Peripheral artery disease

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What you need to know
• Most people with peripheral artery disease are asymptomatic
• Peripheral artery disease is associated with a high risk of vascular complications such as myocardial infarction, stroke, vascular dementia, renovascular disease, and mesenteric disease
• Few patients with intermittent claudication develop limb-threatening complications (1-3% in 5 years)
• Management of risk factors—including smoking, diabetes, and dyslipidaemia—is key to reducing the risk of vascular complications
• Patients with critical limb ischaemia are at high risk of limb amputation and premature death

Peripheral artery disease affects around 13% of the Western population who are more than 50 years old.1 It is most commonly due to atherosclerosis, where an atherosclerotic plaque causes arterial stenosis or occlusion. This results in a reduction in blood flow to the affected limb. Most patients are asymptomatic, but many experience intermittent claudication (pain on walking). Critical limb ischaemia occurs when the reduction in blood flow is so severe that it causes pain on rest or tissue loss (ulceration or gangrene).1

Atherosclerosis is a systemic disease. Some 60% of patients with peripheral artery disease will have ischaemic heart disease, and 30% have cerebrovascular disease.2 Within five years of diagnosis, 10-15% of patients with intermittent claudication will die from cardiovascular disease.1 Therefore, management begins with identification and modification of risk factors that are common to peripheral artery disease, heart disease, and stroke.

Who is at risk?
The development of peripheral artery disease is multifactorial. Two large population studies found that over 95% of patients have at least one cardiovascular risk factor.4 5

Smoking
Results from a systematic review of 17 studies including 20 278 patients suggest that half of all peripheral artery disease can be attributed to smoking. It concluded that heavier smokers are more likely to develop peripheral artery disease than light smokers and that former smokers have a persistently increased risk compared with never smokers.6

Diabetes
The TASC II guidelines conclude that, for all patients with diabetes, the relative risk of developing peripheral artery disease is similar that of people who smoke.37 A prospective cohort study of 1894 diabetic participants found that poor diabetes
control was associated with an increased risk of peripheral artery disease. Patients with diabetes are more likely to be asymptomatic because of the co-existence of neuropathy in a substantial proportion. Peripheral artery disease in this population is more likely to be found in more distal vessels in the calf. Population studies have found that around half of patients with a diabetic foot ulcer have peripheral artery disease.  

Other

The prevalence of peripheral artery disease increases with advancing age; one population study of 2174 participants found an increase from 1% of 40-49 year olds to 15% of those aged over 70. The same study found that black ethnicity increased the risk of peripheral artery disease (odds ratio 2.8, 95% confidence interval 1.4 to 5.4). This difference persists after correcting for conventional risk factors. TASC II guidelines conclude that men are affected at a younger age than women, but overall there is no clear distinction in risk. They also concluded that high fasting serum cholesterol level, hypertension, and chronic kidney disease each increase in the risk of peripheral artery disease by 1.5 times. Peripheral artery disease is also associated with high serum homocysteine.

What are the long term outcomes?

If left untreated, peripheral artery disease does not inevitably lead to amputation. A prospective population study showed that most patients with claudication have stable or improved disease. Asymptomatic disease is a marker of sedentary lifestyle rather than less severe disease and outcomes are similar to those with claudication. Up to 25% of symptomatic patients will need intervention, but fewer than 5% will progress to critical limb ischaemia. Within five years from diagnosis of peripheral artery disease, the risk of amputation is 1-3.3% and all-cause mortality is 20%. If a patient develops critical limb ischaemia, overall survival is worse than for many cancers. In patients with critical limb ischaemia the one-year risk of limb amputation is 30% and five-year all-cause mortality is 50%. A cross sectional study of 2730 742 patients with peripheral artery disease found mortality rates for all patients requiring leg amputation were twice as high as for those without amputation (P≤0.001). A study of 136 patient records found that patients with diabetes were more likely to require amputation (odds ratio 5.4, 95% confidence interval 3.3 to 9.3) compared with those without diabetes.

What are the symptoms?

Most patients with peripheral artery disease are asymptomatic. Claudication is an aching or burning in the muscles of the leg. It is reliably reproduced at a set distance of walking and is relieved within minutes on rest. It is never present at rest or exacerbated by position. The site of pain provides an indication of the site of disease. Stenosis or occlusion of the aorta is likely to cause bilateral buttock, thigh, and calf claudication. Occlusion of the common iliac, common femoral, and superficial femoral arteries cause unilateral buttock, thigh, and calf claudication respectively (see infographic). There are several key differential diagnoses in anybody presenting with lower limb pain related to exercise (infographic). Critical limb ischaemia is often resistant to opiate analgesia and may be difficult to distinguish from neuropathy. Patients describe hanging their leg over the edge of the bed to relieve the pain. Acute limb ischaemia is rare but important not to miss as delays increase the risk of limb amputation. This classically presents with sudden onset symptoms and one or more of the “six Ps” (see infographic and Boxed Text on page 2box 1).

What assessments are needed?

When assessing such patients, answering the following three questions will direct management in primary and secondary care:

1. Does this patient have peripheral artery disease?
   - Symptoms
   - Impalpable or reduced pulses
   - Reduced ankle-brachial pressure index (ABPI) ≤0.9

2. Is the disease acute or chronic?
   - Duration of onset
   - Risk factors (such as atrial fibrillation for acute ischaemia, smoking for peripheral artery disease)

3. What is the severity of disease?
   - Claudication
   - Critical limb ischaemia
   - Acute limb threatening ischaemia

Lack of a palpable pulse is the most sensitive clinical sign. Examine pulses in the leg working distally from the groin. Capillary refill and foot characteristics (hair loss, colour) are of little diagnostic importance. Look particularly for hidden tissue loss on the heel or between toes (infographic). Identification of peripheral neuropathy with a monofilament is useful in those at risk (such as people with diabetes) as it often coexists. An ankle-brachial pressure index (ABPI) test is the ratio of blood pressure at the ankle to blood pressure at the arm. It should always be done in cases of suspected peripheral artery disease, but it has limitations. Although a value of ≤0.9 or less is diagnostic of peripheral artery disease, falsely elevated (>1.2) and unreliable values are often seen in patients with diabetes and renal failure because of arterial calcification. A normal ABPI in the presence of tissue loss does not exclude critical limb ischaemia and such a patient would still require urgent care:
referral (see infographic and Boxed Text on page 2box 1).23
Toe brachial index is an alternative if available (a value <0.7
indicates peripheral artery disease).

Other investigations are detailed in Boxed Text on page 3box 2. These often reveal coexisting disease (such as diabetes or
abdominal aortic aneurysm) that requires separate management.

### How can peripheral artery disease be managed in primary care?

Asymptomatic patients and those with claudication can both be
managed in primary care (Boxed Text on page 3box 3). In
England, the Quality and Outcomes Framework (QOF) requires
that patients with peripheral artery disease are established on a
register in primary care.29 Registries also exist in Europe.

Documenting the distance walked until onset of symptoms
allows progression of the disease to be monitored. Intervention
is unnecessary if there is no impairment in quality of life, but
risk factor identification and management must take place.

Evidence from large population studies have found less than
half of these patients have adequate risk factor modification by
the time of referral.

### Risk factor modification

Patients with peripheral artery disease have persistently worse
outcomes if they continue to smoke. Multiple cohort studies
have shown that, compared with former smokers, patients who
still smoke have a higher risk of amputation, and their chance
of surviving five years from diagnosis is halved compared with
non-smokers.25,26 Patients must be informed of this association
and directed to relevant smoking cessation services at all
interactions. Combining behavioural counselling with
medication (varenicline is most effective) increases the
proportion of successful quitting attempts compared with
standard care.25,30 Smoking cessation may prevent a decline in
symptoms.

Antiplatelets reduce the risk of major cardiovascular events. A
randomised control trial (RCT) of 19 185 patients with
atherosclerotic vascular disease showed that clopidogrel 75 mg
was significantly better than aspirin 325 mg for prevention of
vascular complications (P=0.043, 95% CI 0.3 to 16.5) at a mean
follow up of 1.91 years.23 If clopidogrel is contraindicated,
aspirin remains an acceptable alternative.23,31,32 A network
meta-analysis of 49 RCTs revealed that, although dual
antiplatelet therapy can reduce the rate of major amputations
(relative risk 0.68, 95% CI 0.46 to 0.99), it causes an
unacceptable increase in risk of severe bleeding (relative risk
1.48, 1.05 to 2.10) compared with aspirin alone, and clopidogrel
has the most favourable benefit-harm profile (79% cumulative
rank probability best and 77% cumulative rank probably
safest).23,30,31 Warfarin is usually reserved for those with limb
ischaemia due to arterial emboli.33

A meta-analysis of two RCTs and 12 observational studies
showed that statin therapy reduces all-cause mortality (odds
ratio 0.77, 95% CI 0.68 to 0.86) and the incidence of stroke
(odds ratio 0.77, 0.67 to 0.89) in patients with peripheral artery
disease.40 A cohort study found no effect on limb
amputations (P=0.84).41 Three RCTs have not resolved whether statins affect
walking distance.42-44 NICE recommends reducing non-HDL
cholesterol concentration in patients with peripheral artery
disease by 40%.45

Multiple studies have shown that improved glycaemic control
in patients with diabetes reduces the risk of microvascular
complications, but it seems to have little effect on the risk of
limb amputations.46,47 NICE recommends a target HbA1c
level <48 mmol/mol for all patients with diabetes.48

### Investigations

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Hypertension management lowers cardiovascular risk, and ramipril is recommended as first line therapy in guidelines worldwide. A systematic review and meta-analysis of four RCTs did not show that it improved claudication symptoms in patients with symptomatic peripheral artery disease. All patients who are overweight (body mass index >25) should be given an optimal diet plan and a goal for weight loss.

Symptom management

Exercise

Several meta-analyses of RCTs have found that supervised exercise improves walking distance in patients with peripheral artery disease compared with unsupervised regimens (relative risk 0.48, 95% CI 0.32 to 0.64, at 6 months). Improvement occurs in the absence of improved ABPI. The benefit to walking ability and quality of life is similar whether patients undergo supervised exercise therapy or angioplasty. The most effective therapy is walking for more than 30 minutes, at least three times a week, to near maximal pain, for at least six months.

NICE recommends a supervised exercise programme is offered to all patients (2 hours a week for 3 months) if available. This is more cost effective than either unsupervised exercise or angioplasty. However, it is estimated that 70% of clinical commissioning groups in the UK do not provide this service, which costs £255 per person for three months.

Vasoactive drugs

Naftidrofuryl oxalate and cilostazol both improve walking distance in patients with claudication by 86 m (95% CI 13 to 156 m, P=0.021). Meta-analysis of four RCTs found that angiotensin converting enzyme (ACE) inhibitors also modestly improved pain-free walking distances in patients with claudication by 86 m (95% CI 13 to 156 m, P=0.021). NICE recommends it when supervised exercise does not result in satisfactory improvement and the patient prefers not to be referred to secondary care. If there is no benefit after 3-6 months, it should be stopped. A meta-analysis of four RCTs found that angiotensin converting enzyme (ACE) inhibitors also modestly improved pain-free walking distances in patients with claudication by 86 m (95% CI 13 to 156 m, P=0.021). NICE recommends a supervised exercise programme is offered to all patients (2 hours a week for 3 months) if available. This is more cost effective than either unsupervised exercise or angioplasty. However, it is estimated that 70% of clinical commissioning groups in the UK do not provide this service, which costs £255 per person for three months.

When should patients be referred to vascular surgery?

Urgently refer any patient presenting with critical limb ischaemia or acute limb ischaemia (Boxed Text on page 2box 1) to a vascular centre for specialist assessment. Urgently refer those with a diabetic foot ulcer and peripheral artery disease to the diabetic foot multidisciplinary team (see ). Refer patients with claudication that affects their quality of life and who do not improve after three months of supervised exercise therapy to a vascular surgeon for consideration of revascularisation procedures.

What are the treatment options in secondary care?

Revascularisation

Limb revascularisation is risky and can itself result in amputation. In cases of claudication, it is recommended only when there is significant impairment in function and quality of life. This contrasts with critical limb ischaemia, for which revascularisation is an urgent limb-saving and lifesaving procedure. Patients referred to vascular surgery will undergo further imaging with Duplex ultrasound or cross-sectional imaging (magnetic resonance or computed tomography angiography).

Where the atherosclerotic lesions are favourable (a small, singular stenosis or occlusion) an “endovascular first” strategy is often used. This may involve placement of a stent. Angioplasty is generally avoided below the level of the knee because of its poor durability in people with claudication. Open surgery is considered in patients with debilitating symptoms who are unsuitable for primary angioplasty (multiple or large occlusions) or in whom angioplasty has failed.

Non-invasive interventions

Non-invasive interventions are ineffective in peripheral artery disease. Prostanoid infusions (such as iloprost) may be used in vasospastic conditions (such as Raynaud’s phenomenon), but they provide only short term improvement in symptoms. There are few indications for their use in critical limb ischaemia.

Future directions for vascular surgery

Future developments in vascular surgery are aimed at improving endovascular techniques and technology. Drug eluting technologies are currently being evaluated in randomised trials (BASIL-3). The BASIL-2 trial is assessing revascularisation options in patients with peripheral artery disease below the knee (typically seen with diabetes). Other devices enabling endovascular removal of atheroma—cryoplasty, laser, and bio-absorbable vascular scaffolds—are also under investigation.
61 Henning DR, Siano KA. Diagnosis and treatment of peripheral arterial disease. Am Fam Physician 2013;88:306-10.24010393
67 ISRCTN Registry. ISRCTN27728689: Bypass v angioplasty in severe ischaemia of the leg. 2017. www.isrctn.com/ISRCTN27728689. Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions

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### Table 1: Differential diagnoses of intermittent claudication

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<th>Condition</th>
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<tr>
<td><strong>Non-vascular</strong></td>
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<tr>
<td>Spinal stenosis</td>
<td>Relieved by position change, may have leg weakness</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Not quickly relieved by rest</td>
</tr>
<tr>
<td>Lumbar nerve root irritation</td>
<td>Straight leg raise test is positive</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Venous claudication</td>
<td>History of deep vein thrombosis, pain relief on leg elevation, oedema, venous skin changes</td>
</tr>
<tr>
<td>Buerger’s disease (thromboangiitis obliterans)</td>
<td>Young male smokers</td>
</tr>
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Ischaemic right foot demonstrating discoloration and tissue loss at the tip of the hallux

Figures

Peripheral artery disease (PAD)

- **Asymptomatic**
  - ABPI <0.9
  - Absent/reduced pulses
  - Risk factor management and exercise
  - Monitor

- **Intermittent Claudication**
  - ABPI <0.9
  - Absent/reduced pulses
  - Risk factor management and supervised exercise
  - Stable or improved
  - Monitor

- **Critical limb ischaemia**
  - Rest pain or tissue loss or ABPI <0.5
  - Risk factor management + Refer urgently to vascular surgery
  - Worsening symptoms Failure of supervised exercise
  - Refer to vascular surgery

- **Diabetic foot ulcer**
  - 50% have PAD
  - Refer urgently to diabetic foot MDT with vascular assessment

**ABPI** = ankle-brachial pressure index. **MDT** = multidisciplinary team.

Primary care decisions flowchart. For further information about diabetic foot ulcers see NICE guidelines. Patients should also be referred if there is diagnostic uncertainty.