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PRACTICE

CLINICAL UPDATES

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

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.

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.

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

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).

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 probability 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

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=5HUJ9i15QiQ
- Video of measuring ankle-brachial pressure index (ABPI). www.youtube.com/watch?v=3tU2kU1Fklg

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/iffp/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.

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- 1 Crawford F, Welch K, Andras A, Chappell FM. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. *Cochrane Database Syst Rev* 2016;9:CD010680.27623758
- 2 Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women ≥62 years of age. *Am J Cardiol* 1994;74:64-5. doi:10.1016/0002-9149(94)90493-68017309
- 3 Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease. *Int Angiol* 2007;26:81-157.17489079
- 4 Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 2004;110:738-43. doi:10.1161/01.CIR.0000137913.26087.F015262830
- 5 Joosten MM, Pai JK, Bertola ML, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA* 2012;308:1660-7. doi:10.1001/jama.2012.1341523093164

- 6 Willigendael EM, Tejjink JA, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg* 2004;40:1158-65. doi:10.1016/j.jvs.2004.08.04915622370
- 7 Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141:421-31. doi:10.7326/0003-4819-141-6-200409210-0000715381515
- 8 Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharratt AR. HbA1c and peripheral arterial disease: the Atherosclerosis Risk in Communities study. *Diabetes Care* 2006;29:877-82. doi:10.2337/diacare.29.04.06.dc05-201816567831
- 9 Armstrong DG, Cohen K, Couric S, Bharara M, Marston W. Diabetic foot ulcers and vascular insufficiency: our population has changed, but our methods have not. *J Diabetes Sci Technol* 2011;5:1591-5. doi:10.1177/1932296811005006362226282
- 10 Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* 2003;26:491-4. doi:10.2337/diacare.26.2.49112547887
- 11 Criqui MH, Fronck A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71:510-5. doi:10.1161/01.CIR.71.3.510156006
- 12 Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995;91:1472-9. doi:10.1161/01.CIR.91.5.14727867189
- 13 Vitalis A, Lip GY, Kay M, Vohra RK, Shantsila A. Ethnic differences in the prevalence of peripheral arterial disease: a systematic review and meta-analysis. *Expert Rev Cardiovasc Ther* 2017;15:327-38. doi:10.1080/14779072.2017.130589028290228
- 14 Kullo IJ, Bailey KR, Kardia SL, Mosley TH Jr, Boerwinkle E, Turner ST. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Vasc Med* 2003;8:237-42. doi:10.1191/1358863x03vm511oa15125483
- 15 Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005;112:2703-7. doi:10.1161/CIRCULATIONAHA.105.54650716246968
- 16 Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996;25:1172-81. doi:10.1093/ije/25.6.11729027521
- 17 Garcia LA. Epidemiology and pathophysiology of lower extremity peripheral arterial disease. *J Endovasc Ther* 2006;13(Suppl 2):II3-9. doi:10.1177/15266028060130S20416472007
- 18 Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J* 2013;165:809-15. 815.e1. doi:10.1016/j.ahj.2012.12.00223622919
- 19 Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care* 2001;24:1433-7. doi:10.2337/diacare.24.8.143311473082
- 20 Alahdab F, Wang AT, Elraiyah TA, et al. A systematic review for the screening for peripheral arterial disease in asymptomatic patients. *J Vasc Surg* 2015;61(Suppl):42S-53S. doi:10.1016/j.jvs.2014.12.00825721066
- 21 Boyko EJ, Ahroni JH, Davignon D, Stensel V, Pigeon RL, Smith DG. Diagnostic utility of the history and physical examination for peripheral vascular disease among patients with diabetes mellitus. *J Clin Epidemiol* 1997;50:659-68. doi:10.1016/S0895-4356(97)00005-X9250264
- 22 Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA* 2006;295:536-46. doi:10.1001/jama.295.5.53616449619
- 23 National Institute for Health and Care Excellence. Clinical knowledge summaries: Peripheral arterial disease. 2015. <https://cks.nice.org.uk/peripheral-arterial-disease>.
- 24 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification (clinical guideline CG181). 2017. www.nice.org.uk/guidance/cg181.
- 25 National Institute for Health and Care Excellence. NICE Quality and Outcomes Framework indicator: the contractor establishes and maintains a register of patients with peripheral arterial disease. 2016. www.nice.org.uk/standards-and-indicators/qofindicators/the-contractor-establishes-and-maintains-a-register-of-patients-with-peripheral-arterial-disease.
- 26 Bhatt DL, Steg PG, Ohman EM, et al. REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-9. doi:10.1001/jama.295.2.18016403930
- 27 Khan S, Flather M, Mister R, et al. Characteristics and treatments of patients with peripheral arterial disease referred to UK vascular clinics: results of a prospective registry. *Eur J Vasc Endovasc Surg* 2007;33:442-50. doi:10.1016/j.ejvs.2006.11.01017196851
- 28 Osborne NH, Upchurch GR Jr, Mathur AK, Dimick JB. Explaining racial disparities in mortality after abdominal aortic aneurysm repair. *J Vasc Surg* 2009;50:709-13. doi:10.1016/j.jvs.2009.05.02019703760
- 29 Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. *Med J Aust* 1983;1:217-9.6835125
- 30 Lassila R, Lepäntalo M. Cigarette smoking and the outcome after lower limb arterial surgery. *Acta Chir Scand* 1988;154:635-40.3232481
- 31 Willigendael EM, Tejjink JA, Bartelink ML, Peters RJ, Büller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg* 2005;42:67-74. doi:10.1016/j.jvs.2005.03.02416012454
- 32 Armstrong EJ, Wu J, Singh GD, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg* 2014;60:1565-71. doi:10.1016/j.jvs.2014.08.06425282696
- 33 van de Graaf RC, van Schayck OC. [Helping people to give up smoking; efficacy and safety of smoking cessation interventions]. *Ned Tijdschr Geneesk* 2017;161:D1131.28224877
- 34 Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;163:608-21. doi:10.7326/M15-017126389650
- 35 Ebbert JO, Wyatt KD, Hays JT, Klee EW, Hurt RD. Varenicline for smoking cessation: efficacy, safety, and treatment recommendations. *Patient Prefer Adherence* 2010;4:355-62. doi:10.2147/PPA.S1062021049087
- 36 Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2016;(5):CD006103.27158893
- 37 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39. doi:10.1016/S0140-6736(96)09457-38918275
- 38 Katsanos K, Spiliopoulos S, Saha P, et al. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One* 2015;10:e0135692. doi:10.1371/journal.pone.013569226274912
- 39 Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl):e669S-90S. doi:10.1378/chest.11-230722315275
- 40 Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis. *Vascul Pharmacol* 2014;63:79-87. doi:10.1016/j.vph.2014.09.001125446168
- 41 Suckow BD, Kraiss LW, Schanzer A, et al. Vascular Study Group of New England. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg* 2015;61:126-33. doi:10.1016/j.jvs.2014.05.09325037607
- 42 Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108:1481-6. doi:10.1161/01.CIR.0000090686.57897.F512952839
- 43 Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 2003;92:711-2. doi:10.1016/S0002-9149(03)00833-612972114
- 44 Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;114:359-64. doi:10.1016/S0002-9343(03)00010-X12714124
- 45 Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;75:894-903. doi:10.1016/S0002-9149(99)80683-37732997
- 46 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. doi:10.1016/S0140-6736(98)07019-69742976
- 47 Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycaemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care* 2002;25:894-9. doi:10.2337/diacare.25.5.89411978687
- 48 National Institute for Health and Care Excellence. Diabetic foot problems: prevention and management (NICE guideline NG19). 2016. www.nice.org.uk/guidance/ng19.
- 49 Gerhard-Herman MD, Gornik HL, Barrett C, 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. *J Am Coll Cardiol* 2017;69:1465-508. doi:10.1016/j.jacc.2016.11.00827851991
- 50 Shahin Y, Mazari F, Chetter I. Do angiotensin converting enzyme inhibitors improve walking distance in patients with symptomatic lower limb arterial disease? A systematic review and meta-analysis of randomised controlled trials. *Int J Surg* 2011;9:209-13. doi:10.1016/j.ijsu.2010.12.00621195215
- 51 Fokkenrood HJP, Bendermacher BLW, Lauret GJ, Willigendael EM, Prins MH, Tejjink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2013;23:CD005263.23970372
- 52 Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2014;(7):CD000990.25037027
- 53 Lyu X, Li S, Peng S, Cai H, Liu G, Ran X. Intensive walking exercise for lower extremity peripheral arterial disease: A systematic review and meta-analysis. *J Diabetes* 2016;8:363-77. doi:10.1111/1753-0407.1230425940390
- 54 Frans FA, Bipat S, Reekers JA, Legemate DA, Koelmaer MJ. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. *Br J Surg* 2012;99:16-28. doi:10.1002/bjs.765621928409
- 55 Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA* 1995;274:975-80. doi:10.1001/jama.1995.035301200670437674529
- 56 NHS Employers. 2016/17 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): Guidance for GMS contract 2016/17. 2016. www.nhsemployers.org/~media/Employers/Documents/Primarycarecontracts/QOF/2016-17/2016-17QOFguidancedocuments.pdf.
- 57 Stevens JW, Simpson E, Harman S, et al. Systematic review of the efficacy of cilostazol, nafidofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. *Br J Surg* 2012;99:1630-8. doi:10.1002/bjs.889523034699
- 58 Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhaliidis DP, Stansby G. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev* 2014;(10):CD003748.25358850
- 59 Meng Y, Squires H, Stevens JW, et al. Cost-effectiveness of cilostazol, nafidofuryl oxalate, and pentoxifylline for the treatment of intermittent claudication in people with peripheral arterial disease. *Angiology* 2014;65:190-7. doi:10.1177/000331971247433523378195
- 60 Barrons RW, Woods JA. The roles of ACE inhibitors in lower extremity peripheral artery disease. *Am J Ther* 2016;23:e7-15. doi:10.1097/MJT.00000000000001124768850
- 61 Hennion DR, Siano KA. Diagnosis and treatment of peripheral arterial disease. *Am Fam Physician* 2013;88:306-10.24010393
- 62 Hess CN, Norgren L, Ansel GM, et al. A structured review of antithrombotic therapy in peripheral artery disease with a focus on revascularization: a TASC (InterSociety Consensus for the Management of Peripheral Artery Disease) Initiative. *Circulation* 2017;135:2534-55. doi:10.1161/CIRCULATIONAHA.117.02446928630267
- 63 Jaff MR, White CJ, Hiatt WR, et al. TASC Steering Committee. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Vasc Med* 2015;20:465-78. doi:10.1177/1358863X1559787726268268
- 64 Antoniou GA, Georgiadis GS, Antoniou SA, Makar RR, Smout JD, Torella F. Bypass surgery for chronic lower limb ischaemia. *Cochrane Database Syst Rev* 2017;4:CD002000.28368090

- 65 Pope J, Fenlon D, Thompson A, et al . Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000;(2):CD000953.10796395
- 66 Huisstede BM, Hoogvliet P, Paulis WD, et al . Effectiveness of interventions for secondary Raynaud's phenomenon: a systematic review. *Arch Phys Med Rehabil* 2011;92:1166-80. doi:10.1016/j.apmr.2011.01.02221704799

- 67 ISRCTN Registry. ISRCTN27728689: Bypass v angioplasty in severe ischaemia of the leg. 2017. www.isrctn.com/ISRCTN27728689.

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Table

Table 1 | Differential diagnoses of intermittent claudication

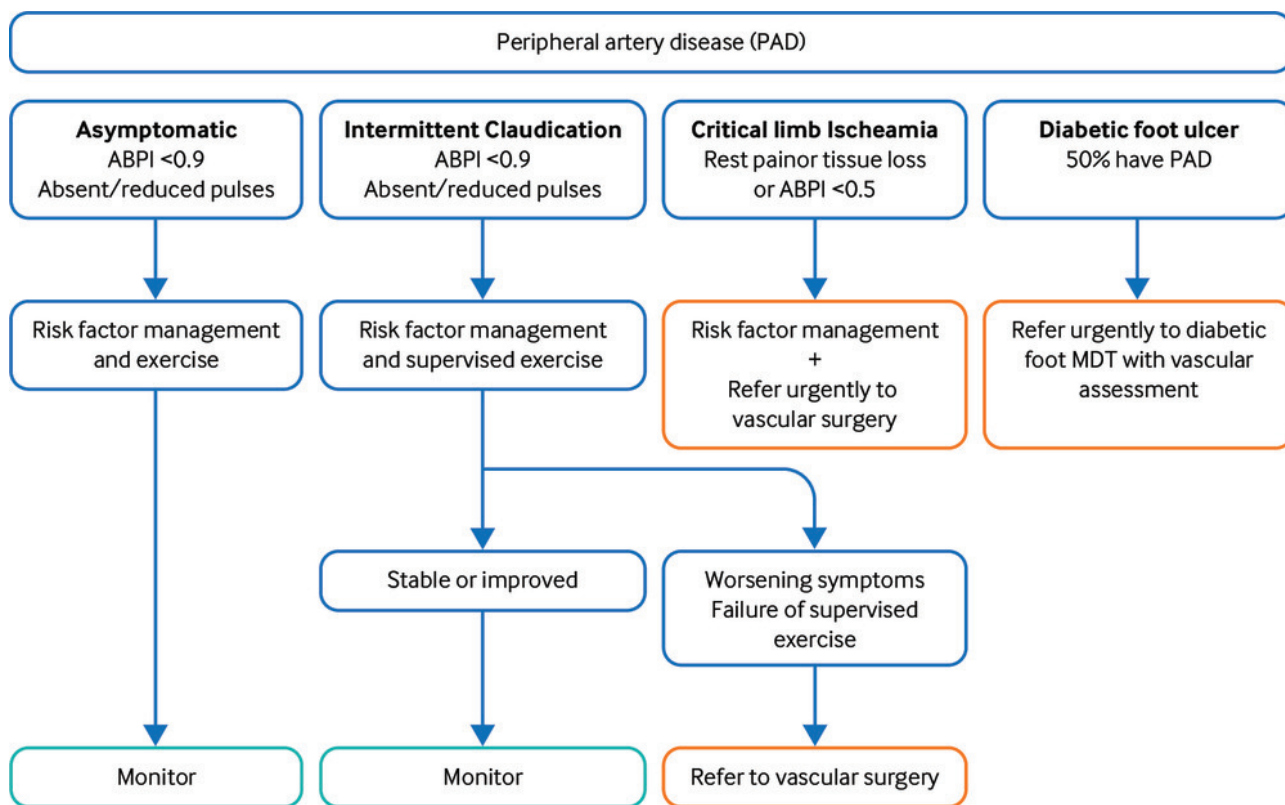
Condition	Differentiation
Non-vascular	
Spinal stenosis	Relieved by position change, may have leg weakness
Osteoarthritis	Not quickly relieved by rest
Lumbar nerve root irritation	Straight leg raise test is positive
Vascular	
Venous claudication	History of deep vein thrombosis, pain relief on leg elevation,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

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