SIGN

Scottish Intercollegiate Guidelines Network

NHS Quality Improvement Scotland

89

Diagnosis and management of peripheral arterial disease

A national clinical guideline

October 2006

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population*; or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results*; or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results*; or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4*; or* Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Peripheral arterial disease (PAD) in the legs, sometimes known as peripheral vascular disease, is caused by atheroma (fatty deposits) in the walls of the arteries leading to insufficient blood flow to the muscles and other tissues. Patients with PAD may have symptoms but can also be asymptomatic. The commonest symptom, intermittent claudication, is characterised by leg pain and weakness brought on by walking, with disappearance of the symptoms following rest. Patients diagnosed as having PAD, including those who are asymptomatic, have an increased risk of mortality, myocardial infarction and stroke. Relative risks are two to three times that of age and sex matched groups without PAD.[1,2] Management of PAD provides an opportunity for secondary prevention of cardiovascular events. Both lifestyle changes and therapeutic interventions to reduce risk need to be considered.

Patients with claudication can have a significantly reduced quality of life due to their restricted mobility.[3] Careful consideration needs to be given to drug and lifestyle management of claudication so that patients can achieve an optimum quality of life within the limitations of their condition.

In the primary care setting, the methods of diagnosis and the criteria for referral to a specialist vary between general practitioners, while in secondary care the use of diagnostic investigations and the routine follow up of patients varies between specialists. These differences in clinical practice suggest that, where feasible, guidance is required on the best approach to managing patients with PAD.

1.2 REMIT OF THE GUIDELINE

This guideline provides recommendations based on evidence for best practice in the management of patients with lower limb PAD. It considers the modification of cardiovascular risk, management of symptoms and prevention of disease progression and major complications. The complex issue of when to refer a patient with PAD for intervention is discussed, as are possible diagnostic criteria and indications for follow up.

The guideline pertains to patients with symptomatic PAD in the form of intermittent claudication but not to prevention of disease in individuals without evidence of existing vascular disease nor to individuals with critical limb ischaemia – a severe manifestation of PAD characterised by chronic ischaemic rest pain, ulcers or gangrene.

This guideline will be of interest to vascular surgeons and physicians, general physicians, podiatrists, physiotherapists, occupational therapists, nurses, interventional and diagnostic radiologists, general practitioners and patients with PAD.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. However, it is advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4 REVIEW AND UPDATING

This guideline was issued in 2006 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

2 Cardiovascular risk reduction

2.1 INTRODUCTION

This section addresses the effect of cardiovascular risk modification in people with PAD on the incidence of subsequent cardiovascular events. The impact of risk factor modification on symptoms of PAD and the effectiveness of exercise therapy are considered in section 4.

2.1.1 REFERRAL WITHIN PRIMARY CARE

The importance of risk factor management is less well appreciated in those with PAD than those with coronary heart disease (CHD). A number of studies suggest that risk factor management is treated less aggressively for those patients with PAD as opposed to those with CHD.[4-6] | 3

☑ Patients shown to have peripheral arterial disease should be referred within primary care to the practice cardiovascular clinic so that risk factor modification and long term follow up can be properly monitored.

☑ When the diagnosis of peripheral arterial disease is made the patient should have a full cardiovascular risk factor assessment carried out.

2.2 SMOKING CESSATION

There is a paucity of evidence on the effects of smoking cessation therapy for patients with PAD. One systematic review was identified but contained only four cohort studies, none of which demonstrated statistically significant changes in outcome for patients with intermittent claudication undergoing smoking cessation.[7] In another observational study of patients with symptomatic PAD a statistically significant increase in cardiovascular events was found in smokers compared to non-smokers (odds ratio, OR 1.43, 90% confidence interval, CI 1.12 to 1.81).[8] | 2+

There is clear evidence that smoking is associated with increased risks of a wide range of vascular and non-vascular diseases[9] so that smoking cessation is strongly advised for everyone. Health Scotland provides information on smoking cessation strategies which are as relevant to patients with PAD as to others in the community.[10] | 4

D **Patients with peripheral arterial disease should be actively discouraged from smoking.**

☑ Smoking cessation methods, including nicotine replacement therapy and counselling, should follow national evidence based guidelines recommended by Health Scotland.

2.3 CHOLESTEROL LOWERING

One good quality meta-analysis[11] and two good quality randomised controlled trials (RCTs)[12,13] assessed the impact of cholesterol lowering on cardiovascular events in people with peripheral arterial disease. In the meta-analysis, three small trials of lipid lowering in patients with peripheral arterial disease included all cause mortality and/or non-fatal cardiovascular events as outcomes.[14-16] Lipid lowering produced a marked, but non-significant, reduction in mortality (OR 0.21, 95% CI 0.03-1.17), but little change in non-fatal events (OR 1.21, 95% CI 0.80-1.83). These results should be interpreted with caution because they were based on a relatively small number of events.

In the Heart Protection Study 20,536 high risk individuals with a total cholesterol level of at least 3.5 mmol/l were randomised to either simvastatin 40 mg daily or placebo.[12] A 25% (95% CI 16-33%) relative risk reduction in first major vascular event among participants with no history of coronary heart disease at baseline was recorded in those taking lipid lowering therapy. Among a subgroup of individuals with peripheral arterial disease, there was also a significant reduction in vascular events ($p < 0.0001$). 1++ 1+

In the LEADER study, 1,568 men with peripheral arterial disease were randomised to either bezafibrate 400 mg daily or placebo.[13] Treatment with bezafibrate had a beneficial effect on the incidence of non-fatal coronary events (relative risk, RR 0.60, 95% CI 0.36-0.99) but did not reduce the incidence of total fatal and non-fatal cardiovascular events (coronary artery disease and stroke; RR 0.96, 95% CI 0.76-1.21).

A **Lipid lowering therapy with a statin is recommended for patients with peripheral arterial disease and total cholesterol level > 3.5 mmol/l.**

2.4 GLYCAEMIC CONTROL

People with both peripheral arterial disease[1,2] and diabetes mellitus[17-19] are at increased risk of subsequent cardiovascular events. No clinical trials have been set up specifically to investigate glycaemic control in diabetic patients with peripheral arterial disease. In all subjects with Type 2 diabetes, increasing glycaemia (measured as glycosylated haemoglobin, HbA_{1C}) was associated with an increased risk of cardiovascular morbidity and mortality.[20] Modelling of data from the same observational study indicated that each 1% lowering of HbA_{1C} has been associated with a 21% (95% CI 15-27%) reduction in the risk of diabetes-related death and specifically a 14% reduction in fatal and non-fatal myocardial infarction (MI) over 10 years. No lower threshold can be demonstrated.[21] 2++ 3 4

B **Optimal glycaemic control is recommended for patients with peripheral arterial disease and diabetes in order to reduce the incidence of cardiovascular events.**

☑ Management of diabetic cardiovascular disease should follow SIGN guideline no. 55: Management of diabetes.[22]

2.5 WEIGHT REDUCTION

No studies were identified which investigated the effects of reducing obesity specifically in patients with peripheral arterial disease. Obesity (defined as a body mass index > 30 kg/m^2) has been adversely associated with a number of cardiovascular risk factors (blood pressure, plasma cholesterol, triglycerides, glucose tolerance and thrombogenesis)[23,24] and with an increased risk of mortality.[25] 2++ 4

D **Obese patients with peripheral arterial disease should be treated to reduce their weight.**

☑ Management of obesity should follow UK National Obesity Forum guidelines.[26]

2.6 BLOOD PRESSURE CONTROL

Elevated blood pressure is a well established risk factor for mortality, cardiovascular and cerebrovascular events. Blood pressure may be elevated above a desirable upper limit of 140/90 mm Hg in around one third to one half of patients with PAD such that these patients would be considered hypertensive. The treatment of hypertension to reduce cardiovascular risk in the population as a whole has been subject to national guidelines.[27] In PAD patients treatment has often been considered difficult because of concerns that antihypertensives, especially beta blockers, may have adverse effects on PAD due to possible drug induced peripheral vasoconstriction leading to further ischaemia in the leg.

In a Cochrane systematic review of the treatment of hypertension in PAD, 46 relevant studies were identified in which cardiovascular events and/or progression of PAD were assessed as outcomes.[28] Only two studies met quality criteria and neither of these assessed cardiovascular events. The reviewers did not find any strong evidence to suggest that beta blockers should not be used in the presence of PAD, although no study was sufficiently large and of adequate quality to demonstrate a definite absence of adverse effect. This issue may be irrelevant with the advent of vasodilator and vasoneutral beta blockers. 1++

The impact of ramipril, an angiotensin converting enzyme (ACE) inhibitor, on the prevention of cardiovascular events has been evaluated in the Heart Outcomes Prevention Evaluation (HOPE) study.[29] In a subgroup analysis, the effects on patients with symptomatic PAD and those with asymptomatic PAD (ankle brachial pressure index ≤ 0.9) plus an additional coronary risk factor were analysed. Only 50% of the patients were defined as hypertensive. In both PAD groups, ramipril was associated with an approximately 25% reduction in the primary combined outcome of cardiovascular mortality, myocardial infarction or stroke. In the HOPE study the ankle brachial pressure index (ABPI) was measured unconventionally using palpation of peripheral pulses. For this reason and for the purposes of replication, further studies of ACE inhibitors are required, including differentiation of effects in normotensive and hypertensive subjects with PAD. 1+

Hypertensive patients with PAD are also at considerably increased risk of renovascular disease and serum creatinine should be measured to assess renal function. This is particularly important before and after the initiation of ACE inhibitors and angiotensin receptor antagonists.

A **Hypertensive patients with peripheral arterial disease should be treated to reduce their blood pressure.**

☑ Blood pressure control should follow the British Hypertension Society guidelines.[27]

2.7 HOMOCYSTEINE LOWERING

An elevated plasma homocysteine level has been implicated as an independent risk factor for atherosclerotic disease. Homocysteine levels can be reduced in most patients by the administration of co-factors/co-substrates of homocysteine, eg folic acid and vitamin B6.

While observational studies involving patients with intermittent claudication have demonstrated a relationship between high homocysteine levels and cardiovascular events[30] and all-cause and vascular mortality,[31] no randomised controlled trials have evaluated homocysteine-lowering in patients with symptomatic PAD. 2++

One randomised controlled trial investigated homocysteine-lowering treatment with folic acid plus vitamin B6 in healthy subjects (66% of whom had elevated homocysteine levels).[32] At the outset of the study, 36% of participants were found to have asymptomatic PAD. The study demonstrated no apparent effect of vitamin treatment on peripheral arterial abnormalities, as assessed by ABPI and duplex scanning of femoral and carotid arteries, but a separate analysis was not conducted on those with asymptomatic peripheral arterial disease at baseline. Major cardiovascular events were not assessed. 1+

There is currently insufficient evidence to make a recommendation on homocysteine-lowering therapy for patients with PAD.

☑ Routine measurement of plasma homocysteine is not required.

2.8 ANTIPLATELET THERAPY

Studies investigating the risks of major cardiovascular events over time in patients with PAD have found that on adjusting for cardiovascular risk factors an increased risk still exists. This suggests that risk factor control is itself inadequate in reducing risk to normal and that other therapeutic measures may be of benefit.

By decreasing the risk of thrombosis formation, antiplatelet therapy may reduce the occurrence of acute cardiovascular events. In a major systematic review of randomised controlled trials conducted by the Antithrombotic Trialists Collaboration antiplatelet drugs were found to reduce the risk of any serious vascular event by one quarter, non-fatal myocardial infarction by one third, non fatal stroke by one quarter and vascular mortality by one sixth in a wide range of atherosclerotic cardiovascular diseases.[33] Among patients with PAD a 23% reduction occurred in serious vascular events ($p = 0.004$) with similar benefits among those with intermittent claudication and those having peripheral vascular grafting and angioplasty (although the result was only statistically significant for claudication). Similar results were also found in a second systematic review of the effects of antiplatelet therapy in patients with PAD.[34] 1++

In comparing the effects of different antiplatelet drugs, the Antithrombotic Trialists found overall no clear evidence of any differences in effects between the antiplatelet drugs. In the CAPRIE trial, the only large trial comparing aspirin and clopidogrel in patients with a history of myocardial infarction, stroke or PAD, clopidogrel reduced serious vascular events by 8.7% (95% CI 0.3 to 16.5%) compared to aspirin.[35] Over 1.8 years the absolute risk reduction was 1.9% (95% CI 0.6 to 3.2%).[36] A subgroup analysis of patients with PAD indicated a 23.8% relative risk reduction (8.9 to 36.2, $p = 0.0028$) in favour of clopidogrel, however caution should be exercised in the interpretation of this result as the trial was not powered to detect a realistic treatment effect in any subgroup. 1++

In a subgroup, but not in the main analysis of the CHARISMA trial, patients with documented cardiovascular disease, of whom only one quarter had PAD, showed a marginal benefit of dual therapy with clopidogrel plus aspirin compared to aspirin alone (primary endpoint 6.9% for dual therapy vs 7.9% for aspirin alone; RR 0.88, 95% CI 0.77 to 0.998, $p = 0.046$). The risk of moderate bleeding was higher in the dual therapy group (RR 1.62; 95% CI, 1.27 to 2.10; $p < 0.001$).[37] 1+

The cost effectiveness of clopidogrel for the prevention of vascular events in patients with PAD has not been conclusively demonstrated.[38] 1+

In trials comparing different aspirin regimens in patients with cardiovascular disease, doses of 75-150 mg were as effective as higher doses: overall aspirin produced a 23% reduction in vascular events.[33] The gastrotoxic side effects from aspirin appear to be greater with increasing dose, so that 75-150 mg is the dose of choice. 1++

A **Antiplatelet therapy is recommended for patients with symptomatic peripheral arterial disease.**

3 Referral, diagnosis and investigation

3.1 DEFINITIONS

The Fontaine Classification[39] describes PAD as follows:

Stage I asymptomatic

Stage II intermittent claudication

Stage III rest pain / nocturnal pain

Stage IV necrosis / gangrene

This guideline presents evidence in relation to stage II of the Fontaine classification.

3.2 DIAGNOSTIC FEATURES OF INTERMITTENT CLAUDICATION

The characteristic feature in the history of a patient with intermittent claudication is muscle pain brought on by exercise and relieved by rest. The location of the pain is determined by the anatomical level of disease, and is most commonly seen in the calf. This usually reflects disease in the femoropopliteal segment. Disease at aorto-iliac level typically produces pain in the buttock, hip or thigh, and is sometimes associated with erectile dysfunction in males. The pain is usually reproduced after approximately the same walking distance.

3.3 INVESTIGATIONS IN PRIMARY CARE

3.3.1 CLINICAL EXAMINATION

In most instances the diagnosis is clear from the clinical history. The clinical examination should include:

- examination of peripheral pulses: femoral/popliteal/foot
- abdominal palpation for aneurysm.

Many patients do not present with a classical history, or present with multiple pathology, which is often far more relevant to the patient's quality of life (QoL) than the intermittent claudication.

The presence of good foot pulses does not exclude PAD and patients with a classic history of claudication will require further investigation. Specific questionnaires that have been validated for use in patients with intermittent claudication may be useful for determining health status (eg the King's College questionnaire).[40]

☑ Individuals with a history of intermittent claudication should have an examination of peripheral pulses and palpation of the abdomen for an aortic aneurysm.

3.3.2 ANKLE BRACHIAL PRESSURE INDEX

Objective evidence to substantiate the presence or absence of significant PAD may be obtained reliably (except in those with heavily calcified vessels) by obtaining an ankle brachial pressure index at the initial visit in both legs. This is the ratio of the ankle to brachial systolic pressure and can be measured easily using a sphygmomanometer and handheld Doppler device. This will help to differentiate patients with exercise leg pain due to other causes from those with true arterial causes.

A resting ABPI cut-point of 0.9 has been shown in several clinical studies to be up to 95% sensitive in detecting angiogram positive disease and around 99% specific in identifying supposedly healthy subjects.[41] Although highly sensitive and specific for PAD, a normal ABPI at rest, in combination with classic symptoms, will necessitate referral for an ABPI measurement after exercise and/or imaging to confirm or refute a possible diagnosis.

Calculating the ABPI using different techniques can produce significantly different results.[42,43] A common method is to relate the highest pressure at the ankle to the higher systolic pressure of the right and left brachial arteries. Intraobserver error can be reduced by utilising experienced practitioners.[44] As district nurses are trained to perform ABPI for venous ulceration, there is a pool of expertise for measuring ABPI in the community *(see Annex 1 for a method of measuring ankle pressure recommended by the Society of Vascular Technology)*. 3

☑ Ankle brachial pressure index should be measured in all patients suspected of peripheral arterial disease.

☑ Measurement of ankle brachial pressure index should be taken by properly trained practitioners who should endeavour to maintain their skills.

There is no strict definition of what constitutes a normal ABPI. In practice, an ABPI of <0.9 is considered to be abnormal.[45] The ABPI of patients with intermittent claudication typically lies between 0.5 and 0.9.

Critical limb ischaemia (Fontaine stage III or IV) is generally associated with an ABPI of <0.5. Care must be taken in interpreting the results in patients with heavily calcified vessels, such as some patients with diabetes and advanced chronic renal failure, where the ABPI may be misleadingly high. For values above 1.5, the vessels are likely to be incompressible, and the result cannot be relied on to guide clinical decisions.

Imaging may be appropriate to exclude PAD when there is a discrepancy between clinical presentation and ABPI.

3.3.3 TOE PRESSURE MEASUREMENT

There is much less calcification of the toe arteries, and toe / brachial index can be measured in patients with medial sclerosis. The technique is unsuitable for primary care.[46] It may be helpful for patients with an abnormally high ABPI such as those with diabetes in the secondary care setting if the expertise and equipment is available. 3

3.3.4 EXERCISE ANKLE BRACHIAL PRESSURE INDEX

The technique of measuring ABPI before and after exercise is unlikely to be adopted in primary care, and is not recommended in this setting. In secondary care it may be helpful in evaluating patients with classic symptoms and a normal resting ABPI in the vascular laboratory.

3.3.5 TREADMILL TESTING

As treadmills are not widely available in primary care, largely due to the need for resuscitation equipment, treadmill testing of patients with intermittent claudication in primary care is not recommended. There may be a limited role for treadmill testing in patients in whom there is a discrepancy between history and clinical signs, as it provides objective evidence of a patient's maximum walking distance.

3.3.6 PULSE OXIMETRY

Despite the increasing availability of pulse oximeters in primary care for the management of people with asthma, no evidence was identified for their usefulness in the detection of early PAD.[47] 3

3.3.7 NEAR–INFRARED SPECTROSCOPY

Methods of measuring tissue oxygen saturation are becoming available. While there is evidence that they may be able to detect PAD during exercise,[48] no evidence was identified that they could detect PAD at rest. While this technique may be a good research tool, at present it is not an appropriate investigation in primary care. 2^+

3.4 REFERRAL

There is convincing evidence that PAD is a marker for systemic arterial damage. The main danger to the patient with claudication is not that they will require an amputation, but that they have a greatly increased risk of a fatal or non-fatal cardiovascular event. There is an inverse relationship between the level of ABPI, and the risk of cardiovascular morbidity and mortality. Individuals with an ABPI of 0.9 or less have an increased risk of cardiovascular morbidity and mortality independent of age, sex, existing coronary disease and diabetes.[49] 2++

3.4.1 CRITERIA FOR REFERRAL

The rate of decline of ABPI over a five year period was measured in a cohort study as being three times faster in the patient with claudication compared to the normal population; however this was still only a drop of 0.09 over five years.[50] Establishing grounds for referral is very difficult from the available literature. The decision to refer a patient with claudication is usually dependent on issues involving the patient's quality of life. 2+

Patients with claudication often have comorbidity which significantly impacts on their quality of life, such as hypertension, and chronic knee, hip and back pain, which are unrelated to the claudicant's PAD.[51]

☑ Patients with suspected peripheral arterial disease should be referred to secondary care if:

- the primary care team is not confident of making the diagnosis, lacks the resources necessary to institute and monitor best medical treatment or is concerned that the symptoms may have an unusual cause, or;
- risk factors are unable to be managed to recommended targets, or;
- the patient has symptoms which limit lifestyle and objective signs of arterial disease (clinical signs and low ABPI).

☑ Young and otherwise healthy adults, presenting prematurely with claudication, should be referred to exclude entrapment syndromes and other rare disorders.

3.5 CONDITIONS WITH SIMILAR PRESENTATIONS TO PERIPHERAL ARTERIAL DISEASE

Symptoms of chronic compartment syndrome, venous claudication, neurogenic claudication and osteoarthritis of the hip may all mimic claudication.

Chronic compartment syndrome causes a tight, bursting pain in the calf muscles, typically in heavy muscled athletes. It starts after much exercise, subsides very slowly and relief is speeded by elevation.

Venous claudication produces a tight, bursting pain which can affect the entire leg, but is usually worse in the thigh and groin, typically in people with a past history of iliofemoral deep vein thrombosis (DVT). It occurs during walking and subsides slowly with rest, while relief is hastened by elevation of the limb.

Neurogenic claudication causes weakness more than pain. Felt in hip, thigh or buttocks in a dermatomic distribution, it occurs usually in people with a history of back problems. It starts on walking or after standing for the same length of time. It is relieved by stopping if walking and by lumbar spine flexion (sitting or stooping forward).

Hip arthritis causes an aching discomfort, after a variable degree of walking. It is not quickly relieved by rest, and can occur at rest, but is usually more comfortable if sitting, and the weight taken off the legs.

3.6 INVESTIGATIONS IN SECONDARY CARE

3.6.1 INTRODUCTION

Major technical advances have been made in recent years in the development of non-invasive imaging modalities. Unfortunately there is a paucity of high quality trials on the new and evolving techniques particularly in relation to determining the accuracy of magnetic resonance angiography (MRA), duplex ultrasound and computed tomography angiography (CTA) in the investigation of peripheral arterial disease.

The decision to image is a decision to intervene if a suitable lesion is identified and is only applicable to a minority of patients with intermittent claudication, and then only after risk factors have been addressed and medical management followed. There is also a role for imaging in the small group of patients in whom there is a discrepancy between the history and objective clinical signs. The purpose of imaging is to assess the anatomical location, morphology and extent of disease in order to determine suitability for intervention and occasionally to differentiate atherosclerotic PAD from other causes such as neurogenic claudication and entrapment. The options for imaging are as follows:

- digital subtraction angiography (DSA)
- duplex ultrasound
- magnetic resonance angiography
- computed tomography angiography

3.6.2 DIGITAL SUBTRACTION ARTERIOGRAPHY

This has been the traditional first line imaging investigation for patients with PAD for many years and, although it is a two dimensional technique, is still considered the gold standard against which other techniques are compared. As a gold standard, the technique suffers from a number of flaws:

- it may not be possible to determine haemodynamic significance even with multiple projections
- it may overestimate the length of occlusions
- it may not always demonstrate patent crural vessels.

The advantage of digital subtraction arteriography as an imaging modality is that it provides a complete arterial map of the lower limb circulation which is easily interpretable. Pressure gradients can be measured to determine haemodynamic significance and it may be used to guide endovascular intervention.

Disadvantages include complications of catheterisation which may occur both within the vessel and at the puncture site. Although it has been estimated that 1.7% of complications may be severe, improvements in catheter and guidewire technology have reduced their incidence significantly.[52] Allergic reactions to iodinated contrast occur, with around 0.1% of these being severe.[53] There is a risk of nephrotoxicity from iodinated contrast and this is increased in elderly patients, infants, and those with pre-existing renal impairment. The procedure involves exposure to ionising radiation and short stay recovery facilities. 4

D **Digital subtraction arteriography is not recommended as the primary imaging modality for patients with peripheral arterial disease.**

☑ In patients with intermittent claudication the use of subtraction arteriography should only be necessary as an immediate prelude to intervention during the same procedure.

3.6.3 DUPLEX ULTRASOUND

Duplex scanning combines both B-mode ultrasound and colour doppler ultrasound to identify haemodynamically significant lesions. Although a number of parameters in the doppler waveform are affected by stenoses the peak systolic velocity ratio is the most widely adopted measurement.[54,55] A peak systolic velocity ratio of greater than two indicates a stenosis of greater than 50%. Studies report high accuracy of duplex ultrasound in comparison to DSA. One study reported duplex sensitivity of 92% and specificity 99% when compared with arteriography.[56] A meta-analysis produced a pooled sensitivity of 87% and pooled specificity of 94% for duplex ultrasound compared with angiography.[57] 2+

When used by experienced operators and in suitable patients, duplex ultrasound can produce a map of significant stenotic disease from aorta to feet. It may also determine the significance of equivocal lesions identified by other modalities and is relatively inexpensive and well tolerated as an outpatient procedure by patients. There are limitations to the visualisation of iliac vessels in the pelvis (due to body habitus and bowel gas) and extensive calcification may produce incomplete examinations. As yet there is no direct comparison between duplex ultrasound and current magnetic resonance angiography techniques. The technique is operator dependent and there is a shortage of trained operators.

3.6.4 MAGNETIC RESONANCE ANGIOGRAPHY

There have been major technical advances in recent years and these continue to evolve. Three dimensional contrast enhanced magnetic resonance angiography has largely replaced two dimensional techniques and the development of moving tabletops enable whole limb examinations with a single contrast injection. The latest contrast agents have improved resolution. The reported accuracy of MRA may be adversely affected by using digital subtraction angiography as the gold standard.

There have been a number of meta-analyses and systematic reviews supporting the diagnostic accuracy of magnetic resonance angiography in recent years.[57-59] One meta-analysis determined that 3-D contrast enhanced MRA is superior to 2-D time of flight MRA.[58] Another meta-analysis identified pooled sensitivity of 97% and pooled specificity of 96% for MRA and concluded that MRA has superior diagnostic performance to duplex ultrasound when each modality is compared separately to DSA. There was no direct comparison between MRA and duplex ultrasound in any of the studies cited in this meta-analysis.[57] 1++

A well conducted systematic review concluded that MRA is accurate for detecting haemodynamically significant stenoses (greater than 50%) and that it is cost effective in comparison to digital subtraction angiography when both are available locally.[60]

Magnetic resonance angiography, in comparison with DSA and CTA, eliminates exposure to ionising radiation and there is no risk of contrast nephropathy when gadolinium is used in recommended doses. Unlike ultrasound and CTA it is unaffected by arterial calcification. Magnetic resonance angiography is performed as a fast non-invasive outpatient procedure (< 15 minutes). Three dimensional images of the whole arterial tree are presented in a maximum intensity projection format produced on a workstation. Relative disadvantages include a tendency to overestimate stenosis, although this will err in the patient's favour. Venous contamination can obscure arteries below the knee. A significant number of patients are too claustrophobic to tolerate the examination and the presence of some metallic implants (such as pacemakers) or foreign bodies may preclude the examination or produce artefacts.

3.6.5 COMPUTED TOMOGRAPHY ANGIOGRAPHY

The introduction of spiral acquisition and multidetector CT scanners in recent years has dramatically improved arterial resolution and a moving tabletop enables examination from aorta to feet in a single contrast injection. Volumetric data are then reconstructed at a workstation and normally represented in maximum intensity projection format producing easily interpretable arteriographic images.

The pace of technological developments means that little literature is available on the newest technology. One cohort study demonstrated sensitivity of 90% and specificity of 92% based on the examination of 444 arterial segments in 18 patients using digital subtraction angiography as the gold standard.[61] A further study of 1,137 segments in 50 patients yielded sensitivity of 96% and specificity of 93%.[62] A randomised study comparing CTA with MRA showed no significant difference in accuracy between the two techniques.[63] 1+ 2+

Computed tomography angiography is also excellent for assessment of aneurysms and acute arterial trauma. Disadvantages include the presence of extensive calcification which commonly obscures arterial stenoses and may render the examination non-diagnostic. There is the same risk of an allergic reaction to contrast, nephrotoxicity and exposure to ionising radiation as for DSA.

A **Non-invasive imaging modalities should be employed in the first instance for patients with intermittent claudication in whom intervention is being considered.**

4 Treatment of symptoms

4.1 INTRODUCTION

Peripheral arterial disease, and its most common manifestation, intermittent claudication, are associated with considerable morbidity and mortality.[64] Patients with PAD, even in the absence of myocardial infarction or ischaemic stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease.[65] Therefore, for patients with PAD, the focus must be on the cardiovascular complications of atherosclerosis, ie vascular risk factor management. Peripheral arterial disease is also associated with significant pain and a poor quality of life that can equate to that seen in cancer patients.[66] Patients with PAD have a similar mortality to patients with angina and management of ischaemic muscle pain in the leg should receive as much attention as the aetiologically similar pain of angina.

This section of the guideline addresses the management of claudication symptoms. This includes drug therapy for claudication, exercise, angioplasty and surgery. In the light of the significant and well recognised placebo response in this patient group, only randomised controlled trials and meta-analyses of such trials were evaluated.

There are many postulated pharmaceutical interventions for alleviation of the leg pain produced by intermittent claudication. These drugs/remedies can be subdivided into three groups:

- drugs with a UK licence for the treatment of intermittent claudication
- drugs/procedures with no licence but which have been studied in research protocols and published in peer review journals
- alternative therapies.

4.2 LICENSED DRUG THERAPY FOR PERIPHERAL ARTERIAL DISEASE

There are five drugs licensed in the UK for the symptomatic treatment of intermittent claudication:

- cilostazol
- naftidrofuryl
- oxpentifylline
- inositol nicotinate
- cennarizine

4.2.1 CILOSTAZOL

Cilostazol is reported to have both antiplatelet and vasodilator effects.[67] Cilostazol inhibits phosphodiesterase III and increases the level of cyclic adenosine monophosphate causing vasodilatation.[68] It also attenuates the proliferative response to a variety of pro-atherogenic growth factors.[69]

Two large systematic reviews of RCTs assessed the effectiveness of cilostazol in improving mean walking distance and quality of life. A range of increase in walking distance was detected of between 50% and 76% compared with 20% with placebo (95 m ± 272 m vs 27 m ±113 m). There appeared to be a sliding scale of benefit with the best results being achieved in patients with short distance claudication. The drug produced adverse effects which led to its withdrawal in up to 16% of the study population (versus 8% with placebo).[70,71] The systematic reviews also indicated significant improvements in QoL although these were not evaluated in all included studies. Cilostazol (100 mg) has been licensed within the UK for the symptomatic relief of intermittent claudication. 1++

A **Patients with intermittent claudication, in particular over a short distance, should be considered for treatment with cilostazol.**

A **If cilostazol is ineffective after three months, or if adverse effects prevent compliance with therapy, the drug should be stopped.**

The Scottish Medicines Consortium advice (October 2005) is that the clinical and cost effectiveness of cilostazol is not demonstrated and therefore it is not recommended for use in NHSScotland.[72]

4.2.2 NAFTIDROFURYL

Naftidrofuryl is reported to have vasodilator effects. It is thought to act at tissue level improving tissue oxygenation, increasing adenosine triphosphate levels and reducing lactic acid.[73] The drug is given in a dose of 100 mg three times a day initially, increasing to 200 mg three times a day.

There are numerous RCTs evaluating this drug in patients with claudication. A significant number of studies were excluded from consideration because of poor study design (eg lack of intention to treat, non-standard assessment of claudication). Four studies were of sufficient quality to indicate a robust effect. Two used walking distance endpoints[74,75] although only one used a validated outcome, and two used QoL endpoints.[76,77] In one study patients who had already undertaken exercise training improved their walking distance by 92% in the naftidrofuryl group compared to 17% in a placebo group.[74] These data are supported by a positive effect on QoL.[76,77] 1+

A **Patients with intermittent claudication and who have a poor quality of life may be considered for treatment with naftidrofuryl.**

4.2.3 OXPENTIFYLLINE

Oxpentifylline and its metabolites are vasodilators, and are also claimed to improve the flow properties of blood by decreasing its viscosity,[78] and increasing blood cell deformability.[79] A further postulated beneficial effect is reduction in plasma fibrinogen levels.[80] The recommended dose is 400 mg three times daily.

A number of RCTs were considered unsound by current standards. A meta-analysis,[7] supported by a RCT, shows no increase in maximum walking distance in patients using oxpentifylline compared to placebo.[81] 1++

A **Oxpentifylline is not recommended for the treatment of intermittent claudication.**

4.2.4 INOSITOL NICOTINATE

The reported mechanisms of action of this drug include vasodilatation, lysis of fibrin and a mild hypolipidaemic effect. It is also said to inhibit oxidative metabolism in hypoxic tissues. The dose of this drug is 3-4 g daily.

Four double blind randomised placebo controlled trials have been reported.[82-85] Three trials used subjective and questionable objective criteria for assessment without treadmill use[82-84] and only one trial used a treadmill with 10% gradient.[85] The methodology of these trials is poor and none showed clear evidence of benefit over placebo for this drug. 1- 1+

B **Inisitol nicotinate is not recommended for the treatment of intermittent claudication.**

4.2.5 CINNARIZINE

The reported mechanism of action of this drug is via antagonism of vasoconstrive substances such as noradrenaline, serotonin and angiotensin.[86,87] Whilst there are a number of placebo controlled single dose or short term studies,[88,89] the majority assess blood flow rather than walking distance. The short term nature of these studies ($\leq$ 7 days) and their poor methodology means they cannot be used in support of this drug. A number of controlled studies evaluated cinnarizine over a period ranging from four weeks to six months but standardised treadmill walking distances were not measured. There are no studies of cinnarizine measuring currently recognised clinical endpoints in intermittent claudication.

It is not possible to make a recommendation for the use of cinnarizine in the treatment of intermittent claudication.

4.3 UNLICENSED RESEARCH DRUGS AND PROCEDURES

There are a number of compounds or procedures currently under investigation as treatments for the symptomatic management of intermittent claudication. These include therapies that may already be prescribed for the patient with intermittent claudication such as statins; compounds that have been evaluated for critical limb ischaemia and extrapolated to the patient with intermittent claudication such as prostaglandins; the novel area of growth factor application through genetically modified compounds; vitamin derived compounds such as carnitine, and other therapies used more widely in Europe such as polyconasol, sulodexide and padma. Procedures include those such as pneumatic compression, chelation therapy and immune modulation.

4.3.1 STATINS

Two studies evaluating statin therapy as a treatment for intermittent claudication symptom relief were identified.[90,91] These studies show some improvement in symptoms although only one used a standard test as endpoint[91] in a small number of subjects, (the other evaluated pain free walking time), and the evidence for benefit is inconclusive. Further work is required to validate the benefit of statins for intermittent claudication symptom relief but these data add strength to the recommendation that statin treatment should be considered as a first line treatment in this group of patients *(see section 2.3)*. 1+

A **Statins should be given for risk factor management in patients with intermittent claudication and total cholesterol level > 3.5 mmol/l.**

4.3.2 PROSTAGLANDINS

It was not possible to consider prostaglandins as a class as individual studies describe different routes of administration, along with different formulations of prostaglandins. Beraprost, an oral prostaglandin has been evaluated in large RCTs with no statistical differences seen between the treatment group and placebo.[92,93] ASO-13 is a PGE1 derivative which has been evaluated in only one trial which showed a significant improvement in maximum walking distance following prostaglandin administration.[94] This study is small and the compound requires to be given by daily intravenous injection, which is impractical. Further studies to investigate optimal dosing regimen and duration of clinical benefit are required. 1+

A **The use of oral prostaglandin therapy in patients with intermittent claudication is not recommended.**

4.3.3 GENETICALLY MODIFIED GROWTH FACTORS

One paper was identified evaluating the use of vascular endothelial growth factor (VEGF) in patients with intermittent claudication.[95] As this failed to show an effect VEGF treatment is not recommended. 1+

Only one intermittent claudication trial of fibroblast growth factor (rFGF-2) was identified.[96] In this study, patients receiving placebo increased pain free walking time by 14% compared to patients who received the growth factor who increased pain free walking time by 34% ($p = 0.034$). 1+

rFGF-2 therapy is not recommended for the treatment of intermittent claudication as the evidence base rests on a single study. There may be concern about the applicability of genetically modified treatment. This is a research area with considerable potential, and further work is recommended.

4.3.4 PROPIONYL- L- CARNITINE THERAPY

Propionyl- L-carnitine therapy is not recommended as a treatment for intermittent claudication as the evidence base consists of three studies, all of which have significant methodological problems.[97-99] 1-

4.3.5 OTHER DRUGS

There is insufficient evidence to recommend either polyconasol[100] or sulodexide.[101] A single RCT was identified which evaluated padma but this failed to establish a clinical benefit.[102] 1+ 1++

4.3.6 IMMUNE MODULATION THERAPY

One small trial of immune modulation suggested that it may be effective in improving walking distance of patients with short distance claudication. Concerns about whether this trial was sufficiently powered to reveal a significant effect mean that there is insufficient evidence to support a recommendation in immune modulation.[103] 1+

4.3.7 PNEUMATIC COMPRESSION

Pneumatic compression has been studied in one RCT[104] which used a complex treatment regimen. The study was too small to assess the clinical impact of the intervention. 1+

4.3.8 CHELATION

Chelation therapy involves the administration of a man-made amino acid, ethylenediamine tetraacetic acid (EDTA), into the veins. Chelation has been studied in only one robust trial of patients with intermittent claudication,[105] which showed no difference between experimental and placebo groups, leaving no evidence on which to base a recommendation. Adverse effects are potentially serious. 1+

4.4 ALTERNATIVE THERAPIES

A number of unlicensed alternative therapies have been evaluated in patients with intermittent claudication. Only a few have been studied in RCTs. These include Gingkho biloba and vitamin E.

4.4.1 GINGKO BILOBA

A meta-analysis of Gingko biloba studies was found to have inconsistency in the endpoints of the studies evaluated. Concern was expressed by the authors regarding the quality of the studies evaluated.[106] It was considered that too small a beneficial effect was detected to make a major impact on the treatment of this disease. 1+

It is not possible to make a recommendation concerning the Gingkho biloba therapy of the meta-analysis as the evidence base rests on studies with non-standard endpoints, and the effect size is not considered to be clinically relevant.

4.4.2 VITAMIN E

There is one systematic review which evaluated vitamin E therapy for the symptoms of intermittent claudication.[107] In total, 265 patients were studied. The authors of the systematic review comment on inconsistency in endpoint evaluation and the variety of doses of vitamin E studied. They express concern regarding poor study quality leaving insufficient evidence on which to make a recommendation. 1+

4.5 EXERCISE THERAPY

In patients suffering from intermittent claudication it has long been thought that increasing exercise can result in improved performance. This has led to the traditional advice to patients on diagnosis to "stop smoking and keep walking". Unsupervised exercise requires significant motivation on the part of the patient and studies have failed to show significant benefits with this approach. In recent years studies have looked at the role of supervised exercise classes.

A Cochrane review of seven trials which directly compared supervised with unsupervised exercise therapy in patients with intermittent claudication showed that supervised exercise therapy produced statistically significant differences in improvement of maximal treadmill walking distance compared with unsupervised exercise therapy regimens, with an overall effect size of 0.58 (95% confidence interval 0.31 to 0.85) at three months.[108] This translates to a difference of approximately 150 metres increase in walking distance in favour of the supervised group. While most of the trials indicated that quality of life scored more highly in the supervised exercise therapy groups than the unsupervised exercise therapy groups, these trends were mostly non-significant and conclusions about the effect of exercise on quality of life must be made with caution. Further research is needed in this area. 1++

Two meta-analyses[109,110] and five randomised controlled trials with sufficient methodological quality were identified that looked at the role of exercise therapy.[111-115] All the studies were small and investigated a range of exercise types and regimens including treadmill walking, polestriding, upper limb exercise and exercise classes. An improvement in exercise tolerance ranging from 60% - 337% after a period of three to six months of supervised exercise was seen. Study design was variable using different endpoints and levels of supervision, making it difficult to compare results. While the results look encouraging, long term benefit for supervised exercise programmes is still unproven. The evidence for one type of programme being more effective than another is currently not available. 1+

A **Patients with intermittent claudication should be encouraged to exercise.**

4.6 VASCULAR INTERVENTION

The natural history of intermittent claudication gives an estimated risk of limb loss of 1% per year and a required intervention rate for critical ischaemia of 6 -10% per year. Vascular intervention for stable claudication is rarely required as the risk to the limb is low. Although there is evidence to support modification of risk factors and some non-invasive pharmacotherapies there is little evidence from RCTs with which to judge the efficacy of endovascular and surgical interventions. There are some clinical situations in which intervention may be considered such as where disability is severe.

In the absence of a body of good trial evidence for both endovascular and surgical intervention, the guidelines drafted by the TransAtlantic Inter-society Consensus on the management of peripheral arterial disease (TASC) should be considered.[116] The TransAtlantic Inter-society Consensus has grouped lesions with similar morphology which are suitable for intervention into four categories (A to D; *see Annex 2*). 4

4.6.1 ANGIOPLASTY AND STENTING

Angioplasty is used in some patients with severe disability and impaired quality of life. Despite a lack of trial evidence, angioplasty is recommended by TASC for these patients if they have a short stenosis in the common or external iliac arteries of less than three cm in length (TASC A). Good technical success rates have been reported and exceed 90% for the iliac arteries. Primary and secondary patency rates are higher for iliac stenosis compared to lesions of the superficial femoral artery. Quality of life may be improved in the short term following angioplasty but there is little evidence that improved walking distances are maintained in the long term. A Cochrane review of the efficacy of angioplasty for intermittent claudication could only find two RCTs, both included small numbers of patients and showed no long term benefit for angioplasty when compared to exercise or best medical therapy.[116,117] 1++ 4

Recent developments allow more extensive lesions (TASC B and C) to be treated by angioplasty or arterial stenting with a reasonable technical success rate but this is not recommended by TASC due to a lack of evidence.

4.6.2 BYPASS SURGERY

There is little evidence to support the use of surgical intervention for intermittent claudication. One trial of 264 patients randomised to vascular intervention, exercise training or no intervention showed a benefit for surgical intervention at 12 months but there was no longer term follow up.[118] TASC recommend that surgery rather than angioplasty is the treatment of choice for selected patients with extensive diffuse or multilevel disease (TASC D). 1++

The TASC guideline offers the following indications for invasive therapy in patients with intermittent claudication:[116] 4

Before offering a patient with intermittent claudication the option of any invasive treatment, endovascular or surgical, the following considerations must be taken into account:

- a predicted or observed lack of adequate response to exercise therapy and risk factor modification
- the patient must have a severe disability, either being unable to perform normal work or having very serious impairment of other activities important to the patient
- absence of other disease that would limit exercise even if the claudication was improved (eg angina or chronic respiratory disease)
- the individual's anticipated natural history and prognosis
- the morphology of the lesion must be such that the appropriate intervention would have low risk and a high probability of initial and long term success.

D

- **Endovascular and surgical intervention are not recommended for the majority of patients with intermittent claudication.**
- **For those with severe disability or deteriorating symptoms, referral to a vascular specialist is recommended.**
- **The TransAtlantic Inter-society consensus guidelines should be used when advising patients about possible interventions.**

5 Follow up

5.1 BENEFITS OF FOLLOW UP

Patients with PAD live with a chronic disease which in the main can only be controlled and not cured. The follow up of patients with PAD, as with other chronic diseases, should be evidence based but the evidence base to guide the establishment of structured long term follow up is incomplete.

It is generally recognised that structured care and follow up should be offered to patients with chronic diseases. Structured follow up may offer the opportunity to:

- provide advice on and monitoring of risk factor modification to help patients manage their condition
- assess the clinical condition for improvement or deterioration
- identify if further intervention is appropriate
- audit the outcome of invasive interventions (in line with guidance from the Royal College of Surgeons of England).[119]

However, it has been suggested that a significant proportion of follow up visits are clinically unnecessary, particularly those in secondary care.[120] The evidence suggests that less than a quarter of patients with intermittent claudication have deterioration in symptoms.[121] 4

5.1.1 FOLLOW UP OF SECONDARY PREVENTION

No literature was identified that examined the benefit of follow up for patients after conservative management. As the underlying pathology of PAD and CHD are the same, the majority of patients with PAD will also have coronary disease. Many of the recommendations in this guideline refer to elements of secondary prevention that are already integral to the management of patients with CHD. These include: monitoring of smoking cessation success, compliance with medication (antihypertensive, lipid-lowering, antiplatelet therapy) and weight management.

☑ Primary care staff should ensure that all patients with peripheral arterial disease be included in systematic disease management arrangements for the optimal management of risk factors.

5.1.2 FOLLOW UP OF ENDOVASCULAR PROCEDURES

No literature was identified that examined the benefit of follow up for patients after endovascular procedures. It is recognised that structured follow up may offer the opportunity to identify if further intervention is appropriate.

5.1.3 FOLLOW UP OF SURGICAL PROCEDURES

Graft failure may occur early, within the first three months from surgery, (when it may be associated with errors in technique) or late, within three to eighteen months from surgery (as a result of progression of atherosclerosis). Epidemiological data suggest that approximately 20 - 30% of vein bypass grafts will develop stenosis within the first eighteen months after surgery and may be associated with graft occlusion.[122,123] Graft surveillance has been advocated in order to identify failing grafts allowing intervention. 3 4

The use of surveillance has been the subject of much debate. A number of studies have been conducted to assess whether surveillance improves outcomes for patients. Three randomised controlled trials,[124-126] and one poor quality meta-analysis were identified.[127] The meta-analysis included heterogeneous studies (including case series) which used different modes of surveillance and assessed a variety of outcome measures. The three RCTs investigated the utility of surveillance following infra-inguinal vein graft with one study[124] including follow up of vein and synthetic grafts. The quality of these studies was limited, for example, by small sample sizes, lack of blinding and lack of adherence to the surveillance protocol. The results of these studies are conflicting and do not provide adequate evidence to inform how patients should be followed up after surgical intervention. The majority of subjects were patients with critical limb ischaemia and only 5-20% of subjects had graft surgery because of intermittent claudication. 1-

In a study evaluating 594 patients (30% of whom had surgery for intermittent claudication) in a multi-centre, prospective randomised controlled trial,[128] all patients received vein grafts and were randomised to either duplex ultrasound or clinical follow up. Eighteen months following surgery there was no difference between the groups in terms of graft failure or amputation rate, but the duplex surveillance incurred greater costs. While further research is required to clarify whether clinical follow up improves outcome compared to no follow up, this trial suggests intensive surveillance with duplex ultrasound scanning does not accrue additional benefit to clinical follow up. 1+

5.2 WHO SHOULD CARRY OUT FOLLOW UP?

The existing arrangements for the follow up of patients with PAD may occur in primary or secondary care. As described previously, studies examining whether follow up improves outcomes for patients do not inform the evidence base. Similarly, no literature was identified which examined who should carry out follow up. Nevertheless, it is recognised that high quality care can usually best be provided by appropriately trained multidisciplinary teams and should take place in the right healthcare setting – specified by local protocols.[120] Automatic secondary care follow up should only be used where necessary and clinically appropriate.

6 Information for discussion with patients and carers

6.1 SAMPLE INFORMATION LEAFLET

An example information sheet for patients with peripheral arterial disease is given below. Healthcare professionals may wish to adapt this for use in their own departments, remembering to insert the relevant local details.

INFORMATION FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

What is Peripheral Arterial Disease (PAD)?

Peripheral arterial disease (PAD), also known as peripheral vascular disease (PVD) or peripheral arterial occlusive disease (PAOD) causes your legs to be sore, particularly when you walk. The pain is usually in the calves of the leg but may be in the thigh or buttock. It usually comes on when you walk and settles when you stop.

Other signs that you have the problem may include:

- cold or numb toes or feet
- sores on toes, feet or legs that won't heal
- loss of hair from feet, toes or legs.

If your legs do not hurt when you are at rest but you find you cannot walk as far as you used to without feeling pain in your calves, then you may have PAD or intermittent claudication as the symptoms are sometimes called.

What causes PAD?

PAD is caused by narrowing of the arteries following the development of fatty patches, called atheroma or plaques in the artery walls - a bit like the scale forming on the inside of water pipes. The amount of blood getting to the muscles of the legs is reduced and pain is the result. The presence of the fatty deposits can also block the artery completely. This process is exactly the same as can happen to the arteries carrying blood to your heart (coronary arteries).

Cigarette smoking is a very important contributor to PAD. Other medical problems that can contribute to PAD are high blood pressure and diabetes.

What can be done?

Your general practitioner may advise you to make some changes to your lifestyle, for example, by taking more exercise. You will definitely be advised to stop smoking. The doctor may also suggest taking a drug to reduce the amount of cholesterol in your blood - this is the main cause of the build up of the fatty deposits. Also the doctor may prescribe a drug, eg aspirin, to reduce the chance of a blood clot developing.

There are also drugs available which may relieve the pain of intermittent claudication.

If your PAD gets worse and causes a lot of pain your GP may refer you to a specialist - probably a vascular specialist.

There are many tests to find out the extent of your disease and you may have the blood pressure measured in your legs (just like having it done in your arm), an ultrasound scan of the arteries (just like a pregnant mother has in order to visualise the baby, but in this case the blood vessels, and any blockages, are visualised) or an angiogram (an X-ray examination of the blood vessels).

If you have significant narrowing of the arteries the specialist may talk to you about the possibility of angioplasty, a method of blowing up a balloon in the narrow area and widening the artery, or bypass surgery, inserting a piece of a blood vessel or plastic to get round (or bypass) the narrowed section of the artery. These procedures are usually only carried out in patients with more severe disease.

One in five people with PAD have diabetes, so it is important that checks are made to see if you are suffering from diabetes – if so, your GP will help you to keep it under control.

What can you do to help?

PAD is a disease which can usually be stabilised and as with many other problems associated with the circulation, you will be actively discouraged from smoking. Over 90% of people with PAD are smokers. That sends out a very clear-cut message. To greatly reduce the chances of getting the disease or to improve your situation once PAD appears - stop smoking. Regular exercise, and controlling your weight if you are obese, will also help. Modifying all of these will also help reduce high blood pressure (as will the drugs prescribed by your doctor if appropriate) if this is a contributing factor to your PAD.

What is the likely outcome of having PAD?

Most people with PAD who make these changes to their lifestyle either stabilise or improve their symptoms.

With this reasonable outlook it is very important to follow the advice above and that given to you by your GP/Nurse in relation to taking medication to decrease the risk factors for the disease. Importantly, sometimes when you have disease in your leg arteries, you also have it in the heart or brain vessels, so taking prescribed tablets can prevent heart attacks, and strokes.

6.2 SOURCES OF FURTHER INFORMATION FOR PATIENTS

British Heart Foundation
4 Shore Place
Edinburgh EH6 6UU
Tel: 0131 555 5891 • Fax: 0131 555 5014
e-mail: scotland@bhf.org.uk • www.bhf.org.uk

Circulation Foundation (formerly the British Vascular Foundation)
c/o Royal College of Surgeons of England
35-43 Lincolns Inn Fields
London WC2A 3PE
Tel: 0207 304 4779
www.circulationfoundation.org.uk

Patient UK
www.patient.co.uk

A useful web site with links to leaflets, support groups, information about medicines and tests and much more.

7 Development of the guideline

7.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practicing clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50; A Guideline Developer's Handbook", available at **www.sign.ac.uk**

7.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Gerry Fowkes (Chair)	*Professor of Epidemiology, Public Health Sciences University of Edinburgh*
Ms Margaret Armitage	*Vascular Liaison Nurse, Greater Glasgow Primary Care Trust*
Professor Jill Belch	*Professor of Vascular Medicine, Ninewells Hospital and Medical School, Dundee*
Mr Graham Bell	*Lay representative, Penicuik*
Ms Julie Brittenden	*Senior Lecturer and Consultant Vascular Surgeon, Aberdeen Royal Infirmary*
Dr Henry Doig	*Lay representative, Glasgow*
Dr Ian Gillespie	*Vascular (Interventional) Radiologist, Royal Infirmary of Edinburgh*
Ms Margaret Greene	*Vascular Technologist, Southern General Hospital, Glasgow*
Ms Alison Howd	*Consultant Vascular Surgeon, Queen Margaret Hospital, Dunfermline*
Dr Gordon Isbister	*General Practitioner, Beith*
Dr Moray Nairn	*Programme Manager, SIGN Executive*
Dr Jackie Price	*Clinical Lecturer, Public Health Sciences, University of Edinburgh*
Ms May Roseburgh	*Clinical Nurse Specialist, Royal Infirmary of Edinburgh*
Ms Mairi Ross	*Senior Vascular Physiotherapist, Raigmore Hospital, Inverness*
Ms Helen Scott	*Superintendent Physiotherapist WESTMAR, Southern General Hospital, Glasgow*
Ms Valerie Sinclair	*Vascular Nurse, Stirling Royal Infirmary*
Ms Christine Smith	*Vascular Liaison Nurse, Raigmore Hospital, Inverness*
Mrs Ailsa Stein	*Information Officer, SIGN Executive*
Dr Tasmin Sommerfield (Resigned from group November 2004)	*Specialist Registrar, Directorate of Public Health and Health Policy, Lothian NHS Board*
Dr Rebecca Walton	*Specialist Registrar in Public Health, Lothian NHS Board*
Dr Olivia Wu	*Health Economist, Reproductive and Maternal Medicine, Division of Developmental Medicine, University of Glasgow*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

7.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following members of the guideline development group for their contribution to this guideline.

Dr John Forbes	*Health Economist, Public Health Sciences, University of Edinburgh*
Mr John Hamley	*Chief Pharmacist, Primary Care Division, NHS Tayside*

7.4 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl and the Cochrane Library. The year range covered was 1994-2004. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, NELH Guidelines Finder, and the US National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN Website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group. All selected papers were evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

7.5 CONSULTATION AND PEER REVIEW

7.5.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group present its draft recommendations for the first time. The national open meeting for this guideline was held on 11 October 2004 and was attended by representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

7.5.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Alan Begg	*General Practitioner, Montrose*
Mr Peter Bell	*Lay Representative, British Vascular Foundation*
Dr Chris Burton	*CSO Research Training Fellow, University of Edinburgh*
Dr San Chackraverty	*Consultant in Radiology, Ninewells Hospital and Medical School, Dundee*
Ms Mairghread Ellis	*Lecturer in Podiatry, Queen Margaret University College, Edinburgh*
Mr Douglas Forrest	*Podiatrist, Southern General Hospital, Glasgow*
Dr Peter Gaines	*Consultant Vascular Radiologist, Northern General Hospital, Sheffield*
Ms Karen Gallacher	*Chief Vascular Scientist, Royal Infirmary of Edinburgh*
Dr Dugald Glen	*Consultant Radiologist, Stirling Royal Infirmary*
Dr Jeff Hussey	*Consultant Radiologist, Aberdeen Royal Infirmary*
Dr Jon Moss	*Consultant Interventional Radiologist, Gartnavel General Hospital, Glasgow*
Dr David Nichols	*Consultant Radiologist, Raigmore Hospital, Inverness*
Ms Ruth Robbins	*Vascular Nurse, Queen Margaret Hospital, Dunfermline*

Dr Peter Thorpe	*Consultant Interventional Radiologist, Aberdeen Royal Infirmary*
Mr Mike Yapanis	*Consultant Vascular Surgeon, Stirling Royal Infirmary*

7.5.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Professor Gordon Lowe	*Chair of SIGN; Co-Editor*
Dr David Alexander	*General Practitioner, Nethertown Surgery, Dunfermline*
Professor Ian Campbell	*Consultant Physician, Victoria Infirmary, Kirkcaldy*
Mr Chris Oliver	*Consultant Trauma Orthopaedic Surgeon, Royal Infirmary of Edinburgh*
Dr Safia Qureshi	*SIGN Programme Director; Co-Editor*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

8 Implementation, audit and resource implications

8.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

8.2 RESOURCE IMPLICATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of the implementation of the recommendations within the guideline. Where current practice is in line with the recommendations there are unlikely to be resource implications.

The following recommendations are likely to have significant resource implications if implemented across Scotland. Resource implications associated with good practice points have not been considered.

FROM SECTION 3.6.5

A **Non-invasive imaging modalities should be employed in the first instance for patients with intermittent claudication in whom intervention is being considered.**

Most centres have access to MRA and CTA. Duplex scanning is limited by the availability of vascular technologists. Additional vascular technologists will be required which will have training and staff cost implications.

FROM SECTION 4.5

A **Patients with intermittent claudication should be encouraged to exercise.**

Supervised exercise programmes for patients with intermittent claudication are not currently widespread. Implementation of this recommendation will require a significant increase in dedicated staff and facilities to provide structured programmes for all patients with intermittent claudication.[129]

8.3 KEY POINTS FOR AUDIT

- The proportion of patients considered for surgical intervention who receive non-invasive investigation.
- The implementation of cardiovascular risk reduction methods (including smoking cessation, cholesterol lowering, blood pressure control, glycaemic control, weight loss and antiplatelet therapy).

8.4 RECOMMENDATIONS FOR RESEARCH

- Large multicentre trials are needed to compare exercise with endovascular intervention and with exercise + intervention (and surgery for TASC C and D lesions) in patients who do not respond to standardised risk factor management.
- Comparison of latest technology MRA vs CTA vs US vs DSA in terms of diagnostic accuracy, cost effectiveness and patient acceptability.
- Trials of sufficient duration (at least five years) are needed to consider the effects of different forms of exercise therapy (supervised vs unsupervised and different forms of supervision) including effects on quality of life.
- Effectiveness of smoking cessation therapies should be established in patients with PAD.
- Effectiveness of homocysteine-lowering therapies should be established in patients with PAD.
- Large multicentre RCTs are required to establish the clinical and cost effectiveness of clopidogrel in patients with PAD.
- Large RCTs of pharmacological therapies for intermittent claudication using robust outcome measures (including maximum walking distance).
- Trials of follow up of patients following endovascular or surgical interventions, including graft surveillance are required.
- Effectiveness and feasibility of pulse oximetry in the community versus ABPI for the assessment of intermittent claudication.

Abbreviations

ABPI	ankle brachial pressure index
ACE	angiotensin-converting enzyme
ATA	anterior tibial artery
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial
CHD	coronary heart disease
CI	confidence interval
CIA	common iliac artery
CFA	common femoral artery
CTA	computed tomography angiography
CVD	cardiovascular disease
DPA	dorsalis pedal artery
DSA	digital subtraction angiography
DVT	deep vein thrombosis
EDTA	ethylenediamine tetraacetic acid
EIA	external iliac artery
GP	general practitioner
HbA_{1c}	glycosylated haemoglobin
HOPE	Heart Outcomes Prevention Evaluation trial
LEADER	Lower Extremity Arterial Disease Event Reduction trial
MI	myocardial infarction
MRA	magnetic resonance angiography
OR	odds ratio
PAD	peripheral arterial disease
PAOD	peripheral arterial occlusive disease
PERA	peroneal artery
PTA	posterior tibial artery
PVD	peripheral vascular disease
QoL	quality of life
RCT	randomised controlled trial
rFGF-2	fibroblast growth factor
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
TASC	TransAtlantic Inter-society Consensus
VEGF	vascular endothelial growth factor

Annex 1

A recommended method for measurement of ankle brachial pressure index

MEASUREMENT OF THE BRACHIAL SYSTOLIC PRESSURE

Step 1: Wrap the cuff firmly around the upper arm, as high as possible, with the bladder of the cuff over the brachial artery (ie over the antecubital fossa).

Step 2: Cover the end of the probe with ultrasonic gel. Hold the probe like a pencil and rest the lateral edge of the hand against the patient's bare skin (which helps to keep the probe absolutely still). Locate the signal from the brachial artery (*see figure 1*). The brachial artery will often be located in the small groove at the medial edge of the distal biceps muscle. Make very small and subtle adjustments in both position and angulation of the probe until the Doppler signal sounds at its strongest.

To achieve the optimum Doppler signal, an angle of 45 – 60° between the direction of the arterial flow and the ultrasound beam is required (*see figure 2*).

Figure 1: Location of brachial artery

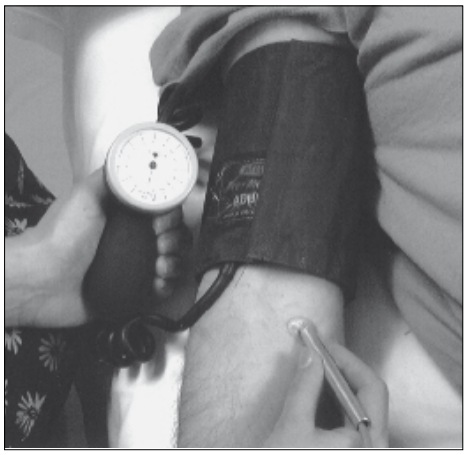
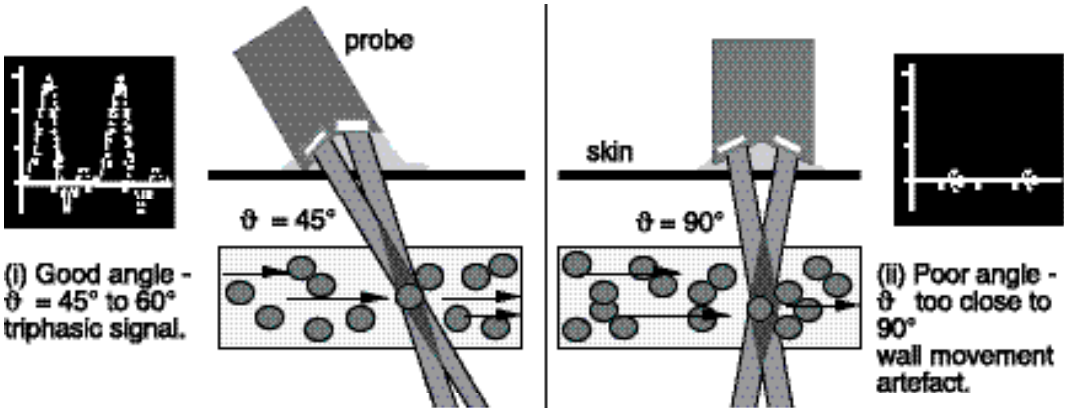


Figure 2: Angulation between Doppler beam and arterial blood flow



If the signal is not sharp and triphasic but damped, this arm should not be used to measure the brachial pressure. Damped signals suggest that the patient has subclavian or axillary artery disease, and the pressure maintained will not be a true representation of the systemic pressure.

Step 3: Keep the probe absolutely still and inflate the cuff until the artery is occluded and the Doppler signal disappears. The signal should not get softer – if it does, the probe is probably slipping off the artery. If you do slip off the artery, stop inflating the cuff, readjust the probe to find the best signal and then continue to inflate the cuff. There is no need to deflate the cuff and start again from zero pressure.

As the artery occludes glance at the pressure dial and make a mental note of the reading. In order to be sure of cessation of flow, the cuff should be inflated at least 20 mm Hg above the pressure at which the last Doppler arterial signal was heard.

Step 4: Deflate the cuff slowly (ie approximately 4 mm Hg per second). Slower deflation rates will be needed for patients with bradycardia or an irregular heartbeat. The arterial Doppler signal should return suddenly and sharply as the systolic blood pressure equals, and then exceeds the pressure in the cuff. At this point, note the pressure reading from the pressure gauge and deflate the cuff.

The pressure at which the Doppler signal returns on deflation of the cuff is often lower than the pressure at which the Doppler signal disappears on inflation. It is the former that is the true measurement of the systolic pressure – only in the deflation mode is cuff pressure truly representative of arterial pressure within the limb.

Do not move the probe. You should still be able to hear the Doppler signal, which will reassure you that you have not slipped off the artery.

Step 5: Deflate the cuff completely and remove it. Make a written record of the pressure measurement.

Step 6: Repeat steps 1-5 on the other arm. Use the highest reading of the two when calculating ankle brachial pressure index.

MEASUREMENT OF THE ANKLE SYSTOLIC PRESSURE

Step1: Place the cuff around the right ankle, just above, but not covering, the malleolus (*see figure 3*)

Figure 3A: Correct application – cuff low but not over the malleolus

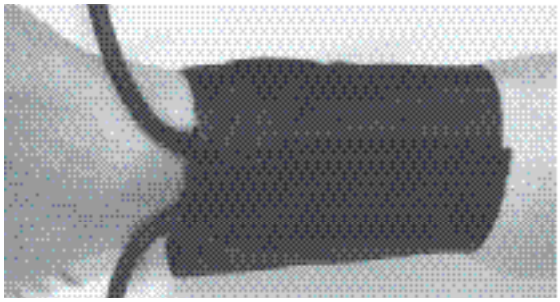
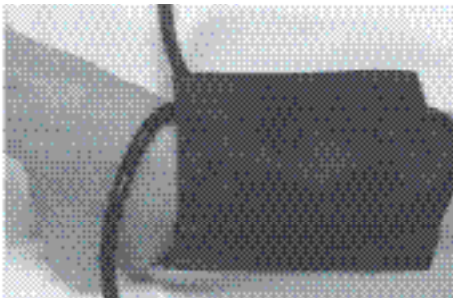


Figure 3B: Incorrect application - cuff wrapped too low - covering malleolus - will give artificially high reading.



Step 2: Locate the posterior tibial artery (PTA). It is usually found behind or along the posterior edge of the medial malleolus on a line between the medial malleolus and the heel (*see figure 4A*). Adjust the probe on the skin to achieve the best Doppler signal but remember that, around the ankle, the arteries may not run parallel to the skin surface and what may look like a poor angle of interrogation may actually be very good (*see figure 5*).

Figure 4A: Location of right posterior tibial artery.

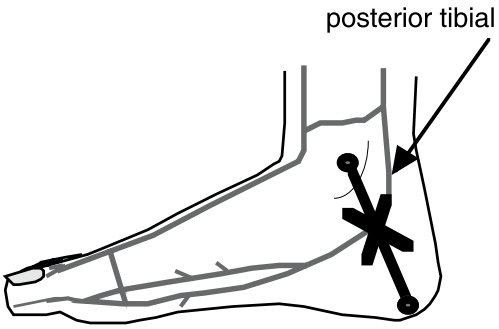
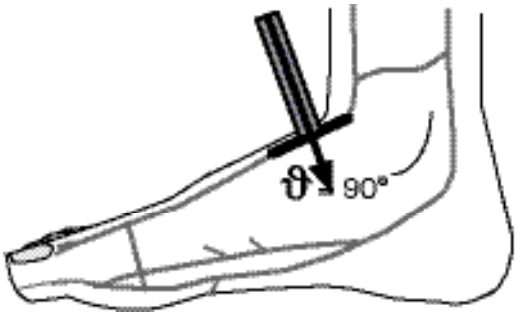
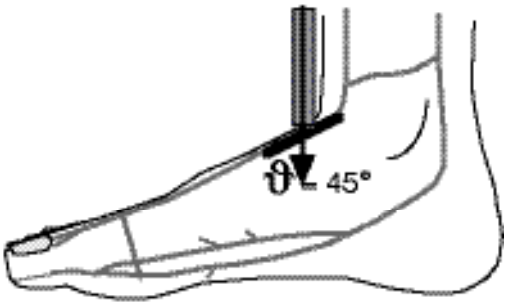


Figure 4B: Doppler probe fits snugly into soft spot behind medial malleolus. Note angulation of probe to achieve a good angle of interrogation.

Figure 5: Illustration of how skin surfaces may be misleading with regard to direction of artery.



Looks like a good angle, but signal is poor because Doppler beam is actually at 90° to flow.



Looks like poor angle, but signal is good because artery curves away and Doppler beam is actually at a good angle to flow.

Step 3: Hold the probe absolutely still and inflate the cuff until the artery is occluded (and the Doppler signal disappears). Make a mental note of the pressure at which this occurs. Now inflate the cuff at least 20 mm Hg above the pressure at which the Doppler arterial signal was heard in order to be sure of cessation of flow.

Step 4: Slowly deflate the cuff, making sure not to move the Doppler probe, and note the pressure reading when the Doppler signal returns.

Step 5: Rapidly deflate the cuff. Make a written record of the Doppler pressure reading.

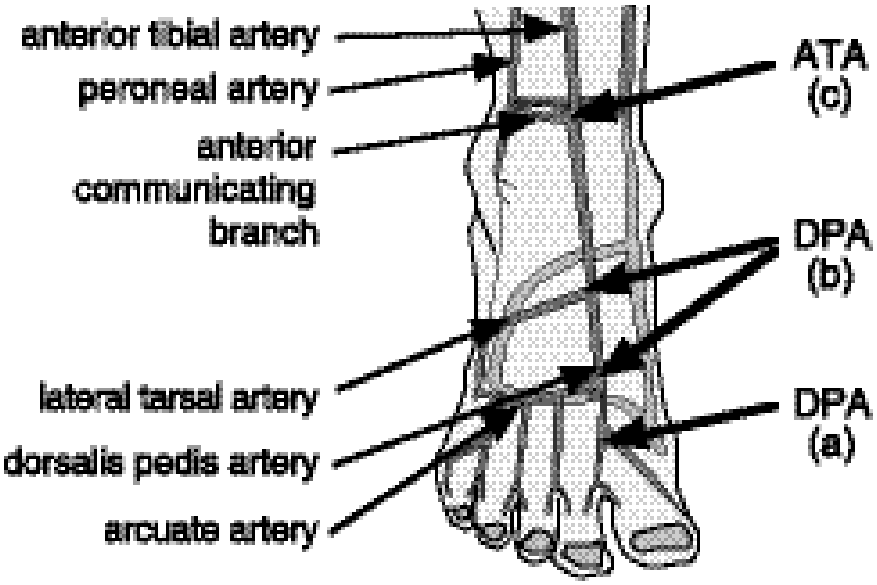
Step 6: Locate the dorsalis pedal artery (DPA) (*see figure* 6) usually found either:

- in the soft spot between the base of the hallux and the second toe (position a)
- on top of the arch of the foot (position b).

or the anterior tibial artery (ATA) – usually found on the creaseline between the foot and the leg (position c).

Take a pressure reading from the best of these sites.

Figure 6: Location of right dorsalis pedis artery and anterior tibial artery



Step 7: If no signal can be found at either the PTA or DPA/ATA sites, locate the peroneal artery (PERA) – usually found either:

- on the lower leg just above the lateral malleolus
- on the foot arch.

Take an ankle pressure reading from the peroneal artery as described previously for other arteries.

Step 8: For the ankle brachial pressure index (ABPI) calculation use the highest pressure reading obtained at the ankle (whether it comes from the PTA, DPA/ATA or PERA) in order to quantify objectively the optimal source of blood flow to the foot.

Step 9: Repeat steps 1-8 on the left leg

CALCULATING THE ANKLE BRACHIAL PRESSURE INDEX

The ankle brachial pressure index for a specific leg is calculated according to the following formula:

ABPI = Highest pressure obtained from the ankle vessels for that leg / Highest brachial pressure of the two arms

Adapted from Vascular Laboratory Practice, Part III. Society for Vascular Technology / Institute of Physics and Engineering. York, 2002.

Annex 2

Morphological stratification of iliac lesions defined in the transatlantic inter-society consensus (TASC)

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 3–10 cm in length, not extending into the common femoral artery (CFA).

Total of two 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 -10 cm long stenosis of the CIA and/or EIA, not extending into the CFA.

Unilateral EIA occlusion not extending into the CFA.

Unilateral EIA stenosis 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).

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.

References

1 Dormandy JD, Heeck L, Vig S. The natural history of claudication: risk to life and limb. In Rutherford R B (Ed). Seminars in Vascular Surgery 1999; 12: 123-137.

2 Fowkes FGR. Epidemiology of atherosclerotic disease in the lower limbs. Eur J Vasc Surg 1988; 2:283-91.

3 Dumville JC, Lee AJ, Smith FB, Fowkes FGR. The health related quality of life of people with peripheral arterial disease in the community: Edinburgh Artery Study. British Journal of General Practice 2004; 54: 826-31.

4 Meijer WT, Cost B, Bernsen RMD, Hoes AW. Incidence and management of intermittent claudication in primary care in The Netherlands. Scand J Prim Health Care 2002;20(1):33-4.

5 Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286(11):1317-24.

6 Cassar K, Coull R, Bachoo P, Macaulay E, Brittenden J. Management of secondary risk factors in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2003; 26(3):262-6.

7 Girolami, B., E. Bernardi, et al. (1999). Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Archives of Internal Medicine. 159(4): 337-45.

8 Violi F, Criqui M, Longoni A, Castiglioni C. Relation between risk factors and cardiovascular complications in patients with peripheral vascular disease. Results from the A.D.E.P. study. Atherosclerosis. 1996: 120(1-2): 25-35.

9 Department of Health. Smoking Kills: A White Paper on Tobacco. The Stationery Office, 1998.

10 Health Scotland and ASH Scotland. Smoking cessation guidelines for Scotland. Edinburgh: Health Scotland, 2004.

11 Leng, GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis. (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

12 Heart Protection Study Collaborative Group . MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high risk individuals: A randomised placebo controlled trial. Lancet 2002: 360(9326): 7-22.

13 Meade T, Zuhrie R, Cook C, and Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. BMJ 2002; 325(7373): 1139.

14 Nye ER, Macbeth WAAG. The treatment of intermittent claudication with beta-pyridy carbinol over two years. Atherosclerosis 1973;17:95-106.

15 Holme I, Malmaeus I, Olsson AG, Nilsson S, Walldius G. Repeated measurements over time: statistical analysis of the angiographic outcomes in the Probucol Quantitative Regression Swedish Trial (PQRST). Clin Trials Meta-Analysis 1993;28:95-108.

16 Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, Sanmarco ME, Selzer RH, et al. Effects of colestipol-niacin therapy on human femoral atherosclerosis. Circulation 1991;83:438-47.

17 Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. BMJ 1989; 299: 1127-31.

18 Bell DS. Stroke in the diabetic patient. Diabetes Care 1994; 17: 213-9.

19 Kanters SD, Banga JD, Stolk RP, Algra A. Incidence and determinants of mortality and cardiovascular events in diabetes mellitus: a meta-analysis. Vasc Med 1999; 4: 67-75.

20 Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus (UKPDS 23). United Kingdom Prospective Diabetes Study Group. BMJ 1998; 316: 823-8.

21 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

22 Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. Edinburgh: SIGN; 2001. (SIGN publication no. 55).

23 Larsson B. Obesity and body fat distribution as predictors of coronary heart disease. In: Marmot M, Elliott P editors. Coronary heart disease epidemiology: from aetiology to public health. Oxford: Oxford University Press; 1992. p.233-41.

24 Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. BMJ 1997; 314: 1311-7.

25 Hoffmans MD, Kromhout D, de Lezenne Coulander C. The impact of body mass index of 78,612 18 year old Dutch men on 32 year mortality from all causes. J Clin Epidemiol 1988; 41: 749-56.

26 National Obesity Forum Guidelines on Management of Adult Obesity and Overweight in Primary Care. Available from url: http://www.nationalobesityforum.org.uk [cited 9 June 2006].

27 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. British Hypertension Society Guidelines. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 – BHS IV. Journal of Human Hypertension 2004; 18: 139-185.

28 Lip G Y H, Makin A J. Treatment of hypertension in peripheral arterial disease (Cochrane review). In The Cochrane Library, Issue 3, 2004. Oxford: Update Software.

29 Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S for the HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J 2004; 25: 17-24.

30 de Jong SC, Stehouwer CD, Mackaay AJ, van den Berg M, Bulterijs EJ, Visser FC, et al. High prevalence of hyperhomocysteinemia and asymptomatic vascular disease in siblings of young patients with vascular disease and hyperhomocysteinemia. Arteriosclerosis 1997, Thrombosis & Vascular Biology. 17(11): 2655-62.

31 Taylor LM Jr, Moneta GL, Sexton GJ, Schuff RA, Porter JM. Prospective blinded study of the relationship between plasma homocysteine and progression of symptomatic peripheral arterial disease. J Vasc Surg. 1999;29(1):8-19.

32 Vermeulen EG, Stehouwer CD, Twisk JW, van den Berg M, de Jong SC, Mackaay AJ, et al. Effect of homocysteine-lowering treatment with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomised, placebo-controlled trial. Lancet 2000; 355: 517-22.

33 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. Br Med J 2002; 324: 71-86.

34 Robless P, Mikhailidis D P, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. Br J Surg 2001; 88: 787-800.

35 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-39.

36 British Medical Journal. Clinical Evidence 2001; 6: 118.

37 Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Engl J Med. 2006;;354(16):1706-17.

38 Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. Health Technol Assess. 2004;8(38): 1-196.

39 Fontaine R, Kim M, Kieny R. Die chirurgische Behandlung der peripheren Durch-blutungsstörungen. Helv Chir Acta. 1954;21(5-6):499-533.

40 Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. J Vasc Surg. 2001; 33(4):679-87.

41 Fowkes FGR. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol 1988;17:248-54.

42 Aboyans V, Lacroix P, Preux PM, Vergnenegre A, Ferrieres J, Laskar M. Variability of ankle-arm index in general population according to its mode of calculation. Int Angiol 2002;21(3):237-43.

43 Jeelani NU, Braithwaite BD, Tomlin C, MacSweeney ST. Variation of method for measurement of brachial artery pressure significantly affects ankle-brachial pressure index values. Eur J Vasc Endovasc Surg. 2000;20(1):25-8.

44 Kaiser V, Kester ADM, Stoffers H, Kitslaar P, Knottnerus JA. The influence of experience on the reproducibility of the ankle-brachial systolic pressure ratio in peripheral arterial occlusive disease. Eur J Vasc Endovasc Surg. 1999;18(1):25-9.

45 Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis. 1997;131(1):115-25.

46 Mackaay AJ, Beks PJ, Dur AH, Bischoff M, Scholma J, Heine RJ, et al. Is toe pressure a better parameter of peripheral vascular integrity than ankle pressure? Comparison of diabetic with nondiabetic subjects in Dutch epidemiological study. J Vasc Technol. 1995;19(1):5-9.

47 Jawahar D, Rachamalla HR, Rafalowski A, Ilkhani R, Bharathan T, Anandarao N. Pulse oximetry in the evaluation of peripheral vascular disease. Angiology 1997;48(8):721-4.

48 Comerota AJ, Throm RC, Kelly P, Jaff M. Tissue (muscle) oxygen saturation (StO2): a new measure of symptomatic lower-extremity arterial disease. J Vasc Surg. 2003;38(4):724-9.

49 Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 2005;25:1463-9.

50 Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996; 313(7070):1440-4.

51 Breek JC, Hamming JF, De Vries J, van Berge Henegouwen DP, van Heck GL. The impact of walking impairment, cardiovascular risk factors, and comorbidity on quality of life in patients with intermittent claudication. J Vasc Surg 2002;36(1):94-9.

52 Hessel SJ, Adams DF, Abrams HL. Complications of angiography. Radiology 1981;138(2):273-81.

53 Waugh JR, Sacharias N. Arteriographic complications in the DSA era. Radiology 1992;182(1):243-6.

54 Sensier Y, Hartshorne T, Thrush A, Nydahl S, Bolia A, London NJ. A prospective comparison of lower limb colour-coded Duplex scanning with arteriography. Eur J Vasc Endovasc Surg 1996;11(2):170-5.

55 Winter-Warnars HA, van der Graaf Y, Mali WP. Interobserver variation in duplex sonographic scanning in the femoropopliteal tract. J Ultrasound Med. 1996;15(6):421-8.

56 Aly S, Sommerville K, Adiseshiah M, Raphael M, Coleridge Smith PD, Bishop CC. Comparison of duplex imaging and arteriography in the evaluation of lower limb arteries. Br J Surg. 1998;85(8):1099-102.

57 Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US - a meta-analysis. Radiology 2000; 216(1):67-77.

58 Nelemans PJ, Leiner T, de Vet HC, van Engelshoven JM. Peripheral arterial disease: meta-analysis of the diagnostic performance of MR angiography. Radiology 2000;217(1):105-14.

59 Koelemay MJ, Lijmer JG, Stoker J, Legemate DA, Bossuyt PM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. JAMA 2001;285(10):1338-45.

60 Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, et al. The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review. Health Technology Assessment 2002;6(7):1-165.

61 Ofer A, Nitecki SS, Linn S, Epelman M, Fischer D, Karram T, et al. Multidetector CT angiography of peripheral vascular disease: a prospective comparison with intraarterial digital subtraction angiography. Am J Roentgenol. 2003;180(3):719-24.

62 Catalano C, Fraioli F, Laghi A, Napoli A, Bezzi M, Pediconi F, et al. Infrarenal aortic and lower extremity arterial disease: Diagnostic performance of multi-detector row CT angiography. Radiology 2004;231:555-563.

63 Ouwendijk R, de Vries M, Pattynama PM, van Sambeek MR, de Haan MW, Stijnen T, et al. Imaging peripheral arterial disease: a randomized controlled trial comparing contrast-enhanced MR angiography and multi-detector row CT angiography. Radiology 2005;236(3):1094-103.

64 Regensteiner JG, and Hiatt WR. Current medical therapies for patients with peripheral arterial disease: A critical review. Am J Med 2002; 112(1):49-57.

65 Belch JJF, Topol EJ, Agnelli G, Bertrand M, Califf, RM, Clement DL, et al. Prevention of Atherothrombotic Disease Network. Critical issues in peripheral arterial disease detection and management: a call to action. Arch Intern Med 2003; 163 (8): 884-92.

66 Klevsgard R, Hallberg IR, Risberg B, Thomsen MB. Quality of life associated with varying degrees of chronic lower limb ischaemia. Eur J Vasc Endovasc Surg 1999;17:319-325.

67 Takahashi S, Oida K, Fujiwara R, Maeda H, Hayashi S, Takai H, et al. Effect of Cilostazol, a cyclic AMP phosphodiesterase inhibitor, on the proliferation of rat aortic smooth muscle cells in culture. J Cardiovasc Pharm 1992;20:900-906.

68 Matousovic K, Grande JP, Chini CC, Chini EN, Dousa TP. Inhibitors of cyclic nucleotide phosphodiesterase isoenzyme type-III and type-IV suppress mitogenesis of rat mesangial cells. J Clin Invest 1995;96:401-410.

69 Reilly MP and Mohler IE. Cilostazol: Treatment of intermittent claudication. Ann Pharmacother 2001;35(1):48-56.

70 Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol. 2002;90(12):1314-9.

71 Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman J, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc. 2002;50(12):1939-46.

72 Scottish Medicines Consortium. Cilostazol 100mg tablets (Pletal). Glasgow;SMC:2005. (SMC Advice 86/04) [cited 1 Aug 2006] Available from url: http://www.scottishmedicines.org.uk/updocs/cilostazol%20100mg%20tablets%20_Pletal_%20RESUBMISSION%20_86-04_.pdf

73 Lehert P, Comte S, Gamand S, Brown TM. Naftidrofuryl in intermittent claudication: a retrospective analysis. J Cardiovasc Pharmacol. 1994;23 Suppl 3:S48-52.

74 Boccalon H, Lehert P, Mosnier M. Effect of naftidrofuryl on physiological walking distance in patients with intermittent claudication. Ann Cardiol Angeiol. 2001;50(3):175-82.

75 Kieffer E, Bahnini A, Mouren X, Gamand S. A new study demonstrates the efficacy of naftidrofuryl in the treatment of intermittent claudication. Findings of the Naftidrofuryl Clinical Ischemia Study (NCIS). Int Angiol. 2001;20(1):58-65.

76 D'Hooge D, Lehert P, Clement DL. Naftidrofuryl in quality of life (NIQOL). A Belgian study. Int Angiol. 2001;20(4):288-94.

77 Spengel F, Clement D, Boccalon H, Liard F, Brown T, Lehert P. Findings of the Naftidrofuryl in Quality of Life (NIQOL) European study program. Int Angiol. 2002;21(1):20-7.

78 Hess H, Franke I, Jauch M. Drug-induced improvement of blood flow properties. Effective principle in the treatment of arterial occlusive diseases. Fortschr Med 1973; 91: 743-8.

79 Ehrly AM. Improvement of the flow properties of blood: A new therapeutical approach in occlusive arterial disease. Angiology 1976; 27: 188-96.

80 Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. Am J Obstet Gynecol 1985; 151: 1094-7.

81 Dawson DL, Cutler BS, Hiatt WR, Hobson RW 2nd, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000;109(7):523-30.

82 Tyson VC. Treatment of intermittent claudication. Practitioner 1979; 223: 121-6.

83 Head A. Treatment of intermittent claudication with inositol nicotinate. Practitioner 1986; 230: 49-54.

84 Kiff RS, Quick CR. Does inositol nicotinate (Hexopal) influence intermittent claudication? A controlled trial. Br J Clin Pract 1988; 42: 141-5.

85 O'Hara J, Jolly PN, Nicol CG. The therapeutic efficacy of inositol nicotinate (Hexopal) in intermittent claudication: a controlled trial. Br J Clin Pract 1988; 42: 377-83.

86 Schaper WK, Jageneau AH, Xhonneux R, Vannueten J, Janssen PA. Cinnarizine, a specific angiotensin - blocking coronary vasodilator. Life Sci 1963;12: 963-74.

87 Van Neuten JM, Janssen PA. Effect of cinnarizine on peripheral circulation in dogs. Eur J Pharmacol1972; 17: 103-6.

88 Ellis F, Hyams DE, Jageneau AH, Loots W. Vascular effects of cinnarizine in patients with intermittent claudication. J Int Med Res 1975; 3: 93-100.

89 Caesar K. Relationship between blood flow values of the upper and the lower extremities and effects of a vasoactive agent in persons with normal circulation and patients with vascular diseases. Med Welt. 1971;14:559-62.

90 Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003;108(12):1481-6.

91 Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, 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(5):359-64.

92 Lievre M, Morand S, Besse B, Fiessinger JN, Boissel JP. Oral Beraprost sodium, a prostaglandin I(2) analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group. Circulation. 2000;102(4):426-31.

93 Mohler ER 3rd, Hiatt WR, Olin JW, Wade M, Jeffs R, Hirsch AT. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I2 analogue: a double-blinded, randomized, controlled trial. J Am Coll Cardiol. 2003;41(10):1679-86.

94 Belch JJ, Bell PR, Creissen D, Dormandy JA, Kester RC, McCollum RD, et al. Randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AS-013, a prostaglandin E1 prodrug, in patients with intermittent claudication. Circulation. 1997;95(9):2298-302.

95 Rajagopalan S, Mohler ER 3rd, Lederman RJ, Mendelsohn FO, Saucedo JF, Goldman CK, et al. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. Circulation. 2003;108(16):1933-8.

96 Lederman RJ, Mendelsohn FO, Anderson RD, Saucedo JF, Tenaglia AN, Hermiller JB, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. Lancet. 2002;359(9323):2053-8.

97 Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication. J Am Coll Cardiol. 1999;34(5):1618-24.

98 Brevetti G, Perna S, Sabba C, Martone VD, Di Iorio A, Barletta G. Effect of propionyl-L-carnitine on quality of life in intermittent claudication. Am J Cardiol. 1997;79(6):777-80.

99 Hiatt WR, Regensteiner JG, Creager MA, Hirsch AT, Cooke JP, Olin JW, et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. Am J Med. 2001;110(8):616-22.

100 Castano G, Mas R, Roca J, Fernandez L, Illnait J, Fernandez JC, Selman E. A double-blind, placebo-controlled study of the effects of policosanol in patients with intermittent claudication. Angiology. 1999;50(2):123-30.

101 Coccheri S, Scondotto G, Agnelli G, Palazzini E, Zamboni V; Arterial Arm of the Suavis (Sulodexide Arterial Venous Italian Study) group. Sulodexide in the treatment of intermittent claudication. Results of a randomized, double-blind, multicentre, placebo-controlled study. Eur Heart J. 2002;23(13):1057-65.

102 Sallon S, Beer G, Rosenfeld J, Anner H, Volcoff D, Ginsberg G, et al. The efficacy of Padma 28, a herbal preparation, in the treatment of intermittent claudication: A controlled double-blind pilot study with objective assessment of chronic occlusive arterial disease patients. J Vasc Invest 1998:4;129-136.

103 McGrath C, Robb R, Lucas AJ, Stewart AH, Underwood CL, Horridge JK, et al. A randomised, double blind, placebo-controlled study to determine the efficacy of immune modulation therapy in the treatment of patients suffering from peripheral arterial occlusive disease with intermittent claudication. Eur J Vasc Endovasc Surg. 2002;23(5):381-7.

104 Delis KT, Nicolaides AN, Wolfe JH, Stansby G. Improving walking ability and ankle brachial pressure indices in symptomatic peripheral vascular disease with intermittent pneumatic foot compression: a prospective controlled study with one-year follow-up. J Vasc Surg. 2000;31(4):650-61.

105 van Rij AM, Solomon C, Packer SG, Hopkins WG. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. Circulation. 1994;90(3):1194-9.

106 Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med. 2000;108(4):276-81.

107 Kleijnen J, Mackerras D. Vitamin E for intermittent claudication (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

108 Bendermacher BLW, Willigendael EM, Teijink JAW, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. The Cochrane Database of Systematic Reviews 2006.

109 Brandsma JW, Robeer BG, van den Heuvel S, Smit B, Wittens CH, Oostendorp RA. The effect of exercises on walking distance of patients with intermittent claudication: a study of randomized clinical trials. Phys Ther 1998;78(3):278-86.

110 Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication(Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Chichester: John Wiley & Sons Ltd.

111 Cheetham DR, Burgess L, Ellis M, Williams A, Greenhalgh RM, Davies AH. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial. Eur J Vasc Endovasc Surg 2004;27(1):17-23.

112 Fowler B, Jamrozik K, Norman P, Allen Y, Wilkinson E. Improving maximum walking distance in early peripheral arterial disease: randomised controlled trial. Aust J Physiother 2002;48(4):269-75.

113 Gibellini R, Fanello M, Bardile AF, Salerno M, Aloi T. Exercise training in intermittent claudication. Int Angiol 2000;19(1):8-13.

114 Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. J Vasc Surg 1997;25(2):312-8.

115 Pinto BM, Marcus BH, Patterson RB, Roberts M, Colucci A, Braun C. On-site versus home exercise programs: psychological benefits for individuals with arterial claudication. J Aging Phys Act 1997;5: 311-28.

116 TransAtlantic Inter-Society Consensus (TASC). TASC consensus paper: Management of Peripheral Arterial Disease (PAD). [cited 9 June 2006]. Available from url: http://www.tasc-pad.org/html/index.html

117 Fowkes FGR, Gillespie I. Angioplasty (versus non surgical management) for intermittent claudication Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Chichester: John Wiley & Sons Ltd.

118 Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements. Eur J Vasc Endovasc Surg. 2001;22(2):107-13.

119 Royal College of Surgeons of England, Mansfield A, Collins C, Phillips H, Ridley S, Smith J. Good Surgical Practice. London: The Royal College of Surgeons of England; 2002. [cited 9 June 2006]. Available from url: http://www.rcseng.ac.uk/rcseng/content/publications/docs/good_surgical_practice.html

120 10 High Impact Changes for service improvement and delivery: a guide for NHS leaders. NHS Modernisation Agency; 2004. [cited 9 June 2006]. Available from url: http://www.content.modern.nhs.uk/NR/rdonlyres/6E0D282A-4896-46DF-B8C7-068AA5EA1121/654/HIC_for_web.pdf

121 Fowkes G. Health Care Needs Assessment. Peripheral vascular disease. [cited 9 June 2006]. Available from url: http://hcna.radcliffe-oxford.com/pvdframe.html

122 Mills JL. Mechanisms of vein graft failure: the location, distribution and characteristics of lesions that predispose graft failure. Semin Vasc Surg 1993; 6(2):78-91.

123 Szilagyi DE, Elliot JP, Hageman JH, Smith RF, Dall'olmo CA. Biologic fate of autogenous vein implants as arterial substitutes: clinical, angiographic and histopathologic observations in femoro-popliteal operations for atherosclerosis. Ann Surg 1973; 178: 232-246.

124 Lundell A, Lindblad B, Bergqvist D, Hansen F. Femoropopliteal-crural graft patency is improved by an intensive surveillance program: a prospective randomized study. J Vasc Surg. 1995;21(1):26-33.

125 Ihlberg L, Luther M, Tierala E and Lepantalo M. The utility of duplex scanning in infrainguinal vein graft surveillance: results from a randomised controlled study. Eur J Vasc Endovasc Surg. 1998;16:19-27.

126 Ihlberg L, Luther M, Alback A, Kantonen I and Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein-graft failure? Eur J Vasc Endovasc Surg. 1999;18:395-400.

127 Golledge J, Beattie DK, Greenhalgh RM, Davies AH. Have the results of infrainguinal bypass improved with the widespread utilisation of postoperative surveillance? Eur J Vasc Endovasc Surg. 1996;11(4):388-92.

128 Davies AH, Handon AJ, Sydes MR and Thompson SG. Is duplex surveillance of value after leg vein bypass grafting?: principle results of the vein graft surveillance randomised trial (VGST) Circulation 2005;112(13): 1985-1991.

129 Prevalence of IC in Northern European Countries 8% and 7% (men and women 55-64), 16% and 11% (men and women 65-74) and >30% (men and women > 75). Source: Oxford Textbook of Medicine, Volume 2. Warrell DA, Cox TM, Firth JD & Benz EJ eds. Oxford University Press, 2003.

INVESTIGATIONS IN PRIMARY CARE

☑
- Individuals with a history of intermittent claudication should have an examination of peripheral pulses and palpation of the abdomen for an aortic aneurysm.
- Ankle brachial pressure index should be measured in all patients with suspected PAD.

REFERRAL AND INVESTIGATIONS

☑ Patients with suspected PAD should be referred to secondary care if:

- the primary care team is not confident of making the diagnosis, lacks the resources necessary to institute and monitor best medical treatment or is concerned that the symptoms may have an unusual cause
- risk factors are unable to be managed to recommended targets
- they have symptoms which limit lifestyle and objective signs of arterial disease (clinical signs and a low ankle brachial pressure index).

Young and otherwise healthy adults, presenting prematurely with claudication, should be referred to exclude entrapment syndromes and other rare disorders.

A **Non-invasive imaging modalities should be employed in the first instance for patients with intermittent claudication in whom intervention is being considered.**

D **Digital subtraction arteriography is not recommended as the primary imaging modality for patients with PAD.**

TREATMENT

DRUG THERAPY

A
- **Patients with intermittent claudication, in particular over a short distance, should be considered for treatment with cilostazol.**
- **Cilostazol should be stopped after three months if it is ineffective, or if adverse effects reduce compliance.**

A **Patients with intermittent claudication and who have a poor quality of life may be considered for treatment with naftidrofuryl.**

A **Oxpentifylline is not recommended for the treatment of intermittent claudication.**

B **Inisitol nicotinate is not recommended for the treatment of intermittent claudication.**

A **Statins should be given for risk factor management in patients with intermittent claudication and total cholesterol level > 3.5 mmol/l.**

A **The use of oral prostaglandin therapy in patients with intermittent claudication is not recommended.**

EXERCISE THERAPY

A **Patients with intermittent claudication should be encouraged to exercise.**

VASCULAR INTERVENTION

D
- **Endovascular and surgical intervention are not recommended for the majority of patients with intermittent claudication.**
- **For those with severe disability or deteriorating symptoms, referral to a vascular specialist is recommended.**
- **The TransAtlantic Inter-society consensus guidelines should be used when advising patients about possible interventions.**

CARDIOVASCULAR RISK REDUCTION

Patients with PAD have an increased risk of mortality, myocardial infarction and stroke. Management of PAD is an opportunity for secondary prevention of cardiovascular events.

☑
- On diagnosis of PAD, patients should have a full cardiovascular risk factor assessment.
- Patients should be referred to the practice cardiovascular clinic for monitoring and long term follow up of risk factor modification.

SMOKING CESSATION

D **Patients with PAD should be actively discouraged from smoking.**

CHOLESTEROL LOWERING

A **Lipid lowering therapy with a statin is recommended for patients with PAD and total cholesterol level > 3.5 mmol/l.**

GLYCAEMIC CONTROL

B **Optimal glycaemic control is recommended for patients with PAD and diabetes to reduce the incidence of cardiovascular events.**

WEIGHT REDUCTION

D **Obese patients with PAD should be treated to reduce their weight.**

BLOOD PRESSURE CONTROL

A **Hypertensive patients with PAD should be treated to reduce their blood pressure.**

ANTIPLATELET THERAPY

A **Antiplatelet therapy is recommended for patients with symptomatic PAD.**