BMJ Best Practice

Peripheral arterial disease

The right clinical information, right where it's needed

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Summary

- The most common cause is atherosclerosis.
- Most patients are asymptomatic.
- Patients require aggressive risk factor control.
- Long-term patency of lower-extremity revascularisation should be monitored with a surveillance programme.
- First line of therapy for patient with lifestyle-limiting claudication is a supervised 12-week exercise programme and medication. Revascularisation should be considered if these therapies fail.
- Death from a cardiac cause has a relative risk of 3 to 6 in patients with peripheral vascular disease.

BASICS

Definition

Peripheral arterial disease (PAD) includes a range of arterial syndromes that are caused by atherosclerotic obstruction of the lower-extremity arteries.

Epidemiology

The prevalence of PAD increases with age, beginning after 40 years of age.[2] [3] [4] [5] [6] According to the Centers for Disease Control and Prevention, PAD, as defined by abnormal ankle brachial index of <0.90, was prevalent in 1.0% among a 40- to 49-year-old population. However, with increasing age the prevalence increased. [CDC: peripheral arterial disease fact sheet] In the age group of 50 to 59 years the prevalence was around 3.0% to 5.0%, in the age group of 60 to 69 years it was around 5.0%, and in those over the age of 80 years it was >20.0% (and even >25.0% in men).

A study in Sweden showed a prevalence of 7.9% in the age group 60 to 65 years, increasing to 47.2% in those aged 85 to 90 years.[3] In the UK, one-fifth of people aged 65 to 75 years have evidence of PAD on clinical examination.[5] A US study found black people to have a higher prevalence of PAD, even after accounting for other risk factors, and Asian people have a lower prevalence compared with white people.[7]

In high-income countries, the prevalence of PAD is equal between women and men.[8] PAD is often under-recognised and under-treated.[6] [9]

Aetiology

PAD is most commonly caused by atherosclerosis. Rarer causes of claudication are aortic coarctation, arterial fibrodysplasia, arterial tumour, arterial dissection, arterial embolism, thrombosis, vasospasm, and trauma. Other rare causes are Takayasu's arteritis, temporal arteritis, thoracic outlet obstruction, and Buerger's disease. Adventitial cystic disease, occluded limb aneurysms, popliteal artery entrapment, iliac endofibrosis, ergot toxicity, radiation fibrosis, and retroperitoneal fibrosis can also cause PAD. These can usually be distinguished based on clinical history and examination.

Pathophysiology

The pathophysiology of PAD is as diverse as the diseases it encompasses, but it centres on damage, inflammation, and structural defects of blood vessels. It includes atherosclerosis, degenerative diseases, dysplastic disorders, vascular inflammation, and thrombosis as well as thromboembolism.

The pathophysiology of intermittent claudication is most likely to be due to haemodynamic compromise. Other factors include deconditioning, metabolic changes such as accumulation of acylcarnitines and ADP, impaired synthesis of phosphocreatine, and skeletal muscle injury characterised by muscle fibre loss.[10]

Classification

Fontaine stages

There are 4 increasing stages of severity:[1]

- Stage I: asymptomatic
- Stage IIa: mild claudication
- Stage IIb: moderate to severe claudication
- Stage III: ischaemia rest pain
- Stage IV: ulceration or gangrene.

Rutherford categories

There are a total of 7 increasing categories of severity:[1]

- Grade 0, category 0: asymptomatic
- Grade I, category 1: mild claudication
- Grade I, category 2: moderate claudication
- Grade I, category 3: severe claudication
- Grade II, category 4: ischaemia rest pain
- Grade III, category 5: minor tissue loss
- Grade IV, category 6: major tissue loss.

Asymptomatic/claudication/critical limb ischaemia/acute limb ischaemia

The American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines use the following divisions:[2]

Asymptomatic:

- Absence of leg claudication symptoms.

Claudication:

- Inadequate blood flow during exercise, causing fatigue, discomfort, or pain.

Critical limb ischaemia:

- Compromise of blood flow to extremity, causing limb pain at rest. Patients often have ulcers or gangrene.

Acute limb ischaemia:

- A sudden decrease in limb perfusion that threatens limb viability. Associated with the "6 Ps": pain, paralysis, paraesthesias, pulselessness, pallor, and perishing with cold.

Primary prevention

Reduction of cardiovascular risk factors is the cornerstone in primary prevention of PAD. Smoking cessation and control of hypertension, diabetes, and hyperlipidaemia are key. A healthy lifestyle with daily exercise and low consumption of fat is also important. Taking up weight loss programmes and maintenance of an optimal weight are essential.[36]

Screening

According to the American College of Cardiology/American Heart Association guideline, it is reasonable to measure the ankle brachial index (ABI) in people at increased risk of PAD but who have no history or physical examination findings suggestive of PAD.[2] This group comprises of people:

- Who are 65 years or older
- Who are 50 to 64 years old with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidaemia, hypertension) or a family history of PAD
- Who are less than 50 years old with diabetes mellitus and one additional risk factor for atherosclerosis
- With known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).

Secondary prevention

All patients regardless of their symptoms should have aggressive risk factor modification.[2]Since patients with PAD have significantly increased cardiovascular mortality and morbidity, it is crucial to modify cardiovascular risk factors. Risk factor modifications should include control of blood pressure, diabetes, and cholesterol and smoking cessation.[2]

Case history

Case history #1

A 50-year-old male diabetic smoker presents complaining of leg pain with exertion for 6 months. He notices that he has bilateral calf cramping with walking. He states that it is worse on his right calf than his left and that it goes away when he stops walking. He has noticed that he is able to walk less and less before the onset of symptoms.

Case history #2

A 75-year-old woman with hypertension and hyperlipidaemia presents with abnormal ankle brachial index on a routine screening. She is able to walk without any discomfort and is active.

Other presentations

Patients with a previously diagnosed history of PAD can also present with sudden onset of leg numbness and paralysis. Non-healing leg or foot ulcers may also be the first presentation of PAD.

Step-by-step diagnostic approach

Peripheral vascular disease (PAD) is often under-recognised and under-treated.[6] [9] Many patients with PAD are asymptomatic, but will have 1 or more risk factors.[2] [6] The resting ankle brachial index (ABI) is the initial diagnostic test for PAD.[2] It is recommended in all patients with suspected lower limb disease with a history of exertional leg symptoms, non-healing wounds/foot ulcers, or abnormal lower extremity pulse examination. The toe brachial index is useful in those patients where the ABI is unreliable (e.g., non-compressible arteries in patients with diabetes and advancing age, as well as in many renal patients on dialysis). Other tests used to establish diagnosis include:[2]

- Segmental pressure examination
- Duplex ultrasound
- Pulse volume recording (PVR)
- Continuous wave Doppler ultrasound
- Exercise ABI
- Angiography.

Patients at risk

Classic claudication symptoms occur in a minority of patients and it is reasonable to measure the ABI in people at increased risk of PAD but who have no history or physical examination. This includes people:[2]

- Aged 65 years or older
- Aged 50 to 64 years with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidaemia, hypertension) or a family history of PAD

- Who are less than 50 years old with diabetes mellitus and one additional risk factor for atherosclerosis
- With known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).

Other symptoms and signs

Further symptoms and signs may lead to a diagnosis of PAD in the presence of risk factors:

- Calf or foot cramping with walking that is relieved with rest
- Thigh or buttock pain with walking that is relieved with rest
- Erectile dysfunction
- Pain worse in one leg
- Diminished pulse.

Critical limb ischaemia should be suspected with the following:

- Leg pain at rest
- Gangrene
- Non-healing wound/foot ulcer
- Muscle atrophy
- Dependent rubor
- Pallor when the leg is elevated
- Loss of hair over the dorsum of the foot
- Thickened toenails
- Shiny/scaly skin.

Acute limb ischaemia should be suspected with the following:

- The classic 6 signs of acute limb ischaemia which are pain, paralysis, paraesthesias, pulselessness, perishingly cold, and pallor.

Ankle brachial index (ABI)

Should be performed in patients who have symptoms or answered positively to a review of questions regarding PAD.[37] An ABI ≤0.9 is diagnostic for presence of PAD. The resting ABI should be used to establish the diagnosis of PAD in patients with exertional low-extremity claudication, rest pain, chronic limb ischaemia, or non-healing wounds/foot ulcers. It is a cheap and quick surgery-based test.[2] [6] ABI is performed by measuring the systolic pressure of the left and right brachial arteries and the left and right posterior tibial and dorsalis pedis arteries pressure. The ABI is the highest of the dorsalis pedis and posterior tibial arteries' pressure divided by the higher of the left and right arm brachial artery pulse pressure.

The test may not be accurate in patients with non-compressible arteries (e.g., patients with long-standing diabetes mellitus, or renal patients on dialysis). Patients with either severely stenotic or totally occluded arteries may also have normal ABI if there is abundant collateral system present.[37] The ABI is a marker of peripheral atherosclerosis, as well as a predictor of vascular events.[38]

Toe brachial index (TBI)

The TBI should be used to establish the diagnosis of PAD in patients in whom lower extremity PAD is clinically suspected, but in whom the ABI test is not reliable due to non-compressible vessels (usually patients with long-standing diabetes or advanced age).[2]

Further tests

Depending on the patient's symptoms, other diagnostic tests may be needed, including a more thorough assessment of the lower-extremity vasculature.[2] [6] If the ABI/TBI is abnormal, the next test to guide the therapeutic decision should be duplex ultrasonography of the lower-extremity arteries. The duplex ultrasound is both cost-effective and non-invasive, and should be done first to verify stenoses. If this is also abnormal (i.e., it shows stenoses or occlusions) an angiography is warranted. An exercise ABI can also be performed, but it does not provide information about the location of the lesion. It is useful, however, in establishing the diagnosis of lower extremity PAD in symptomatic patients when resting ABIs are normal or borderline.[2]

Computed tomography (CT) angiography and magnetic resonance angiography (MRA) comprise the gold standard for establishing diagnosis, but require IV contrast, and their spatial resolution may be lower than digital subtraction angiography.

- The location and degree of stenosis can also be assessed by duplex ultrasound. This is the preferred and most widely used modality to assess stenoses. The accuracy is diminished in tortuous, calcified prosthetic bypass grafts, and in vessels with multiple stenoses. In the aortoiliac arterial segment, accuracy can also be diminished due to bowel gas and body habitus.
- Evaluation of the arterial pressure waveform using pulse volume recording via a pneumoplethysmographic device. It is less accurate at anatomical localisation of the disease and is a technique that is now used less often.
- Walking limitations can be measured with exercise ABI, along with the onset of symptoms and the total walking time.
- Visualisation of tissue surrounding the artery using CT angiogram can demonstrate stenosis due to aneurysms, popliteal entrapment, or cystic adventitial disease that cannot be detected by angiography.
- Revascularisation is guided by angiography. It is the only accepted modality and is considered the gold standard in assessing vascular anatomy and stenosis.

Further tests can assess characteristics of any stenoses. Segmental pressure examination and pulse volume recording may be performed in addition to duplex ultrasound. If the duplex ultrasound is positive then digital subtraction angiography should be performed to locate and better visualise lesions. Alternative, emerging, procedures include MRA, which may be performed to better describe the exact degree, location, and length of the lesion:

- Location and severity of PAD, using continuous wave Doppler ultrasound, is measured through a decrease in pulsatility index between adjacent proximal and distal anatomical segments. Pulsatility index is calculated as Vmax - Vmin/Vmean, where Vmax = peak systolic velocity, Vmin = minimum diastolic velocity, and Vmean = mean blood flow velocity.
- Location and magnitude of stenosis can be determined with segmental pressure examination, based on pressure gradients between adjacent segments. Segmental pressure measurement may be artefactually elevated in patients with non-compressible arteries.

- Digital subtraction angiography technique provides superior resolution since it eliminates bony and dense body tissue artefacts. However, it is an invasive procedure requiring contrast.
- Anatomical location and stenosis can be diagnosed using MRA, although patients with pacemakers, defibrillators, and some cerebral aneurysm clips cannot be scanned safely. Gadolinium has caused nephrogenic systemic fibrosis (NSF) in patients with chronic renal insufficiency.

Risk factors

Strong

smoking

- Since the most common aetiology of PAD is atherosclerosis, the risk factors for PAD are similar to those of coronary artery disease (CAD). However, smoking is 2 or 3 times more likely to cause PAD than CAD.[2] [6] Smoking is the most powerful predictor and is independently associated with the development of PAD; an almost 4-fold increased risk of PAD due to smoking has been reported (odds ratio (OR) per year 3.83; 95% CI 2.49 to 5.91). Additionally, a dose-dependent association between smoking and the severity of PAD has been supported.[11] Both active and passive cigarette smoking impair flow-mediated endothelium-dependent peripheral arterial vasodilation (arterial stiffness). Smoking cessation is therefore essential to prevent disease progression, as well as to decrease clinical deterioration (i.e., walking distance) and amputation rates.[12] [13] [14] [15]

diabetes

- Another powerful predictor of PAD. In large epidemiology studies, diabetes has been shown to increase the risk by 2- to 4-fold.[2] Diabetes also increases the risk of intermittent claudication by 3- to 9-fold. The risk is proportional to the severity and duration of diabetes. Patients with both PAD and diabetes are 7 to 15 times more likely to undergo limb amputation. The UK Prospective Diabetes Study Group showed that each 1% increase in glycosylated haemoglobin levels is associated with a 28% increased risk of incident PAD and with a 28% increased risk of death, independent of other variables, such as blood pressure, serum cholesterol, age, or smoking status. Thus, aggressive control of hyperglycaemia in diabetes mellitus is essential to prevent disease progression and reduce cardiovascular risk.[16] [17] [18]

hypertension

- Hypertension is a recognised risk factor for PAD, with odds ratios for hypertension ranging from 1.5 to 2.2.[19] In the Framingham Heart Study, PAD was increased by the severity of hypertension and the risk of intermittent claudication overall was increased 2- to 4-fold.[20] An even higher population risk attributable to hypertension of 41% was reported in the Health Professionals Follow-up Study.[2] [21]
- Risk factor modifications should include control of blood pressure.[22] [23] The Heart Outcomes Prevention Evaluation (HOPE) study found that treatment with the angiotensin-converting enzyme inhibitor (ACEI) ramipril was associated with a reduced risk of vascular death, myocardial infarction, and stroke in a broad range of patients who were at high risk for cardiovascular events, including those with PAD.[24] [25]
- The Appropriate Blood Pressure Control in Diabetes study demonstrated the superiority of intensive over moderate blood pressure control.[26] Patients with diabetes receiving intensive antihypertensive treatment had significantly fewer cardiovascular events compared with those patients on moderate blood pressure-lowering treatment.

hyperlipidaemia

- Elevated total cholesterol, LDL, triglycerides, and lipoprotein(a) have been associated with increased risk of PAD.[2] Decreased levels of HDL have also been associated with increased risk. The risk of PAD increased by 5% to 10% for each 10 mg/dL rise in total cholesterol. Therefore, aggressive pharmacological management of lipid abnormalities in patients with peripheral arterial disease (PAD) (e.g., with statins) is crucial.[27]
- Achieving the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines for low-density lipoprotein cholesterol (LDL-C) levels (<2.59 mmol/L [<100 mg/dL]) not only reduces the atherosclerosis burden in these patients (thus decreasing disease progression), but also reduces cardiovascular event, morbidity, and mortality rates.[28] [29]
- High-dose statin therapy has been shown to be more effective at preventing PAD than moderate-dose therapy.[30]

age >40 years

- Prevalence increases from 0.9% in 40- to 49-year-olds to 14.5% in people over 70 years of age.[31]

history of coronary artery disease/cerebrovascular disease

- A personal or family history of these conditions increases the risk of developing PAD.[2]

low levels of exercise

- Individuals who do not take regular physical exercise are at increased risk of developing PAD. Regular exercise produces favourable alterations in cardiovascular risk factor profile.[33]

Weak

elevated C-reactive protein

- Physicians' Health Study found a 2.5-fold increased risk of developing PAD in those men whose CRP was in the highest quartile.[2]

hyperhomocysteinaemia

- The association of hyperhomocysteinaemia with PAD is stronger than with CAD. Approximately 30% to 40% of patients with PAD have high levels of homocysteine.[2] Elevated levels of homocysteine increase the risk of progression of PAD. There is, however, no evidence to support treatment of hyperhomocysteinaemia in PAD.[32]

vasculitis/inflammatory conditions

- The presence of a vasculitis such as Buerger's disease or Takayasu's arteritis, particularly in combination with smoking, can increase the risk of developing peripheral vascular disease.[34]

arterial fibrodysplasia

- This can affect any artery, but often involves the femoral, iliac, and popliteal arteries and can contribute to peripheral vascular disease, particularly in younger patients.[35]

trauma

- Traumatic limb injuries involving vascular injury can result in stenosis formation, which in turn can contribute to the development of PAD.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include smoking, diabetes, hyperlipidaemia, and a history of coronary artery disease or cerebrovascular disease.

asymptomatic (common)

- Most patients with PAD are asymptomatic and diagnosis is based on risk factors.

intermittent claudication (common)

- It is important to assess patients with detailed questions on walking impairment, claudication symptoms, ischaemic rest pain, or presence of non-healing wound/foot ulcer. Classic claudication symptoms occur in a minority of patients.[2]

thigh or buttock pain with walking that is relieved with rest (common)

- Intermittent claudication can also occur in the larger muscles groups of the upper leg. This is indicative of narrowing of the deep femoral artery.

diminished pulse (common)

- Key component of physical examination includes assessment of pulse in all extremities. Palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial artery is essential. Also, auscultation of carotid, femoral, and abdomen is essential to assess for bruit.

sudden onset of severe leg pain accompanied by numbness, weakness, pale, and cold leg (uncommon)

- The classic 6 signs of acute limb ischaemia are: pain, paralysis, paraesthesias, pulselessness, perishingly cold, and pallor.

no pulse in lower extremity (uncommon)

- Sign of acute limb ischaemia (detected with Doppler ultrasound).

Other diagnostic factors

erectile dysfunction (common)

- May be an early sign of PAD. Erectile dysfunction may be the symptom of narrowing of the internal iliac arteries.[39]

pain worse in one leg (common)

- Most patients are able to localise severity of leg pain to one leg.[2]

leg pain at rest (uncommon)

- May be a sign of critical limb ischaemia.[2] The pain is severe and will be associated with chronic ischaemic signs on their physical examination. The pain is worse when the patient is supine and may be better when the leg is dependent.

gangrene (uncommon)

- Necrosis that may involve one or more toes. This is a sign of critical limb ischaemia.[2]

non-healing wound/ulcer (uncommon)

- A non-healing wound/ulcer in the lower extremities below the level of the knee may be a sign of critical limb ischaemia.[2]

muscle atrophy (uncommon)

- Muscle atrophy of one lower extremity (reduced circumference compared with the contralateral extremity) may be a sign of critical limb ischaemia.[2]

dependent rubor (uncommon)

- Sign of critical limb ischaemia.

pallor when the leg is elevated (uncommon)

- Sign of critical limb ischaemia.

loss of hair over the dorsum of the foot (uncommon)

- Sign of critical limb ischaemia.[2]

thickened toenails (uncommon)

- Sign of critical limb ischaemia.[2]

shiny/scaly skin (uncommon)

- Sign of critical limb ischaemia.[2] Due to loss of subcutaneous tissue.

pale extremity (uncommon)

- Sign of acute limb ischaemia.[2]

nerve loss (uncommon)

- Sign of acute limb ischaemia.[2]

Diagnostic tests

1st test to order

Test	Result
ankle brachial index (ABI) • Sensitivity of 95% and specificity of 100%. May not be accurate in patients with non-compressible arteries (e.g., patients with long-standing diabetes mellitus, or renal patients on dialysis). Patients with either severely stenotic or totally occluded arteries may also have normal ABI if there is abundant collateral system present.[37]	**ABI ≤0.90**

Other tests to consider

Test	Result
toe brachial index (TBI) • The TBI should be used to establish the diagnosis of PAD in patients in whom lower extremity PAD is clinically suspected, but in whom the ABI test is not reliable due to non-compressible vessels (usually patients with long-standing diabetes, advanced age, or renal patients on dialysis). • TBI should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.[2]	**TBI <0.6**
segmental pressure examination • Arterial pressure can be measured with plethysmographic cuffs sequentially placed along the limb at various levels.[2] Unlike ABI, the segmental pressure analysis is able to determine the location and magnitude of stenosis. It is also cheap and quick.	**gradient of >20 mmHg between adjacent segments**
duplex ultrasound • Peak systolic velocity ratio >2.0 = stenosis >50%. • Is the most widely used modality to assess location and degree of stenosis as well as patency of bypass grafts.[2] The sensitivity and specificity of ≥50% stenosis from the iliac artery to popliteal artery are 90% and 95%.	**peak systolic velocity ratio >2.0**
pulse volume recording (PVR) • Now used less because of the emergence of duplex ultrasound.[2] Evaluates the arterial pressure waveform via the use of pneumoplethysmographic device. Accurate in patients with non-compressible arteries; however, its measurements are qualitative, not quantitative. Diagnostic accuracy is in the range of 90% to 95%. May not be accurate in diagnosing stenosis of the distal segments. Abnormal in patients with low cardiac stroke volume.	**any qualitative sequential decrease in pulsatility of the waveform**
continuous wave Doppler ultrasound • Provides an accurate location and severity of PAD.[2] Limited accuracy in tortuous, calcified, and overlapping vessel and lower sensitivity for iliac artery disease. Also, in patients with superficial femoral artery stenosis, there is lowered specificity. • Pulsatility index might be normal distal to the stenosis, which can also diminish test sensitivity.	**pulsatility index decrease between adjacent proximal and distal anatomical segments**
exercise ABI • The magnitude of the walking limitations can be assessed and it is a good measure of therapeutic benefit.[2] Useful in establishing the diagnosis of lower extremity PAD in symptomatic patients when resting ABIs are normal or borderline.[2] Typically, a motorised treadmill is used and patients are exercised on Naughton, Hiatt, or Gardner-Skinner protocol.	**post-exercise ABI < pre-exercise ABI**
angiography • Digital subtraction technique provides superior resolution since it eliminates bony and dense body tissue artefacts. However, it is an invasive procedure requiring contrast.	**stenosis**

Test	Result
CT angiogram • One of the gold standard tests for diagnosis. However, still requires IV contrast, although there is less radiation than with traditional angiography.[2] It can also reconstruct the images into 3D images. The new 64-slice CT can have sensitivity from 89% to 100% and specificity from 92% to 100% for >50% stenosis. • However, its spatial resolution is lower than digital subtraction angiography and venous opacification can obscure arterial filling.	**presence of significant stenosis**
MR angiography (MRA) • One of the gold standard tests for diagnosis. MRA is useful to diagnose anatomical location and stenosis.[2] Sensitivity and specificity of MRA in a meta-analysis to detect a stenosis >50% was 90% to 100%, with the greatest accuracy when gadolinium was used. However, it does have several limitations. MRA tends to overestimate stenosis and occlusions. Metal clips can mimic occlusions, thus limiting its use in post-surgical patients. Also, patients with pacemakers, defibrillators, and some cerebral aneurysm clips cannot be scanned safely. • Gadolinium has caused nephrogenic systemic fibrosis (NSF) in patients with chronic renal insufficiency.	**stenosis**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Spinal stenosis	• Patients with history of back pain complain of hip, thigh, buttock, or leg pain. It is usually in a dermatomal distribution and may be associated with motor weakness. The pain may occur on standing alone and is relieved by position change such as sitting or stooping forwards (lumbar spine flexion).	• Ankle brachial index (ABI) will be normal and exercise ABI will show no decrease in post-exercise ABI. • No significant disease seen with arterial imaging tests. • Plain spinal x-ray: degenerative changes or spondylolisthesis. • MRI spine: compression of the neural elements and soft tissue.
Arthritis	• Patients complain of hip, thigh, or buttock pain that is localised to hip and gluteal region. It can occur at rest or starts after exercise and is not quickly relieved.	• ABI will be normal and exercise ABI will show no decrease in post-exercise ABI. • No significant disease seen with arterial imaging tests. • X-ray of affected joint: new bone formation (osteophytes), joint space narrowing, and subchondral sclerosis and cysts.

Condition	Differentiating signs / symptoms	Differentiating tests
Venous claudication	• Patients usually have history of iliofemoral DVT, signs of venous congestion, and oedema. They may complain of entire leg pain that is usually worse in the thigh and groin region. The pain is described as tight or bursting, and starts after walking and is relieved slowly. Pain relief usually occurs once the leg is elevated.	• ABI will be normal and exercise ABI will show no decrease in post-exercise ABI. • No significant disease seen with arterial imaging tests.
Chronic compartment syndrome	• Occurs in athletes. They complain of tight bursting calf pain after exercise that subsides slowly after leg elevation. Usually these patients are very muscular.	• Duplex ultrasound scanning will show no significant arterial stenosis. • Compartment pressure measurement: differential pressure ≤20 mmHg.
Symptomatic Baker's cyst	• Patients complain of pain in the calf and behind the knee. The area is usually swollen, sore, and tender. The pain is present at rest and worse with exercise.	• ABI will be normal and exercise ABI will show no decrease in post-exercise ABI. • No significant disease seen with arterial imaging tests. • Duplex ultrasound of the leg: cystic mass in the posterior-medial popliteal fossa.
Nerve root compression	• Patients have pain that radiates down the leg. Often have a history of back problems.	• ABI will be normal and exercise ABI will show no decrease in post-exercise ABI. • No significant disease seen with arterial imaging tests.

Diagnostic criteria

Ankle brachial index (ABI)

This is a ratio of the blood pressure at the ankle compared with the arm while resting:[2]

- 0.90 to 1.09 is normal
- <0.90 is abnormal and indicates presence of PAD
- 0.41 to 0.90 indicates mild to moderate PAD
- <0.40 is severe
- >1.40 indicates abnormal, calcified arteries.

TransAtlantic Inter-Society Consensus (TASC): morphological stratification of iliac lesions[40]

TASC type A iliac lesions:

- Single stenosis <3 cm of the common iliac artery (CIA) or external iliac artery (EIA) (unilateral/bilateral).

TASC type B iliac lesions:

- Single stenosis 3 to 10 cm in length, not extending into the common femoral artery (CFA)
- Total of 2 stenoses <5 cm long in the CIA and/or EIA and not extending into the CFA
- Unilateral CIA occlusion.

TASC type C iliac lesions:

- Bilateral 5 to 10 cm long stenosis of the CIA and/or EIA, not extending into the CFA
- Unilateral EIA occlusion not extending into the CFA
- Bilateral CIA occlusion.

TASC type D iliac lesions:

- Diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (usually >10 cm long)
- Unilateral occlusion involving both the CIA and EIA
- Bilateral EIA occlusions
- Diffuse disease involving the aorta and both iliac arteries
- Iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery.

TransAtlantic Inter-Society Consensus (TASC): morphological stratification of femoropopliteal lesions[40]

TASC type A femoropopliteal lesions:

- Single stenosis <3 cm of the superficial femoral artery or popliteal artery.

TASC type B femoropopliteal lesions:

- Single stenosis 3 to 10 cm in length, not involving the distal popliteal artery
- Heavily calcified stenoses ≤3 cm in length
- Multiple lesions, each <3 cm (stenoses or occlusions)
- Single or multiple lesions in the absence of continuous tibial run-off to improve inflow for distal surgical bypass.

TASC type C femoropopliteal lesions:

- Single stenosis or occlusion longer than 5 cm
- Multiple stenoses or occlusions, each 3 to 5 cm in length, with or without heavy calcification.

TASC type D femoropopliteal lesions:

- Complete common femoral artery or superficial femoral artery occlusions or complete popliteal and proximal trifurcation occlusions.

TransAtlantic Inter-Society Consensus (TASC): morphological stratification of infrapopliteal lesions[41]

TASC type A infrapopliteal lesions:

- Single focal stenosis in the target tibial artery ≤5 cm in length, with occlusion of similar or worse severity in the other tibial arteries.

TASC type B infrapopliteal lesions:

- Multiple stenoses, each ≤5 cm in length, or total length ≤10 cm, or single occlusion ≤3 cm in length, with occlusion of similar or worse severity in the other tibial arteries.

TASC type C infrapopliteal lesions:

- Multiple stenoses in the target tibial artery and/or single occlusion with total lesion length >10 cm, with occlusion of similar or worse severity in the other tibial arteries.

TASC type D infrapopliteal lesions:

- Multiple occlusions involving the target tibial artery with total lesion length >10 cm or dense lesion calcification or non-visualisation of collaterals. The other tibial arteries are occluded or have dense calcification.

Step-by-step treatment approach

All patients regardless of their symptoms should have aggressive risk factor modification. Control of blood pressure (<130/80 mmHg),[42] lipid control (LDL <2.59 mmol/L [<100 mg/dL]),[28] smoking cessation,1[C]Evidence and diabetes control (HgA1c <7.0).[1] [2] 2[A]Evidence

Patients with mild-to-moderate claudication should be advised to keep walking, and people who are fit enough should be encouraged to enrol in an exercise intervention.[33]

Antiplatelet therapy is recommended for all patients.

Acute limb ischaemia

Acute limb ischaemia is a medical emergency.[2] Patients who have sudden decrease in limb perfusion with threatened tissue viability require urgent history and physical examination to determine symptom onset. They need rapid assessment by a vascular surgeon with a view to restoring arterial blood flow as soon as possible.[2] Emergency vascular study assessment should be performed with ankle brachial index (ABI) or duplex ultrasound. Once the diagnosis is established, patients should be started on systemic anticoagulation with heparin, unless contraindicated, together with appropriate analgesia.[1] [2] For acute ischaemic pain, paracetamol and an opioid (weak or strong) are recommended depending on the severity of pain.[43]

Aetiologies of acute limb ischaemia are embolic, progressive PAD with in situ thrombosis, bypass graft thrombosis, arterial trauma, popliteal cyst or entrapment, hypercoagulable state, or phlegmasia cerulea dolens.

Non-viable limb:

- These patients will have signs of tissue loss, nerve damage, and sensory loss and will require amputation.

Viable limb:

- These patients will have no significant tissue loss, nerve damage, or significant sensory loss.
- Patients should have arterial anatomy defined and undergo revascularisation.
- Options for revascularisation include: percutaneous catheter-directed thrombolytic therapy; percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolysis); and surgical thrombectomy, bypass, and/or arterial repair.[1] Endovascular therapy is often preferred, especially in patients with severe comorbidities.
- Randomised controlled trials and case series suggest that intra-arterial thrombolytic therapy is as effective as surgery, and it has become the modality of choice. Factors influencing choice depend on the presence of a neurological deficit, duration of ischaemia, its localisation, comorbidities, type of conduit (artery or graft), and risks related to treatment.[1] Urokinase is the most widely studied thrombolytic in acute limb ischaemia but it is no longer available in the US. Alternatives include alteplase, reteplase, and tenecteplase.[2] [44] Although there are a number of comparative studies, no single thrombolytic has emerged as the drug of choice. Streptokinase is no longer used due to lower efficacy, increased bleeding rate, and antigenicity issues.

Claudication (not lifestyle-limiting)

Patients with mild-to-moderate claudication should be advised to keep walking.[33]

For patients with claudication and established PAD, antiplatelet therapy (aspirin alone or clopidogrel alone) is recommended to reduce risk of myocardial infarction, stroke, and vascular death.[2] Follow-up visits, at least annually, are required to monitor development of coronary, cerebrovascular, or leg ischaemic symptoms.[2]

Claudication (lifestyle-limiting)

Patients with lifestyle-limiting symptoms should undergo both a supervised exercise programme and pharmacological therapy for symptom relief.[2] 3[C]Evidence Exercise therapy has been shown in multiple studies (but of limited quality) to improve walking time and relieve symptoms.[33] [45]

A supervised exercise training programme consists of 30 to 45 minutes per session, 3 times a week for 12 weeks. If supervised exercise therapy is not feasible, community-based walking programmes have also shown some benefit.[46]

Symptom relief can be achieved with pentoxifylline, cilostazol, or naftidrofuryl.[47] [48] Cilostazol may improve pain-free walking distance in patients with intermittent claudication,[49] [50] and has been shown to be more effective than pentoxifylline.4[B]Evidence One meta-analysis demonstrated that the addition of cilostazol to antiplatelet therapy after peripheral vascular interventions is associated with a reduced risk of restenosis, amputation, and target lesion revascularisation.[51] Cilostazol also reduces angiographic restenosis after percutaneous transluminal angioplasty and stenting for femoropopliteal lesions.[52] However, cilostazol is contraindicated in: congestive heart failure; unstable angina, recent myocardial infarction, or coronary intervention (within 6 months); patients with a history of severe tachyarrhythmia; and patients who are receiving 2 or more other anticoagulants or antiplatelet agents. According to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, it should be restricted to second-line use in patients for whom lifestyle modifications and other appropriate interventions have failed to sufficiently improve their symptoms. [MHRA: cilostazol drug alert] Patients taking cilostazol should be assessed for benefit 3 months after starting treatment, and treatment ceased if there is not a clinically-relevant improvement in walking distance. Pentoxifylline is also widely used; however, it is no more effective than placebo in randomised controlled trials, and is contraindicated in patients with recent cerebral and/or retinal haemorrhage and in patients with intolerance of methylxanthines (theophylline). Patients with intermittent claudication may improve their walking distance with naftidrofuryl therapy.[53] Naftidrofuryl was shown to be more effective than cilostazol in a systematic review.[54]

If there is clinical improvement with an exercise programme and medication, follow-up visits are recommended. However, if there is no improvement, patients should be referred to a vascular specialist and have their anatomy defined and assessed for revascularisation. Studies have shown that revascularisation in combination with exercise therapy is more effective than exercise therapy alone.[55] [56]

Some patients choose to take a herbal supplement (L-arginine, propionyl L-carnitine, ginkgo biloba). However, the clinical benefit of these supplements is not well established.[2] [57]

Chronic severe limb ischaemia (critical limb ischaemia)

These patients have chronic ischaemic leg symptoms such as ischaemic rest pain, gangrene, and non-healing wounds/foot and leg ulcers.[2] For these patients, ischaemic aetiology must be established

urgently by physical examination and vascular studies. If patients have documented PAD, they should be immediately referred to a vascular specialist for revascularisation.

Risk stratification may be considered based on the Wound, Ischaemia, and Foot Infection (WiFi) score.[58]

Patients who have been able to walk before the episode of critical limb ischaemia, have a life expectancy of >1 year, and are able to withstand surgery may be candidates for revascularisation.

In patients with inoperable chronic critical limb ischaemia facing amputation of the leg, spinal cord stimulation may be a helpful treatment option in addition to standard conservative treatment. There is evidence that spinal cord stimulation is associated with higher rates of limb salvage and more prominent pain relief compared with standard conservative treatment alone.[59] There is also some evidence for autologous bone marrow stem cell transplantation as an option for patients with critical limb ischaemia.[60] However, other studies have failed to show benefit.[61]

If the patient is not a candidate for revascularisation, they should be assessed for amputation where necessary and be on appropriate risk factor reduction medication.

Revascularisation referral

The following patients should be referred to a vascular specialist to have their anatomy defined and assessed:

- Patients with lifestyle-limiting claudication who continue to have limiting symptoms despite exercise
- Patients with critical limb ischaemia symptoms (ischaemic rest pain, gangrene, non-healing wounds/foot ulcers)
- Patients with acute limb ischaemia (sudden decrease in limb perfusion with threatened tissue viability).

Revascularisation is recommended if patients have lifestyle-limiting claudication, and have failed to achieve benefit from medications combined with an exercise programme. Endovascular and surgical procedures should not be performed in patients with PAD solely to prevent progression to chronic limb ischaemia.[2]

Endovascular or surgical revascularisation

Endovascular techniques include percutaneous transluminal angioplasty (PTA) with balloon dilation, stents, atherectomy, laser, cutting balloons, and drug-coated balloons.[62] [63]

For aortoiliac disease, endovascular revascularisation is recommended for stenoses that are <10 cm in length and chronic occlusions that are <5 cm.[2] For other lesions with stenosis >10 cm, chronic occlusions >5 cm, heavily calcified lesions, and lesions associated with aortic aneurysm, surgery is recommended, but endovascular approaches also have high rates of technical success. Surgery should not be offered to patients with a large amount of tissue loss or extensive infection.[64] Common femoral endarterectomy is frequently performed for common femoral artery lesions. This surgery has a high patency rate but may be associated with significant complications.[65]

For femoropopliteal artery stenosis, endovascular therapy is recommended if there is a discrete stenosis <10 cm or calcified stenosis <5 cm.[2]

Surgical revascularisation is recommended for lesions involving the common femoral artery, lesions >10 cm, heavily calcified lesions >5 cm, lesions involving the ostium of superficial femoral artery, and lesions involving the popliteal artery. Endovascular therapy can also be performed for longer lesions, as newer technologies such as drug-coated balloons have begun to suggest patency rates similar to that of surgical bypass.[66]

For infrapopliteal artery lesions, endovascular treatment has been limited to threatened limb loss only. Surgical revascularisation patency rate for infrapopliteal artery is poor but may be slightly better with in situ technique. Regardless of the procedure selected, all patients undergoing surgical or endovascular revascularisation should receive lifelong aspirin treatment (75-100 mg/day).[67] [68] Current evidence has not yet established whether bypass surgery or endovascular intervention is superior for initial treatment or critical limb ischaemia, although many operators have adopted an 'endovascular first' strategy, given that this approach is associated with lower morbidity among patients with concomitant comorbidities.[69]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)

Patient group	Tx line	Treatment
acute limb ischaemia	**1st**	**urgent assessment for revascularisation or amputation**
	plus	**antiplatelet therapy**
	plus	**analgesia**
	plus	**anticoagulation**
	plus	**continued risk factor modification**
■ **viable limb**	**adjunct**	**endovascular revascularisation and intra-arterial thrombolysis**
■ **viable limb**	**adjunct**	**surgical revascularisation**
■ **non-viable limb or failed revascularisation**	**adjunct**	**amputation**

Ongoing (summary)

Patient group	Tx line	Treatment
claudication (not lifestyle-limiting)	**1st**	**antiplatelet therapy**
	plus	**exercise**
	plus	**risk factor modification**

Ongoing (summary)

claudication (lifestyle-limiting)	**1st**	**antiplatelet therapy**
	plus	**exercise**
	plus	**symptom relief**
	plus	**continued risk factor modification**
	adjunct	**revascularisation**
chronic severe limb ischaemia (critical limb ischaemia)	**1st**	**assessment for revascularisation**
	plus	**antiplatelet therapy**
	plus	**continued risk factor modification**
	adjunct	**endovascular revascularisation**
	adjunct	**surgical revascularisation**
	adjunct	**spinal cord stimulation**
	adjunct	**autologous bone marrow stem cell transplantation**
	adjunct	**amputation**

Treatment options

Acute

Patient group	Tx line	Treatment
acute limb ischaemia	**1st**	**urgent assessment for revascularisation or amputation** » Acute limb ischaemia is a medical emergency.[2] » Patients who have sudden decrease in limb perfusion with threatened tissue viability require urgent history and physical examination to determine symptom onset. They need rapid assessment by a vascular surgeon with a view to restoring arterial blood flow as soon as possible. Emergency vascular study assessment should be performed with ABI or duplex ultrasound. If there is severe PAD, then the patient should immediately be assessed for aetiology of acute limb ischaemia.[2] » Non-viable limb: these patients will have signs of tissue loss, nerve damage, and sensory loss and will require amputation. » Viable limb: these patients will have no significant tissue loss, nerve damage, or significant sensory loss. Patients should have arterial anatomy defined and undergo revascularisation.
	plus	**antiplatelet therapy** » Antiplatelet therapy with aspirin is recommended. Clopidogrel is recommended as an effective alternative antiplatelet therapy to aspirin.2[A]Evidence **Primary options** » aspirin: 75-325 mg orally once daily European guidelines recommend a lower dose of 75-100 mg/day. **OR** **Primary options** » clopidogrel: 75 mg orally once daily
	plus	**analgesia** » For acute ischaemic pain, paracetamol and an opioid (weak or strong) are recommended, depending on the severity of pain. Consult

Acute

Patient group	Tx line	Treatment
		local guidance for selection of an appropriate analgesic.[43]
	plus	**anticoagulation**
		» In patients with acute limb ischaemia, systemic anticoagulation with unfractionated heparin should be administered, unless contraindicated.
		Primary options
		» heparin: consult specialist for guidance on dose
	plus	**continued risk factor modification**
		» All PAD patients regardless of their symptoms should have aggressive risk factor modification.
		» Since patients with PAD have significantly increased risk of cardiovascular mortality and morbidity, it is crucial to modify their cardiovascular risk factors.
		» This should include: control of blood pressure according to the ACC/AHA guideline (<130/80 mmHg);[42] for patients with diabetes, HbA1c <7.0%, and foot care; hyperlipidaemia control according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (LDL <2.59 mmol/L [<100 mg/dL]);[28] cessation of smoking;1[C]Evidence dietary advice to reduce CVD risk and control weight;[2] and increase exercise.[2] 3[C]Evidence
		» Statins are indicated in all patients to achieve LDL <2.59 mmol/L (<100 mg/dL).5[B]EvidenceLipid-lowering therapy reduces cardiovascular events, improves walking distance, and reduces the progression of the disease.[29] [70] [71] [72] Fibrates (e.g., gemfibrozil) can be used if patients have low HDL, normal LDL, and elevated triglycerides.
		» Beta-blockers (e.g., bisoprolol, metoprolol, propranolol) are effective at reducing cardiovascular risk factors, especially if patients have a history of CAD, CHF, or angina. No one class of antihypertensive medication or strategy is superior for lowering blood pressure in PAD.[2]
		» ACE inhibitors can also be used: in the Heart Outcomes Prevention Evaluation Study (high-risk patients ≥55 years of age who had evidence of vascular disease or diabetes mellitus plus one cardiovascular risk factor), treatment with ramipril reduced the rates of

Acute

Patient group	Tx line	Treatment
		death from cardiovascular causes by 26%, the risk of myocardial infarction by 20%, the risk of stroke by 32%, and the risk of death from any cause by 16% compared with placebo.[24] One randomised, double-blind, placebo-controlled trial demonstrated that treatment with ramipril for 24 weeks was associated with an increase in mean pain-free and maximum walking time compared with placebo in patients with intermittent claudication.[73]
viable limb	adjunct	**endovascular revascularisation and intra-arterial thrombolysis** » For patients who continue to have symptoms, revascularisation is recommended. Endovascular revascularisation is often preferred to bypass surgery in patients with severe comorbidities. Percutaneous transluminal angioplasty (PTA) with balloon dilation, stents, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolysis) are available techniques. » Localised intra-arterial infusion of thrombolytics is used with or without the concomitant use of a mechanical thrombectomy device.[2] » Urokinase is the most widely studied thrombolytic in acute limb ischaemia. Alternatives are alteplase, reteplase, and tenecteplase.[2] [44] Although there are a number of comparative studies, no single thrombolytic has emerged as the drug of choice. Streptokinase is no longer used due to lower efficacy, increased bleeding rate, and antigenicity issues. » Consult specialist for guidance on dose. **Primary options** » urokinase: consult specialist for guidance on dose **OR** **Secondary options** » alteplase: consult specialist for guidance on dose **OR** **Secondary options**

Acute

Patient group	Tx line	Treatment
		» reteplase: consult specialist for guidance on dose
		OR
		Secondary options
		» tenecteplase: consult specialist for guidance on dose
viable limb	**adjunct**	**surgical revascularisation** » For patients who continue to have symptoms, revascularisation is recommended. Options for surgical revascularization include surgical thrombectomy and bypass. » Surgical revascularisation is recommended for aortoiliac disease if stenosis >10 cm, chronic occlusion >5 cm, heavily calcified lesions, or lesions associated with aortic aneurysm. » Surgical revascularisation is recommended for common femoral artery disease if lesion >10 cm, heavily calcified lesions >5 cm, lesions involving the ostium of superficial femoral artery, and lesions involving the popliteal artery.[2] » Common femoral endarterectomy is frequently performed for common femoral artery lesions. This surgery has a high patency rate but may be associated with significant complications.[65] » Unlike femoropopliteal lesions or aortoiliac lesions, failed endovascular intervention can preclude surgical revascularisation. Therefore, careful selection is essential. Surgical revascularisation patency rate for infrapopliteal artery is poor but may be slightly better with in situ technique.
non-viable limb or failed revascularisation	**adjunct**	**amputation** » If part of a limb is clearly non-viable from the outset or attempts at revascularisation should fail, amputation is required. Careful consideration of the most appropriate type and level of amputation should be made in consultation with the patient, bearing in mind factors such as likelihood of successful healing, patient motivation and social circumstances, and the patient's potential functional outcomes with an appropriate prosthesis, if required.

Ongoing

Patient group	Tx line	Treatment
claudication (not lifestyle-limiting)	**1st**	**antiplatelet therapy**

» Antiplatelet therapy with aspirin is recommended. Clopidogrel is an effective alternative to aspirin.2[A]Evidence Evidence suggests that antiplatelet therapy significantly reduces cardiovascular event rates in patients with claudication.[74] Co-prescription of a proton-pump inhibitor may be recommended to reduce the risk of an upper gastrointestinal bleed, especially in patients aged 75 years or older. [75]

Primary options

» aspirin: 75-325 mg orally once daily
European guidelines recommend a lower dose of 75-100 mg/day.

OR

Primary options

» clopidogrel: 75 mg orally once daily

plus **exercise**

» Exercise therapy has been shown to improve walking time and relieve symptoms in multiple studies (limited quality). A supervised exercise training programme consists of 30 to 45 minutes per session, 3 times a week for 12 weeks.[2]

plus **risk factor modification**

» All PAD patients regardless of their symptoms should have aggressive risk factor modification.

» Since patients with PAD have significantly increased risk of cardiovascular mortality and morbidity, it is crucial to modify their cardiovascular risk factors.

» This should include: control of blood pressure according to the ACC/AHA guideline (<130/80 mmHg);[42] for patients with diabetes, HbA1c <7.0%, and foot care; hyperlipidaemia control according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline (LDL <2.59 mmol/L [<100 mg/dL]);[28] cessation of smoking;1[C]Evidence dietary advice to reduce CVD risk and control weight; and increase exercise.[2] 3[C]Evidence

Ongoing

Patient group	Tx line	Treatment
		» Statins are indicated in all patients to achieve LDL <2.59 mmol/L (<100 mg/dL).5[B]EvidenceLipid-lowering therapy reduces cardiovascular risk factors, improves walking distance, and reduces the progression of the disease.[70] [29] [71] Fibrates (e.g., gemfibrozil) can be used if patients have low HDL, normal LDL, and elevated triglycerides. » Beta-blockers (e.g., bisoprolol, metoprolol, propranolol) are effective at reducing cardiovascular events, especially if patients have a history of CAD, CHF, or angina. No one class of antihypertensive medication or strategy is superior for lowering blood pressure in PAD.[2] » ACE inhibitors can also be used: in the Heart Outcomes Prevention Evaluation Study (high-risk patients ≥55 years of age who had evidence of vascular disease or diabetes mellitus plus one cardiovascular risk factor), treatment with ramipril reduced the rates of death from cardiovascular causes by 26%, the risk of myocardial infarction by 20%, the risk of stroke by 32%, and the risk of death from any cause by 16% compared with placebo.[24] One randomised, double-blind, placebo-controlled trial demonstrated that treatment with ramipril for 24 weeks was associated with an increase in mean pain-free and maximum walking time compared with placebo in patients with intermittent claudication.[73]
claudication (lifestyle-limiting)	**1st**	**antiplatelet therapy** » Antiplatelet therapy with aspirin is recommended. Clopidogrel is an effective alternative to aspirin.2[A]Evidence Evidence suggests that antiplatelet therapy significantly reduces cardiovascular event rates in patients with claudication.[74] Co-prescription of a proton-pump inhibitor may be recommended to reduce the risk of an upper gastrointestinal bleed, especially in patients aged 75 years or older. [75] **Primary options** » aspirin: 75-325 mg orally once daily European guidelines recommend a lower dose of 75-100 mg/day. **OR**

Ongoing

Patient group	Tx line	Treatment
		Primary options
		» clopidogrel: 75 mg orally once daily
	plus	**exercise**
		» Patients with lifestyle-limiting symptoms should undergo a supervised exercise programme for 3 months.[2] 3[C]Evidence Exercise therapy has been shown to improve walking time and relieve symptoms in multiple studies (limited quality). A supervised exercise training programme consists of 30 to 45 minutes per session, 3 times a week for 12 weeks.[2]
	plus	**symptom relief**
		» Symptom relief can be achieved with pentoxifylline, cilostazol, or naftidrofuryl.[47] Cilostazol may improve pain-free walking distance in patients with intermittent claudication,[49] [50] and has been shown to be more effective than pentoxifylline.4[B]Evidence One meta-analysis demonstrated that the addition of cilostazol to antiplatelet therapy after peripheral vascular interventions is associated with a reduced risk of restenosis, amputation, and target lesion revascularisation.[51] Cilostazol also reduces angiographic restenosis after percutaneous transluminal angioplasty and stenting for femoropopliteal lesions.[52] However, cilostazol is contraindicated in: congestive heart failure; unstable angina, recent myocardial infarction, or coronary intervention (within 6 months); patients with a history of severe tachyarrhythmia; and patients who are receiving 2 or more other anticoagulants or antiplatelet agents. According to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, it should be restricted to second-line use in patients for whom lifestyle modifications and other appropriate interventions have failed to sufficiently improve their symptoms. [MHRA: cilostazol drug alert] Patients taking cilostazol should be assessed for benefit 3 months after starting treatment, and treatment ceased if there is not a clinically-relevant improvement in walking distance.
		» Pentoxifylline is also widely used; however, it is no more effective than placebo in randomized controlled trials, and is contraindicated in patients with recent cerebral and/or retinal hemorrhage and in patients with intolerance of methylxanthines (theophylline).

Ongoing

Patient group	Tx line	Treatment
		» Patients with intermittent claudication may improve their walking distance with naftidrofuryl therapy.[53] Naftidrofuryl was shown to be more effective than cilostazol in a systematic review.[54]
		Primary options
		» cilostazol: 100 mg orally twice daily
		OR
		Primary options
		» naftidrofuryl: 200 mg orally three times daily
		OR
		Secondary options
		» pentoxifylline: 400 mg orally three times daily for at least 8 weeks
	plus	**continued risk factor modification**
		» All PAD patients regardless of their symptoms should have aggressive risk factor modification.
		» Since patients with PAD have significantly increased risk of cardiovascular mortality and morbidity, it is crucial to modify their cardiovascular risk factors.
		» This should include: control of blood pressure according to the ACC/AHA guideline (<130/80 mmHg);[42] for patients with diabetes, HbA1c <7.0%, and foot care; hyperlipidaemia control according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline (LDL <2.59 mmol/L [<100 mg/dL]);[28] cessation of smoking;1[C]Evidence dietary advice to reduce CVD risk and control weight; and increase exercise.[2] 3[C]Evidence
		» Statins are indicated in all patients to achieve LDL <2.59 mmol/L (<100 mg/dL).5[B]EvidenceLipid-lowering therapy reduces cardiovascular events, improves walking distance, and reduces the progression of the disease.[70] [29] [71] Fibrates (e.g., gemfibrozil) can be used if patients have low HDL, normal LDL, and elevated triglycerides.
		» Beta-blockers (e.g., bisoprolol, metoprolol, propranolol) are effective at reducing cardiovascular risk factors, especially if patients have a history of CAD, CHF, or angina. No one

Ongoing

Patient group	Tx line	Treatment
		class of antihypertensive medication or strategy is superior for lowering blood pressure in PAD.[2] » ACE inhibitors can also be used: in the Heart Outcomes Prevention Evaluation Study (high-risk patients ≥55 years of age who had evidence of vascular disease or diabetes mellitus plus one cardiovascular risk factor), treatment with ramipril reduced the rates of death from cardiovascular causes by 26%, the risk of myocardial infarction by 20%, the risk of stroke by 32%, and the risk of death from any cause by 16% compared with placebo.[24] One randomised, double-blind, placebo-controlled trial demonstrated that treatment with ramipril for 24 weeks was associated with an increase in mean pain-free and maximum walking time compared with placebo in patients with intermittent claudication.[73]
	adjunct	**revascularisation** » Patients with lifestyle-limiting claudication who have had no improvement with exercise and symptom relief should be referred to a vascular specialist to have their arterial anatomy defined and assessed. Studies have shown that revascularisation in combination with exercise therapy is more effective than exercise therapy alone.[55] [56] » Endovascular revascularisation treatment may include either percutaneous transluminal balloon angioplasty (PTA) or bypass surgery. PTA can lead to an immediate increase in the calibre of the arterial lumen and has become an increasingly viable option for patient management.[62] » Endovascular revascularisation is recommended for aortoiliac disease with stenosis <10 cm and chronic occlusions that are <5 cm.[2] » For femoropopliteal artery stenosis, endovascular therapy is recommended if there is a discrete stenosis <10 cm, or calcified stenosis <5 cm.[2] » For infrapopliteal artery lesions, endovascular treatment has been limited to threatened limb loss only. Unlike femoropopliteal lesions or aortoiliac lesions, failed endovascular intervention can preclude surgical revascularisation. Therefore, careful selection is essential.

Ongoing

Patient group	Tx line	Treatment
		» Surgical revascularisation is recommended for aortoiliac disease if stenosis >10 cm, chronic occlusion >5 cm, heavily calcified lesions, or lesions associated with aortic aneurysm. » Surgical revascularisation is recommended for common femoral artery disease if lesion >10 cm, heavily calcified lesions >5 cm, lesions involving the ostium of superficial femoral artery, and lesions involving the popliteal artery.[2]
chronic severe limb ischaemia (critical limb ischaemia)	**1st**	**assessment for revascularisation** » Patients with critical limb ischaemia symptoms (ischaemic rest pain, gangrene, non-healing wounds/foot and leg ulcers) should be referred to a vascular specialist to have their arterial anatomy defined and assessed. » Consider risk stratification based on the Wound, Ischemia, and Foot Infection (WiFi) score.[58]
	plus	**antiplatelet therapy** » Antiplatelet therapy with aspirin is recommended. Clopidogrel is an effective alternative to aspirin.2[A]Evidence Evidence suggests that antiplatelet therapy significantly reduces cardiovascular event rates in patients with claudication.[74] Co-prescription of a proton-pump inhibitor may be recommended to reduce the risk of an upper gastrointestinal bleed, especially in patients aged 75 years or older. [75] **Primary options** » aspirin: 75-325 mg orally once daily European guidelines recommend a lower dose of 75-100 mg/day. **OR** **Primary options** » clopidogrel: 75 mg orally once daily
	plus	**continued risk factor modification** » All PAD patients regardless of their symptoms should have aggressive risk factor modification. » Since patients with PAD have significantly increased risk of cardiovascular mortality

Ongoing

Patient group	Tx line	Treatment
		and morbidity, it is crucial to modify their cardiovascular risk factors. » This should include: control of blood pressure according to the ACC/AHA guideline (<130/80 mmHg);[42] for patients with diabetes, HbA1c <7.0%, and foot care; hyperlipidaemia control according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline (LDL <2.59 mmol/L [<100 mg/dL]);[28] cessation of smoking;1[C]Evidence dietary advice to reduce CVD risk and control weight; and increase exercise.[2] 3[C]Evidence » Statins are indicated in all patients to achieve LDL <2.59 mmol/L (<100 mg/dL).5[B]EvidenceLipid-lowering therapy reduces cardiovascular events, improves walking distance, and reduces the progression of the disease.[70] [29] [71] Fibrates (e.g., gemfibrozil) can be used if patients have low HDL, normal LDL, and elevated triglycerides. » Beta-blockers (e.g., bisoprolol, metoprolol, propranolol) are effective at reducing cardiovascular risk factors, especially if patients have a history of CAD, CHF, or angina. No one class of antihypertensive medication or strategy is superior for lowering blood pressure in PAD.[2] » ACE inhibitors can also be used: in the Heart Outcomes Prevention Evaluation Study (high-risk patients ≥55 years of age who had evidence of vascular disease or diabetes mellitus plus one cardiovascular risk factor), treatment with ramipril reduced the rates of death from cardiovascular causes by 26%, the risk of myocardial infarction by 20%, the risk of stroke by 32%, and the risk of death from any cause by 16% compared with placebo.[24] One randomised, double-blind, placebo-controlled trial demonstrated that treatment with ramipril for 24 weeks was associated with an increase in mean pain-free and maximum walking time compared with placebo in patients with intermittent claudication.[73]
	adjunct	**endovascular revascularisation** » Endovascular techniques include: balloon dilation (angioplasty); stents; and atherectomy. » These techniques continue to evolve and now include covered stents, drug-eluting stents (DES), cutting balloons, and drug-coated balloons.[76]

Ongoing

Patient group	Tx line	Treatment
		» The technique chosen will relate to lesion characteristics (e.g., anatomical location, lesion length, degree of calcification) and operator experience. » Endovascular revascularisation is recommended for aortoiliac disease with stenosis <10 cm and chronic occlusions that are <5 cm.[2] » For femoropopliteal artery stenosis, endovascular therapy is recommended if there is a discrete stenosis <10 cm, or calcified stenosis <5 cm.[2] » For infrapopliteal artery lesions, endovascular treatment has been limited to threatened limb loss only. Unlike femoropopliteal lesions or aortoiliac lesions, failed endovascular intervention can preclude surgical revascularisation. Therefore, careful selection is essential.
	adjunct	**surgical revascularisation** » Bypass surgery is one of the mainstay treatments for patients with critical lower limb ischaemia (CLI). It may confer improved patency rates up to 1 year but there may be longer hospital stay and peri-interventional complications, and it is less suitable than endovascular treatment in high-risk surgical patients.[77] » Surgical revascularisation is recommended for aortoiliac disease if stenosis >10 cm, chronic occlusion >5 cm, heavily calcified lesions, or lesions associated with aortic aneurysm. » Surgical revascularisation is recommended for common femoral artery disease if lesion >10 cm, heavily calcified lesions >5 cm, lesions involving the ostium of superficial femoral artery, and lesions involving the popliteal artery.[2] » Common femoral endarterectomy is frequently performed for common femoral artery lesions. This surgery has a high patency rate but may be associated with significant complications.[65]
	adjunct	**spinal cord stimulation** » In patients with inoperable chronic critical limb ischaemia facing amputation of the leg, spinal cord stimulation may be a helpful treatment option in addition to standard conservative

Ongoing

Patient group	Tx line	Treatment
		treatment. There is evidence that spinal cord stimulation is associated with higher rates of limb salvage and more prominent pain relief compared with standard conservative treatment alone.[59] [78]
	adjunct	**autologous bone marrow stem cell transplantation** » There is some evidence for this as an option for patients with critical limb ischaemia.[60] However, other studies have failed to show benefit.[61]
	adjunct	**amputation** » Patients with critical limb ischaemia who are unsuitable for revascularisation will be those unable to walk before the episode of critical limb ischaemia, and who have a limited life expectancy.

Emerging

Therapeutic angiogenesis

Therapeutic angiogenesis (administration of vascular growth factors) has emerged as a possible alternative treatment for PAD. Preliminary evidence suggests that autologous bone marrow mononuclear cells implantation in PAD patients with critical limb ischaemia may improve lower limb ischaemic symptoms.[79] [80] This is also supported by the results of two systematic reviews.[81] [82] However, further data from larger studies are required before reaching any firm conclusions.

Balloon catheter

The US Food and Drug Administration (FDA) has approved the Lutonix® 035 drug-coated balloon percutaneous transluminal angioplasty (PTA) catheter, the IN.PACT Admiral® paclitaxel-coated PTA balloon catheter, and the Stellarex® drug-coated angioplasty balloon for the treatment of femoropopliteal lesions.[83] [84] [85] [86] These drug-coated balloons may improve long-term angioplasty outcomes without necessitating a permanent scaffold implant.

Vorapaxar

A thrombin receptor antagonist that acts as a potent antiplatelet agent. In clinical trials that included patients with recent myocardial infarction or PAD, the addition of vorapaxar on a background of aspirin and/or clopidogrel was associated with a reduction in major adverse cardiovascular events during long-term follow-up. A subgroup analysis of patients with PAD also suggested that vorapaxar was associated with a reduction in acute limb ischaemia.[87]

Rivaroxaban

A direct-acting oral anticoagulant that inhibits factor Xa. Rivaroxaban has been extensively studied for the treatment of venous thromboembolism as well as stroke prevention among patients with atrial fibrillation. A large, multinational randomised trial demonstrated that the addition of rivaroxaban to low-dose aspirin therapy reduced the occurrence of both major adverse cardiovascular events and major adverse limb events among patients with PAD.[88]

FOLLOW UP

Recommendations

Monitoring

For those patients who have PAD who are not functionally limited, an annual follow-up visit to monitor for development of coronary, cerebrovascular, and extremity disease is warranted. For patients with PAD with lifestyle-limiting claudication who benefited from conservative treatment, annual visits are recommended.

For those who required revascularisation either for claudication or for limb ischaemia, careful surveillance is required.[2] Long-term patency of aortoiliac and infra-inguinal endovascular revascularisation should be monitored routinely with follow-up careful history and physical examination, ankle brachial index (ABI), and a duplex ultrasound at regular intervals. The recommendations have been for a follow-up visit immediately in the post-endovascular period; at 1, 3, 6, 12, 18, and 24 months postoperatively; and annually thereafter. The intervals of follow-up have varied between different groups.

For infra-inguinal vein bypass grafts, patients should have a routine follow-up with careful history and physical examination, ABI, and duplex.[2] [6] The surveillance should begin immediately post-operation and at regular intervals for 2 years. For femoral-popliteal and femoral-tibial venous conduit bypass, the ACC/AHA guideline recommends follow-up visits at 3, 6, 12, and 24 months. Patients should have annual follow-up visits thereafter.

For infra-inguinal prosthetic grafts, similar surveillance applies.[2] Patients should have a routine follow-up with careful history and physical examination, ABI, and duplex. The surveillance should begin immediately post-operation; at regular intervals of 3, 6, 12, 18, and 24 months; and annually thereafter.

Restenosis after endovascular therapy is a pervasive issue. Restenosis is a manifestation of the reparative response to vessel injury and is characterised by late elastic recoil, smooth muscle cell proliferation, neo-intimal hyperplasia, and positive vessel wall remodelling.[90] Stents were traditionally used to bail out a failed angioplasty (e.g., in cases of acute thrombosis, flow-limiting dissection, or significant residual stenosis >30%). Increasingly, however, stents are used as primary implants to inhibit positive vessel wall remodelling and prolong target lesion patency rates. Stents, however, also suffer from neo-intimal hyperplasia, so identifying those patients with restenosis requiring target lesion revascularisation is of particular importance. Recurrent symptoms of claudication usually precede the onset of limb- or life-threatening events in patients with lower-extremity arterial disease, and it is the recurrence of these symptoms that typically drives patient assessment.[90]

Patient instructions

Patients should be educated regarding the importance of smoking cessation, blood pressure control, diabetes control, and cholesterol control. Diabetic patients should also have a thorough foot care education.

Advice about avoiding the cold and avoiding vasoconstrictive medications (e.g., pseudoephedrine) should also be given.

Complications

Complications	Timeframe	Likelihood
leg/foot ulcers	**long term**	**medium**
Treatment can be difficult. Therefore, it is important to instigate appropriate treatment promptly.		

Complications	Timeframe	Likelihood
gangrene	**long term**	**low**
This occurs in non-viable limb. Therefore, it is important to act quickly on critical and acute limb ischaemia.		
permanent limb weakness/numbness	**long term**	**low**
This occurs in non-viable limb. Therefore, it is important to act quickly on critical and acute limb ischaemia.		
permanent limb pain	**long term**	**low**
This occurs in non-viable limb. Therefore, it is important to act quickly on critical and acute limb ischaemia.		

Prognosis

PAD is related to morbidity and mortality from other types of atherosclerotic disease, even after adjustment for known common risk factors.[19] This explains the importance of general cardiovascular prevention in patients with PAD.[2]

Ankle brachial index (ABI) is a marker for cardiovascular events beyond the diagnosis of PAD.[1] A more rapid deterioration in ABI carries a worse prognosis for all-cause mortality and cardiovascular disease mortality, independent of baseline ABI and potential confounding variables.[19]

Claudication

For the most part, claudication symptoms remain stable and do not worsen rapidly. Two clinical risk factors, significantly reduced ABI and diabetes, increase the risk for chronic limb ischaemia.[2]

Critical limb ischaemia

At 1 year, 25% of patients with critical limb ischaemia will have died and 30% will have undergone amputation. At 5 years, more than 60% of patients with critical limb ischaemia will have died.[89]

Acute limb ischaemia

The long-term prognosis for the limb is dependent on speed and completeness of revascularisation prior to onset of permanent tissue and nerve damage.

Diagnostic guidelines

Europe

2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases

Published by: European Society of Cardiology; European Society for Vascular Surgery **Last published:** 2017

Summary: A comprehensive guideline encompassing all arterial diseases (other than coronary arteries and the aorta) and provides guidance on diagnosis.

Peripheral arterial disease: diagnosis and management

Published by: National Institute for Health and Care Excellence (NICE) **Last published:** 2012

Summary: Evidence-based recommendations on the diagnosis of lower limb peripheral arterial disease.

International

A supplement to the inter-society consensus for the management of peripheral arterial disease

Published by: TASC II Working Group **Last published:** 2015

Summary: This publication provides a complete anatomical lower limb TASC lesion classification, including the infrapopliteal segment.

Inter-society consensus for the management of peripheral arterial disease (TASC II)

Published by: TASC II Working Group **Last published:** 2007

Summary: Diagnostic tests including segmental limb systolic pressure measurement, pulse volume recording, toe pressure and toe-brachial indices, Doppler velocity wave form analysis, angiography, colour-assisted duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography.

North America

2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease

Published by: American College of Cardiology; American Heart Association **Last published:** 2017

Summary: This is a comprehensive guideline for diagnosis of patients with lower extremity PAD.

Follow-up of lower extremity arterial bypass surgery

Published by: American College of Radiology **Last published:** 2013

Summary: Discusses appropriate imaging to follow up patients who have had lower-extremity arterial bypass surgery.

North America

Recurrent symptoms following lower extremity angioplasty

Published by: American College of Radiology **Last published:** 2012

Summary: Discusses appropriate imaging for patients with restenosis after surgery for peripheral arterial disease.

Treatment guidelines

Europe

2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases

Published by: European Society of Cardiology; European Society for Vascular Surgery **Last published:** 2017

Summary: A comprehensive guideline encompassing all arterial diseases (other than coronary arteries and the aorta) and provides guidance on management.

Antithrombotics: indications and management

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2012

Peripheral arterial disease: diagnosis and management

Published by: National Institute for Health and Care Excellence (NICE) **Last published:** 2012

Summary: Evidence-based recommendations on the diagnosis of lower limb peripheral arterial disease.

Cilostazol, naftidrofyryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

Published by: National Institute for Health and Care Excellence **Last published:** 2011

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events

Published by: National Institute for Health and Care Excellence **Last published:** 2010

Summary: Recommendations on when to use clopidogrel, modified-release dipyridamole alone or in combination with aspirin for the prevention of occlusive vascular events.

Identifying and supporting people most at risk of dying early

Published by: National Institute for Health and Care Excellence **Last published:** 2008

International

A supplement to the inter-society consensus for the management of peripheral arterial disease

Published by: TASC II Working Group **Last published:** 2015

Summary: This publication provides an updated literature review of new endovascular techniques and practice patterns employed by vascular specialists today.

Inter-society consensus for the management of peripheral arterial disease (TASC II)

Published by: TASC II Working Group **Last published:** 2007

Summary: Treatment of intermittent claudication, critical limb ischaemia, acute limb ischaemia, aorto-iliac occlusive disease, and infra-inguinal arterial occlusive disease. Antiplatelet and anticoagulant therapies. New and advancing therapies.

North America

2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease

Published by: American College of Cardiology; American Heart Association **Last published:** 2017

Summary: This is a guideline for management of patients with lower extremity PAD. It supersedes recommendations related to lower extremity PAD in previous ACC/AHA guidelines.

Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication

Published by: Society for Vascular Surgery **Last published:** 2015

Summary: This is a guideline on the diagnosis and management of peripheral arterial disease from asymptomatic through to severe limb ischaemia.

The use of antiplatelet therapy in the outpatient setting

Published by: Canadian Cardiovascular Society **Last published:** 2011

Summary: Discusses secondary prevention in patients discharged from hospital following acute coronary syndromes, post-percutaneous coronary intervention, or post-coronary artery bypass grafting; patients with a history of transient cerebral ischaemic events or strokes; and patients with peripheral arterial disease. Also discusses primary prevention.

Oceania

Physical activity in patients with cardiovascular disease: management algorithm and information for general practice#

Published by: National Heart Foundation of Australia **Last published:** 2006

Summary: Evidence-based recommendations on physical activity for people with cardiovascular conditions, including PAD.

Online resources

1. CDC: peripheral arterial disease fact sheet *(external link)*
2. MHRA: cilostazol drug alert *(external link)*

Evidence scores

1. No adequate systematic reviews or randomised controlled trials evaluating the evidence on stopping smoking for PVD have been found.
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

2. Cardiovascular events: there is good-quality evidence that antiplatelet agents (aspirin, clopidogrel, aspirin plus dipyridamole, or ticlopidine) reduce major cardiovascular events over an average of about 2 years compared with control treatment.
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

3. Distance walked: there is poor-quality evidence that regular exercise at least 3 times weekly for between 3 and 6 months may improve total walking distance and maximal exercise time after 3 to 12 months compared with no exercise in people with chronic stable claudication.
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

4. Distance walked: there is medium-quality evidence that cilostazol is more effective at improving initial and absolute claudication distance compared with pentoxifylline after 24 weeks.
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

5. Cardiovascular events: there is medium-quality evidence that statins (simvastatin, atorvastatin, and pravastatin) reduce major cardiovascular events compared with placebo in people with peripheral arterial disease.
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

Key articles

- Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014 Oct 31;(10):CD003748. Full text Abstract
- Fakhry F, Spronk S, van der Laan L, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. JAMA. 2015 Nov 10;314(18):1936-44. Abstract
- Chowdhury MM, McLain AD, Twine CP. Angioplasty versus bare metal stenting for superficial femoral artery lesions. Cochrane Database Syst Rev. 2014 Jun 24;(6):CD006767. Full text Abstract
- 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 Feb;141(2 Suppl):e669S-e690S. Abstract
- Abu Dabrh AM, Steffen MW, Asi N, et al. Bypass surgery versus endovascular interventions in severe or critical limb ischemia. J Vasc Surg. 2016 Jan;63(1):244-53. Full text Abstract
- Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007 Apr;45(4):645-54. Full text Abstract
- Fadini GP, Agostini C, Avogaro A. Autologous stem cell therapy for peripheral arterial disease: meta-analysis and systematic review of the literature. Atherosclerosis. 2010 Mar;209(1):10-7. Abstract
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