the Cochrane Library and Google Scholar from the establishment of these databases up to February 2012. The search was performed by using the keywords ‘peripheral arterial disease’ and one of the following words: ‘management’, ‘investigations’, ‘risk factors’, ‘epidemiology’, ‘revascularization’, ‘cryoplasty’, ‘atherectomy’ and ‘gene therapy’. Studies were limited to those published in English language.

Areas of agreement: Aggressive risk factors modification is needed to reduce cardiovascular-related mortality in PAD patients.

Areas of controversy: Choice of endovascular or surgical intervention remains controversial in an ever-evolving field.

Growing points: There is a rapid expansion of endovascular technologies aiming to improve the effectiveness of this modality.

Areas timely for developing research: The advances in the fields of gene therapy and therapeutic angiogenesis mean these are potential future treatments. Tissue engineering is a developing area and aims to produce grafts with similar patency and infection profiles to those of autologous material. Further elucidation of the pathophysiology of atherosclerosis is required to provide new targets for pharmacotherapy.

Keywords: peripheral arterial disease/atherosclerosis/revascularization/bypass surgery/atherectomy

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Peripheral arterial disease

Background and epidemiology

Despite a fall in the number of deaths due to circulatory diseases over the last decade, they remain the commonest cause of death in England and Wales. There is increasing recognition that peripheral arterial disease (PAD) is an independent risk factor for both myocardial infarction and stroke. Further, treatment of PAD reduces this risk. This review of the literature highlights the recent developments in the management of lower limb PAD.

PAD is a term used to describe the impairment of blood flow to the extremities usually as a result of atherosclerotic occlusive disease. Generally speaking, the presence of symptoms in PAD depends on the metabolic demands of the ischaemic tissue during exercise, the degree of collateral circulation and the size and location of the affected artery.

The incidence of PAD varies in the general population from 3 to 10% in people younger than 70 years to 15–20% in people older than 70 years. However, ~40% of PAD patients are asymptomatic, while only 10% of them present with typical intermittent claudication (IC). One third of PAD patients will have a complete occlusion of a major artery to the leg at first presentation.

Pathophysiology and risk factors

PAD results from any disease causing stenosis or occlusion of the lower limb arteries, with atherosclerosis disease being the most common aetiology.

Atherosclerosis is a complex process that involves endothelial dysfunction, lipid disturbances, platelet activation, thrombosis, oxidative stress, vascular smooth muscle activation, altered matrix metabolism, re-modelling and genetic factors. Also, the role of inflammation in all stages of atherosclerosis development has been widely recognized. It usually affects arterial bifurcations due to the effect of flow disturbance leading to impaired endogenous athero-protective mechanisms. Whilst this has allowed the identification of multiple potential circulating biomarkers, the complex and interwoven pathophysiology of plaque formation has limited the success of pharmacomodulating agents.

Atherosclerosis development commences in the teenage years as a result of endothelial dysfunction with the formation of a fatty streak, an inflammatory lesion that affects the intima, causing the formation of foam cells. This progresses with time to development of a
fibro-proliferative atheroma and finally advanced lesion, containing a necrotic lipid core covered by a fibrous cap which may thin and rupture.12

Risk factors for atherosclerosis include race; male gender; increasing age; smoking; diabetes mellitus; hypertension; dyslipidaemia; hypercoagulable and hyperviscous states; hyperhomocysteinaemia; systemic inflammatory conditions and chronic renal insufficiency.4

Overall, PAD increases with smoking, African-American ethnicity, renal insufficiency, diabetes mellitus and hypercholesterolaemia,5 while it has been documented that developing critical limb ischaemia (CLI) is more likely with ankle–brachial index (ABI) <0.7, age over 65 years, smoking, and hypercholesterolaemia.13

Details of non-atherosclerotic causes of PAD are beyond the scope of this review but are listed in Table 1.

**Table 1 Non-atherosclerotic causes of PAD.**

<table>
<thead>
<tr>
<th>Peripheral emboli</th>
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<tbody>
<tr>
<td>Aneurysm thrombosis or thromboembolism (aortic, popliteal)</td>
</tr>
<tr>
<td>Arteritis</td>
</tr>
<tr>
<td>Takayasu's disease</td>
</tr>
<tr>
<td>Thromboangiitis obliterans (Buerger's disease)</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td>Prior trauma or irradiation injury</td>
</tr>
<tr>
<td>Aortic coarctation</td>
</tr>
<tr>
<td>Endofibrosis of the external iliac artery (iliac artery syndrome in cyclists)</td>
</tr>
<tr>
<td>Primary vascular tumours</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
</tr>
<tr>
<td>Young patients</td>
</tr>
<tr>
<td>Adventitial cyst of the popliteal artery</td>
</tr>
<tr>
<td>Popliteal entrapment</td>
</tr>
<tr>
<td>Persistent sciatic artery</td>
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</table>

Morbidity and mortality

Only ~25% of patients with IC will significantly deteriorate, most frequently (7% to 9%) in the first year following diagnosis compared with 2–3% per year thereafter.4 The reported incidence of CLI is around 200–400 new cases every year per million population,14,15 and ~1 out of every 100 patients with IC will present with CLI per year.16

Although major amputation is a relatively rare outcome of claudication, with only 1–3% of claudicants needing it over a 5-year period,4 limbs with ulceration due to arterial insufficiency treated without revascularization will have a 19% risk of amputation at 6 months and 23% risk at 1 year.17
Cardiovascular risk varies with the severity of PAD and is closely correlated with both reduced and increased ankle brachial pressure index. The relationship between ABI and mortality over a period of 10 years in the Strong Heart Study is shown in Figure 1. Mortality in claudicants at 5, 10 and 15 years is 30, 50 and 70%, respectively, and similar rates are found in asymptomatic patients. Twenty-five per cent of CLI patients will die within a year of diagnosis. 

Clinical presentation of PAD and classification

Although 65–75% of patients with PAD are asymptomatic, the classic presenting symptom is IC which is usually described as muscle cramps, fatigue or pain in the lower legs induced by exercise and rapidly relieved by rest; often the symptom location indicates the level of arterial involvement. 

Less commonly, patients may present with critical limb ischaemia. The European Society of Vascular Surgeons defined CLI as a recurring ischaemic rest pain requiring analgesia for >2 weeks or ulceration or gangrene of foot or toes with ankle systolic pressure <50 mmHg or toe systolic pressure <30 mmHg (Fontaine’s III and IV). 

Fontaine’s classification, proposed in 1954, remains a popular way of staging PAD. It divides patients into groups according to their clinical presentation. A similar clinical classification developed more recently by Rutherford has the advantage of including haemodynamic data, helping to ensure that any rest pain or tissue loss is directly related to PAD (Table 2).
Clinical history

A careful history and examination will generally distinguish IC from non-vascular causes that may mimic claudication (Table 3). It is also important to look for other co-morbidities in the history and to explore the degree of limitation caused by the disease. Attention should be paid to signs and symptoms of atherosclerosis in other vascular beds (coronary, cerebrovascular and renal).

Rest pain is an alarming sign of CLI and often presents at night when the blood supply to the foot is affected by both gravity and the increased metabolic requirement caused by warmth. This is almost always experienced in the most distal part of the limb as numbness or a burning sensation. Sufferers of rest pain often sleep with the affected limb dangling off the bed side, or in a chair in an attempt to improve the blood supply and to cool down the foot.

Physical examination

A full cardiovascular examination should be performed with the patient’s lower legs and feet fully exposed. On inspection attention should be paid to thin and shiny skin, hair loss and trophic skin changes. Patients should also be checked for tissue loss, ulceration (especially at pressure areas) and gangrene (dry or wet). Skin pallor occurring after elevating the foot to around 45° and the onset of erythema after lowering the leg from the elevated position is also suggestive of PAD (Buerger’s test).

The abdomen should be examined to exclude an abdominal aortic aneurysm. The common femoral, popliteal, dorsalis pedis and posterior tibial pulses should all be assessed in both legs. Both feet should be palpated to check the temperature and capillary refill time and arrhythmias should be looked for when assessing the pulses.

Table 2 Fontaine’s and Rutherford’s classification of PAD.

<table>
<thead>
<tr>
<th>Fontaine’s</th>
<th>Rutherford’s</th>
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<tbody>
<tr>
<td>Stage</td>
<td>Clinical presentation</td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>II</td>
<td>Intermittent claudication</td>
</tr>
<tr>
<td></td>
<td>IIa: on walking &gt; 200 m</td>
</tr>
<tr>
<td></td>
<td>IIb: on walking &lt; 200 m</td>
</tr>
<tr>
<td>III</td>
<td>Rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
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Hand-held Doppler assessment of the pedal arteries is a reproducible, inexpensive and non-invasive tool. Waveform analysis provides broad information regarding arterial status but the ABI allows repeated measures over time and an objective measure of revascularization success. The normal range is 0.9–1.3 with the deviation above or below this being significant. ABI ≤0.9 in symptomatic patients has 95% sensitivity in detecting PAD and almost 100% specificity in identifying healthy individuals. Further, a drop in the pressure by ~20% following exercise suggests a significant arterial disease in patients with palpable pulses at rest.

ABI can be falsely elevated in the presence of arterial calcification, and heavily calcified vessels may be incompressible. In this circumstance, the toe–brachial index is useful in diagnosing PAD as digital vessels are spared from calcification. The normal toe pressure is >0.70.4

Another method of assessing PAD when ABI measurements are unreliable is by evaluating the ischaemic angle (pole test). This is determined by the level at which a pedal Doppler signal disappears on elevating the foot.

### Table 3 Differential diagnosis of arterial claudication.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Past history</th>
<th>Pain description</th>
<th>Onset of pain</th>
<th>Relief of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic claudication</td>
<td>Back pain</td>
<td>Tightness buttock&gt;calf associated paraesthesia</td>
<td>After walking or standing for similar time period</td>
<td>Sitting or stooping rather than standing</td>
</tr>
<tr>
<td>Venous claudication</td>
<td>DVT (iliac)</td>
<td>Bursting pain in leg, usually thigh</td>
<td>Walking</td>
<td>Delayed relief with rest; improved with elevation</td>
</tr>
<tr>
<td>Chronic compartment syndrome</td>
<td>Often muscular</td>
<td>Bursting pain in muscle compartment</td>
<td>Heavy periods exertion</td>
<td>Delayed relief with rest; improved with elevation</td>
</tr>
<tr>
<td>Hip osteoarthritis</td>
<td></td>
<td>Aching</td>
<td>Variable degree of walking; morning stiffness</td>
<td>Delayed on sitting or resting joint</td>
</tr>
</tbody>
</table>

### Acute limb ischaemia

Acute limb ischaemia (ALI) is defined as a sudden decrease in the blood supply of a previously stable leg of <2 weeks duration, resulting in rest pain and other features of severe ischaemia and threatening limb viability. This may be subdivided into acute (onset <24 h) and sub-acute (onset 24 h–2 weeks). The classical clinical presentation of ALI is pain, paralysis, paraesthesia, pallor, pulselessness and perishing.
cold leg. At presentation, the presence or absence of sensory and motor function, mottling (blanching or non-blanching) and muscle tenderness will determine whether the limb is viable, threatened or non-viable. Emboli used to be the most common cause of ALI; however, this is now more likely to be caused by thrombosis at a site of underlying severe stenosis.

Clinical presentation will usually determine the most appropriate treatment of ALI, but immediate anticoagulant therapy with intravenous heparin is indicated in all patients. All cases require emergency referral to a vascular specialist for definitive management and in patients with classical acute limb ischaemia it is important that revascularization is accomplished within 6 h to prevent irreversible muscle damage. The 30-day mortality and major amputation rates remain high (15–20 and 10–30%, respectively).

**Investigations**

**Haematological investigations**
Blood tests may identify cardiovascular risk factors. Full blood count (anaemia, polycythaemia and thrombocythaemia), biochemical profile (diabetes mellitus and renal dysfunction) and fasting lipid profile can all guide medical therapy. Occasionally, with unusual presentation or patients <50 years, a thrombophilia screen and vasculitis screen should be considered and homocysteine levels checked.

**Radiological investigations**
Colour-assisted duplex ultrasound scan is safe, non-invasive and non-expensive and, if done by an expert hand, able to provide anatomical as well as functional information. It is often used in surveillance following angioplasty or reconstruction. However, the accuracy of this investigation is highly operator dependent. Other disadvantages include the length of examination and the challenge in imaging crural arteries.

Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) could be used to confirm and localize suspected disease, especially where intervention is being considered. Both techniques have been shown to be sensitive and specific for PAD evaluation. They are similar in terms of diagnostic accuracy, clinical outcome and ease of use. National Institute for Health and Clinical Excellence (NICE) has recently published new guidelines on PAD recommending duplex ultrasound as first-line imaging to all people with PAD for whom revascularization is being considered. The guidelines further recommend to offer contrast-enhanced MRA (or CTA if MRA is contraindicated)
to patients with PAD who need further imaging (after duplex ultrasound) before considering revascularization.24

Although MRA is a more expensive investigation than CTA, it has the advantage of avoiding the nephrotoxic iodinated contrast material and radiation, as well as the ability to provide rapid high-resolution 3D images of the abdomen, pelvis and lower limbs in one setting. As a result, MRA has become the preferred imaging technique for the diagnosis and treatment-planning of patients with PAD in many centres. However, MRA is contraindicated in patients with implanted devices such as pacemakers and metallic clips and in those with claustrophobia.23 Previous arterial stents cause signal dropout making assessments of patency or in-stent stenosis difficult. In addition, a recent retrospective study showed a link between the contrast agent used for MRA, gadolinium and nephrogenic systemic fibrosis.25

Despite the fact that catheter-based digital subtraction angiography is considered the ‘gold standard’ investigation for PAD,4,26 this is usually only performed when a concurrent endovascular intervention is anticipated due to its invasive nature. The risks related to catheter angiography include nephrotoxicity induced by the iodinated contrast, allergic reaction to the contrast, arterial dissection, arterial spasm, embolization and access site complications such as haematoma, pseudoaneurysm and arterio-venous fistula.4

The use of non-toxic contrast agents such as gadolinium27 and carbon dioxide28 has been recommended in patients with renal impairment to reduce the risk of nephrotoxicity seen with conventional contrast media.29

Management and treatment

Lifestyle modification

Exercise therapy
The overall improvement in walking ability is found to be around 50–200%, with most of the studies recommending a thrice-weekly programme of 30-min walking sessions to near-maximal pain for a period of at least 6 months.30,31 Supervised exercise regimes are required to achieve best possible results.8,32 A recent randomized trial showed equivalent outcomes for supervised exercise, angioplasty or both, at 12 months.33

Smoking cessation
Smoking has been associated with PAD severity, risk of amputation, graft occlusion and increased mortality,8 and cessation is recommended by trans-Atlantic inter-society consensus for the management of
peripheral arterial disease (TASC II). Although smoking cessation has not been shown to significantly improve overall walking distance, it does reduce the risk of cardiovascular events and slows the progression to CLI. A combination approach of behavioural therapy, nicotine replacement and medication has more effect in stopping smoking than a single modality approach.

Modification of risk factors

Lipid control
Placebo-controlled trials with both simvastatin and atorvastatin have shown some improvement in treadmill walking distance in patients with PAD. More importantly, in the Heart Protection Study, simvastatin reduced vascular mortality by 17%, coronary artery events by 24% and strokes by 27% in a subgroup of patients with PAD at 5 years. In contrast bezafibrate had no effect on total fatal and non-fatal cardiovascular events in a similar subgroup. Statins should be prescribed for all PAD patients irrespective of cholesterol level of >3 mmol/l.

Hypertension control
The target blood pressure in patients with PAD is <140/90 mmHg (<130/80 mmHg in diabetic or renal failure patients). It is noted that most PAD patients will require more than one type of anti-hypertensive to control their blood pressure.

The Heart Outcomes Prevention Evaluation (HOPE) study showed blood pressure modification in patients with ABI <0.90 was twice as effective in preventing major adverse cardiovascular events compared with those with ABI >0.90. Further, ramipril treatment was associated with a 25% reduction in the primary combined outcome of cardiovascular mortality, myocardial infarction or stroke in patients with PAD, independent of blood pressure lowering. Earlier studies suggest that ACE inhibitors may also improve walking distance, especially in high-risk groups. However, a recent systematic review suggested that there is not enough evidence to support their routine use and further research is required.

Beta blockers were thought to worsen PAD symptoms but this has been refuted by a Cochrane review; they can be safely used in claudicants, especially in the presence of coronary arterial disease.

Diabetic control
Diabetes mellitus increases the risk of PAD by three to four times, and doubles the risk of claudication. Although strict glycaemic control
reduces the risk of microvascular complications it does not reduce the PAD complications (which are thought to be mediated by dyslipidaemia). However, strict glycaemic control does reduce myocardial infarction, stroke and vascular death in patients with type 2 diabetes, and an HbA1c level of <7% should be targeted.4

**Antiplatelets and anticoagulants**

Antiplatelet therapy has not been shown to improve claudication but is important in reducing the risk of cardiovascular disease related to atherosclerosis and PAD.40 The Antithrombotic Trialists’ Collaboration showed that the use of antiplatelet therapy in patients with PAD reduces the risk of adverse cardiovascular outcomes by 23%.4

There is no strong evidence to support superiority of any one antiplatelet agent. In the CAPRIE study (patients at risk of ischaemic events), long-term use of clopidogrel in PAD patients was more effective than aspirin in reducing the combined risk of myocardial infarction, stroke or vascular-related death.40 Conversely, the CHARISMA trial was unable to demonstrate benefit for clopidogrel plus aspirin over aspirin alone in reducing this risk.41

In the WAVE trial, investigating the efficacy and safety of adding oral anticoagulants (warfarin or acenocoumarol) to antiplatelet therapy in patients with PAD, combination therapy added no benefit but led to higher rates of life-threatening bleeding.42

Currently, it is recommended that patients with symptomatic PAD should be on long-term low-dose aspirin or clopidogrel to minimize the rate of serious vascular events.40

**Homocysteine**

Although hyperhomocysteinaemia is implicated in both PAD and coronary artery disease, there is no evidence that lowering levels with folate influences walking distance or vascular risk.

**Other pharmaceutical therapies**

A number of drugs have been marketed with the aim of improving walking distance in patients with IC: naftidrofuryl oxalate, a 5-hydroxytryptamine type 2 antagonist; cilostazol, a phosphodiesterase III inhibitor; pentoxifylline, a vasodilator; inositol nicotinate, a vasodilator. All have randomized controlled evidence of some improvement in walking distance.

A recent systematic review has assessed the effectiveness and cost-effectiveness of these agents for IC.43 Naftidrofuryl oxalate and cilostazol both appear to be effective treatments with minimal adverse effects.
but only naftidrofuryl is cost-effective. UK NICE technology guidance (May 2011) recommends naftidrofuryl oxalate as an option for the treatment of IC on this basis, although patients should not be converted from other agents if these have been already been commenced with good effect. Other medications with supporting evidence in improving treadmill walking distance in claudicants are carnitine and propionyl-L-carnitine which interact with the skeletal muscle oxidative metabolism. A meta-analysis of iloprost, a prostacycline analogue, demonstrated a reduction in death and major amputation at 6 months (35 versus 55% in controls). Other adjuncts with limited evidence for use in CLI include spinal cord stimulation and lumbar chemical sympathectomy.

Revascularization

Revascularization is indicated for IC impacting on the quality of life or preventing employment, for rest pain and tissue loss. The outcomes of revascularization are dependent on the site and extent (length and number of lesions) of disease, quality of inflow and run-off vessels, patient co-morbidities and the type of procedure performed. Generally, interventions are endovascular (percutaneous balloon angioplasty and/or stent) or surgical (bypass using autologous vein or synthetic conduits). The choice of an endovascular or surgery first approach is guided by the TASC II classification of disease, but this has to be tailored to local expertise and patient factors.

Supra-inguinal revascularization

Aorto-iliac angioplasty has been reported to have an initial clinical success rate of >90% with reported 5-year primary patency rates ranging from 72 to 79%. Studies also suggested that the use of a stent in aorto-iliac occlusive disease improves technical success rates and reduces the risk of long-term failure by almost 39%, with a similar complication rate, when compared with angioplasty. Endovascular techniques are the first-line treatment for most patients with supra-inguinal disease. Although an aorto-bifemoral bypass appears to have better long-term patency than the endovascular strategy with reported 5-year primary patency rates of up to 94%, there is significant morbidity and mortality.
related to this surgery. It is therefore reserved for diffused aorto-iliac disease or where an endovascular intervention has failed.48

Infra-inguinal revascularization for claudication

There is little evidence to support any infra-inguinal endovascular intervention for claudication over best medical therapy and supervised exercise alone. Despite this there are increasing numbers of endovascular interventions being performed worldwide. Standard angioplasty of superficial femoral artery disease has patency rates of 50–60% at 3 years, compared with femoro-AK popliteal bypass with vein (75% at 4 years) and PTFE (50–55% at 4 years),4 despite being used to treat more focal disease. This has led to trials of numerous adjuvant technologies in an attempt to achieve patency rates with endovascular therapy similar to those of open surgery:

Stent insertion
The FAST trial randomized PTA versus primary stenting in short SFA lesions in a cohort of mainly claudicants. It showed no difference in re-stenosis or clinical outcomes at 1 year.49 Two trials involving longer lesions demonstrated improved walking distance at 1 year in the primary stent group and with lower target lesion re-stenosis50,51 but clinical benefit was lost in the stent arm of the ABSOLUTE trial by 2 years, suggesting bare stents are not going to improve long-term patency of endovascular interventions.50

However, recently published 3-year follow-up data from the RESILIENT study (a multi-centre prospective randomized trial of PTA versus Nitinol stent for claudicants with moderate length disease) demonstrated sustained benefits in both radiological patency and symptom relief with stenting. This suggests that the newer generation stents with improved flexibility and reduced fracture rates may increase stent longevity.52

Drug-eluting stents
The Achilles’ heel of both angioplasty and bare metal stents (BMSs) is the development of neo-intimal hyperplasia causing re-stenoses and subsequent thrombosis. Drug-eluting stents are now used routinely in the coronary circulation in small-diameter vessels. The SOROCCO trial compared sirolimus-eluting stents and bare stents in claudicants with moderate length SFA disease (8.5 and 8.1 cm, respectively). Clinical improvement and re-stenosis rates were similar between groups
and sustained at 2 years. The lack of additional benefit with drug-eluting stents may be explained by the much lower re-stenosis rates in the bare stent arm of this trial than in the previously discussed BMS trials (21 versus 49% in ABSOLUTE at 2 years).

More recently, the Zilver PTX trial compared a polymer-free paclitaxel-coated nitinol drug-eluting stent with PTA and provisional BMS placement in patients with femoro-popliteal disease. The study suggested that treatment with the paclitaxel-eluting stent was associated with a superior primary patency (83.1 versus 32.8%; \( P \leq 0.001 \)) and 12-month event-free survival (90.4 versus 82.6%; \( P = 0.004 \)) compared with PTA and provisional BMS placement.

Covered stents

ePTFE covered stents have been proposed to improve patency over non-covered stents. Initial reports suggest that patency is 70% at 2 years for TASC A and B lesions (preferentially endovascular) but drops to 50% at 2 years in more extensive TASC C and D lesions. These may be an option for patients with no vein available for bypass, as patency rates equate to PTFE bypasses with reduced morbidity and length of hospital stay.

Atherectomy

An alternative to standard endovascular techniques is the removal of the obstructing arterial plaque using atherectomy devices. There are several types of these, including directional (SilverHawk), orbital, rotational (Rotablator) and laser atherectomy devices (Excimer Laser). In theory, atherectomy minimizes stretch injury on arterial walls thereby limiting acute dissection and elastic recoil and potentially reducing the rate of re-stenosis. However, there have not been adequate studies showing any significant long-term benefit of atherectomy over PTA alone in the peripheral arteries, despite promising results in some single-centre experiences.

A recent randomized trial compared primary balloon angioplasty with SilverHawk atherectomy and adjunctive balloon angioplasty for \textit{de novo} infrainguinal disease. It was found that target lesion and vessel revascularization rates at 1 year were statistically similar in both groups, but atherectomy with adjunctive PTA significantly reduced stent use compared with PTA alone.

More promising results have been documented with the use of endovascular Excimer Laser atherectomy techniques in treating complex infrainguinal vascular disease. The success rate reached around 80% with very low complication rates and a need for surgery of <2%.

In February 2011 NICE published new guidelines on percutaneous atherectomy of femoro-popliteal arterial lesions with plaque excision
devices, suggesting further auditing and research in the form of well-conducted trials should take place because of the inadequate evidence on the efficacy and safety of this procedure currently.\textsuperscript{60}

**Controversies in open surgery**

In surgical bypass, available prosthetic grafts include polytetrafluoroethylene (PTFE), polyester (Dacron) and various biological grafts.\textsuperscript{47} It is widely accepted that autologous grafts have better patency and infection profiles compared with synthetic ones for both above- and below-knee femoro-popliteal bypass.\textsuperscript{61}

The choice of prosthetic material for femoro-popliteal bypass has been controversial over the last decade. Dacron is commonly used for aorto-bifemoral bypass grafts, with a 5-year patency rate of over 90\% and a peri-operative mortality of up to 5\%.\textsuperscript{62} In a randomized trial using heparin-bonded, collagen-sealed Dacron (HBD) for femoro-popliteal bypass grafting, there was a significantly better patency rate for HBD compared with PTFE (55–42\% at 3–4 years) with a significant improvement in limb salvage.\textsuperscript{63}

Recently, a randomized trial showed that using heparin-bonded PTFE in femoro-femoral or femoro-popliteal bypasses significantly reduced the overall risk of primary graft failure by 37\%. The study also estimated the risk reduction to be around 50\% in femoro-popliteal bypass cases and in cases with CLI.\textsuperscript{64}

Finally, various studies showed a significant reduction in early wound infection rates when using rifampicin-bonded grafts, and their use is recommended when there is a high risk of graft infection.\textsuperscript{65}

**Infra-inguinal revascularization for CLI**

In CLI, with multilevel disease, there is less clarity as to choice of therapy. This is further confused by the reduced life-expectancy of this cohort of patients. The BASIL trial randomized to an endovascular-first or surgery-first approach in patients suitable for both and showed that there were generally similar amputation-free survival outcomes at 6 months.\textsuperscript{66} However, in those surviving >2 years the durability of open surgery reduced the need for further interventions suggesting that life expectancy was the best guide to a surgery or endovascular first policy.

**Amputation**

Amputation may be necessary in situations where tissue is beyond salvage or there is extensive tissue death. Major amputation is
considered in the presence of non-reconstructible PAD with significant infection or severe pain, where amputation can help improve the quality of life. Amputation should not always be seen as a failure and can be a very positive life event. However, there is high morbidity and mortality following major amputation. Almost 30% of amputees will end up losing the other leg in 2 years, and 50% of them die within 5 years.

Discussion, developments and future options

PAD is responsible for a significant degree of morbidity and mortality. Early diagnosis and the modification of risk factors will improve the prognosis of the disease and can help in reducing the rate of amputation and therefore mortality. In patients with claudication it is vital to ensure appropriate risk factor modification and secondary preventative therapies to minimize vascular morbidity and mortality. This takes precedence over thoughts of revascularization for almost all claudicants given the natural history of the disease process. One hopes that current research will lead to pharmacotherapy that will alter the current relentless progression of the atherosclerotic process and high vascular mortality in this patient cohort.

The difficulty in treating long and complex infra-inguinal arterial lesions has led to the development of new endovascular techniques. The addition of cryoplasty to balloon angioplasty has been considered in recent years but studies suggest poor patency rates and poor relief from claudication at 1 year. The rapid development of new technologies and improvements in current techniques will lead to improved results from endovascular therapies in the future. Similarly, increased understanding of the pathophysiology of neointimal hyperplasia may open avenues for pharmacomodulation.

Similarly, in open surgery, concerns regarding reduced patency rates and increased infection risk with current prosthetic graft materials are driving research into tissue-engineered grafts and prosthetic grafts which more closely mimic the biomechanics of human arteries.

In view of the poor results of current therapies, especially for CLI, there is an ongoing search for emerging alternative treatment options. Triggered by the fact that the development of collateral vessels can have a major impact on symptoms, many studies have tried to determine the mechanism which regulates new vessel formation. In normal tissues there is a fine balance between pro- and antiangiogenic pathways. This balance is strongly influenced by the activation of local inflammatory pathways caused by vascular disease.
Potential future treatments include gene therapy and therapeutic angiogenesis as there have been many recent advances in these fields. However, despite encouraging outcomes in pre-clinical trials using a variety of pro-angiogenic growth factors, there are no clinical studies that have shown a significant benefit of gene therapy when compared with placebo therapy. Therefore, more studies will be needed to address the overall value and methods of administrating angiogenic factors in the treatment of CLI.

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