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Morley, R. L., Sharma, A., Horsch, A. D., & Hinchliffe, R. J. (2018). Peripheral artery disease. *BMJ*, *360*, [j5842]. https://doi.org/10.1136/bmj.j5842

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thebmj

BMJ 2018;360:j5842 doi: 10.1136/bmj.j5842 (Published 1 February 2018)

PRACTICE

CLINICAL UPDATES

Peripheral artery disease

Rachael L Morley *academic foundation doctor*[1 2], Anita Sharma *general practitioner, clinical director in vascular care Oldham CCG*[3] *GP member of NICE Quality Standards Advisory Committee*[3], Alexander D Horsch *consultant interventional and diagnostic radiologist*[1], Robert J Hinchliffe *professor of vascular surgery*[1 2]

[1]North Bristol NHS Trust, Bristol, Bristol, UK; [2]Bristol Centre for Surgical Research, NIHR Bristol BRC, University of Bristol, UK; [3]South Chadderton Health Centre, Oldham, UK

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.[3] Therefore, management begins with identification and modification of risk factors that are common to peripheral artery disease, heart disease, and stroke.

Sources and selection criteria

We used Healthcare Databases Advanced Search (HDAS) to search Embase, Medline, and PubMed for the most up to date systematic reviews and meta-analyses or alternative highest level of evidence on peripheral artery disease or intermittent claudication. Searches were performed during September 2017 with no date limits applied.

We also consulted national and international guidelines, particularly those published by the National Institute for Health and Care Excellence (NICE) and the Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Artery Disease (TASC II). TASC guidelines are developed by a worldwide working group and are based on the best evidence available in vascular surgery.

Relevant citations were also drawn from the content of initially identified papers.

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.[3 7] A prospective cohort study of 1894 diabetic participants found that poor diabetes control was associated with an increased risk of peripheral artery disease.[8] Patients with diabetes are more likely to be asymptomatic because of the co-existence of neuropathy in a

Correspondence to: R J Hinchliffe robert.hinchliffe@bristol.ac.uk

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substantial proportion. Peripheral artery disease in this population is more likely to be found in more distal vessels in the calf.[3] Population studies have found that around half of patients with a diabetic foot ulcer have peripheral artery disease.[9 10]

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.[4 11 12] The same study found that black ethnicity increased the risk of peripheral artery disease (odds ratio 2.83, 95% confidence interval 1.48 to 5.42).[4] This difference persists after correcting for conventional risk factors.[4 13-15] TASC II guidelines conclude that men are affected at a younger age than women, but overall there is no clear distinction in risk.[3] 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.[3]

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 symptoms at five years from diagnosis.[16] 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.[3 17] Within five years from diagnosis of peripheral artery disease, the risk of amputation is 1-3.3% and all-cause mortality is 20%.[3]

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%.[3] A cross sectional study of 2 730 742 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).[18] A study of 136 patient records found that patients with diabetes were more likely to require amputation (odds ratio 5.4, P<0.0001) or die (odds ratio 3.1, P<0.002) compared with those non-diabetic patients.[19]

What are the symptoms?

Most patients with peripheral artery disease are asymptomatic.[1 20] 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 (table 1).

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 box 1).

Box 1: Symptoms in common vascular presentations

Intermittent claudication

Claudication in calf, thigh, or buttock

Critical limb ischaemia

One or more of:
- Ulceration
- Gangrene
- Rest pain in foot for >2 weeks

Acute limb ischaemia

Sudden onset of one or more of*:
- Pain
- Pallor
- Pulseless
- Paraesthesia
- Paralysis
- "Perishingly" cold
- Sudden deterioration of claudication

*Not all of the "six Ps" need to be present for diagnosis

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.[21 22] Look particularly for hidden tissue loss on the heel or between toes (fig 1). 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 referral (see infographic and box 1).[23] Toe brachial index is an alternative if available (a value <0.7 indicates peripheral artery disease).

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

Box 2: History, examinations, and investigations for suspected peripheral artery disease

History

- Previous manifestations of:
  - Coronary artery disease
  - Cerebrovascular disease
- Hypertension
- Diabetes
- Smoking

Examinations

- Palpation of peripheral pulses (including abdominal aortic aneurysm)
- Peripheral neuropathy (if at risk)

Investigations

- Ankle-brachial pressure index (ABPI)
- Blood pressure
- Electrocardiography
- Full blood count
- Urea and electrolytes
- Random blood glucose or HbA_{1c}
- Serum cholesterol
- Thrombophilia screen if patient <50 years old

How can peripheral artery disease be managed in primary care?

Asymptomatic patients and those with claudication can both be managed in primary care (box 3). In England, the Quality and Outcomes Framework (QOF) requires that patients with peripheral artery disease are established on a register in primary care.[25] 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 time of referral.[26-28]

Box 3: Key aspects of managing peripheral artery disease in primary care

All patients should receive the following (where applicable) before referral to secondary care

Risk factor modification

- Smoking cessation therapy
- HbA_{1c} control (target value <48 mmol/mol)
- Blood pressure control (target <140/90 mm Hg*)
- Clopidogrel (or aspirin) 75 mg lifelong
- Atorvastatin 80 mg† lifelong

Symptom control

- Supervised exercise therapy for 3 months

*Target blood pressure is for patients <80 years old. If >80 years, target is 150/90 mm Hg.

†Dose for secondary prevention of cardiovascular disease.[24]

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.[29-32] 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.[33-36] 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 37], [38] 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).[38] Warfarin is usually reserved for those with limb ischaemia due to arterial emboli.[39]

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%.[24]

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.[45-47] NICE recommends a target HbA_{1c} level <48 mmol/mol for all patients with diabetes.[48]

Hypertension management lowers cardiovascular risk, and ramipril is recommended as first line therapy in guidelines worldwide.[3 23 49] A systematic review and meta-analysis of four RCTs did not show that it improved claudication symptoms in patients with symptomatic peripheral artery disease.[50]

All patients who are overweight (body mass index >25) should be given an optimal diet plan and a goal for weight loss.[3]

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).[51-53] Improvement occurs in the absence of improved ABPI.[52] The benefit to walking ability and quality of life is similar whether patients undergo supervised exercise therapy or angioplasty.[54] 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.[55]

NICE recommends a supervised exercise programme is offered to all patients (2 hours a week for 3 months) if available.[23] This is more cost effective than either unsupervised exercise or

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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.[56]

Vasoactive drugs

Naftidrofuryl oxalate and cilostazol both improve walking distance in patients with intermittent claudication. [57-59] Naftidrofuryl oxalate is the most cost effective and efficacious (up to 60% improvement).[57,59] 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.[23] 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).[60]

When should patients be referred to vascular surgery?

Urgently refer any patient presenting with critical limb ischaemia or acute limb ischaemia (box 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 fig 2).[48]

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.[23 61]

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.[62] 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.[63] 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.[20 64]

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.[65 66] 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).[67] Other devices enabling endovascular removal of atheroma—cryoplasty, laser, and bio-absorbable vascular scaffolds—are also under investigation.[63]

Questions for future research

- Is it possible to prevent critical limb ischaemia?
- What is the optimal medical therapy to reduce cardiovascular risk in patients with peripheral artery disease?

Additional educational resources

- National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management (clinical guideline CG147). 2012. www.nice.org.uk/guidance/cg147
- Gerhard-Herman et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e686-e725.
- Norgren et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;45:S5-S67.
- Video of peripheral arterial examination. www.youtube.com/watch?v=5HUJ9iI5QiQ
- Video of measuring ankle-brachial pressure index (ABPI). www.youtube.com/watch?v=3tU2kU1FkIg

Information resources for patients

- Circulation Foundation vascular charity. www.circulationfoundation.org.uk
- Treating intermittent claudication. In: National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management (clinical guideline CG147). 2012. www.nice.org.uk/guidance/cg147/ifp/chapter/treating-intermittent-claudication

Education into practice

- What proportion of your patients with peripheral artery disease have appropriate cardiovascular risk factor modification?
- What proportion of your patients with intermittent claudication are offered supervised exercise therapy as first line management?

How patients were involved in the creation of this article

No patients were involved in the creation of this article.

Contributors: RLM performed the literature search and wrote the article. AS and ADH contributed ideas for specific content and format of the final article. RJH is the guarantor.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; externally peer reviewed.

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Table

Table 1| Differential diagnoses of intermittent claudication

Condition	Differentiation
Non-vascular	
Spinal stenosis	Relieved by position change, may have leg weakness
Osteoarthritis	Not quickly relieved by rest
Lumbar nerve root irritation	Straight leg raise test is positive
Vascular	
Venous claudication	History of deep vein thrombosis, pain relief on leg elevation, oedema, venous skin changes
Buerger's disease (thromboangiitis obliterans)	Young male smokers

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Figures

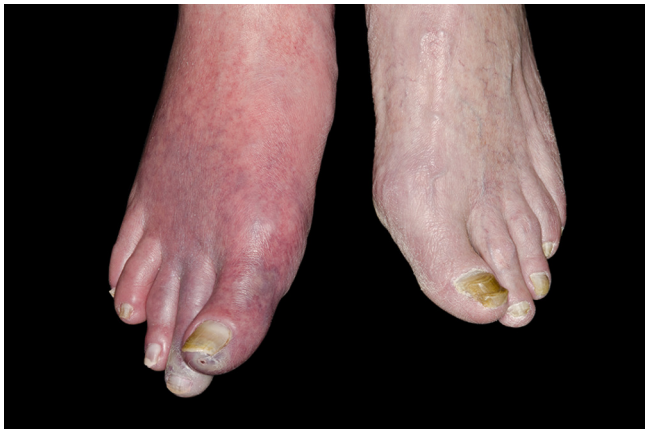
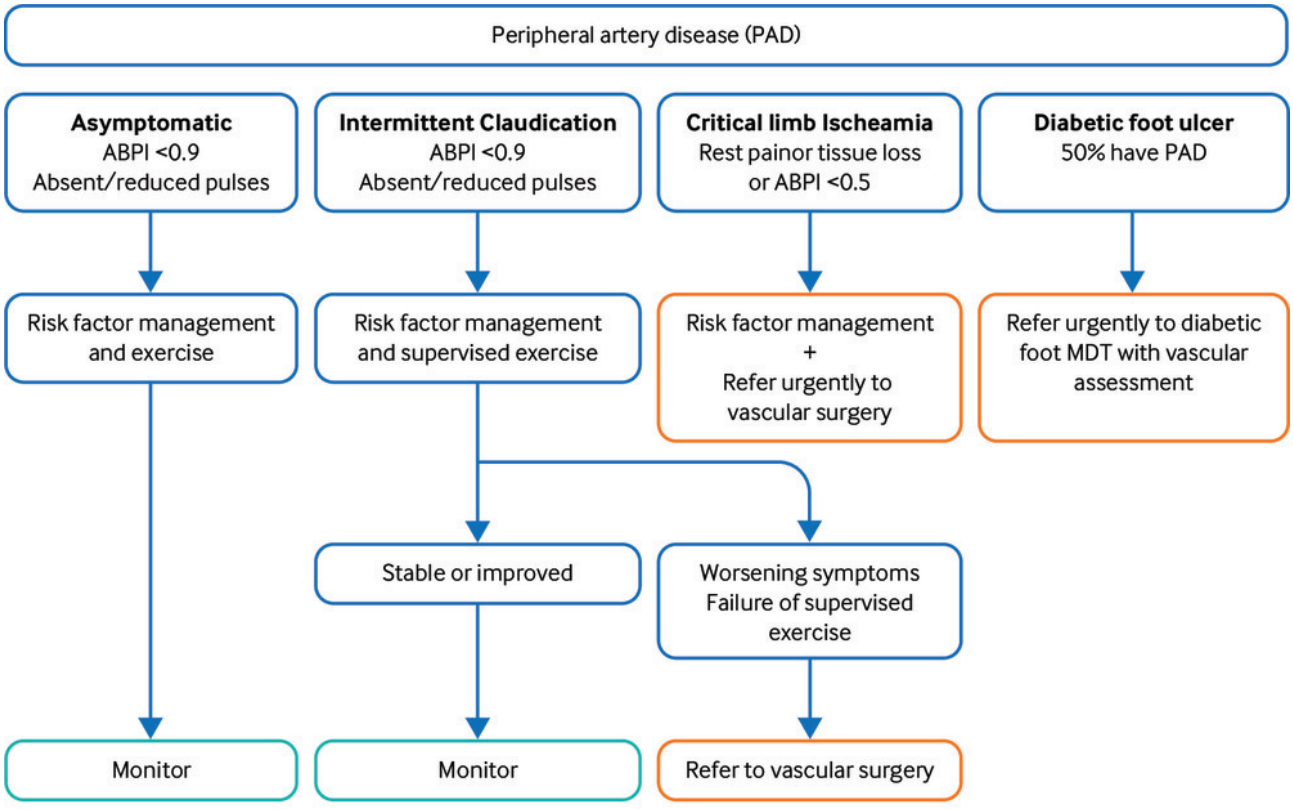


Fig 1 Ischaemic right foot demonstrating discoloration and tissue loss at the tip of the hallux

[Image: DR P. MARAZZI/SCIENCE PHOTO LIBRARY]



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

Fig 2 Primary care decisions flowchart. For further information about diabetic foot ulcers see NICE guidelines.[48] Patients should also be referred if there is diagnostic uncertainty

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