NCGC National Clinical Guideline Centre

Stakeholder consultation draft

Lower limb peripheral arterial disease

Diagnosis and management

NICE Clinical Guideline <…>

Methods, evidence and recommendations

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Draft for Consultation

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1 Abbreviations

ABPI	Ankle brachial pressure index
BMS	Bare metal stents
BMT	Best medical treatment
CCA	Cost-consequences analysis
CE-MRA	Contrast-enhanced magnetic resonance angiography
CLI	Critical limb ischaemia
CEA	Cost-effectiveness analysis
CI	Confidence interval
CTA	Computed tomography angiography
DES	Drug eluting stents
DUS	Duplex ultrasound scanning
EQ-5D	EuroQol-5D
GDG	Guideline development group
GRADE	Grading of recommendations assessment, development and evaluation
HRQoL	Health-related quality of life
HTA	Health technology assessment or appraisal
IC	Intermittent claudication
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
ITT	Intention-to-treat analysis
MI	Myocardial infarction
MID	Minimal important difference
MWD	Maximum walking distance
NCGC	National clinical guideline centre
NICE	National institute for health and clinical excellence
NNT	Numbers needed to treat
NPV	Negative predictive value
PAD	Peripheral arterial disease
PC MRA	Phase-contrast magnetic resonance angiography
PFWD	Pain free walking distance
PICO	Patient, intervention, comparison, outcome
PPV	Positive predictive value
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SFA	Superficial femoral artery
TA	Technology appraisal
TLR	Target lesion revascularisation
TOF MRA	Time of flight magnetic resonance angiography
UNG	Understanding NICE guidance

1 Introduction

1.1 Background and incidence

The most common initial symptom of peripheral arterial disease (PAD) is pain in the leg on walking known as intermittent claudication (IC). The incidence of PAD increases with age. Population studies have found that about 20% of people aged over60 years have some degree of PAD.[1] In the majority of those with IC the symptoms remain stable but approximately 20% will progress to develop increasingly severe symptoms with the development of critical limb ischaemia (CLI). Those with CLI are at significant risk of developing irreversible ischaemic damage to the leg or foot if they do not receive appropriate treatment and this may lead to the need for amputation. Overall approximately 1% to 2% of people with IC will eventually undergo amputation,[2] although the risk is higher (about 5%) in people with diabetes.[3]

The incidence of PAD is high among people who smoke, people with diabetes, and people with coronary artery disease. Even in the absence of clinical symptoms the presence of PAD (as indicated by reduced ankle brachial pressure index, ABPI) has been shown to identify people who are at increased risk of cardiac and cerebrovascular morbidity and mortality.[4]

Many people will have undetected and asymptomatic PAD. In post-mortem studies, there is a significant incidence of such disease that has never led to lifetime symptoms. The development of symptoms will depend both upon the extent of disease and activity levels of the individual.

Of those presenting with IC over a 5-year period approximately 70 - 80% will remain with stable claudication, 10 – 20% will go on to have worsening symptoms and 5 – 10% will go on to develop CLI. Approximately 10 – 15% die of cardiovascular causes within 5 years and a further 20% will have a non-fatal cardiovascular event.[5]

Of those who develop CLI there is a high mortality with approximately 25% dying within a year and about 1/3 will require a major lower limb amputation within a year.[6]

1.2 Specific risk factors

There are a number of associated risk factors. Some people may require investigation and treatment for risk factors and associated diseases.

There is an association between diabetes and the development of PAD and there is a correlation between the level of haemoglobin A1c and the level of increase in the risk of asymptomatic PAD.[7] There is also evidence that those with diabetes who develop PAD have less favourable outcomes for both the disease and its treatment. Asymptomatic PAD is common in people with diabetes. NICE has produced a number of guidelines relating to the management of diabetes (see section 2.6), particularly in relation to foot problems. This guideline is not intended to replace any current recommendations within those guidelines.

Smoking is an important risk factor with the Edinburgh Artery Study[1] suggesting that current smokers are almost four times as likely to develop asymptomatic PAD as non-smokers.

As with other forms of cardiovascular disease there are also associations of PAD with hypertension and dyslipidaemia.

Other associations with the prevalence or severity of PAD include raised homocysteine, chronic renal insufficiency and various hyperviscosity and hypercoagulable states.

1.3 Definitions and classification systems

Whilst there are a number of definitions and classification systems for PAD, these are not used consistently in either clinical practice or research settings. The evidence reviewed within this guideline often utilises different criteria, some of which are based on anatomical distribution of disease and others on symptom severity. To address this, the guideline development group (GDG) identified general definitions for PAD, IC and CLI (see Table 1).

Table 1: Guideline definitions of peripheral arterial disease

Term	Definition
Peripheral arterial disease (PAD)	• Infra-renal atherosclerosis • Also known as Peripheral Arterial Occlusive Disease (PAOD) or Peripheral Vascular Disease (PVD).
Asymptomatic PAD	Clinically significant PAD without symptoms of intermittent claudication or rest pain.
Intermittent claudication (IC)	Walking (exercise) induced pain in the lower limbs caused by diminished circulation.
Critical limb ischaemia (CLI)	People with severely impaired circulation, at imminent risk of limb loss without undergoing revascularisation.

Severe Limb Ischaemia

The term severe limb ischemia has been used in some research in preference to CLI to indicate those people who are clinically thought to be at significant risk of limb loss due to their circulatory disease.

1.3.1 Classification of PAD based on symptom severity

Standard classifications such as the Fontaine or Rutherford scales[8] are commonly used in research settings and do not correlate well with the degree of disability experienced by patients. Both categorise PAD in term of symptoms (asymptomatic, intermittent claudication, ischemic rest pain or ulceration and/or gangrene) and severity (mild, moderate, severe). The Fontaine classification is based upon the distance that a person can walk before pain occurs (pain free walking distance, PFWD) dividing into two groups based upon a PFWD of greater than or less than 200 metres. The Rutherford classification uses three groups based upon a combination of the results of a treadmill exercise test and ABPI values.

1.3.2 Classification of PAD based on anatomical distribution of disease

Treatment options and outcomes can be dependent on the anatomical distribution of disease. However, the anatomical disease site may not correlate closely with symptoms experienced by the patient. For the purposes of this guideline, the broad anatomical definitions in Table 2 have been used.

Table 2: Broad anatomical definitions of peripheral arterial disease

Arterial segment	Main site of blood flow limitation
Aorto-iliac	Above the groin
Femoro-popliteal	Between the groin and the knee
Infra-geniculate	Below the knee

There are more complex classifications dealing with the anatomical distribution and extent of arterial occlusive disease and TASC definitions[6] are quite widely quoted, particularly in research studies. The TASC classification gives some indication of the site, extent and distribution of disease.

Other terms relating to the anatomical distribution include infra-inguinal to describe disease anywhere below the groin and tibial or peroneal to describe the specific vessels below the knee.

Arterial disease to the lower limbs often affects more than one site and there may be short discrete narrowings or more extensive disease with long or multiple segments of occluded arteries.

1.3.3 Issues surrounding definitions of PAD

1.3.3.1 Ankle Brachial Pressure Index (APBI)

Various definitions and classifications often use ABPI as an indicator of disease severity, with the use of a threshold value for ABPI of below 0.5 for CLI and <0.9 for PAD. There are, however, a significant group of people, particularly those with diabetes mellitus, who may have significant impairment of the circulation, non-healing ulceration of infection and be at significant risk of limb loss, but who do not fall strictly within these definitions of ABPI.

1.3.3.2 Use of classifications in clinical settings

Whilst such classifications may be helpful in a research setting they are rarely used in clinical practice as they often correlate poorly with the level of disability experienced due to IC or CLI. For example, someone who has an active job or leisure activities that involve significant walking may be very disabled despite falling into the milder categories on such a classification. Other people, who would be classified as severe on such scales, may find that their symptoms have little impact if they have a largely sedentary lifestyle. In practice a term such as “lifestyle limiting claudication” is often more helpful in representing the individual impact of the condition.

1.4 Initial management

Mild symptoms are generally managed in primary care, with referral to secondary care when symptoms do not resolve or deteriorate. There are several treatment options for people with IC. This includes advice to exercise, management of cardiovascular risk factors for example, aspirinor statins) and vasoactive drug treatment for example, naftidrofuryl oxalate).

There is considerable variation in the provision of these treatment options. Whilst supervised exercise programmes can improve walking distance and quality of life, access to such programmes is variable, and many are not funded by the NHS. Treatments for secondary prevention are less commonly offered to people with PAD than for those with other cardiac and cerebrovascular risk factors.

1.5 Secondary care

People with severe symptoms that are inadequately controlled are often referred to secondary care for assessment for endovascular (such as angioplasty or stenting), surgical revascularisation and amputation. In recent years, there has been a move away from invasive investigation by catheter angiography to non-invasive investigation by duplex ultrasonography, magnetic resonance angiography or computed tomography angiography. Treadmill walking tests and segmental pressures are other commonly used investigations.

The risks and outcomes of these procedures vary according to the nature of the procedure, the presenting symptoms, comorbidities, and the site and extent of the disease. However, the current trend is toward less invasive treatment.

1.6 Importance to the NHS

PAD is a marker for an increased risk of potentially preventable cardiovascular events even when it is asymptomatic. If it becomes symptomatic it can lead to significant impairment of quality of life through limiting mobility and in its more severe manifestations may lead to severe pain, ulceration and gangrene and is the largest single cause of lower limb amputation in the UK.

The management of PAD of the lower limb remains controversial and treatments range from watchful waiting, through medical management, exercise training, endovascular treatment or surgical reconstruction. Rapid changes in diagnostic methods, endovascular treatments and vascular services, associated with the emergence of new subspecialities in surgery and vascular radiology, has resulted in considerable uncertainty and variation in practice. This guideline aims to resolve that uncertainty and variation.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the quick reference guide (QRG) presents recommendations in a suitable format for health professionals
- information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce a clinical guideline on the diagnosis and management of lower limb peripheral arterial disease.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on GDG membership and acknowledgements).

NICE funds the NCGC and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Jonathan Michaels in accordance with guidance from the NICE.

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry (see Appendix B). At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analyses and cost-effectiveness analyses where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

This guideline covers adults presenting with symptoms of lower limb peripheral arterial disease. The key clinical areas covered in this guideline were:

- Information requirements for people with peripheral arterial disease
- Secondary prevention measures
- Diagnosis of peripheral arterial disease
- Imaging for revascularisation
- Management of intermittent claudication through exercise, drug treatment, angioplasty, stenting and bypass surgery
- Management of critical limb ischaemia through angioplasty, stenting and bypass surgery
- Management of pain associated with critical limb ischaemia
- Major amputation for critical limb ischaemia.

For further details please refer to the scope in Appendix A and review questions in section 3.1.

2.5 What this guideline does not cover

This guideline does not cover the following:

- Children and young people
- Screening of asymptomatic PAD
- Adults who have acute ischaemia of the lower limb.

2.6 Relationships between the guideline and other NICE guidance

Related NICE Health Technology Appraisals:

- Cilostazol, naftidrofyryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. NICE technology appraisal guidance 223 (2011). Available from http://publications.nice.org.uk/cilostazol-naftidrofuryl-oxalate-pentoxifylline-and-inositol-nicotinate-for-the-treatment-of-ta223.
- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal guidance 210 (2010). Available from http://guidance.nice.org.uk/TA210.
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal guidance 159 (2008). Available from http://publications.nice.org.uk/spinal-cord-stimulation-for-chronic-pain-of-neuropathic-or-ischaemic-origin-ta159.
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from http://publications.nice.org.uk/ezetimibe-for-the-treatment-of-primary-heterozygous-familial-and-non-familial-ta132.
- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from http://publications.nice.org.uk/varenicline-for-smoking-cessation-ta123.
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from http://publications.nice.org.uk/statins-for-the-prevention-of-cardiovascular-events-ta94.
- Guidance on the use of patient-education models for diabetes. NICE technology appraisal guidance 60 (2003). Available from http://guidance.nice.org.uk/TA60

Related NICE Interventional Procedures:

- Endovascular stent-grafting for popliteal aneurysms. NICE interventional procedure guidance IPG390 (2011). Available from http://publications.nice.org.uk/endovascular-stent-grafting-of-popliteal-aneurysms-ipg390.
- Percutaneous atherectomy of femoro-popliteal arterial lesions with plague incision devices. NICE intervention procedure guidance IPG380 (2010). Available from http://publications.nice.org.uk/percutaneous-atherectomy-of-femoropopliteal-arterial-lesions-with-plaque-excision-devices-ipg380

Related NICE Clinical Guidelines:

- Patient experience in adult NHS services. NICE clinical guideline 138 (2012). Available from http://publications.nice.org.uk/patient-experience-in-adult-nhs-services-improving-the-experience-of-care-for-people-using-adult-cg138
- Hypertension: Clinical management of primary hypertension in adults. NICE clinical guideline CG127 (2011). Available from http://publications.nice.org.uk/hypertension-cg127.
- Diabetic foot problems - inpatient management of people with diabetic foot ulcers and infection. NICE clinical guideline CG119 (2011). Available from http://publications.nice.org.uk/diabetic-foot-problems-cg119.
- Medicines adherence. NICE clinical guideline 76 (2009). Available from http://publications.nice.org.uk/medicines-adherence-cg76.
- Lipid modification. NICE clinical guideline 67 (2008). Available from http://publications.nice.org.uk/lipid-modification-cg67.
- Type 2 diabetes. NICE clinical guideline 66 (2008). Available from http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983
- Obesity. NICE clinical guideline 43 (2006). Available from http://publications.nice.org.uk/obesity-cg43.

- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from http://publications.nice.org.uk/type-1-diabetes-cg15
- Type 2 diabetes – footcare. NICE clinical guideline 10 (2004). Available from http://publications.nice.org.uk/type-2-diabetes-cg10

Related NICE Public Health Guidance:

- Preventing type 2 diabetes: population and community-level interventions in high-risk groups and the general population. NICE public health guidance 35 (2011). Available from http://publications.nice.org.uk/preventing-type-2-diabetes-population-and-community-level-interventions-in-high-risk-groups-and-the-ph35
- Prevention of cardiovascular disease. NICE public health guidance 25 (2010). Available from http://publications.nice.org.uk/prevention-of-cardiovascular-disease-ph25
- Preventing the uptake of smoking by children and young people. NICE public health guidance 14 (2008). Available from http://publications.nice.org.uk/mass-media-and-point-of-sales-measures-to-prevent-the-uptake-of-smoking-by-children-and-young-ph14
- Promoting physical activity in the workplace. NICE public health guidance 13 (2008). Available from http://publications.nice.org.uk/workplace-health-promotion-how-to-encourage-employees-to-be-physically-active-ph13
- Smoking cessation services. NICE public health guidance 10 (2008). Available from http://publications.nice.org.uk/smoking-cessation-services-in-primary-care-pharmacies-local-authorities-and-workplaces-ph10
- Physical activity and the environment. NICE public health guidance 8 (2008). Available from http://publications.nice.org.uk/promoting-and-creating-built-or-natural-environments-that-encourage-and-support-physical-activity-ph8.
- Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006). Available from http://publications.nice.org.uk/four-commonly-used-methods-to-increase-physical-activity-brief-interventions-in-primary-care-ph2
- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006). Available from http://publications.nice.org.uk/brief-interventions-and-referral-for-smoking-cessation-in-primary-care-and-other-settings-ph1

3 Methods

This chapter sets out in detail the methods used to generate the recommendations that are presented in the subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.[9]

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient/population, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy (see Table 3). This was to guide the literature searching process and to facilitate the development of recommendations by the GDG. They were drafted by the NCGC technical team and refined and validated by the GDG. The review questions were based on the key clinical areas identified in the scope (Appendix A). The review question protocols can be found in Appendix C. The review questions and outcome measures examined are presented in Table 3.

Table 3: List of guideline review questions

Chapter	Review questions	Outcomes
Chapter 5	What are peoples' experiences of living with PAD and preferences for information requirements for PAD?	• Experiences of living with PAD • Information people with PAD wanted or found useful • If there are specific information requirements for people with PAD • If information received changed the perception of PAD
Chapter 7 Section 7.2	In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining the diagnosis and severity of PAD?	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio • Reproducibility.
Chapter 7 Section 7.3	In people with suspected PAD undergoing ABPI, do different methods result in different diagnostic accuracy?	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood

		ratio • Inter- and intra-operative reliability • Applicability.
Chapter 8	What is most clinical and cost-effective method of assessment of PAD (intermittent claudication and critical limb ischemia)?	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio.
Chapter 9 Section 9.2	What is the clinical and cost effectiveness of supervised exercise therapy compared to unsupervised exercise therapy for the treatment of PAD in adults with intermittent claudication?	• Amputation free survival (all) • CV events • Quality of life • Walking distance (all) • Adverse events • Exercise at follow up • Withdrawal rates from exercise programme • Change in ABPI
Chapter 9 Section 9.3	What is the clinical and cost effectiveness of naftidrofuryl oxalate compared to exercise therapy, angioplasty or stents for the treatment of PAD in adults with intermittent claudication?	• Mortality • Amputation free survival (all) • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates • Change in ABPI
Chapter 9 Section 9.4	What is the clinical and cost effectiveness of endovascular or surgical techniques compared to or in combination with exercise or usual care for the treatment of PAD in adults with intermittent claudication?	• Amputation free survival (all) • CV events • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates • Exercise at follow up • Withdrawal rates • Change in ABPI
Chapter 9 Section 9.4.7	What is the clinical and cost effectiveness of angioplasty compared to bypass surgery for the treatment of PAD in adults with intermittent claudication?	• Mortality • Amputation free survival (all) • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates

		• Change in ABPI
Chapter 9 Section 9.5	What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with intermittent claudication?	• Mortality • Amputation free survival (all) • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates • Change in ABPI
Chapter 9 Section 9.6	What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with intermittent claudication?	• Mortality • Amputation free survival (all) • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates • Change in ABPI
Chapter 9 Section 9.7	What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in adults with intermittent claudication?	• Mortality • Amputation free survival (all) • Quality of life • Walking distance (all) • Adverse events • Re-intervention rates • Change in ABPI
Chapter 10 Section 10.2	What is the clinical and cost effectiveness of angioplasty compared to bypass surgery compared to amputation for the treatment of PAD in adults with critical limb ischaemia?	• Mortality • Amputation free survival (all) • Quality of life • Adverse events • Re-intervention rates • Change in ABPI
Chapter 10 Section 10.3	What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with critical limb ischaemia?	• Mortality • Amputation free survival (all) • Quality of life • Adverse events • Re-intervention rates • Change in ABPI
Chapter10 Section 10.4	What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with critical limb ischaemia?	• Mortality • Amputation free survival (all) • Quality of life • Adverse events • Re-intervention rates • Change in ABPI
Chapter 10 Section 10.5	What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in	• Mortality • Amputation free

	adults with critical limb ischaemia?	survival (all) • Quality of life • Adverse events • Re-intervention rates • Change in ABPI
Chapter 11	What is the clinical and cost effectiveness of chemical sympathectomy, opiates, gabapentin, pregabalin or tricyclic antidepressants compared to each other in any combination for the management of pain in adults with critical limb ischemia?	• Mortality • Quality of life • Adverse events • Pain measures • Duration of pain control • Patient satisfaction
Chapter 12	What are the clinical indications for major amputation for the management of pain in people with critical limb ischemia and does major amputation improve the quality of life in people with critical limb ischemia?	• Clinical indications for major amputation • Quality of life before and after scores (both must be reported)

3.11 Clinical outcomes not considered

Patency

The final scope for this guideline identified graft and vessel patency (primary and secondary) as an outcome to be considered in the clinical and cost effectiveness evidence reviews. The use of patency as an outcome measure for PAD was discussed by the GDG at length. The GDG were aware that it has been used in many clinical trials as a surrogate endpoint for studies of treatments for PAD, particularly endovascular treatments. The GDG were of the opinion that patency was not a good surrogate outcome and should not therefore be included as an outcome.

The major concern was that there was no clear evidence to make the link between patency and clinical outcomes of relevance to people with PAD. The GDG noted that some treatments that are known to have an effect upon symptoms in people with PAD have no effect upon patency. Their clinical experience and knowledge of the literature suggests that it is common for people to develop recurrent symptoms despite a patent segment of vessel or to develop re-stenosis or re-occlusion without having recurrent symptoms. They therefore considered that the results of treatment were far better measured by outcomes of relevance to patients such as symptoms, quality of life and the need for further interventions.

Another consideration in respect to the use of patency as an outcome is the variability in definitions used in the literature, which may be based upon different modalities of measurement or differing degrees of narrowing. A threshold for degree of narrowing (e.g. 50% based upon a chosen imaging modality) leads to the anomaly that changes in narrowing of a few percent close to the threshold determine "success", but are likely to have little or no clinical significance. It was also noted that patency focused specifically on technical outcomes for disease at a specific site in an artery, whereas PAD often occurs at multiple sites. The GDG felt that outcomes that consider the impact of disease and treatment on the limb or the patient are of greater relevance.

The use of patency as a surrogate outcome also leads to difficulties in undertaking comparisons with other treatments, such as exercise or drug treatment, where an effect on patency is not to be expected.

3.1.12 Health related quality of life

Two types of instrument are available for measuring health related quality of life: disease specific and generic questionnaires. The former focuses on problems associated with individual diseases, while the latter include questions that span a number of physical and emotional dimensions common to all people. Generic measurements of quality of life can be further divided into two major classes: health profiles and utility measures.

Several disease specific and generic health profiles have been used to measure quality of life in people with IC. These include, but are not limited to: the SF-36; Nottingham Health Profile; Sickness Impact Profile; Walking Impairment Questionnaire; and VascuQol.

Utility measures are designed to reflect preferences for different treatment processes and outcomes and comprise the primary measure of effectiveness in cost-utility analyses. In cost-utility analyses, measures of health benefit are valued in terms of quality adjusted life years (QALYs). The QALY is a measure of a person's length of life weighted by a valuation of their HRQoL over that period. The utility weighting comprises two elements: the description of changes in HRQoL and an overall valuation of that description. Generic utility measures include: the EQ-5D; HUI 2; and SF-6D.

The different methods of measuring quality of life are not mutually exclusive; each may be useful for under certain circumstances and for specific purposes. Early in the guideline development process, the GDG decided that they wished to inform the economic analyses with health related quality of life obtained directly from the included clinical studies. Changes in disease specific functional disability would be captured by including walking distance as an outcome. The NICE reference case[10] specifies that the EQ-5D is the preferred method of QALY measurement. Therefore, only EQ-5D values or health state descriptions which could be mapped to EQ-5D were included as measures of health related quality of life. Disease specific questionnaires and other generic health profiles were not included as outcomes in the review.

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per the Guidelines Manual 2009.[9] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. In addition, PsychInfo database was used for the patient information review question. All searches were updated on the 9th January 2012. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)

- National Library for Health (www.library.nhs.uk/).

3.2.11 Call for evidence

The GDG decided to initiate a 'call for evidence' for randomised controlled trials comparing the effectiveness of drug eluting stents to bare metal stents for the treatment of peripheral arterial disease as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

3.2.12 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to people with peripheral arterial disease in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2010, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on the 9th January 2012. No papers published after this date were considered.

3.3 Evidence of effectiveness

The research fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C)
- Critically appraised relevant studies using the appropriate checklist as specified in the Guidelines Manual 2009[9]
- Extracted key information about the study's methods and results into evidence tables (clinical evidence tables are included in Appendix H)
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: data presented as a range of values in GRADE profiles
  - Diagnostic studies: data presented as a range of values in adapted GRADE profiles
  - Qualitative studies: each study summarised in adapted GRADE profiles.

3.3.1 Inclusion/exclusion

The inclusion/exclusion of studies was based on the review protocols (Appendix C). The GDG were consulted about any uncertainty regarding inclusion/exclusion of selected studies.

3.3.12 Methods of combining clinical studies

3.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: mortality, amputation free survival, cardiovascular events, adverse events, re-intervention rates and withdrawal rates. The continuous outcomes: quality of life, walking distance, exercise level at follow up, change in ABPI pain measures, duration of pain control and patient satisfaction were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio.

Three network meta-analyses were considered for the guideline. The three proposed networks were for the outcome of walking distance in the IC population, mortality in the CLI population and amputation free survival in the CLI population. None of the network meta-analyses were methodologically possible to conduct due to lack of evidence to build complete networks for the outcomes proposed.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out sensitivity analysis based on the quality of studies if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For continuous outcomes, the means and standard deviations were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies summarised results by only presenting means this information was included in the GRADE tables without calculating the relative and absolute effect.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

3.3.2.2 Data synthesis for diagnostic test accuracy review

Evidence for diagnostic data was evaluated by study, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklists.

For diagnostic test accuracy studies, the following data were extracted, either directly from the study report or calculated from other study data: components of the “2x2 table” (true positives, false positives, false negatives and true negatives) and test accuracy parameters: sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios (there are other outcomes that can be included such as area under curve (AUC for ROC curves) reproducibility, applicability and

inter and intra operative reliability). In cases where the outcomes were not reported, 2x2 tables were constructed from raw data to allow calculation of accuracy measures.

Forest plots of sensitivity and specificity with their 95% confidence intervals were presented side-by-side for individual studies using Cochrane Review Manager (RevMan5) software (for RevMan see Appendix J).

When data from 5 or more studies were available, a diagnostic meta-analysis was carried out. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one receiver operating characteristics (ROC) curve in Microsoft EXCEL software (for Excel plots please see Appendix J). A ROC plot shows true positive rate (i.e. sensitivity) as a function of false positive rate (i.e. 1 – specificity). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (in WinBUGS® software - for the program code see Appendix J). This model also assesses the variability by incorporating the precision by which sensitivity and specificity have been measured in each study. A confidence ellipse is shown in the graph that indicates the confidence region around the summary sensitivity / specificity point. A summary ROC curve is also presented. From the WinBUGS® output we report the summary estimate of sensitivity and specificity (plus their 95% confidence intervals) as well as between study variation measured as logit sensitivity and specificity as well as correlations between the two measures of variation. The summary diagnostic odds ratio with its 95% confidence interval is also reported.

3.3 Type of studies

For most intervention evidence reviews in this guideline, RCTs were included. Where the GDG believed RCT data would not be appropriate this is detailed in the protocols in Appendix C. RCTs were included as they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects.

For diagnostic evidence reviews, diagnostic randomised controlled trials, diagnostic cohorts and case controls studies were included in this guideline.

3.4 Types of analysis

Estimates of effect from individual studies were based available case analysis (ACA) where possible or intention to treat (ITT) analysis if this was not possible. ITT analysis is where all participants that were randomised are considered in the final analysis based on the intervention and control groups to which they were originally assigned. It was assumed that participants in the trials lost to follow-up did not experience the outcome of interest (categorical outcomes) and they would not considerably change the average scores of their assigned groups (for continuous outcomes).

It is important to note that ITT analyses tend to bias the results towards no difference. ITT analysis is a conservative approach to analyse the data, and therefore the effect may be smaller than in reality.

3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as one table in the guideline (called clinical evidence profiles). This includes the details of the quality assessment pooled outcome data, and where appropriate, an absolute measure of intervention effect and the summary of quality

of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment.

Each outcome was examined separately for the quality elements listed and defined in Table 4 and each graded using the quality levels listed in Table 5 and Table 6. The main criteria considered in the rating of these elements are discussed below (see section 3.3.6 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The GRADE toolbox is currently designed only for RCTs and observational studies but however, for the purposes of this guideline, the quality assessment elements and outcome presentation was adapted for diagnostic accuracy and qualitative studies.

Table 4: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 5: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by one level.
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels.

Table 6: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

3.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below (see Table 7). Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias were rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.3.5 to 3.3.10.

3.3.5 Study limitations

The main limitations for RCTs are listed in Table 7.

The GDG accepted that investigator blinding in surgical intervention studies was impossible and participant blinding was also difficult to achieve in most situations. Nevertheless, open-label studies for surgery were downgraded to maintain a consistent approach in quality rating across the guideline.

Table 7: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of un-validated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials.

3.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I-squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results

contributed by the inconsistency in the results. In addition to the I-square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

3.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

3.3.10 Imprecision

The minimal important difference (MID) in the outcome between the two groups were the main criteria considered.

The thresholds of important benefits or harms, or the MID for an outcome are important considerations for determining whether there is a “clinically important” difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as “the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, ether beneficial or harmful, and that would lead the patient or clinician to consider a change in the management.[11-14] An effect estimate larger than the MID is considered to be “clinically important”.

The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of “clinical importance”; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as outlined in Table 8 and illustrated in Figure 1.

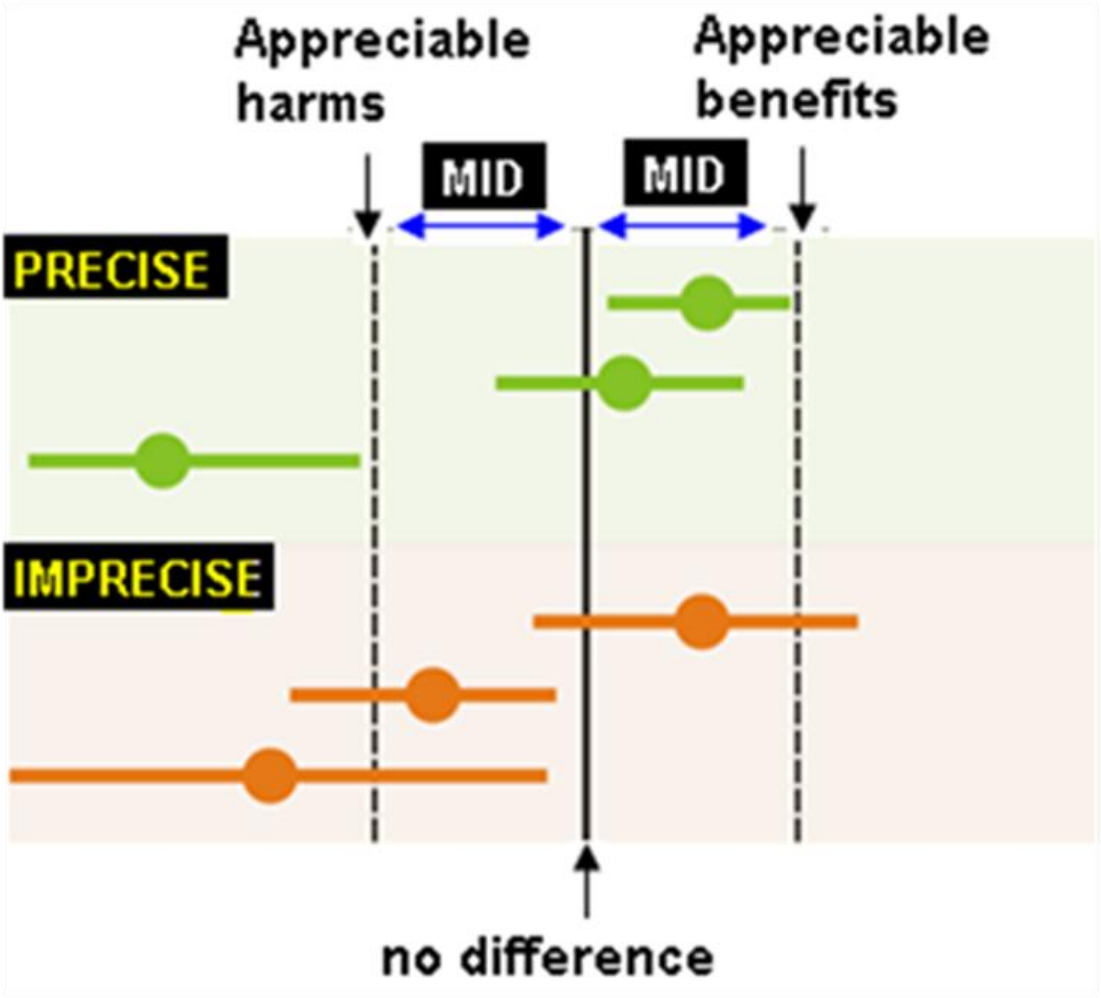
Table 9 presents the MID thresholds used for the specified outcomes for this guideline as specified by the GDG.

Table 8: Criteria applied to determine precision

Dichotomous and continuous outcomes	
The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect:	
‘no serious imprecision’	Does not cross either of the two minimal important difference (MID) thresholds (the threshold lines for appreciable benefit or harm); defined as precise.
‘serious’	Crosses one of the two MID thresholds (appreciable benefit or appreciable harm); defined as imprecise.
‘very serious’	Crosses both of the two MID thresholds (appreciable

	benefit and appreciable harm); defined as imprecise.

Figure 1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



Source: Figure adapted from GRADEPro software.

The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

Table 9: Minimal important differences (MIDs) for the outcomes used in this guideline

Outcome	MID
Mortality	1%
Amputation free survival	1%
CV events for people with IC	5%
Quality of life (EQ5D)	Change of 0.05 (mean difference, continuous outcome)
Maximum walking distance	Doubling in baseline distance (mean difference, continuous outcome)
Pain free walking distance	Doubling in baseline distance (mean difference, continuous outcome)
Major adverse events	10%

Minor adverse events	10%
Re-intervention rate	10%
Change in ABPI	Change of 0.15 (mean difference, continuous outcome)
Pain measures (as reported in papers)	0.5 standardised mean difference
Duration of pain	0.5 standardised mean difference
Patient satisfaction	0.5 standardised mean difference

3.4 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the treatment options in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them.[9] Thus, if the evidence suggests that an intervention provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- A systematic review of the economic literature
- New cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies (see below for details)
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual 2009[9]
- Extracted key information about the study's methods and results into evidence tables (included in Appendix I)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country, except for American studies, which were considered 'partially applicable').

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly

applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section and included in the list of excluded studies in Appendix F.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist.[9]

When no relevant economic analysis was identified in the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

3.4.192 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates (see Table 10). The economic evidence profile includes an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for each assessment. These assessments were made by the health economist using the economic evaluation checklist from the Guidelines Manual 2009.[9] It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio, as well as information about the assessment of uncertainty in the analysis.

Several of the pair wise clinical comparisons conducted in the IC population concerned the same decision question. Due to the nature of the question and the difficulty of considering multiple-comparator evaluations in a pair wise context, the clinical and economic evidence for these questions were presented in separate sections.

All costs converted into 2009/10 pounds sterling using the appropriate purchasing power parity.[15]

Table 10: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with

	one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (i.e. QALYs gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist from The Guidelines Manual[9]

3.42 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in priority selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified the treatment of IC using exercise and endovascular interventions as the highest priority areas for original economic modelling. Specifically, these areas include the cost effectiveness of supervised compared to unsupervised exercise, and exercise compared to angioplasty for the treatment of IC.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case[10]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible
- When published data was not available GDG expert opinion was used to populate the model
- Model inputs and assumptions were reported fully and transparently
- The results were subject to sensitivity analysis and limitations were discussed
- The model was peer-reviewed by another health economist at the NCGC.

Additional data for the analysis was identified as required through additional literature searches undertaken by the health economist and in discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Full methods for the original health economic analyses undertaken for this guideline are described in Appendices K and L.

3.43 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[9,16]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'recommendations and link to evidence' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[16]

3.4.4 In the absence of cost-effectiveness evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between comparators and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I
- Summary of clinical and economic evidence and quality (as presented in chapters 5-12)
- Forest plots, diagnostic meta-analysis and summary ROC curves (Appendix J)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix K and L).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 3.5.1).

The main considerations specific to each recommendation are outlined in the recommendations and link to evidence section following the clinical and economic evidence reviews.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- The importance to patients or the population
- National priorities
- Potential impact on the NHS and future NICE guidance
- Ethical and technical feasibility.

3.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are

responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.53 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.54 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.55 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Algorithms

To be completed post-consultation.

4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected 8 key priorities for implementation. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients
- Have a high impact on reducing variation in care and outcomes
- Lead to a more efficient use of NHS resources
- Promote patient choice
- Promote equality.

In addition to this, the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Relates to an intervention that is not part of routine care
- Requires changes in service delivery
- Requires retraining of staff of the development of new skills and competencies
- Highlights the need for practice change
- Affects an needs to be implemented across a number of agencies or settings (complex interactions)
- May be viewed as potentially contentious, or difficult to implement for other reasons.

The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

4.2.1 The recommendations identified as priorities for implementation are:

Information requirements for people with peripheral arterial disease

- Offer all people with peripheral arterial disease verbal and written information about their condition and discuss it with them so they can share decision-making, understand the course of the disease and what they can do to help prevent disease progression. Information should include:
  - the causes of their symptoms, such as level of stenosis or occlusion
  - the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and exercise
  - the risks and benefits of all relevant treatment options
  - how they can access support for dealing with depression and anxiety

  Ensure that information, tailored to the individual needs of the person, is available at diagnosis and subsequently as required, to allow people to make decisions throughout the course of their treatment.

- Offer all people with peripheral arterial disease appropriate information, advice and support in line with NICE guidance (see related NICE guidance section 2.6) on:

- smoking cessation
- diet, weight management and exercise
- lipid modification and statin therapy
- the prevention, diagnosis and management of diabetes
- the prevention, diagnosis and management of high blood pressure
- drug therapy with anti-platelet agents.

Diagnosis

- Assess people with suspected peripheral arterial disease by:
  - using structured questioning about the symptoms of intermittent claudication and critical limb ischaemia
  - examining the leg and foot for evidence of critical limb ischaemia, for example ulceration
  - examining the femoral, popliteal and foot pulses
  - measuring the ankle brachial pressure index (see recommendation below).

- Measure ankle brachial pressure index in the following manner:
  - The person should be resting and supine where possible.
  - Systolic blood pressure is recorded with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, the peroneal arteries.
  - Measurements should be taken manually using a Doppler probe of suitable frequency in preference to an automated system.
  - Document the nature of the Doppler ultrasound signals in the foot arteries.
  - The index in each leg is calculated by dividing the highest foot artery pressure by the highest arm pressure.

Imaging for revascularisation

- Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging before considering an intervention.

Management of intermittent claudication

- Offer a supervised exercise programme to all people with intermittent claudication.

Management of critical limb ischaemia

- Ensure that all people with critical limb ischaemia are reviewed by a vascular multidisciplinary team before treatment decisions are made.
- Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team.

4.3 Full list of recommendations

4.3.1 Information requirements

1. Offer all people with peripheral arterial disease verbal and written information about their condition and discuss it with them so they can share decision-making, understand the course of the disease and what they can do to help prevent disease progression. Information should include:
   - o the causes of their symptoms, such as level of stenosis or occlusion
   - o the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and exercise
   - o the risks and benefits of all relevant treatment options
   - o how they can access support for dealing with depression and anxiety.

   Ensure that information, tailored to the individual needs of the person, is available at diagnosis and subsequently as required, to allow people to make decisions throughout the course of their treatment.
2. NICE has produced guidance on the components of good patient experience in adult NHS services. Follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138).

4.3.2 Secondary prevention of cardiovascular disease in PAD

3. Offer all people with peripheral arterial disease appropriate information, advice and support in line with NICE guidance (see related NICE guidance section 2.6) on:
   - o smoking cessation
   - o diet, weight management and exercise
   - o lipid modification and statin therapy
   - o the prevention, diagnosis and management of diabetes
   - o the prevention, diagnosis and management of high blood pressure
   - o drug therapy with anti-platelet agents.

4.3.3 Diagnosis

4. Assess people with suspected peripheral arterial disease by:
   - o using structured questioning about the symptoms of intermittent claudication and critical limb ischaemia,
   - o examining the leg and foot for evidence of critical limb ischaemia, for example ulceration,
   - o examining the femoral, popliteal and foot pulses,
   - o measuring the ankle brachial pressure index (see recommendation 5).

5. Measure ankle brachial pressure index in the following manner:
   - o the person should be resting and supine where possible
   - o systolic blood pressure is recorded with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, the peroneal arteries
   - o measurements should be taken manually using a Doppler probe of suitable frequency in preference to an automated system
   - o document the nature of the Doppler ultrasound signals in the foot arteries
   - o the index in each leg is calculated by dividing the highest foot artery pressure by the highest arm pressure.

4.3.4 Imaging for revascularisation

6. Offer duplex ultrasound as first-line imaging to all people with peripheral arterial disease in whom revascularisation is being considered.

7. Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging before considering an intervention.

8. Offer computed tomography angiography in people with peripheral arterial disease where contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.

4.3.5 Management of intermittent claudication

4.3.5.1 Supervised exercise

9. Offer a supervised exercise programme to all people with intermittent claudication.

4.3.5.2 Angioplasty and stenting

10. Offer angioplasty for the treatment of intermittent claudication when:
    - advice on the benefits of modifying risk factors has been reinforced (see recommendation 3)
    - supervised exercise has not led to a satisfactory improvement in symptoms, and
    - imaging has confirmed the person as appropriate for angioplasty.

11. Do not offer primary stent placement for the treatment of intermittent claudication caused by aorto-iliac stenosis (as opposed to complete occlusion) or femoro-popliteal disease.

12. Consider primary stent placement for the treatment of intermittent claudication due to aorto-iliac occlusion (as opposed to stenosis).

13. Use bare metal stents where stenting is indicated for the treatment of intermittent claudication.

4.3.5.3 Bypass surgery and graft types

14. Offer bypass surgery for the treatment of severe lifestyle-limiting intermittent claudication only when:
    - angioplasty has been unsuccessful or is unsuitable, and
    - imaging has confirmed that the person is suitable for bypass surgery.

15. Use autologous vein whenever possible for people with intermittent claudication having infra-inguinal bypass surgery.

4.3.5.4 Naftidrofuryl oxalate

16. Consider naftidrofuryl oxalate for the treatment of intermittent claudication, starting with the least costly preparation when:
    - supervised exercise has not lead to satisfactory improvement, and
    - the patient prefers not to be referred for consideration of angioplasty or bypass surgery.

Review progress after 3-6 months and discontinue naftidrofuryl oxalate if there has been no symptomatic benefit.

4.3.16 Management of critical limb ischaemia

17. Ensure that all people with critical limb ischaemia are reviewed by a vascular multidisciplinary team before treatment decisions are made.

18. Offer angioplasty or bypass surgery (see also recommendation 22) to people with critical limb ischaemia requiring revascularisation, based on:
    - comorbidities
    - pattern of disease
    - availability of vein, and
    - patient preference.

19. Do not offer primary stent placement for the treatment of critical limb ischaemia caused by aorto-iliac stenosis (as opposed to complete occlusion) or femoro-popliteal disease.

20. Consider primary stent placement using for the treatment of critical limb ischaemia caused by aorto-iliac occlusion (as opposed to stenosis).

21. Use bare metal stents where stenting is indicated for the treatment of critical limb ischaemia.

22. Use autologous vein bypass whenever possible in people with critical limb ischaemia having infra-inguinal bypass surgery.

4.3.27 Management of critical limb ischaemic pain

23. Offer paracetamol and either weak or strong opioids to people with critical limb ischaemic pain depending on the severity of pain.

24. Offer drugs such as laxatives and anti-emetics to manage the adverse effects from strong opioids, in line with the patient's needs and preferences, and review on a regular basis.

25. Refer to a specialist pain management service when critical limb ischaemic pain is not adequately controlled.

26. Do not offer chemical sympathectomy to people with critical limb ischaemic pain, unless in the context of a clinical trial.

4.3.28 Amputation for critical limb ischaemia

27. Do not offer major amputation to people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team.

4.4 Key research recommendations

- What is the clinical and cost effectiveness of a bypass surgery first strategy as compared with an angioplasty first strategy for the treatment of people with critical limb ischaemia due to disease of the infra-geniculate (below the knee) arteries?
- What is the clinical and cost effectiveness of supervised exercise in comparison to unsupervised exercise for peripheral arterial disease, taking into account the effects on long-term outcomes and continuing levels of exercise?

- What is the effect of people's attitudes and beliefs regarding their peripheral arterial disease on the management and outcome of their condition?
- What is the clinical and cost effectiveness of selective stent placement in comparison to angioplasty with primary stent placement in the management of critical limb ischaemia due to disease in the infra-geniculate arteries?
- What is the clinical and cost effectiveness of chemical sympathectomy in comparison with other methods of pain control for the management of critical limb ischaemic pain?

5 Information requirement for people with peripheral arterial disease

5.1 Introduction

Peripheral arterial disease (PAD) is a chronic condition for which the person will require ongoing support and guidance. It is important that the person receives information relevant to their stage of disease that will enable them to make an informed decision about the treatment that is available and the lifestyle choices that may affect the outcome.

People with PAD need to recognise that lifestyle factors e.g. exercise levels, smoking and diet, will have an impact on disease progression and severity (see chapter 6 for further information and recommendations). This information is needed from the time of diagnosis but needs to be offered in a fashion appropriate to the person's background as cultural and social factors have a large influence not just on lifestyle but also on response that will be made to any proposed changes. The patient's baseline understanding must be established and their attitude to any current proposed treatment should be sensitively explored.

The resources available for changing lifestyle will include not only consultation with healthcare professionals but voluntary workshops, self help groups and if possible friends and family. The information might include both written and verbal and if appropriate and available, audio and visual material.

5.1.1 Review question

What are people's experiences of living with PAD and people's preferences for information requirements?

The GDG were interested in identifying people's experiences of living with PAD and any specific information requirements. A qualitative literature search was undertaken, there were no study design filters placed on the search.

5.1.2 Clinical evidence

Four qualitative studies[17-20] were identified which addressed the question and were included in the review. Information from the studies was further synthesised into themes (see Table 11) and has been summarised in modified clinical evidence profiles (see Table 12, Table 13, Table 14, Table 15, Table 16).

Table 11: Themes from qualitative studies on peoples' experiences of peripheral arterial disease and their information needs

Main theme	Sub-themes
Impact of disease	• Disease severity • Pain • Physical function/physical symptoms • Mental health/emotional function • Social/role function • Sense of self
Perceptions and beliefs	No sub-themes
Needs and concerns	• Physical

	• Mental health/emotional • Social • Support • Information
Expectations	No sub-themes
Strategies for adaption/improvement/scoping	No sub-themes

1

Table 12: Evidence profile: Theme 1 – Impact of peripheral arterial disease

No. of studies	Design	Sample	Themes[a]	Quality assessment[b]
Sub theme: Disease severity				
1 Treat-Jacobson, 2002[19]	1:1 interviews	N=38 PAD	• Many people expressed both positive and negative feelings • Those with more severe disease expressed more negative feelings	• High quality • Transferable to population addressed
Sub-theme: Pain				

3
Gibson, 1998; Treat-Jacobson, 2002; Wann-Hansson, 2005[17,19,20]
	1:1 interviews	N=9 post-surgery[c]
		N=38 PAD[d]
		N=24 PAD[e]
			• Pain was a common outcome for most people[c][d][e]
			• Pain was mainly pre-operative[c]
			• Pain resulted in:
			  ○ cramping, aching, burning, fatigue[d]
			  ○ sleep disturbance[c]
			  ○ loss of quality of life[c]
				• High quality
				• Transferable to population addressed

Sub-theme: Physical function / physical symptoms				
3 Gibson, 1998; Treat-Jacobson, 2002; Wann-Hansson, 2005[17,19,20]	1:1 interviews	N=9 post-surgery[c] N=38 PAD[d] N=24 PAD[e]	• Effects on physical function/physical symptoms included: • Altered sensation (e.g. coldness/deadness of limb)[c] • Non-healing wounds[e] • Carrying a hard-to-bear physical burden and struggling for relief[e] • Restricted mobility/walking impairment/walking slowly for short distances (compromising independence and physical activities at home or work, recreational "becoming an invalid"), quality of life, social and emotional function, accomplishing goals[c][d][e] • Fatigue (sleep disturbance, lack of energy)[e]	• High quality • Transferable to population addressed
Sub-theme: Mental health / emotional function				

2 Gibson, 1998; Wann-Hansson, 2005[17,20]	1:1 interviews	N=9 post-surgery[c]
		N=24 PAD[e]
			• Carrying a hard-to-bear emotional burden and struggling for relief[e]
			• Emotional change (often due to lifestyle changes or health status):
			  ○ depression[c][e]
			  ○ mood and temper influenced by pain[e]
			  ○ having to ask for help[e]
			  ○ despair[e]
				• High quality
				• Transferable to population addressed

			○ powerlessness/feeling useless (sometimes due to direct effects of condition and treatment modalities)[c][e]	
Sub-theme: Social/role function				
3 studies Gibson, 1998; Treat-Jacobson, 2002; Wann-Hansson, 2005[17,19,20]	1:1 interviews	N=9 post-surgery[c] N=38 PAD[d] N=24 PAD[e]	• Impact on/changed interaction with relationships and friends[c][e] • Carrying a hard-to-bear social burden and struggling for relief[e] • Isolation and loss of independence (restricting freedom, loneliness, missing previous activities and social activities, loss of interest)[c][d][e] • Limitation in social and role functioning: ○ inadequacy (slowing down friends or family)[d] ○ being a burden to family (other people having to bear responsibility for supporting the family)[d] ○ role and employment limitations (threat of job loss; need to change jobs; loss of opportunity for promotion)[d] ○ homemakers expressed inability to fulfil role (including parenting)[d]	• High quality • Transferable to population addressed
Sub-theme: Sense of self				
2 Gibson, 1998; Treat-Jacobson, 2002[17,19]	1:1 interviews	N=9 post-surgery[c] N=38 PAD[d]	• Compromise of self: • Compromising sense of wholeness[d] • Premature aging[d] • Feeling abnormal (sense of shame)[d] • Unfulfilled desire[d] • Loss of sense of self ("who they are"; loss of the person they used to be, having to give up activities and independence)[c][d]	• High quality • Transferable to population addressed

(a) *Clarification: not all participants reported in the study sample contributed to the themes.*
(b) *Quality assessment included study limitations, indirectness (transferability) and other considerations.*
(c) *Gibson, 1998.*[17]
(d) *Treat-Jacobson, 2002.*[19]
(e) *Wann-Hansson, 2005.*[20]

Table 13: Evidence profile: Theme 2 – Perception and beliefs

No. of studies	Design	Sample	Themes emerged[a]	Quality assessment[b]
1 Gibson, 1998[17]	1:1 interviews	N=9 Post-surgery	Causes of illness: • Role of chance in getting illness in the first place	• High quality • Transferable to population

			• Mostly external factors identified as causes of patients' health problems (1 person identified responsibility due to smoking).	addressed
1 Gibson, 1998[17]	1:1 interviews	N=9 Post-surgery	Treatment and recovery: • Role of chance in getting access to treatment and whether treatment is successful • Perceived a lack of control over course of illness; treatment not guaranteed to work • Believed their best chance of recovery lay in the hands of others and their own role mostly limited to playing by the rules (e.g. modifying lifestyle factors, partly so that medical staff haven't wasted their time) • Some stopped smoking (their side of the "bargain" with medical staff) • Some continued smoking as much as before (disbelieving that smoking caused their condition) • Some reduced smoking but did not stop altogether, accepting that smoking caused their condition but denying (to themselves or others) that they continued to smoke (e.g. smoking in secret, avoiding the subject, convincing themselves that smoking occasionally did not matter).	• High quality • Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Dissatisfaction with body structure and function (particularly women).	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	• Twice as many women as men perceived themselves to be in control in the hospital while twice as many men as women felt lonely and cut off from normal family support • Men were three times more likely to have financial worries due to reduction in income	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods

				• Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Older patients (vs. younger, ≤64 years) perceived: • Less need to follow a special diet • Demonstrated less awareness of the negative relationship between smoking and circulatory pathology	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Most did not relate perceived benefits of dietary management and regular foot care to vascular disease and were not following these practices.	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed

(a) Clarification: not all participants reported in the study sample contributed to the themes.
(b) Quality assessment included study limitations, indirectness (transferability) and other considerations.

Table 14: Evidence profile: Theme 3 – Needs and concerns

No. of studies	Design	Sample	Themes emerged[(a)]	Quality assessment[(b)]
Sub-theme: Physical				
2 Leech, 1982; Treat-Jacobson, 2002[18,19]	Questionnaire Interviews & 1:1 interviews	N=60 pre-surgery[(c)] N=38 PAD[(d)]	Physiological needs (smoking): • Most considered it important to decrease or quit smoking (fear of lung cancer rather than vascular disease)[(c)] • Only 26% had actually stopped[(c)] • Addiction (patients recognised smoking as a serious issue but some were still unable to quit even after being confronted with potential loss of limb or life)[(d)]	• High quality[(d)]; Low quality[(c)] • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods[(c)] • Transferable to population addressed
3 Gibson, 1998;	1:1 interviews	N=9 post-surgery[(e)]	Concerns were mainly physical. The greatest and most frequent personal concerns were:	• High quality • Transferable to population

Treat-Jacobson, 2002; Wann-Hansson, 2005[17,19,20]		N=38 PAD[(d)] N=24 PAD[(f)]	• Fears relating to: increased pain[(e)], loss of function[(d)], amputation[(d)(e)], death[(d)], taking pills and unwanted effects[(f)] • Treatment or operation failure[(e)] • Hospitalisation[(e)] • Need for surgery[(e)]	addressed
Sub-theme: Mental health / emotional				
1 Leech, 1982[18]	Questionnaire Interviews	N=60 pre-surgery[(c)]	Psychosocial needs: • Difficulties coping with alterations in self-concept and role function were closely related • Most people were unhappy with changes that had occurred with the progression of their disease: felt useless, frustration and depression with their situation and with their perceived inability to cope with it. • Less than half of people felt themselves to be in control during hospitalisation. • People perceived a need to have a sense of control over life / the future. • Anxiety about the effect of surgery on disease progression (more than about hospitalisation itself).	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
Sub-theme: Social				
2 Leech, 1982; Treat-Jacobson, 2002[18,19]	Questionnaire Interviews 1:1 interviews	N=60 pre-surgery[(c)] N=38 PAD[(d)]	• Social needs/concerns: ○ Loneliness and separation from families[(c)] ○ Loss of independence[(d)]	• High quality[(d)]; Low quality[(c)] • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods[(c)] • Transferable to population addressed
Sub-theme: Support				
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Need support for: • Difficulties coping with negatively perceived changes in self-concept • Alterations in role relationships • Anxiety about the effect of surgery on disease progression	• Low quality • Poor or no report of study design, data collection and most elements of validity,

			• General operative support measures	analysis and synthesis methods • Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Most people found the following useful: • Pre-operative passive support measures (wanted a friendly, positive atmosphere and emphasised the importance of considering patients as people, not just individuals with a particular disease condition). • Physical and emotional support in pre-operative period (women) • Emotional support in pre-operative period (men) • General nursing support (older people vs younger, ≤64 years)	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Investigator identified the following needs for support: • Active emotional support by nurses • Fostering sense of control • Reducing anxiety • Enhancing family support	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
Sub-theme: Information				
1 Leech, 1982[18]	Questionnaire Interviews	N=60 Pre-surgery	Investigator identified a need for information on: • Preventive health behaviours (diet, smoking, foot care, use of analgesics)	• Low quality • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis methods • Transferable to population addressed
2 Leech, 1982; Treat-Jacobson, 2002[18,19]	Questionnaire Interviews 1:1 interviews	N=60 Pre-surgery[(c)] N=38 PAD[(d)]	People identified needs for information on: • Pre-operative information (to decrease anxiety, but many did not wish to know “too much” and some desired no information at all. Older patients desired less pre-operative information than younger patients (≤64 years)[(c)]	• High quality[(d)]; Low quality[(c)] • Poor or no report of study design, data collection and most elements of validity, analysis and synthesis

			• Aortographic procedures under local anaesthetic (felt they had not been adequately prepared and experienced discomfort)[(c)] • Knowledge of side-effects of analgesics (many people taking large amounts)[(c)] • Knowledge of disease and importance of risk factor management[(d)] • Lack of control[(d)]	methods[(c)] • Transferable to population addressed
1 Treat-Jacobson, 2002[19]	1:1 Interviews	N=38 PAD	Delay in diagnosis and frustration with management of disease: • Person's delay due to not recognising symptoms (e.g. thinking it was a normal part of aging) • Clinician delay (e.g. going to several doctors before getting diagnosis)	• High quality • Transferable to population addressed

(a) Clarification: not all participants reported in the study sample contributed to the themes.
(b) Quality assessment included study limitations, indirectness (transferability) and other considerations.
(c) Leech et al, 1982.[18]
(d) Treat-Jacobson, 2002. [19]
(e) Gibson, 1998[17]
(f) Wann-Hansson, 2005.[20]

Table 15: Evidence profile: Theme 4 – Expectations of people with peripheral arterial disease

No. of studies	Design	Sample	Themes emerged[(a)]	Quality assessment[(b)]
1 Gibson, 1998[17]	1:1 Interviews	N=9 Post-surgery	Cause and management of illness: • The "acute" style of management of PAD led to unrealistic expectations, and gave rise to powerlessness.	• High quality • Transferable to population addressed
1 Gibson, 1998[17]	1:1 Interviews	N=9 Post-surgery	Participation in decisions someone else's problem: • Little evidence of participation in decisions over whether or not to have surgery (accepting medical advice; faith in medical system; expecting "clear results" and surgery to be a cure; sick role; external locus of control).	• High quality • Transferable to population addressed
1 Gibson, 1998[17]	1:1 Interviews	N=9 Post-surgery	Prior to surgery: • Expectations were unrealistic and positive (e.g. belief operation would get things "back to normal" and "that would be it").	• High quality • Transferable to population addressed
1 Gibson, 1998[17]	1:1 Interviews	N=9 Post-surgery	After surgery: • When it became apparent that surgery had not restored their function as much as they hoped, expectations were tempered by	• High quality • Transferable to population addressed

			realism expressed positively (e.g. "it's done what it's meant to do really") or negatively ("I can't see me getting any better") • Concerned and disappointed when pain persisted after they expected to have recovered (may be related to unrealistic hope in the power of medicine to alleviate symptoms and focus on surgery as a cure) • Expected pain to be considerable in the early post-operative period but then to reduce rapidly and not recur.	

(a) Clarification: not all participants reported in the study sample contributed to the themes.
(b) Quality assessment included study limitations, indirectness (transferability) and other considerations.

Table 16: Evidence profile: Theme 5 – Strategies for adaptation/improvement/coping

No. of studies	Design	Sample	Themes emerged[(a)]	Quality assessment[(b)]
2 Gibson, 1998; Wann-Hansson, 2005[17,20]	1:1 Interviews	N=9 post-surgery[(c)] N=24 PAD[(d)]	Acceptance: • Being realistic, facing up to problems, lowering expectations)[(c)] • Trying to create sense of normality[(c)] • Adjusting to changed social relationships[(c)] • Dealing with role changes[(c)] • Reorientation (adjusting activities, taking on new interests [e.g. reading] to compensate for loss of old ones, positive thinking [e.g. others worse off])[(d)] • Resignation (being realistic, facing up to problems, lowering expectations, giving responsibility to healthcare professionals)[(d)] • Struggling against loss of independence (modifying routines to maintain some control [e.g. walking where they could rest])[(c)(d)] • Struggling to not accept limitations but live as normally as possible (e.g. exercises and keeping in good shape)[(d)]	• High quality • Transferable to population addressed
2 Gibson, 1998; Treat-Jacobson, 2002[17,19]	1:1 Interviews	N=9 post-surgery[(c)] N=38 PAD[(e)]	Control: • Tried to maintain control of factors within their remit; maintaining independence (e.g. shopping)[(c)] • Adaptation to the effects of the disease and demonstration of resiliency (adjustment, flexibility)[(e)]	• High quality • Transferable to population addressed
2 Gibson, 1998;	1:1 Interviews	N=9 post-surgery[(c)]	Adaptations to physical limitations: • To deal with pain pre-operatively medication and alteration of	• High quality • Transferable to population

Wann-Hansson, 2005[17,20]		N=24 PAD[(d)]	activity (but had little effect)[(c)] • Learned by trial and error[(c)] • Allowed for day-to-day variations in ability[(c)] • Prioritising activities and carrying them out efficiently with suitable resting places[(c)] • Relieving pain and promoting circulation (pain unpredictable; analgesics used, changing position of leg; distracting activities [e.g. TV])[(d)] • Managing non-healing wounds (looking after wounds, trying different bandages, letting professionals take care of wounds)[(d)]	addressed

(a) Clarification: not all participants reported in the study sample contributed to the themes.
(b) Quality assessment included study limitations, indirectness (transferability) and other considerations.
(c) Gibson, 1998[17]
(d) Wann-Hansson et al, 2005[20]
(e) Treat-Jacobson, 2002[19]

5.12 Economic evidence

No cost effectiveness evidence was identified for this question.

5.13 Evidence statements

5.13.1 Clinical

Four qualitative studies of high to low quality[17-20] with a total of 131 participants, showed the following findings about the experiences and information requirements of people with PAD:

- Pain, restricted mobility/walking impairment, depression, anxiety and sleep disturbance were problems for many people with PAD.
- PAD had a major impact on people's sense of self (who they were) and limitations on their social and role functions (feelings of isolation, loss of independence, burden to friends and family, missing out on previous activities and social activities, limitations on work).
- People with PAD did not feel in control of their illness, many did not believe that modifying lifestyle (including diet and smoking) would help their condition, and often felt that treatment may not work.
- Their concerns were mainly 'physical' and many had fears of: increased pain, loss of function, amputation, failure of operations or other treatment.
- Psychosocial concerns and needs included: loss of independence, loneliness and separation from families, feeling out of control and difficulties coping.
- Most people with PAD and investigators felt support was needed for: coping with negative changes (e.g. control, self, role relationships, family support, anxiety about surgery), and found that pre-operative support measures, physical and emotional support and general nursing support was useful.
- People with PAD had unrealistic expectations of the management of PAD and the results of surgery (particularly on pain and function - which led to feelings of powerlessness), and expected that it would be a cure.
- People often experienced a delay in diagnosis (due to not recognising symptoms and perceived clinician delays), and expressed a need for information on a number of areas including: disease and risk factor management, preventative health behaviours, aortographic procedures, lack of control, pre-operative information to reduce anxiety, and the adverse events of analgesics.
- Strategies people adopted for coping with / adapting to living with PAD included:
  - acceptance
  - re-orientation (e.g. finding new activities they could do and modifying routines and activities to maintain some feeling of control and independence).

5.13.2 Economic

No cost effectiveness evidence was identified for this question.

5.14 Recommendations and link to evidence

Recommendations	**1. Offer all people with peripheral arterial disease verbal and written information about their condition and discuss it with them so they can share decision-making, understand the course of the disease and what they can do to help prevent disease progression. Information should include:**

	• **the causes of their symptoms, such as level of stenosis or occlusion** • **the key modifiable risk factors, such as smoking, managing diabetes, diet, weight and exercise** • **the risks and benefits of all relevant treatment options** • **how they can access support for dealing with depression and anxiety** **Ensure that information, tailored to the individual needs of the person, is available at diagnosis and subsequently as required, to allow people to make decisions throughout the course of their treatment.** **2. NICE has produced guidance on the components of good patient experience in adult NHS services. Follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138).**
Relative values of different outcomes	The aim of the evidence review was to identify: • Experiences of living with PAD • Information people with PAD wanted or found useful • If there are specific information requirements for people with PAD • If information received changed the perception of the disease. A number of important themes emerged from the qualitative evidence review on patient information needs and requirements. In particular, the review highlighted that people with PAD require: • Psychosocial support as well as medical treatment. Such support would address issues with coping, depression and anxiety as well as perceptions and beliefs around the disease management. • Encouraging autonomy and shared decision making. • Managing expectations through ensuring that patients have realistic expectations and understanding of PAD.
Trade off between clinical benefits and harms	Information needs and requirements will change during the course of the disease and must be tailored to this. Healthcare professionals must be aware of the impact of information on patients. This may have a negative impact or may be mis-understood. However, if delivered adequately it should aid in understanding the disease, encourage self-management and involvement in the decision-making.
Economic considerations	The GDG discussed patient information in the context of routine healthcare practice. It was expected that any impact on time and resource use would be minimal and would likely be offset by an improvement in quality of life.
Quality of evidence	The evidence reviewed was either high or low quality by GRADE criteria. A number of the studies were 1:1 interviews, which is considered high quality within qualitative research. The studies reported tended to be small in sample size. In addition, the samples consisted of people at different stages in the treatment pathway and degree of disease severity, which may affect their responses to questionnaires. Therefore, there has to be some caution in

	attributing themes reported to all patients with PAD.
Other considerations	The GDG developed the recommendations based on the clinical evidence presented. The GDG agreed that the NICE Patient Experience (publication to be confirmed) guideline contains general recommendations around communication, treating the patient as an individual that healthcare professionals should follow. Information should be available in a variety of formats (including written and verbal information) and translations should be available where appropriate. In addition to the Patient Experience guideline recommendations, the GDG identified recommendations specific to people with PAD. **Information requirements** From the clinical evidence review, the GDG discussed several aspects of information required by people with PAD and this information informed the recommendations. In particular, • Addressing the disease stage and severity – is it intermittent claudication or critical limb ischaemia? What is the prognosis? • Lifestyle and preventative behaviours - the clinical evidence review did highlight that there is evidence that perception and beliefs need to be challenged. For example, some people did not believe that modifying behaviours such as smoking, diet and exercise would impact on the disease. This behaviour should be explored and patient educated in the importance of these factors and the benefits of lifestyle change • Cardiovascular risk factors - the GDG patient members highlighted that patients are unlikely to ask or be aware of CV risk factors associated with PAD. Therefore, it is important that the healthcare professionals inform and reinforce this information • Understanding of the disease process • Restricted mobility and walking impairment. **Psychosocial aspects of PAD** There was some discussion about around the psychosocial aspects of PAD particularly in relation to experiences of pain, loss of control, and depression and anxiety. This may be related to the belief systems some people hold and by changing attitudes towards PAD may alleviate stress and negative emotions. The GDG patient members also highlighted that some patients may not be aware that they may experience negative emotions. Some of the GDG had the view that depression may not be routinely sought in people with PAD and that this should be considered. NICE have produced a guideline on "Depression in adults with a chronic physical condition", which healthcare professionals can consult as an additional resource when dealing with depression in people with PAD.[21] It was noted that primary care healthcare professionals do undertake some screening of mood and anxiety of people with chronic conditions. **Other discussions** It is important to give simple summary information to patients and then assess the impact of the information on the individual. For example, is it having an effect on behaviours and coping styles. From this the healthcare professional can challenge any negative beliefs. There was a discussion around setting individualised care plans. This did not emerge as a theme from the clinical review and was not a specific review question. The GDG emphasised that all people with PAD should be fully involved in all decision making. The NICE guideline on "Patient Experience in

	adult NHS services (CG138) contains further recommendations relating to this, therefore the GDG did not make a specific recommendation. The GDG felt that it was not appropriate to prepare a standardised patient leaflet but to give some clear recommendations about what should be included in patient discussions. Concern was expressed that people are not always given enough consultation time to discuss the diagnosis and treatment fully. This has been covered within the Patient Experience guideline but was re-emphasised by the GDG. **Key priority for implementation** The GDG identified recommendation 1 about the information requirements for people with PAD as a key priority for implementation. The reason for selecting this recommendation for prioritisation was that there is variability in the information given. In particular, patients may not be given sufficient information on the benefits of secondary prevention of cardiovascular risk factors. By highlighting this as a key priority, variation in care and outcomes will be reduced. This recommendation also promotes patient choice.

5.115 Research recommendation

1. What is the effect of people's attitudes and beliefs regarding their peripheral arterial disease on the management and outcome of their condition?

Why this is important

The evidence reviewed suggested that, amongst people with PAD there is a lack of understanding of the causes of PAD, lack of belief that lifestyle interventions have a positive impact on disease outcomes and unrealistic expectations of the outcome of surgical interventions. Much of the research has been conducted on the subpopulation of people with PAD who have been referred for surgical intervention, but little evidence is available on the majority of people diagnosed with PAD in a primary care setting. Research is required to further investigate attitudes and beliefs in relation to PAD, interventions that might influence these and how these may have an impact on behavioural changes in relation to risk factors for PAD, attitudes to intervention and clinical outcomes.

6 Secondary prevention of cardiovascular risk factors in the treatment of peripheral arterial disease

6.1 Introduction

Peripheral arterial disease (PAD) is strongly associated with cardiovascular disease. The modifiable and non modifiable risk factors for PAD are shared with those for cardiovascular disease. Many individuals with PAD will have evidence of cardiovascular disease, and people diagnosed with PAD are at high risk of further cardiovascular events such as stroke and myocardial infarction. The severity of PAD is a prognostic indicator of cardiovascular risk, those with the most severe symptoms faring worse. In people with CLI, the cardiovascular mortality rate is even higher, with a one in five mortality rate within one year of diagnosis. Although less marked even the asymptomatic group have an increased cardiovascular risk. This observation has led to the main focus of treatment shifting to address cardiovascular risk in people with PAD by attempting to modify their risk factors. There is some qualitative evidence that people with PAD do not associate their symptoms with negative behaviours such as smoking or poor diet[18,19] and often have the perception that disease management is outwith their control.[17] Chapter 5 provides further information on patients beliefs, expectations and coping with PAD. Whilst clinicians recognise and have well established protocols for the management of risk factors in cardiovascular disease these are less well recognised and acted on in PAD.[22]

There is a paucity of evidence to address risk factor modification specifically in PAD and available evidence is usually related to subgroup analysis.[23-25] Nevertheless, the strong association of PAD and cardiovascular disease and common shared risk factors justifies extrapolation to PAD using information from other conditions associated with atherosclerosis.

6.1.1 Reducing cardiovascular risk

6.1.1.1 Smoking

Smoking is the most important risk factor for the development of PAD and even passive smoking increases cardiovascular risk. Excess cardiovascular risk is halved within one year of cessation and is the same as non-smokers within 5 years in those patients that successfully give up smoking. There is no strong evidence for the benefits of smoking cessation to the limb but some observational studies have suggested an improvement in walking distance and a reduction in amputation rates. Smoking cessation advice when combined with nicotine replacement therapy improves quit rates to around 30%.

6.1.1.2 Diabetes

Diabetes is an important risk factor for PAD and the incidence and prevalence of PAD increases with duration of both Type 1 and Type 2 diabetes.[26] The effects of diabetes are compounded by later presentation with more extensive disease[27] neuropathy and risk of infection. The risk of amputation is significantly greater in a diabetic population and over 50% of all amputations occur in people with diabetes. No trials have been set up to examined the role of improved glycaemic control in relation to PAD. There is evidence that improved glycaemic control influences cardiovascular disease progression.[28]

6.1.113 Cholesterol management

There is overwhelming evidence for the benefits of lowering cholesterol in patients with PAD. In the Heart Protection Study (2002),[23] people with PAD with a total cholesterol over 3.5 mmol/l who took simvastatin (a HMG-CoA reductase inhibitor) had a 17.6% reduction in cardiovascular events compared to those on placebo. There was also a reduction in the subsequent need for both cardiac and non-cardiac revascularisation procedures. Based on these results, nearly all people with PAD should be prescribed statin therapy. There is also emerging evidence that statins have a direct effect on atherosclerotic plaque, stabilising it and possibly causing plaque regression in high doses.

6.1.194 Hypertension

Up to 24% of the adult population are hypertensive and hypertension is associated with a 3 fold increase risk of PAD, as well as being a strongly associated with stroke and myocardial infarction. Treatment of hypertension will reduce stroke rates by 38% and cardiovascular deaths by 14%. In the Heart Outcomes Study[29], the angiotensin converting enzyme inhibitor, ramipril, demonstrated an advantage in reducing cardiovascular events, even in those patients whose blood pressure was not elevated. However, there are potential problems with widespread use of ramapril in people with PAD as many will have renal artery disease. At present in those with PAD and hypertension ramipril should be considered as the first line treatment but there is not enough evidence to suggest widespread use in the non-hypertensive patients.

6.1.195 Anti-platelet agents

The Antithrombotic Trialists' Collaboration[27] meta-analysis found that antiplatelet agents (predominantly aspirin, a cyclo-oxygenase inhibitor) reduced the risk of cardiovascular events by 23% in people with PAD. 75mg was as effective as higher doses. Approximately 20% of patients are unable to take aspirin largely due to gastrointestinal disturbance and it is emerging that a similar proportion of patients have aspirin resistance. In these patients usual doses of aspirin do not have the normal effect on patients. In these patients clopidogrel should be used. Clopidogrel is a theopyridine derivative that blocks ADP induced platelet activity. In the Caprie study, clopidogrel (was shown to further reduce cardiovascular events compared to aspirin (particularly in the PAD group) with a relative risk reduction of 8.7%. The NICE TA 210[30] recommends clopidogrel as first line option. Combination therapy of aspirin and clopidogrel should be considered very carefully. In the Charisma study patients on both drugs had a significantly greater risk of bleeding complications which overall exceeded any apparent benefit.

6.1.126 Weight management and exercise

A number of other life style changes should be advocated. Weight reduction and regular exercise have proven cardiovascular benefit. The role of exercise for intermittent claudication is discussed in chapter 9. They also have a positive effect on other risk factors. Omega 3 fatty acids (fish oils) appear to have some beneficial effects but their clinical role in PAD has not been established. Likewise antioxidants and other dietary additives have not been demonstrated to be of benefit.

6.182 Existing NICE guidance and recommendations

The GDG recognised that there are existing NICE recommendations covering many of the aspects for the secondary prevention of cardiovascular disease, which were relevant for people with PAD. Therefore, the GDG agreed that no further evidence review was required and that recommendations for PAD should follow existing NICE guidance.

6.2 Recommendation

Recommendation	**3. Offer all people with peripheral arterial disease appropriate information, advice and support in line with NICE guidance (see related NICE guidance section 2.6) on:** • **smoking cessation** • **diet, weight management and exercise** • **lipid modification and statin therapy** • **the prevention, diagnosis and management of diabetes** • **the prevention, diagnosis and management of high blood pressure** • **drug therapy with antiplatelet agents.**

6.2.1 Key priority for implementation

The GDG identified this recommendation as a key priority for implementation. The GDG were of the opinion that guidance relating to cardiovascular disease and secondary prevention is given in an inconsistent way to people with PAD. The appropriate and consistent application of information on secondary prevention of cardiovascular disease is likely to have high impact on patient outcomes and reducing variation in care and outcome.

7 Diagnosis of peripheral arterial disease

7.1 Introduction

People with suspected PAD most commonly present with pain in the leg muscle brought on by exertion. They may also present with other leg and foot symptoms such as rest pain, foot ulcers or tissue loss. PAD can be found in asymptomatic patients attending, for example, a general examination or diabetic foot screening. They will most likely present to GP's, nurses or allied health professionals in primary care.

The diagnosis of PAD is based on a good clinical history and a clinical examination including the palpation of femoral, popliteal and pedal pulses, and when this is done by an experienced clinician additional diagnostic tests may well be unnecessary. A readily available test which is often performed is the ankle brachial pressure index (ABPI), which is simply the measurement of resting systolic ankle blood pressure divided by the systolic brachial pressure. An ABPI ratio of <0.9 is an indicator of PAD. However, a normal resting ABPI (>0.9) does not exclude its presence. The measurement of ABPI is user dependant and has its limitations when used in patient with swollen limbs or where arterial wall calcification is present, such as in some of the diabetic population. The GDG therefore wished to assess the utility of measurement of ABPI in the diagnostic work-up of suspected PAD.

Other forms of imaging are sometimes utilised to diagnose PAD and are able to delineate the site and severity of arterial lesions producing the signs and symptoms of PAD, but they are usually not necessary for diagnosis per se. This guideline did not consider imaging for diagnosis but did review the evidence for its role in assessment for revascularisation (see chapter 8).

7.2 Methods of diagnosis of peripheral arterial disease

7.2.1 Review question

In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining the diagnosis and severity of PAD?

A literature search was conducted for diagnostic studies that compared the diagnostic accuracy of clinical assessment, ABPI or ABPI with clinical assessment, to the reference standard of imaging in people with suspected PAD.

Suspected PAD was described as symptoms of intermittent claudication (IC), leg ulcers, common foot problems or having cardiovascular risk factors; indirect populations (such as a general population without suspected PAD) and emergency settings were excluded.

7.2.2 Clinical evidence

Five studies[31-35] were identified which addressed the question and were included in the review. Specifically:

- Two studies compared automated manual ABPI using Doppler to angiography[31,32]
- Two studies compared manual ABPI using Doppler to duplex ultrasound[33,34]
- One study compared manual ABPI without Doppler to angiography[31]
- One study compared automated oscillometric method of ABPI to angiography[35]
- Two studies[32,33] considered patients with diabetes. No diagnostic studies were identified comparing ABPI and clinical assessment or clinical assessment alone to imaging. None of studies

reported on subgroups for people with diabetes, asymptomatic PAD or people with renal failure/advanced renal disease for the outcomes.

The studies are summarised in the clinical evidence profiles below (Table 17, Table 18 and Table 19). See also the full study evidence tables in Appendix H. Diagnostic forest plots are presented in Appendix J.

1 **Table 17: Clinical evidence profile: Manual ankle brachial pressure index using Doppler compared to imaging**

Quality Assessment								Summary of Findings				
No of studies	Design	No of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity	Specificity	PPV	NPV	Quality
Reference standard – Angiography; ABPI cut-off <1.0												
1 Baxter, 1993[31]	Cross sectional study	20	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	92%	80%	NR	NR	MODERATE
Reference standard – Angiography; ABPI cut-off <0.5; people with diabetes												
1 Janssen, 2005[32]	Cross sectional study	106	No serious risk of bias	No serious inconsistency	no serious indirectness	serious[(a)]	None	36%	86%	67%	64%	MODERATE
Reference standard – Angiography; ABPI cut-off <0.7; patients with diabetes												
1 Janssen, 2005[32]	Cross sectional study	106	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	59%	67%	58%	68%	MODERATE
Reference standard – Angiography; ABPI cut-off <0.9; patients with diabetes												
1 Janssen, 2005[32]	Cross sectional study	106	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	71%	42%	48%	65%	MODERATE
Reference standard – duplex ultrasound; ABPI cut-off <0.9 patients with diabetes												
1 Premalatha, 2002[33]	Cross sectional study	100	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	70.6%	88.5%	94.1%	53.4%	MODERATE

Quality Assessment								Summary of Findings				Quality
Reference standard – duplex ultrasound; lower ankle pressure ABPI cut-off <0.9												
1 Schroder, 2006[34]	Cross sectional study	216	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	89%	93%	93%	88%	MODERATE
Reference standard – duplex ultrasound; higher ankle pressure ABPI cut-off ≥0.9												
1 Schroder, 2006[34]	Cross sectional study	216	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	68%	99%	99%	74%	MODERATE

(a) No confidence intervals reported.
Abbreviations: PPV=Positive predictive value; NPV=Negative predictive value; NR=Not reported.

Table 18: Clinical evidence profile: Manual ABPI without Doppler compared to angiography

Quality Assessment								Summary of findings				Quality
No of studies	**Design**	**No of patients**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	
Reference standard – Angiography; ABPI cut off <1.0												
1 Baxter, 1993[31]	Cross sectional study	20	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	100%	40%	NR	NR	MODERATE

(a) No confidence intervals reported.
Abbreviations: PPV=Positive predictive value; NPV=Negative predictive value; NR=Not reported.

Table 19: Clinical evidence profile: Automated oscillometric ABPI compared to angiography

Quality Assessment								Summary of findings				Quality
No of studies	Design	No of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity	Specificity	PPV	NPV	
Reference standard – Angiography												
ABPI cut-off 0.53												
1 Guo, 2008[35]	Cross sectional study	298	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	14.3%	100%	NR	NR	MODERATE
ABPI cut-off 0.9												
1 Guo, 2008[35]	Cross sectional study	298	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	76%	90%	NR	NR	MODERATE
ABPI cut-off 0.95												
1 Guo, 2008[35]	Cross sectional study	298	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	91%	86%	NR	NR	MODERATE
ABPI cut-off 1.12												
1 Guo, 2008[35]	Cross sectional study	298	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	100%	40%	NR	NR	MODERATE

(a) No confidence intervals reported.
Abbreviations: PPV=Positive predictive value; NPV=Negative predictive value; NR=Not reported.

7.2.112 Economic evidence

No cost effectiveness evidence was identified in the literature search. In the absence of published economic evaluations, the GDG were asked to estimate the additional resource use associated with obtaining a measure of ABPI compared to performing clinical assessment alone.

The GDG agreed that ABPI is typically performed by a practice nurse or podiatrist while taking a clinical history. It may add between 5 and 15 minutes to the time required for the clinical examination. In some instances patients may be referred to a different healthcare provider if they do not have access to equipment or expertise. Clinicians may attend supervised training placements which may be considered part of the overhead cost associated with ABPI. Similarly, the purchase of a manual or automated device for measuring ABPI incurs a onetime cost to each healthcare centre. With correct care, these devices have a lifespan of many years.

7.222 Evidence statements

7.2.231 Clinical

Manual ABPI using Doppler compared to angiography

- Manual ABPI using Doppler with a cut-off < 1.0 had a sensitivity of 92% and specificity of 80% compared to the reference standard of angiography [1 study, 20 participants, moderate quality evidence][31]
- Manual ABPI using Doppler with a cut-off <0.5 had a sensitivity of 36%; specificity of 86%; positive predictive value of 67% and negative predictive value of 64% compared to the reference standard of angiography [1 study, 106 participants, moderate quality evidence][32]
- Manual ABPI using Doppler with a cut-off <0.7 had a sensitivity of 59%; specificity of 67%; positive predictive value of 58% and negative predictive value of 68% compared to the reference standard of angiography [1 study, 106 participants, moderate quality evidence][32]
- Manual ABPI using Doppler with a cut-off <0.9 had a sensitivity of 71%; specificity of 42%; positive predictive value of 48% and negative predictive value of 65% compared to the reference standard of angiography [1 study, 106 participants, moderate quality evidence][32]

Manual ABPI using Doppler compared to duplex ultrasound

- Manual ABPI using Doppler with a cut-off <0.9 had a sensitivity of 70.6%; specificity of 88.5%; positive predictive value of 94.1% and negative predictive value of 53.4% compared to the reference standard of duplex ultrasound [1 study, 100 participants, moderate quality evidence][33]
- Manual ABPI using Doppler with the lower ankle measurement cut-off <0.9 had a sensitivity of 89%; specificity of 93%; positive predictive value of 93% and negative predictive value of 88% compared to the reference standard of duplex ultrasound [1 study, 216 participants, moderate quality evidence][34]
- Manual ABPI using Doppler with the higher ankle measurement cut-off ≥0.9 had a sensitivity of 68%; specificity of 99%; positive predictive value of 99% and negative predictive value of 74% compared to the reference standard of duplex ultrasound [1 study, 216 participants, moderate quality evidence][34]

Manual ABPI without Doppler compared to angiography

- Manual ABPI without Doppler with cut off <1.0 had a sensitivity of 100% and specificity of 40% compared to the reference standard of angiography [1 study, 20 participants, moderate quality evidence][31]

Automated oscillometric ABPI without Doppler compared to angiography

- Automated oscillometric method of ABPI with cut-off 0.53 had a sensitivity of 14.3% and specificity of 100% compared to the reference standard of angiography [1 study, 298 participants, moderate quality evidence][35]
- Automated oscillometric method of ABPI with cut-off 0.9 had a sensitivity of 76% and specificity of 90% compared to the reference standard of angiography [1 study, 298 participants, moderate quality evidence][35]
- Automated oscillometric method of ABPI with cut-off 0.95 had a sensitivity of 91% and specificity of 86% compared to the reference standard of angiography [1 study, 298 participants, moderate quality evidence][35]
- Automated oscillometric method of ABPI with cut-off 1.12 had a sensitivity of 100% and specificity of 40% compared to the reference standard of angiography [1 study, 298 participants, moderate quality evidence][35]

7.2.2.2 Economic

No cost effectiveness evidence was identified for this question.

7.2.3 Recommendations and link to evidence

Recommendations	**4. Assess people with suspected peripheral arterial disease by:** • **using structured questioning about the symptoms of intermittent claudication and critical limb ischaemia** • **examining the leg and foot for evidence of critical limb ischaemia, for example ulceration** • **examining the femoral, popliteal and foot pulses** • **measuring the ankle brachial pressure index (see recommendation 5).**
Relative values of different outcomes	No evidence was found comparing clinical assessment to ABPI. There was evidence relating to the accuracy of ABPI in comparison to imaging for the diagnosis of PAD. The GDG considered that the most important outcomes were sensitivity and negative predictive values since their main concern was to avoid missing any people with peripheral arterial disease. An ABPI of 0.9 therefore appears to be the best indicator for PAD. The values seen varied between the available studies, and also inevitably varied when different cut-off values of ABPI were used. The GDG concluded that the studies offered some support for the use of ABPI, since it shows acceptable predictive values when compared to the results of the less readily available "gold standard" imaging techniques. Unfortunately none of the trials addressed the key question posed by the GDG, of the added value of ABPI to a careful clinical examination.
Trade off between clinical benefits and harms	ABPI is a non-invasive test and there are no recognised dangers of correct use of equipment. It is important that healthcare professionals are appropriately trained as failure to correctly measure ABPI may result in a mis-diagnosis, thereby delaying referral or treatment.
Economic considerations	The GDG considered the additional resources required for obtaining an ABPI compared to clinical examination alone. Based on expert opinion, the GDG thought that the incremental resource requirements associated with

	measuring ABPI were small compared to the benefit of accurately identifying people with suspected PAD. Accurate diagnosis would be expected to improve quality of life and save costs by ensuring that patients are managed appropriately.
Quality of evidence	The evidence relating to the diagnostic accuracy of ABPI was deemed to be of moderate quality by GRADE criteria, based on the QUADAS checklist. A diagnostic meta-analysis was not undertaken as 4 or more studies are required, as described in the methodology chapter of the guideline. No studies were found comparing clinical assessment alone, or clinical assessment with ABPI, to imaging as a reference standard. The GDG noted the variation in the studies in baseline patient characteristics and healthcare settings, where the diagnostic tests were performed. However, the GDG did not feel these differences biased the results of the studies.
Other considerations	• The GDG made a recommendation based on consensus. It is currently common practice for patients to be misdiagnosed, referred for treatment when they do not have PAD or referral being delayed due to incorrect diagnosis. It was the opinion of GDG that making a diagnosis of PAD requires three forms of assessment. • Structured questioning about the symptoms of PAD is required. This not only aids in the diagnosis but can also be used to indicate whether referral to a specialist service is required i.e. referral for revascularisation if symptoms are severe and lifestyle limiting. There are a number of valid PAD questionnaires available, which can be used. The GDG did not make a recommendation on a specific questionnaire, as an assessment of these was not specified in the scope of the guideline and was not part of the evidence review. • Careful examination of the peripheral pulses is an important and basic principle in diagnosing PAD. The examination should also include an assessment of the signs which might be associated with critical limb ischaemia, such as temperature of the limb, hair loss, or ulceration. • Measuring the ABPI In the opinion of the GDG, neither clinical history, examination nor ABPI alone is sufficient to diagnose PAD. All three methods in combination would be useful. However, even in combination they are not universally accurate, and clinicians should use their judgement and refer if necessary. The GDG were also aware that peripheral arterial disease might be detected without being the primary cause for presentation, and when symptoms are absent or minimal. For example, absent pulses might be detected during an assessment for some other form of leg surgery, or an abnormal ABPI might be round when assessing for compression hosiery. The recommendations which follow in this guideline would equally apply in such cases. **Key priority for implementation** The GDG identified this recommendation as a key priority for implementation as the diagnosis of PAD is currently subject to considerable variability, in particular to the extent in which clinicians measure pulses and ABPI. As such, this recommendation would have the potential to improve the accurate diagnosis of PAD, timely referral and thereby, improving patient outcomes.

7.3 Measuring the ankle brachial pressure index

7.3.1 Review question

In people with suspected PAD undergoing ABPI, do different methods result in different diagnostic accuracy?

A literature search was conducted for diagnostic studies that compared the effectiveness of different techniques for taking an ABPI in people with suspected PAD. The comparisons of types of ABPI considered were:

- Duration of the rest period prior to measurements
- Sitting versus lying down during measurement or seated Doppler ABPI measurement compared to supine Doppler ABPI measurement
- Location of the cuff
- Higher compared to lower vessel measurement
- Automated compared to manual device.

No time limit was placed on the literature search, and there were no limitations on sample size. Suspected PAD was described as symptoms of IC, leg ulcers, common foot problems or having cardiovascular risk factors, indirect populations and emergency settings were excluded.

7.3.1 Clinical evidence

One study was identified which compared seated Doppler ABPI measurement to supine Doppler ABPI measurement.[36] Seated Doppler measurement of ABPI was described as ABPI measured in the seated position after the supine measurements had been taken and additional 5 minute rest period applied. Supine Doppler measurement of ABPI was described as ABPI measured after 10 minutes of rest in the supine position.

No studies were found on the duration of the rest period prior to measurements or the location of the cuff. None of the studies reported on subgroups for people with asymptomatic PAD, diabetes or people with renal failure/advanced renal disease for the outcomes.

The study is summarised in the clinical GRADE evidence profile below (Table 20). See also the full clinical evidence tables in Appendix H. Diagnostic forests plots are presented in Appendix J.

Table 20: Clinical evidence profile: Seated Doppler ABPI compared to supine Doppler ABPI

Quality Assessment								Summary of findings	
No. of studies	**Design**	**No. of patients**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Correlation co-efficient**	**Quality**
1 Gornik, 2008[36]	Cross sectional study	106	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	0.936 ($p < 0.001$)	MODERATE

(a) No confidence intervals reported.

7.3.11 Economic evidence

No cost effectiveness evidence was identified for this question.

The GDG discussed the costs associated with manual and automatic ABPI devices. The acquisition cost of automatic devices is typically two to three times greater than manual devices. The group acknowledged that the manufacturers of these devices often claim that they are time saving and, by extension, that they are cost saving. However, several GDG members had conducted informal evaluations within their centres and found manual devices to be both more reliable and faster than automatic devices; it was their clinical experience that automatic devices often fail to produce a valid reading and cannot be used on a large proportion of people with suspected PAD.

7.3.12 Evidence statements

7.3.21 Clinical

Seated compared to supine Doppler ABPI

The correlation co-efficient between seated and supine Doppler ABPI was 0.936 ($p < 0.001$) [1 study, 106 participants, moderate quality evidence][36]

7.3.25 Economic

No cost effectiveness evidence was identified.

7.3.3 Recommendations and link to evidence

Recommendation	**5. Measure ankle brachial pressure index in the following manner:** • **The person should be resting and supine where possible.** • **Systolic blood pressure is recorded with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, the peroneal arteries .** • **Measurements should be taken manually using a Doppler probe of suitable frequency in preference to an automated system.** • **Document the nature of the Doppler ultrasound signals in the foot arteries .** • **The index in each leg is calculated by dividing the highest foot artery pressure by the highest arm pressure.**
Relative values of different outcomes	This evidence review was conducted to identify the best technique for ABPI measurement. One paper was found comparing seated and supine measurements of ABPI, but this only reported the correlation co-efficient. Although a high correlation was observed, this does not give an indication as to whether seated or supine measurement elicits a more accurate ABPI. No outcome data was available for the duration of the rest period prior to assessment, the optimal cuff location, higher compared to lower vessel measurements.
Trade off between clinical benefits and harms	No evidence was available on benefits versus harms for different methods for ABPI, but this is unsurprising since the measurement is non-invasive and unlikely to cause any harm if carried out correctly. The main concern is that the

	ABPI is accurately measured to avoid a misdiagnosis.
Economic considerations	The GDG discussed the resource use associated with manual and automatic devices for measuring ABPI. Based on clinical experience, the GDG considered hand held Doppler devices to be less expensive and more reliable than automatic devices.
Quality of evidence	The evidence reviewed for this question was rated as moderate quality by GRADE criteria. The recommendations were based on GDG consensus and clinical experience as no definitive evidence was found. The GDG also extrapolated the clinical evidence on automated compared to manual ABPI presented in section 7.2 to inform their recommendation on taking ABPI measurements manually.
Other considerations	The aim of the evidence review was to identify the techniques to measure ABPI. Due to the lack of evidence, the GDG made consensus recommendations on the standard method to measure ABPI. The following areas were discussed and rationale for their inclusion into the recommendation given. **Seated compared to supine measurement** One study compared seated and supine ABPI measurements.[36] However, the study only reported the correlation co-efficient. The GDG agreed that the person should be supine where possible when measuring ABPI. Lying supine equalises the blood pressure in the brachial and lower limb systems. Where it is not possible and the person is seated, the height difference between the arm and ankle should be noted and the reading adjusted appropriately. This adjustment is not being done in routine practice and is a reason for variation in results. Taking a seated ABPI measurement in practice is sometimes necessary, for example, in someone in a wheelchair with significant pain or mobility problems. **Cuff size** The cuff should be placed on the calf. The cuff size is important in the measurement of ABPI, as an incorrect or ill-fitting cuff will lead to an incorrect ABPI measurement. No specific cuff size was recommended; the cuff needs to fit comfortably around the patient's limb. A range of cuff sizes should be available when measuring ABPI. **Rest period prior to ABPI measurement** No evidence was found to recommend a minimum rest period before taking ABPI. The GDG agreed that the rest period should be long enough for blood pressure to return to normal, but be practical for the running of clinics. **Measuring blood pressure** It is considered standard practice that blood pressure be measured in the arms and legs using a Doppler probe. The GDG agreed that it was appropriate to recommend this. Doppler probes may be of different frequencies as they are used for different purposes. To adequately measure the peripheral vessels the recommended range is between 7-10 MHz but that 8MHz is average. A range of Doppler probes should be available when taking an ABPI. **Arteries to be measured** Although no evidence was reviewed to determine which arteries should be

measured, the GDG considered this an important aspect in the correct measurement of ABPI and therefore in the diagnosis of PAD. The GDG recognised that in most clinical practice only two arteries are measured. However, it was noted that some people, particularly those with diabetes, may only have a pulse in the peroneal artery in the foot. Therefore it is important to attempt to measure all three arteries. The GDG recognised that it can be difficult to identify all three, but felt that assessment should, where possible, include the peroneal artery.

Manual compared to automated ABPI measurements

The evidence, as presented in section 7.2, whilst indirect supports the use of manual ABPI measurement over automated and the GDG made a recommendation to use a handheld manual Doppler based on this evidence. In addition to the evidence, the GDG were of the opinion that the automated methods are unreliable and do not always give an accurate reading.

Documenting ABPI measurements

The GDG emphasised that ABPI measurements should always be noted in patient case-notes to allow for future comparison. In addition, the method (i.e. lying down or sitting, level of cuff, length of rest period) should also be noted along with any abnormal signals.

How to calculate ABPI

The GDG considered it necessary to recommend the method of calculation of ABPI. Different values can be obtained depending on whether higher or lower foot or arm pressures are taken. By stipulating a standard method variability will be minimised and improve the diagnosis of PAD.

Other considerations

It is important that people with tissue loss and/or painful limbs should still have an ABPI measured. Falsely elevated ankle pressures can occur in diabetes and renal failure, which should be borne in mind but should not preclude its use.

Key priority for implementation

The GDG identified this recommendation as a key priority for implementation as the measurement of PAD is currently subject to considerable variability. As such, this recommendation would have the potential to improve the accurate diagnosis of PAD, timely referral and thereby, improving patient outcomes.

1

8 Imaging for revascularisation in peripheral arterial disease

8.1 Introduction

In people with PAD when interventional treatment is being considered, further assessment by diagnostic imaging is indicated. This is important as the extent and location of any narrowing (stenosis) or blockage (occlusion) of the arteries to the legs will determine the treatments that may be available or appropriate to improve the blood flow (revascularisation).

Available diagnostic imaging modalities include duplex ultrasound scanning (DUS), magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and digital subtraction angiography (DSA). DUS and MRA resonance imaging offer the least invasive options and avoid the use of ionising radiation. DUS offers the unique advantage of functional assessment of arterial stenosis, but it is the most operator dependent of the available techniques. MRA imaging provides a three dimensional map of the imaged vessels and is able to image the pelvic vessels with more reproducibly than DUS. However, MRA may be contraindicated in some patients, for instance those with pacemakers and advanced renal insufficiency. CTA and DSA both require injection of contrast media, with attendant risks to renal function, and exposure to ionising radiation. DSA requires insertion of a catheter usually via the femoral artery and is now infrequently performed as a primary imaging modality.

The choice of imaging modality used will be influenced to some extent by local expertise and availability of imaging equipment. In general terms, a less invasive and lower cost strategy is preferred. The purpose of imaging people with PAD is to determine the severity and distribution of the lesions affecting the arterial tree and to plan and optimise any therapeutic intervention. As a result of imaging, some people may be excluded from further intervention while others may be selected for surgical or endovascular management.

8.2 Review question

What is most clinical and cost-effective method of assessment of PAD (intermittent claudication and critical limb ischemia)?

The GDG were interested in looking at pre-interventional assessment of stenosis and occlusion for people with PAD. The review question for this clinical guideline updated part of the HTA "A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease".[37] The HTA reviewed the diagnostic accuracy of DUS, MRA and CTA, alone or in combination, for the assessment of lower limb peripheral arterial disease. The review question for this guideline updated the HTA analysis on this objective. The HTA also addressed the impact of assessment method on patient management and outcomes, studies of patient attitude, adverse events and economic evaluations. However, these objectives were not addressed in the review.

The review followed the HTA protocol. A literature search was conducted updating the HTA search from May 2005, for diagnostic cohort or case control studies that compared the effectiveness DUS, MRA and CTA to the reference standard of digital subtraction angiography/arteriography (DSA) in people with symptomatic PAD. Studies were included if they provided sufficient data to calculate a 2x2 table.

8.2.11 Clinical evidence

Seven new studies[38-44] were identified which addressed the question and were added to the HTA review.

A diagnostic meta-analysis (see Appendix J) was performed in outcomes with more than 4 studies per comparison. Where there were less than 4 studies for an outcome, the data was presented as a range of values or for single studies as the results with a 95% confidence interval. A modified GRADE table has been used to present the data from the diagnostic studies (see Table 21, Table 22, Table 23, Table 24). See also the full study evidence tables in Appendix H and the diagnostic forest plots and ROC curves in Appendix J.

Table 21: Clinical evidence profile: Two dimensional PC magnetic resonance angiography (2D PC MRA) and 2D TOF magnetic resonance angiography (2D TOF MRA) compared to digital subtraction angiography/arteriography (DSA)

Study characteristics			Quality Assessment					Summary of findings		
No. of studies	Design	No. of Segments	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity (%)	Specificity (%)	Quality
2D PC MRA										
Whole leg, 50-100% stenosis										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	253	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	97.6 (95% CI 95.1, 99.1)	73.7 (95% CI 51.2, 88.2)	MODERATE
2D TOF MRA										
Whole leg, 50-100% stenosis										
5 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	2668	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(b)]	None	88.07	85.38	MODERATE
Whole leg, ≥70% stenosis										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	206	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	89.8 (95% CI 79.5, 95.3)	96.6 (95% CI 92.3, 98.5)	MODERATE
Whole leg, occlusion										
4 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	2290	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(c)]	None	76.9 to 100	85.1 to 98.3	MODERATE
Above knee										

3 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	800	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(c)]	None	71.4 to 97.3	84.4 to 100	MODERATE
Below knee										
3 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	1823	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	92.53	94.73	HIGH
Foot										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	33	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	86.4 (95% CI 66.7, 95.3)	27.3 (95% CI 9.7, 56.6)	LOW

(a) Wide confidence intervals around specificity.
(b) Wide confidence around pooled effect (see appendix J).
(c) Range of values, no estimate of confidence in effect.
(d) Wide confidence intervals around sensitivity and specificity.

Table 22: Clinical evidence profile: Contrast-enhanced magnetic resonance angiography (CE MRA) compared to digital subtraction angiography/arteriography (DSA)

Study characteristics			Quality Assessment					Summary of findings		
No. of studies	**Design**	**No. of segments**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
CE MRA										
Whole leg, ≥50% stenosis										

10 Collins, 2007; Gjonnaess, 2006; Bueno, 2010; Kos 2009[37,40,42,43]	Diagnostic cohort, data taken from HTA	7710	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	94.96	96.37	HIGH
Whole leg, ≥70% stenosis										
4 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	2773	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	90.9 to 100	96.2 to 99.4	MODERATE
Whole leg, occlusion										
8 Collins, 2007; Bueno, 2010; Kreitner, 2008[37,39,40]	Diagnostic cohort, data taken from HTA	6403	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	91.83	98.71	HIGH
Above knee, ≥50% stenosis										
4 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	742	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	81.4 to 100	91.9 to 95.9	MODERATE
Above knee, ≥70% stenosis										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	576	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	90.5 (95% CI 83, 94.9)	97.3 (95% CI 95.4, 98.4)	HIGH
Above knee, occlusion										

4 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	742	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	86.7 to 100	99.5 to 100	MODERATE
Below knee, ≥50% stenosis										
3 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	721	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	71.1 to 96.5	87 to 95.8	MODERATE
Below knee, ≥70% stenosis										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	298	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	91.3 (95% CI 83.8, 95.5)	93.7 (95% CI 89.5, 96.3)	HIGH
Below knee, occlusion										
2 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	627	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	86.2 to 95.2	92.9 to 96.8	MODERATE
Foot										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	286	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious [(a)]	None	78.7 to 79.4	70.6 to 86.3	MODERATE

1 *(a) Range of values, no estimate of confidence in effect.*

2 **Table 23: Clinical evidence profile: Computed tomography angiography (CTA) compared to digital subtraction angiography/arteriography (DSA)**

Study characteristics			Quality Assessment					Summary of findings		
No. of studies	**Design**	**No. of segments**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
CTA										
Whole leg, ≥50% stenosis										

6 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	4270	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	93.5	91.13	HIGH
Whole leg, ≥70% stenosis										
4 Collins, 2007; Napoli, 2011[37,44]	Diagnostic cohort, data taken from HTA	9599	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	87.4 to 99	97 to 98.5	MODERATE
Whole leg, occlusion										
5 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	3530	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	94.1	99.49	HIGH
Above knee, ≥50% stenosis										
3 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	628	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	94.2 to 96.9	91.2 to 98.1	MODERATE
Above knee, ≥70% stenosis										
3 Collins, 2007; Schernthaner, 2008[37,38]	Diagnostic cohort, data taken from HTA	1150	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	99 to 100	99.4 to 100	MODERATE
Above knee, occlusion										
2Collins, 2007[37]	Diagnostic cohort, data taken from HTA	338	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	95.1 to 96	99.2 to 100	MODERATE
Below knee, ≥50% stenosis										

1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	390	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	89.5 (95% CI 84.1, 93.3)	73.9 (95% CI 67.6, 79.2)	HIGH
Below knee, ≥70% stenosis										
1 Schernthaner, 2008[38]	Diagnostic cohort, data taken from HTA	539	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(b)]	None	98.2	99.7	MODERATE

1 *(a) Range of values, no estimate of confidence in effect.*
2 *(b) No confidence intervals.*

3 **Table 24: Clinical evidence profile: Duplex ultrasound scanning (DUS) compared to digital subtraction angiography/arteriography (DSA)**

Study characteristics			Quality Assessment					Summary of findings		
No. of studies	**Design**	**No. of segments**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (%)**	**Specificity (%)**	**Quality**
DUS										
Whole leg, ≥50% stenosis										
11 Collins, 2007; Bueno, 2010; Gjonnaess, 2006[37,40,42]	Diagnostic cohort, data taken from HTA	8335	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	89.7	95.64	HIGH
Whole leg, occlusion										
9 Collins, 2007; Bueno, 2010[37,40]	Diagnostic cohort, data taken from HTA	7396	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	89.12	97.8	HIGH
Whole leg, other stenosis thresholds										

4 Collins, 2007, Eiberg, 2010[37,41]	Diagnostic cohort, data taken from HTA	3021	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	60.9 to 88	79 to 99.7	MODERATE
Above knee, ≥50% stenosis										
9 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	1970	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	91.54	92.58	HIGH
Above knee, ≥70% stenosis										
2 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	588	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	65.4 to 100	95.2 to 98	MODERATE
Above knee, occlusion										
9 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	1500	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	92.58	97.84	HIGH
Above knee, other stenosis thresholds										
3 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	682	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	82.7 to 94.1	82.8 to 99.3	MODERATE
Below knee, ≥50% stenosis										
4 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	767	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	40.7 to 96.1	79.8 to 98.8	MODERATE
Below knee, occlusion										

6 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	2562	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(b)]	None	79.52	90.57	MODERATE
Below knee, other stenosis thresholds										
2 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	1772	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[(a)]	None	72.3 to 76	67.6 to 77.7	MODERATE
Foot										
1 Collins, 2007[37]	Diagnostic cohort, data taken from HTA	140	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	64.3 (95% CI 53.6, 73.7)	80.4 (95% CI 68.2, 88.7)	LOW

(a) Range of values, no estimate of confidence in effect.
(b) Wide confidence around pooled effect (see Appendix J).
(c) Wide confidence intervals around sensitivity and specificity.

8.2.111 Economic evidence

Four studies were identified that evaluated comparators which were relevant to the review question: a decision analytic model developed as part of the HTA by Collins et al 2007[45] and three trial-based economic evaluations which have been published since the HTA cut-off date (May 2005).[46-48] No single study included all comparators. The results of both the HTA and studies included as part of the guideline update search are summarised in the economic evidence profiles below (see Table 26).

The HTA by Collins 2007 concluded that DUS is the most cost effective choice for both whole leg and below the knee imaging. The analysis shows that 2D TOF MRA is the most cost effective alternative when imaging is confined to areas above the knee. However, this model is subject to several potentially serious limitations:

- Treatment pathway
  - The model assumed that people diagnosed with >50% stenosis could be treated with angioplasty, bypass or amputation. The GDG did not consider bypass and amputation to be appropriate first-line options for treatment of these patients. If only exercise and angioplasty were considered, the consequences of an inaccurate test result would be different than those predicted by the model.
  - People with <50% stenosis were treated with medical management. The GDG considered exercise therapy (supervised and unsupervised) to be the most appropriate treatment options for this patient group. If these options had been included as an option in the model, the consequences of an inaccurate test result would be different to those predicted by the model.
  - The probability of undergoing each interventional treatment was estimated according to the results of each included imaging study. This introduces a confounding factor into the model as it is difficult to determine how much of the difference in cost and quality of life between the different imaging procedures is due to the accuracy of the diagnostic test and how much is due to the treatment pathway (which varies between tests).
  - Similarly, the probability of reintervention and experiencing a change in treatment plan differed for each imaging strategy. The effect of this is to further skew the results of the model as the differences in initial treatment plans (according to diagnostic test) are amplified.
- Cost
  - The costs included in this model were derived from estimates based largely on expert opinion are very different to those derived from current NHS reference costs (Table 25). As a result, the consequences of an inaccurate test result predicted by the HTA model may be different to those which could be expected given current costs.

The three RCT-based studies included as part of the economic update search are pair-wise comparisons of different imaging procedures.[46-48] Each study reported costs that were adjusted to take into account predictive baseline characteristics using multivariable linear and logistic regression. Two[47,48] also adjusted QALYs, allowing for an adjusted ICER to be calculated. Based on the results of the adjusted data, CTA is less costly and more effective than both CE MRA and DSA. However, if the unadjusted figures are used to calculate ICERs, CE MRA is more cost-effective than both CTA and DUS, and DSA is more cost effective than CTA.

It is difficult to draw comparisons between the studies included in this update and the results of the HTA. The RCT-based studies did not report sensitivity and specificity of each intervention, making it impossible to compare the results of these studies to that of the HTA or current clinical review. In addition, two of these studies included investment costs associated with imaging equipment in the total cost of each strategy; this was not a cost considered by the HTA. Moreover, none of the studies included as part of the update search specified the location of the imaging procedure (whole leg, above knee or below knee) or reported results by subgroups.

This area was prioritised for new cost-effectiveness analysis subject to timing and data. Given the time required to complete the network meta-analysis and the fact that the conclusions of the original HTA were essentially unchanged, no new analysis was preformed for this question.

Current unit costs

In order to allow comparison to the costs used in the included studies, relevant UK unit costs are provided below (Table 25).

Table 25: Cost of imaging procedures in the NHS (2010)

Imaging procedure	Most likely average value	Possible range
Contrast-enhanced MRA	£200[(a)]	£229 to £366[(b)]
Duplex ultrasound	£90[(c)]	£61 to £176[(d)]
Computed tomography angiography	£146[(e)]	£112 to £162[(f)]
Catheter angiography	£679[(g)]	£480 to £778[(h)]

Sources:
(a) Expert opinion
(b) RA03Z MRI scan, one area, pre and post contrast & RA05Z MRI scan, two to three areas, with contrast
(c) RA26Z Ultrasound mobile scan/ intra-operative procedures 20 to 40 minutes
(d) RA 25Z Ultrasound mobile scan/intra-operative procedures less than 20 minutes & RA 27Z Ultrasound mobile scan /Intra-operative procedures more than 40 minutes
(e) RA12Z CT scan, two areas with contrast
(f) RA 10Z CT scan, one area, pre and post contrast & RA 13Z CT scan, three areas with contrast
(g) Day case HRG QZ 16C Diagnostic radiology and other transluminal procedures without CC
(h) Day case HRG QZ16 A & QZ 16B NHS reference costs 2009/10

1 **Table 26: Economic evidence profile: Imaging for revascularisation in peripheral arterial disease**

Study	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
2D TOF MRA vs. CE MRA vs. DUS vs. CA							
Collins 2007[45]	Potentially serious limitations[(a)]	Partially applicable[(b)]	• Decision analytic model • Population: People with IC and CLI • Time Horizon: 1 year • Costs: Diagnostic test costs (and secondary CA for inconclusive test results), cost of treatment (angioplasty, bypass, etc) and follow-up costs. The cost of complications associated with CA was also included. Adverse events related to other imaging procedures were not considered relevant for inclusion. • Perspective: UK NHS	**Whole leg**			
				DUS was the least costly of all evaluated strategies	DUS was equally as effective as CA and CE MRA, resulting in a gain of 0.03 QALYs compared to 2D TOF MRA	DUS was the dominant strategy	There was a 95% probability that DUS was the most cost effective strategy at a threshold of £20k.
				Below the knee			
				2D TOF MRA is £362 more costly than DUS	2D TOF MRA was the most effective strategy, resulting in a gain of 0.008 QALYs compared to DUS	2D TOF MRA costs £43, 272 per QALY and is therefore not considered cost-effective. DUS is the most cost effective strategy.	There was a 70% probability that DUS is the most cost-effective strategy at a threshold of £20k.
				Above the knee			
				CE MRA is £155 more costly than 2D MRA	CE MRA was the most effective strategy, resulting in a 0.001 QALY gain	CE MRA costs £143, 389 per QALY and is therefore not considered cost effective. 2D MRA is the	There was a 75% probability that 2D MRA was the most cost effective strategy at a threshold of £20k.

					compared to 2D MRA	most cost effective strategy.	
CE MRA vs. DUS							
de Vries 2007[49]	Potentially serious limitations[(c)]	Partially applicable[(d)]	• RCT-based cost-utility analysis • Population: People with IC and CLI • Time horizon: 6 months • Costs: Initial and additional imaging, procedural and outpatient costs over 6 months. • Perspective: Netherlands, hospital • Other: Approximately equal proportions of patients underwent exercise therapy, angioplasty and bypass in each arm.	CE MRA was £275 more costly than DUS[(e)]	CE MRA resulted in a 0.02 QALY gain compared to DUS[(e)]	CE MRA costs £13, 750 per QALY gain[(e)]	If the investment costs for the MR imager were reduced by 50%, the incremental difference in total costs was reduced to £48, resulting in an ICER of £2, 400.
DSA vs. CTA							
Kock 2007[47]	Potentially serious limitations[(f)]	Partially applicable[(g)]	• RCT-based cost-utility analysis • Population: People with IC and CLI • Time horizon: 6 months • Approximately equal proportions of patients underwent exercise therapy, angioplasty and bypass in each group. • Outcomes: Costs over 4 months, change in quality of life at 6 months, additional imaging, patient comfort.	CTA is £547 less costly than DSA[(h)]	CTA results in a 0.07 QALY gain[(h)]	CTA is the dominant treatment option[(h)]	If the reported unadjusted values are used to calculate the incremental costs and QALYs, CTA is £1, 788 more costly than DSA and results in a 0.04 QALY grain. The ICER is therefore £44, 450. And CTA is not considered cost-effective.
CE MRA vs. CTA							
Ouwendijk 2005 [48]	Potentially serious limitation[(i)]	Partially applicable[(j)]	• Cost-utility analysis based on RCT • Population: people with PAD (symptom group unclear) • Time horizon: 6 months	CTA is £2,425 less costly than CE MRA[(k)]	CTA results in a 0.02 QALY gain[(k)]	CTA is the domain treatment option[(k)]	If the reported unadjusted values are used to calculate incremental costs and QALYs, CE MRA is £2,

			• Approximately one third of patients underwent angioplasty, bypass and conservative treatment in each group. • Outcomes: Costs at 6 months, change in quality of life at 6 months, therapeutic confidence.				710 more costly than CTA and results in a gain of 0.03 QALYs. The ICER is therefore £9, 033 and CE MRA would be considered cost effective. Altering the initial investment costs of imaging equipment does not change the conclusion of the analysis.

(a) Probability of intervention differs according to imaging modality as reported by the studies included in the clinical review; no lifetime analysis of cost and QALY gain (1 year time horizon); intervention outcomes differ from those identified in the literature included in the current clinical review; source of health state descriptions is unclear; resource use and unit cost estimates for downstream interventions differ from those included as part of the economic review; inadequate sensitivity analysis.

(b) Analysis did not include all relevant comparators; downstream consequences differ from those considered appropriate by the GDG.

(c) Cut-off criteria and factors used to determine intervention treatment pathway not reported; sensitivity and specificity not reported (difficult to compare to results of current clinical evidence review); included investment costs for imaging equipment.

(d) Dutch healthcare setting; did not include all possible comparators.

(e) Unadjusted for predictive variables at baseline (disease severity (IC vs. CLI), renal disease, cardiac diseases, cerebrovascular disease, and diabetes mellitus, hospital setting, and study group).

(f) Cut-off criteria and factors used to determine intervention treatment pathway not reported; sensitivity and specificity not reported (difficult to compare to results of current clinical evidence review).

(g) Dutch healthcare setting; did not include all possible comparators; downstream consequences differ from those considered appropriate by GDG.

(h) Adjusted for predictive variables at baseline (disease severity (IC vs. CLI), renal insufficiency, cerebrovascular disease, and diabetes mellitus).

(i) Cut-off criteria and factors used to determine intervention treatment pathway not reported; sensitivity and specificity not reported (difficult to compare to results of current clinical evidence review); included investment costs for imaging equipment.

(j) Dutch healthcare setting; did not include all possible comparators; downstream consequences differ from those considered appropriate by GDG.

(k) Adjusted for predictive variables at baseline (disease severity (IC vs. CLI), renal insufficiency, cardiac diseases, cerebrovascular disease, and diabetes mellitus)

8.2.12 Evidence statements

8.2.2.1 Clinical

Two-dimensional phase-contrast magnetic resonance angiography (2D PC MRA)

In comparison to the reference standard of DSA, the review showed that 2D PC MRA:

- Had a sensitivity of 97.6% (95% CI 95.1 to 99.1) and specificity of 73.7% (95% CI 51.2 to 88.2) for assessment of whole leg, 50-100% stenosis [1 systematic review based on 1 study, 253 segments, moderate quality evidence][37]

Two-dimensional time-of-flight magnetic resonance angiography (2D TOF MRA)

In comparison to the reference standard of DSA, the review showed that 2D TOF MRA:

- Had a sensitivity of 88.07% and specificity of 85.38% assessment of whole leg, 50-100% stenosis [1 systematic review based on 5 studies, 2668 segments, moderate quality evidence][37]
- Had a sensitivity of 89.8% (95% CI 79.5 to 95.3) and specificity of 96.6% (95% CI 92.3 to 98.5) for assessment of whole leg, ≥70% stenosis [1 systematic review based on 1 study, 206 segments, moderate quality evidence][37]
- Had a sensitivity range of 76.9 to 100% and specificity range of 85.1 to 98.3% for assessment of whole leg, occlusion [1 systematic review based on 4 studies, 2290 segments, moderate quality evidence][37]
- Had a sensitivity range of 71.4 to 97.3% and specificity range of 84.4 to 100% for assessment of above knee [1 systematic review based on 3 studies, 800 segments, moderate quality evidence][37]
- Had a sensitivity of 92.53% and specificity of 94.73% for assessment of below knee [1 systematic review based on 3 studies, 1823 segments, high quality evidence][37]
- Had a sensitivity of 86.4% (95% CI 66.7 to 95.3) and specificity of 27.3% (95% CI 9.7 to 56.6) for assessment of the foot [1 systematic review based on 1 study, 33 segments, low quality evidence][37]

Contrast-enhanced magnetic resonance angiography (CE-MRA)

In comparison to the reference standard of DSA, the review showed CE MRA:

- Had a sensitivity of 94.96% and specificity of 96.37% assessment of whole leg, ≥50% stenosis [3 studies and 1 systematic review based on 7 studies, 7710 segments, high quality evidence][37,40,42,43]
- Had a sensitivity range of 90.9 to 100% and specificity range of 96.2 to 99.4% for assessment of whole leg, ≥70% stenosis [1 systematic review based on 4 studies, 2773 segments, moderate quality evidence][37]
- Had a sensitivity of 91.83% and specificity of 98.71% for assessment of whole leg, occlusion [2 studies and 1 systematic review based on 6 studies, 6403 segments, high quality evidence][37,39,40]
- Had a sensitivity range of 81.4 to 100% and specificity range of 91.9 to 95.9 for assessment of above knee, ≥50% stenosis [1 systematic review based on 4 studies, 742 segments, moderate quality evidence][37]
- Had a sensitivity of 90.5% (95% CI 83 to 94.9) and specificity of 97.3% (95% CI 95.4 to 98.4) for assessment of above knee, ≥70% stenosis [1 systematic review based on 1 study, 576 segments, high quality evidence][37]
- Had a sensitivity of range 86.7 to 100% and specificity of range 99.5 to 100% for assessment of above knee, occlusion [1 systematic review based on 4 studies, 742 segments, moderate quality evidence][37]

- Had a sensitivity range of 71.1 to 96.5% and specificity range of 87 to 95.8% for assessment of below knee, ≥50% stenosis [1 systematic review based on 3 studies, 721 segments, moderate quality evidence][37]
- Had a sensitivity of 91.3% (95% CI 83.8 to 95.5) and specificity of 93.7% (95% CI 89.5 to 96.3) for assessment of below knee, ≥70% stenosis [1 systematic review based on 1 study, 298 segments, high quality evidence][37]
- Had a sensitivity range of 86.2 to 95.2% and specificity range of 92.9 to 96.8% for assessment of below knee, occlusion [1 systematic review based on 2 studies, 627 segments, moderate quality evidence][37]
- Had a sensitivity range of 78.7 to 79.4% and specificity range of 70.6 to 86.3% for assessment of the foot [1 systematic review based on 1 study, 286 segments, moderate quality evidence][37]

Computed tomography angiography (CTA)

In comparison to the reference standard DSA, the review showed CTA:

- Had a sensitivity of 93.5% and specificity of 91.13% for assessment of whole leg, ≥50% stenosis [1 systematic review based on 6 studies, 4270 segments, high quality evidence][37]
- Had a sensitivity range of 97 to 98.5% and specificity range of 97 to 98.5% for assessment of whole leg, ≥70% stenosis [1 study and 1 systematic review based on 3 studies, 9599 segments, moderate quality evidence][37,44]
- Had a sensitivity of 94.1% and specificity of 99.49% for assessment of whole leg, occlusion [1 systematic review based on 5 studies, 3530 segments, high quality evidence][37]
- Had a sensitivity range of 94.2 to 96.9% and specificity range of 91.2 to 98.1% for assessment of above knee, ≥50% stenosis [1 systematic review based on 3 studies, 628 segments, moderate quality evidence][37]
- Had a sensitivity range of 99 to 100% and specificity range of 99.4 to 100% for assessment of above knee, ≥70% stenosis [1 study and 1 systematic review based on 2 studies study, 1150 segments, moderate quality evidence][37,38]
- Had a sensitivity range of 95.1 to 96% and specificity range of 99.2 to 100% for assessment of above knee, occlusion [1 systematic review based on 2 studies, 338 segments, moderate quality evidence][37]
- Had a sensitivity of 89.5% (95% CI 84.1 to 93.3) and specificity of 73.9% (95% CI 67.6 to 79.2) for assessment of below knee, ≥50% stenosis [1 systematic review based on 1 study, 390 segments, high quality evidence][37]
- Had a sensitivity of 98.2% and specificity of 99.7% for assessment of below knee, ≥70% stenosis [1 study, 539 segments, moderate quality evidence][38]

Duplex ultrasound scanning (DUS)

In comparison to the reference standard DSA, the review showed that DUS:

- Had a sensitivity of 89.7% and specificity of 95.64% for assessment of whole leg, ≥50% stenosis [2 studies and 1 systematic review based on 9 studies, 8335 segments, high quality evidence][37,40,42]
- Had a sensitivity of 89.12% and specificity of 97.8% for assessment of whole leg, occlusion [1 study and 1 systematic review based on 8 studies, 7396 segments, high quality evidence][37,40]
- Had a sensitivity range of 60.9 to 88% and specificity range of 79 to 99.7% for assessment of whole leg, other stenosis thresholds [1 study and 1 systematic review based on 3 studies, 3021 segments, moderate quality evidence][37,41]
- Had a sensitivity of 91.54% and specificity of 92.58% for assessment of above knee, ≥50% stenosis [1 systematic review based on 9 studies, 1970 segments, high quality evidence][37]

- Had a sensitivity range of 65.4 to 100% and specificity range of 95.2 to 98% for assessment of above knee, ≥70% stenosis [1 systematic review based on 2 studies, 588 segments, moderate quality evidence][37]
- Had a sensitivity of 92.58% and specificity of 97.84% for assessment of above knee, occlusion [1 systematic review based on 9 studies, 1500 segments, high quality evidence][37]
- Had a sensitivity range of 82.7 to 94.1% and specificity range of 82.8 to 99.3% for assessment of above knee, other stenosis thresholds [1 systematic review based on 3 studies, 682 segments, moderate quality evidence][37]
- Had a sensitivity range of 40.7 to 96.1% and specificity range of 79.8 to 98.8% for assessment of below knee, ≥50% stenosis [1 systematic review based on 4 studies, 767 segments, moderate quality evidence][37]
- Had a sensitivity of 79.52% and specificity of 90.57% for assessment of below knee, occlusion [1 systematic review based on 6 studies, 2562 segments, moderate quality evidence][37]
- Had a sensitivity range of 72.3 to 76% and specificity range of 67.6 to 77.7% for assessment of below knee, other stenosis thresholds [1 systematic review based on 2 studies, 1772 segments, moderate quality evidence][37]
- Had a sensitivity of 64.3% (95% CI 53.6 to 73.7) and specificity of 80.4% (95% CI 68.2 to 88.7) for assessment of the foot [1 systematic review based on 1 study, 140 segments, low quality evidence][37]

8.2.202 Economic

- No cost-effectiveness studies were identified that included all relevant comparators.
- For whole leg and below the knee imaging, one economic decision model concluded that DUS was more cost effective than 2D TOF MRA, CE MRA and CA. For above the knee imaging, the same economic decision model found that 2D TOF MRA was more cost effective than DUS, CE MRA and CA. [Partially applicable with potentially serious limitations][45]
- It was difficult to draw conclusions from studies of pair-wise comparisons
  - One RCT determined that CE MRA was more cost effective than DUS [Partially applicable with potentially serious limitations][46]
  - One RCT determined that CTA was more cost effective than DSA [Partially applicable with potentially serious limitations][47]
  - One RCT determined that CTA was more cost effective than DSA [Partially applicable with potentially serious limitations][48]

8.2.233 Recommendations and link to evidence

Recommendations	**6. Offer duplex ultrasound as first-line imaging to all people with peripheral arterial disease in whom revascularisation is being considered.** **7. Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging before considering an intervention.** **8. Offer computed tomography angiography in people with peripheral arterial disease where contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.**
Relative value of different outcomes	It is difficult to make a definitive comparison between the accuracy of these imaging techniques because none of the studies included compared all the

	techniques to each other. In addition, the studies combined results from different disease sites. Furthermore, the reference standard was taken as DSA, but this can occasionally miss vessels which are picked up by other techniques. The HTA (Collins 2007)[37] concluded that CE MRA was superior in diagnostic accuracy than DUS and CTA and would be a suitable alternative to the reference standard of DSA, and having noted the difficulties in interpreting the data the GDG found that the newer evidence did not substantially alter this conclusion, although they noted that differences in sensitivity and specificity were not large.
Trade off between clinical benefit and harms	The GDG noted that all imaging techniques are relatively safe. The avoidance of intravascular contrast media (not required for DUS) and of exposure to ionising radiation (not required for DUS or for CE-MRA) are important considerations. Allergic reactions to contrast medium are rare, but the potential nephrotoxic effects of iodinated contrast media are of concern. There are non-contrast techniques other than DUS e.g. TOF MRA but these are agreed to be less accurate (see below). In addition, the avoidance of unnecessary reduplication of imaging is important (time and cost). Whilst DSA is considered the gold standard, it is much less commonly used in routine practice. It involves both administration of a contrast medium and ionising radiation. In addition, discomfort is experienced by some patients. DUS was not perceived as having any major risks. DUS may be technically more difficult in large or obese patients and/or in the presence of calcification (particularly in diabetic patients) or where there are ulcers and bandaging near the sites of the vessels. Stenosis and occlusion are important with regard to sensitivity of DUS for below knee lesions. CE MRA offers better spatial resolution, is faster to perform and is less dependent on blood flow than DUS. However, it is contraindicated in people with intra-cranial clips and pacemakers. In addition, some people are unable to tolerate MRA due to claustrophobia. CTA is not recommended for people with an eGFR of <30ml/min. The latter is not an absolute contra-indication but would also be considered a relative contra-indication to CE MRA. If the creatinine is <200 CTA could be performed with safeguards.
Economic considerations	The GDG discussed the methods, results and limitations of each study included in the economic evidence review and agreed that it was very difficult to draw a robust conclusion from the current cost-effectiveness evidence base. The group discussed the current costs associated with each imaging modality from an NHS perspective and the costs and consequences of the pathways that they expect patients to follow based on the results of imaging. They agreed that for patients in whom revascularisation may be beneficial, DUS represents the least costly and least invasive method of determining the location and extent of the lesion, and may well provide sufficient information. If the results of DUS are not suitable for planning an intervention, the GDG agreed that CE MRA and CTA represent useful modalities for gathering more detailed information.
Quality of evidence	The quality of the evidence was rated from high quality to low by the GRADE

	criteria. There was concern about using the degree of stenosis as part of this assessment. In practice, treatment is based on severity of symptoms. Although uncommon, sometimes people with <50% stenosis are treated and many people with >50% stenosis will remain asymptomatic. Furthermore, the degree of stenosis is unknown until the imaging has taken place, and it therefore cannot be used as a means of judging which test to do in advance. It was noted that the accuracy of the techniques could be affected by the use of different imaging protocols. The GDG expressed caution when interpreting the results of the HTA. Although the HTA is relatively recent, clinical practice has changed significantly in that short time. The GDG did not consider 2D TOF MRA within the recommendations as it was not thought to be a relevant comparator. 2D TOF MRA is much more prone to artefacts such as movement and is susceptible to non-uniformity of blood flow. Imaging times are longer than for CE-MRA. The recommendations were made based on the clinical and cost effectiveness evidence, and expert opinion.
Other considerations	Based on the clinical and cost effectiveness data, and expert opinion, the GDG agreed that DUS should be used as a first option for people being considered for revascularisation. However, they noted that it might not provide sufficient information, and that ultrasound is easier to perform in some people than others. They therefore felt that other imaging modalities should be available and that the recommendation should reflect this. Most units will have access to MRA in the UK. However the amount of time available on the scanner will vary from site to site and generally it is used much less frequently than DUS; CTA might also utilised more widely. The local expertise may therefore be limited in some units. **Key priority for implementation** The GDG identified the recommendation on offering CE-MRA as a key priority for implementation. There is considerable variability in the investigations used and whilst MRA is considered preferable to CTA, the widespread adoption may have significant implications for training and the availability of expertise and equipment.

9 Management of intermittent claudication

9.1 Introduction

Intermittent claudication (IC) is a tight, cramp like pain in the muscles of the calf, thigh or buttock which comes on only after walking and is relieved by resting. The pain is caused by diminished circulation.

The aim of treatment for intermittent claudication is two-fold. First, as people with PAD are at high risk of other cardiovascular events, the aim is to reduce this risk. The first basic intervention for PAD, is to offer information including general information about cardiovascular risk and potential interventions to reduce this (cardiovascular exercise, quitting smoking, healthy eating, medicines – see chapter 6 for the recommendations relating to this) as well as specific information about risks to the limb. This could be termed best medical treatment for PAD.

The second aim of treatment is to improve walking distance. The decision to directly attempt to improve walking distance should be decided by the patient, balancing the impact their symptoms have on their day to day life, and the chance of success versus the risks of treatment. People with claudication are a heterogeneous group. Many will only be mildly troubled by their symptoms or have other significant co-morbidity that reduces their mobility. Others however may be severely restricted by their claudication which can significantly alter their lifestyle. It is the role of the clinician to help the patient decide on the best therapeutic option for them based on the impact of their symptoms on their quality of life.

The purpose of this chapter is to set out the GDG's consideration of the evidence comparing the various management options for IC. It is assumed that the diagnosis has been correctly established (see chapter 7).

9.1.1 Role of exercise

Physical exercise has been shown to be of benefit to people with established cardiovascular disease (Lipid modification NICE Clinical Guideline 67 May 2008[50]) and increased exercise in people with IC can result in improvements in walking distance. People with IC should be encouraged to walk to near maximal pain. A variety of methods have been employed to support people with IC in exercising, including treadmill walking, exercise classes and gym membership (supervised exercise).

9.1.2 Role of naftidrofuryl oxalate

There are a number of vasoactive drugs currently licensed for treating the symptoms of IC. There is some evidence that vasoactive drugs can increase walking distance compared to placebo.[51] The NICE technology appraisal (TA 223) on "Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease"[51] recommended naftidrofuryl oxalate as the preferred treatment.

From a clinical viewpoint, although there is a small benefit identified in drug treatment, the question remains as to whether drug treatment is preferred to other treatments such as supervised exercise therapy, angioplasty or stents, when patients are suitable for more than one of these options.

9.1.3 Endovascular techniques

A proportion of people with IC will achieve reasonable symptom control after cardiovascular risk prevention measures have been taken and a regular exercise regimen has been established. IC can also be treated using endovascular procedures (angioplasty +/- stent placement) or bypass surgery,

both of which constitute a more direct means of addressing the problem since they are directed at the arterial lesions causing claudication.

9.1.3.1 Angioplasty

In recent years there has been rapid development of endovascular techniques for the management of PAD. These are minimally invasive procedures in which catheters and guide wires are introduced through small punctures in the artery, carried out under local anaesthetic. These techniques are used to introduce devices that can be used to unblock or dilate areas where there are obstructions to blood flow. The most common technique is the use of an inflatable balloon to dilate an area of artery (angioplasty). This has some limitations in that it may not be possible to open up the artery sufficiently or the procedure may lead to complications, such as the development of a flap of the lining of the artery (dissection) or dislodging material that passes further down the artery and causes another blockage (embolisation).

9.1.3.2 Stenting

A treatment that can be used to improve the results of angioplasty is the insertion of a stent. Stents are small spring like structures that are usually made of metal (known as bare metal stents) and can be placed within the artery in order to try and hold it open. The potential benefits of the use of stents are that they may improve the diameter of the treated artery, where angioplasty alone is inadequate. They may also help to prevent or treat complications by pinning down a flap of lining that has developed or preventing embolisation and may alter the risks of long term re-stenosis or re-occlusion of the treated section of artery.

There are two different approaches to the use of stents. One is to use them as an adjunct to angioplasty only in those cases where the result of the initial angioplasty is thought to be sub-optimal. The alternative is to insert a stent as part of an angioplasty procedure, which is termed primary stenting.

Over recent years new drug eluting stents have been developed which have a coating of material containing drugs that are gradually released over a long period of time and are intended to reduce the risk of narrowing of the artery after treatment.

9.1.4 Bypass surgery

The most invasive treatments for people with PAD, who have not been suitable for or responded to other treatments, are open surgical procedures to improve the circulation to the limb.

The most common operations are bypass grafts in which a new blood vessel is created by joining a conduit to above and below the blocked artery. In treating blocked arteries in the leg below the groin there are a number of options for bypass material. The patient's own vein (autologous) can be used in the bypass procedure. This usually involves taking the long saphenous vein from the same leg as the blockage. Autologous grafting has the advantage of being less likely to become infected or cause a serious reaction. However there are not always suitable veins available and because of the valves in the vein it either needs to be completely removed and reversed, resulting in the need for long incision down the leg, or needs to have a procedure to destroy the valves, which may damage the interior of the vein leading to a risk of complications or subsequent narrowing. The other option is to use an artificial artery made out of a prosthetic material, often PTFE or Dacron.

Chapter overview

The GDG wished to know whether the results of angioplasty or bypass surgery were superior to exercise or, since the mechanism of benefit is different to exercise, whether they add anything to the benefit obtained from exercise.

In formulating their review of the evidence, the GDG considered types of treatment that could be used in addition to best medical treatment (i.e. management of secondary cardiovascular risk factors) for PAD. Literature searches were performed to answer a series of questions in which treatment options were compared head-to-head, the options being some form of exercise, surgery, and endovascular therapy. The GDG felt that the first question they needed to answer was how best to help people with PAD achieve an optimal level of exercise - exercise in some form was accepted as beneficial on a priori grounds. For people with PAD the possibilities for exercise therapy range from simple advice on exercise, through individualised plans, to participation in formal supervised exercise sessions. Additional treatment might then consist of nothing more (i.e. exercise alone has successfully controlled symptoms), an endovascular procedure or surgery; the assessment of these measures needed to allow that they might be added to either unsupervised or supervised exercise (depending on the outcome of that first head-to-head comparison). In order to assess all the possibilities using both clinical and health-economic data, papers covering all potential treatment comparisons under the umbrella heading of exercise versus endovascular therapy versus surgery were sought and assessed, and an original health economic model was developed covering all 3 forms of intervention.

The situation is further complicated by questions within each separate general treatment modality. Within endovascular therapy, the GDG wished to know whether angioplasty alone is sufficient or whether stents should also be placed; and if stenting is employed, whether it should be with a bare metal stent or a drug-eluting stent. For the surgical question, it was felt appropriate to compare autologous vein grafts with prosthetic grafts. These different possibilities were also accounted for in the large health-economic model, but to minimise complexity they will be presented separately from the over-arching exercise vs endovascular therapy vs surgery questions.

Finally on intermittent claudication, the GDG needed to incorporate the NICE Technology Appraisal (TA) of vasoactive drugs. It was felt that these drugs are generally used in current practice when other treatment is not possible or when turned down by the person with PAD, and that they do not confer any prognostic advantage nor offer a likely cure for symptoms. Moreover the TA had already considered their cost-effectiveness. They are therefore slightly separate from the other forms of treatment covered by this guideline, and are not included in the direct comparison of the other forms of treatment for intermittent claudication.

9.2 Supervised exercise compared to unsupervised exercise

9.2.1 Review question

What is the clinical and cost effectiveness of supervised exercise therapy compared to unsupervised exercise therapy for the treatment of PAD in adults with intermittent claudication?

For the purpose of this review, unsupervised exercise was defined as advice to exercise for approximately 30 minutes three to five times per week, walking until the onset of symptoms, then resting to recover. Supervised exercise was defined as a community-based exercise including hospital or gym based programme supervised by healthcare professionals (typically two physiotherapists with approximately ten patients per group). A programme typically consists of approximately two hours of classes per week for a period of up to three months during which patients exercise until the onset of symptoms, and then rest and repeat.

Two Cochrane reviews were identified Bendermacher 2006[52] and Watson 2008[53]) comparing unsupervised exercise to supervised exercise for the treatment of intermittent claudication. These studies were not included or updated in the current review as they did not meet the review question protocol defined by the GDG, which had a wider definition of the exercise interventions compared to the Cochrane reviews. However they were used as a source to ensure that studies identified in the Cochrane review which matched the current review protocol had been considered for inclusion.

9.2.171 Clinical evidence

Twelve RCTs comparing supervised and unsupervised exercise[54-65] were included in the clinical review. Table 27 describes the duration and content of the supervised exercise programmes in each included study. These are summarised in the clinical evidence profiles below (Table 28 and Table 29). See also the full clinical evidence tables in Appendix H and forest plots in Appendix J. The reasons for withdrawal from the exercise interventions are summarised in Table 30.

One study reported quality of life as measured by the EQ-5D[56]; five papers (representing an additional four studies) included the SF-36 questionnaire[54-57,59]; and one study included the SF-20 as a measure of health related quality of life.[58] Methods for mapping SF-36 health state descriptions to health state valuations based on the EQ-5D have been developed and reported by Ara and Brazier 2008.[66] Where the results of each dimension score were not reported in full, authors reporting the use of this measure were contacted for additional data and all replied. Cheetham 2004[54] and Nicolai 2010[56] provided average values for each of the 8 dimensions; Pinto 1997[57] replied that although these data were collected they were not available. All available values were mapped to preference based values using Equation 1 as reported by Ara and Brazier[66] and probabilistic simulation methods. A summary of mapped values is presented in Table 31 and Table 32; additional data are reported in the economic modelling report in Appendix K.

Table 27: Study characteristics: Summary of exercise interventions

Study	Unsupervised exercise		Supervised exercise programme			
	Method	Content	Duration	Setting	Method	Content
Cheetham 2004[54]	Advice only	• Written and verbal advice to exercise for half an hour at least 3 times per week to near maximal pain. • Additional exercise such as stair climbing and toe walking also advised. • Progress reviewed every 3 months.	1 x 45 min/week for 6 months	Hospital gym	Weekly education, circuit training	• 5-10 minutes talk about benefits of exercise • 30 minutes exercise. Alternating walking for 2 min and exercise stations for 2 minutes: stair climbing, high-step climbing, tip toe walking, calf raises, and power walking/jogging.
Kakkos 2005[55]	Advice only	• Advised to exercise for at least 45 minutes per day, walking to near maximal pain.	3 x 60 min/week for 6 months	Physiotherapy department	Treadmill walking	• Each class consisted of a 5 minute warm up, 50 minutes of exercise and a 5 minute cool down. • Patients started walking at 2mph and 0% until pain became severe, then rested. Increased speed by 0.5mph or grade by 1%-2% every 10 minutes.
Nicolai 2010[56]	Advice only	• Verbal and written advice to exercise three times per day. • During each session, near maximal pain level should be reached three times.	2-3 x 30 min/week for 12 months	Local physiotherapy practice	Treadmill walking	• Interval training; encouraged to perform at least three walking sessions per day, walking to sub-maximal pain with short intervals. • Also included walking pattern improvement and endurance and strength exercises.
Pinto 1997[57]	Education, advice, exercise journal and weekly in-person support	• Attended weekly lecture and verbally advised to walk for 20-40 minutes at least 3 times per week to near maximal pain. • Asked to record pause durations in home log. • Vascular nurses provided feedback	3 x 30 min/week for 3 months	Not specified	Weekly education, treadmill walking, cycling	• 20 minutes stationary or arm cycling followed by walking. Initially, speed was set to produce maximum pain at 3-5min, then asked to rest. • Exercise log was kept. • Patients also attended a weekly lecture as per the control group.

		prior to weekly lecture.				
Regensteiner 1997[58]	Detailed advice and weekly telephone support	• Detailed, personalised written advice to walk for between 35 to 50 minutes at least three times per week. • Advised to walk to near maximal pain. • Patients contacted weekly by telephone to provide feedback and encouragement.	3 x 60 min/week for 3 months	Hospital gym	Treadmill walking	• Walked until a moderate level of pain developed, then asked to rest. Began at 35 minutes per class, increasing by 5 minutes to a total of 50 minutes while also gradually increasing speed and grade.
Savage 2001[59]	Advice and monthly telephone support	• Verbal advice to exercise 3 times per week, walking to the point of maximal pain, then resting, gradually increasing to 40 minutes each time. • Contacted by telephone every month to provide feedback and encouragement.	3 x 40 min/week for 3 months	Hospital gym	Treadmill walking	• Walked at 2mph at 60% of max intensity achieved in initial test. Walked to the point of intense pain, then rest. Began at 15minutes per class, increasing to a total of 40 minutes.
Stewart 2008[60]	Advice only	Not specified	2 x 60 min/week for 3 months	Hospital gym	Circuit training	• Five different exercises per class with 8 minutes spent at each. Ten minutes warm up & cool down. Patients asked to rest when pain became intolerable. • Exercises could all be performed at home; no treadmills used. • Asked to continue to exercise at home following programme completion.
Tew 2009[61]	Advice only	• Verbal advice on benefits of an active lifestyle.	2 x 20-40 min/week for 3 months	Exercise laboratory	Arm-crank exercise	• Trained in cycles of 2 minutes of crank exercise at a rate of 50 rev. /min, followed by two minutes of rest. • Intensity was increased to maintain a 'somewhat hard' rating of perceived exhaustion.

Tisi 1997[62]	Advice only	• Verbally encouraged to exercise at least 45 minutes each day in the home and walk 1 mile daily.	1 x 60 min/week for 1 month	Not specified	Leg exercises	• Series of active and passive leg exercises performed to the limit of claudication pain. • Also encouraged to exercise for at least 45 minutes per day and walk 1 mile daily.
Treat-Jacobson 2009[63]	Advice, exercise journal, weekly in-person support	• Provided with IC-specific, standardised written exercise instructions and exercise log. • Advised to exercise at moderate intensity exercise (walking), for a minimum of 30 minutes a session, at least three times per week.	3 x 70 min/week for 3 months	Exercise laboratory	Treadmill walking	• Began walking at 2 mph at 0% grade. Walked until onset of moderately severe pain, then asked to rest. Once able to walk for 8 minutes, grade increased by increments of 0.5% until 8-10% grade achieved , then speed increased in increments of 0.1 – 0.2 mph.
Zwierska 2005[64]	Advice only	• Verbally encouraged to exercise regularly.	2 x 40 min/week for 6 months	Exercise laboratory	Arm- and leg- cranking exercises	• Cycles of 2 minutes of exercise at a rate of 50 rev. /min, followed by two minutes of rest. Initial intensity was 9W with power output increased by 7W and 14W per increment in the arm-cranking test and leg-cranking test, respectively.

Table 28: Clinical evidence profile: Supervised exercise compared to unsupervised exercise for people with intermittent claudication due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Supervised exercise**	**Unsupervised exercise**	**Relative (95% CI)**	**Absolute**	
Quality of life at 6 months											
1 Kakkos, 2005[55]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	12	9	See Table 32		LOW

Quality of life at 1 year											
1 Kakkos, 2005[55]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	12	9	See Table 32		LOW
Withdrawal at 3 months											
1 Stewart, 2008[60]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	2/30 (6.7%)	2/30 (6.7%)	RR 1 (0.15 to 6.64)	0 fewer per 1000 (from 57 fewer to 376 more)	VERY LOW
Withdrawal at 6 months (random effects)											
2 Kakkos, 2005; Stewart, 2008[55,60]	RCT	Serious[(a)]	Serious[(d)]	No serious indirectness	Very serious[(c)]	None	7/42 (16.7%)	7/39 (17.9%)	RR 1.03 (0.18 to 5.81)	5 more per 1000 (from 147 fewer to 863 more)	VERY LOW
Withdrawal at 1 year											
1 Kakkos, 2005[55]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	6/12 (50%)	2/9 (22.2%)	RR 2.25 (0.59 to 8.65)	278 more per 1000 (from 91 fewer to 1000 more)	VERY LOW
ABPI at 6 months											
1 Zwierska, 2005[64]	RCT	Serious[(e)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	71	33	-	MD 0.01 lower (0.09 lower to 0.01 higher)	MODERATE

1 *(a) Unclear allocation concealment and blinding.*
2 *(b) No information on variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.*
3 *(c) 95% CI crosses both MIDs.*
4 *(d) Unexplained heterogeneity.*
5 *(e) Unclear randomisation process, allocation concealment and blinding.*

6 **Table 29: Clinical evidence profile: Supervised compared to unsupervised exercise for people with intermittent claudication due to unknown disease.**

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Supervised exercise**	**Unsupervised exercise**	**Relative (95% CI)**	**Absolute**	

Quality of life at 3 months										
3 Cheetham, 2004; Nicolai, 2010; Savage, 2001[54,56,59]	RCT	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	149	142	See Table 31 and Table 32	VERY LOW
Quality of life at 6 months										
3 Cheetham, 2004; Nicolai, 2010; Savage, 2001[54,56,59]	RCT	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	149	142	See Table 31 and Table 32	VERY LOW
Quality of life at 9 months										
2 Cheetham, 2004; Nicolai, 2010[54,56]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	138	132	See Table 31 and Table 32	LOW
Quality of life at 1 year										
2 Cheetham, 2004; Nicolai, 2010[54,56]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	138	132	See Table 31 and Table 32	LOW
Maximum walking distance at 3 months (combined end and change results)										
3 Savage, 2001; Tew, 2009; Treat-Jacobson, 2009[59,61,63]	RCT	Very serious[(d)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	71	42	-	MD 154.49 higher (85.73 to 223.26 higher)	VERY LOW
Maximum walking distance at 6 months (combined end and change results)										
2 Savage, 2001;	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	36	16	-	MD 136.74 higher (51.94 to 221.54	LOW

Treat-Jacobson, 2009[59,63]										higher)	
Pain free walking distance at 3 months (combined end and change results)											
3 Savage, 2001; Tew, 2009; Treat-Jacobson, 2009[59,61,63]	RCT	Very serious[(d)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	71	42	-	MD 74.71 higher (30.48 to 118.95 higher)	VERY LOW
Pain free walking distance at 6 months (combined end and change results)											
2 Savage, 2001; Treat-Jacobson, 2009[59,63]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	36	16	-	MD 76.32 higher (18.37 to 134.26 higher)	VERY LOW
Adverse events at 3 months											
1 Gardener, 2011[65]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Very serious[(g)]	None	3/33 (9.1%)	4/29 (13.8%)	RR 0.66 (0.16 to 2.7)	47 fewer per 1000 (from 116 fewer to 234 more)	VERY LOW
Percentage of sessions attended in 3 months of treatment											
1 Gardener, 2011[65]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	Unsupervised exercise - completed 82.5% of sessions (33 people) Supervised exercise - completed 84.8% of sessions (29 people)				VERY LOW
Withdrawal at 3 months											
2 Pinto, 1997; Treat-Jacobson, 2009[57,63]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Very serious[(g)]	None	7/60 (11.7%)	5/36 (13.9%)	RR 0.87 (0.27 to 2.79)	18 fewer per 1000 (from 101 fewer to 249 more)	VERY LOW
Withdrawal at 6 months											
2	RCT	Very	No serious	No serious	Very	None	20/60	10/36	RR 1.16	44 more per 1000	VERY LOW

Pinto, 1997; Treat-Jacobson, 2009[57,63]		serious[f]	inconsistency	indirectness	serious[g]		(33.3%)	(27.8%)	(0.58 to 2.32)	(from 117 fewer to 367 more)	
Withdrawal at 1 year											
1 Nicolai 2010[56]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[g]	None	16/109 (14.7%)	18/102 (17.6%)	RR 0.83 (0.45 to 1.54)	30 fewer per 1000 (from 97 fewer to 95 more)	LOW
ABPI at 3 months											
4 Regensteiner, 1997; Savage, 2001; Tew, 2009; Tisi, 1997[58,59,61,62]	RCT	Very serious[h]	No serious inconsistency	No serious indirectness	No serious imprecision	None	70	61	-	MD 0.02 lower (0.06 lower to 0.02 higher)	LOW
ABPI at 6 months (random effects)											
2 Savage, 2001; Tisi, 1997[59,62]	RCT	Very serious[f]	Serious[i]	No serious indirectness	Very serious[g]	None	33	27	-	MD 0 lower (0.16 lower to 0.17 higher)	VERY LOW
ABPI at 1 year											
1 Tisi, 1997[62]	RCT	Very serious[f]	No serious inconsistency	No serious indirectness	Serious[e]	None	22	17	-	MD 0.1 lower (0.27 lower to 0.07 higher)	VERY LOW

(a) 1 of 3 studies had unclear methodology; 1 of 3 studies had unclear allocation concealment and blinding; 1 of 3 studies had low risk of bias.
(b) No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
(c) 1 of 2 studies had unclear allocation concealment and blinding and baseline differences; 1 of 2 studies had low risk of bias
(d) 2 of 3 studies had unclear methodology; 1 of 3 studies had unclear allocation concealment and blinding.
(e) 95% CI crosses one MID.
(f) Unclear methodology.
(g) 95% CI crosses both MIDs.
(h) 1 of 4 studies had unclear allocation concealment and blinding; 3 of 4 studies had unclear methodology.
(i) Unexplained heterogeneity.

Table 30: Study characteristics: Reason for withdrawal from exercise programmes

Study	Unsupervised exercise programme (n)	Supervised exercise programme (n)
3 months		
Treat-Jacobson 2009	2/8 Lost to follow-up (1) Study unrelated health problem (1)	4/33: Family crisis (3); Unrelated injury (1)
Stewart 2008	2/30 Withdrawal given without a reason (1) Aggravated back injury (1)	2/30 Fatal stroke (1) Aggravated back injury (1)
6 months		
Treat-Jacobson 2009	2/8 Lost to follow-up (1), Unrelated health problem (1)	12/33 Family crises (3), Unrelated injury (1), Lost to follow-up (2), Unrelated health problem (6)
Stewart 2008	4/30 Fatal stroke (1), Withdrew without giving a reason (2), Aggravated back injury (1)	3/30 Developed leg ulcer (1), Fatal stroke (1), Aggravated back injury (1)
Kakkos 2005	1/9 Due to development of rest pain and had a bypass	4/12[(a)] Due to: Fatigue, Bladder cancer, GI bleeding, Leg injuries, Personal choice
12 months		
Kakkos 2005	2/9 Withdrew consent (1), Developed rest pain and had bypass (1)	6/12 Fatigue, Bladder cancer, GI bleeding, Leg injuries, Personal choice withdrew consent
Nicolai 2010	18/102 Lack of motivation (7), CHD (1), CVA (1), Orthopaedic disease (2) Other concomitant disease (4), Death (3)	16/109 Lack of motivation (3), Progression of PAD (2), CHD (2), Orthopaedic disease (2), Diabetic foot (1), Other concomitant disease (3), Death (4)

(a) Numbers attributed to each reason not reported within the study.

1 **Table 31: EQ-5D: Unsupervised compared to supervised exercise**

Unsupervised exercise					Supervised exercise				
Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Nicolai 2010 & van Asselt 2011[56,67] – Mean (SD)									
0.62 ± 0.23	0.68 ± 0.23	0.69 ± 0.19	0.68 ± 0.23	0.66 ± 0.26	0.66 ± 0.2	0.69 ± 0.21	0.72 ± 0.17	0.73 ± 0.21	0.74 ± 0.2

2 **Table 32: SF 36 individual domain results and mapped EQ-5D values – unsupervised compared to supervised exercise**

	Unsupervised exercise					Supervised exercise				
	Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Cheetham 2004[54] - Median (IQR)										
PF	50 (20)	55 (NR)	55 (NR)	55 (NR)	55 (NR)	60 (20)	65 (NR)	70 (NR)	70 (NR)	70 (NR)
RP	56 (19)	53 (NR)	56 (NR)	56 (NR)	56 (NR)	75 (44)	75 (NR)	84 (NR)	81 (NR)	88 (NR)
BP	70 (36)	71 (NR)	70 (NR)	77 (NR)	71 (NR)	59 (29)	72 (NR)	71 (NR)	72 (NR)	72 (NR)
GH	59 (27)	56 (NR)	59 (NR)	63 (NR)	59 (NR)	67 (22)	65 (NR)	67 (NR)	70 (NR)	62 (NR)
V	53 (12)	53 (NR)	59 (NR)	56 (NR)	53 (NR)	56 (37)	56 (NR)	62 (NR)	65 (NR)	62 (NR)
SF	81 (37)	81 (NR)	81 (NR)	81 (NR)	81 (NR)	88 (50)	88 (NR)	88 (NR)	88 (NR)	88 (NR)
RE	67 (42)	71 (NR)	75 (NR)	67 (NR)	67 (NR)	67 (50)	67 (NR)	67 (NR)	67 (NR)	67 (NR)
MH	70 (40)	70 (NR)	70 (NR)	73 (NR)	70 (NR)	75 (35)	75 (NR)	80 (NR)	80 (NR)	75 (NR)
EQ-5D[(a)]	**0.65 (0.02)**	**0.71 (0.02)**	**0.70 (0.02)**	**0.73 (0.02)**	**0.71 (0.02)**	**0.71 (0.02)**	**0.76 (0.02)**	**0.79 (0.02)**	**0.79 (0.02)**	**0.78 (0.02)**
Kakkos 2005[55] – Median (IQR)										
PF	50 (30)	NR	60 (23)	NR	45 (25)	65 (14)	NR	65 (23)	NR	50 (30)
RP	100 (50)	NR	75 (38)	NR	50 (75)	50 (44)	NR	50 (12)	NR	0 (100)
BP	60 (45)	NR	62 (27)	NR	51 (43)	60 (27)	NR	70 (42)	NR	62 (43)
GH	35 (31)	NR	40 (14)	NR	40 (10)	35 (19)	NR	35 (13)	NR	50 (30)
V	60 (22)	NR	65 (24)	NR	50 (15)	70 (10)	NR	60 (25)	NR	50 (30)
SF	78 (11)	NR	72 (20)	NR	89 (78)	78 (20)	NR	78 (11)	NR	89 (22)
RE	33 (33)	NR	33 (0)	NR	67 (100)	0 (25)	NR	0 (33)	NR	0 (33)
MH	52 (28)	NR	44 (27)	NR	88 (36)	44 (20)	NR	56 (20)	NR	76 (20)
EQ-5D[(b)]	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**

Nicolai 2010[56] – Mean (SD)										
PF	52.4 (15.0)	59.4 (16.6)	61.3 (15.8)	55.4 (18.0)	59.0 (19.0)	52.8 (14.3)	61.7 (16.4)	65.9 (16.7)	62.3 (16.9)	65.1 (16.8)
RP	51.0 (40.8)	56.8 (38.0)	55.2 (39.0)	51.8 (40.8)	55.8 (39.8)	45.8 (39.1)	53.5 (40.7)	58.5 (38.9)	57.9 (39.0)	65.3 (36.2)
BP	52.0 (18.0)	54.5 (19.8)	56.1 (21.7)	51.9 (24.3)	55.8 (22.7)	51.1 (16.6)	57.4 (20.9)	61.2 (22.6)	60.9 (23.6)	64.8 (22.5)
GH	54.9 (13.0)	48.4 (21.5)	55.7 (12.1)	55.6 (12.2)	54.2 (12.8)	53.7 (12.6)	55.6 (12.8)	56.1 (12.1)	55.0 (12.6)	53.6 (14.3)
V	63.0 (20.3)	62.6 (21.1)	60.3 (18.3)	57.9 (21.2)	59.2 (19.8)	61.6 (18.7)	62.2 (18.3)	62.5 (19.2)	60.4 (19.6)	62.0 (18.9)
SF	79.9 (19.6)	79.5 (24.2)	78.6 (24.3)	72.4 (27.3)	75.4 (25.3)	77.1 (22.8)	80.6 (21.6)	79.0 (21.7)	76.7 (23.6)	81.7 (22.8)
RE	85.1 (29.0)	82.5 (34.8)	85.5 (29.4)	82.0 (32.4)	82.4 (34.9)	85.2 (32.6)	87.9 (29.0)	85.2 (30.5)	85.8 (29.6)	86.1 (29.1)
MH	76.4 (17.2)	75.2 (17.8)	72.8 (24.3)	73.5 (17.8)	74.6 (19.1)	75.5 (17.8)	76.4 (18.4)	76.4 (17.6)	74.4 (18.8)	74.9 (20.3)
EQ-5D[(a)]	**0.66 (0.01)**	**0.68 (0.01)**	**0.69 (0.01)**	**0.65 (0.01)**	**0.68 (0.01)**	**0.65 (0.01)**	**0.71 (0.01)**	**0.73 (0.01)**	**0.71 (0.01)**	**0.74 (0.01)**
Savage 2001[59] – Mean (SD)										
PF	45 (17)	61 (10)	54 (27)	NR	NR	54 (14)	60 (16)	56 (14)	NR	NR
RP	47 (47)	68 (43)	47 (46)	NR	NR	84 (30)	77 (34)	84 (19)	NR	NR
BP	50 (13)	72 (23)	64 (14)	NR	NR	59 (20)	70 (18)	65 (19)	NR	NR
GH	67 (9)	65 (17)	65 (19)	NR	NR	71 (17)	64 (14)	66 (18)	NR	NR
V	49 (22)	47 (6)	52 (19)	NR	NR	66 (17)	68 (17)	63 (16)	NR	NR
SF	85 (19)	90 (15)	85 (20)	NR	NR	91 (11)	92 (10)	91 (10)	NR	NR
RE	75 (46)	81 (38)	74 (43)	NR	NR	97 (10)	82 (35)	71 (45)	NR	NR
MH	83 (13)	74 (17)	65 (31)	NR	NR	79 (16)	82 (12)	73 (17)	NR	NR
EQ-5D[(a)]	**0.66 (0.03)***	**0.76 (0.03)***	**0.68 (0.04)***	**NA**	**NA**	**0.68 (0.03)***	**0.74 (0.03)***	**0.69 (0.03)***	**NA**	**NA**

(a) Mapped based on algorithm (Equation1) reported by Ara and Brazier 2008[66]
(b) Not estimable based on median values of 0.
Abbreviations: PF = physical function; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role emotional; MH = mental health; SD= standard deviation; IQR = interquartile range; NA = not applicable; NR = not reported.

9.2.112 Economic evidence

Two cost-utility analyses were included from the economic literature search. Both studies were based on clinical trials with a time horizon of one year. The analysis by van Asselt 2011[67] was based on an RCT included in the current clinical review. Using bootstrap analysis, this study reported there was only a 35% probability that supervised exercise was cost effective at a threshold of £20, 000. The study by Lee 2007[68] concluded that supervised exercise is cost effective compared to unsupervised exercise in a UK NHS setting. However, the evidence used to inform this analysis was taken from a non-randomised trial with a non-preference based method of QALY calculation. Study characteristics and a summary of results are presented in Table 33. Detailed economic evidence tables can be found in appendix I.

The GDG considered compliance to the prescribed exercise programme (i.e. the proportion of people continue to exercise long-term following either intervention) to be a key factor for determining the long term cost-effectiveness of supervised exercise. Neither of the included studies was thought to sufficiently capture the long-term compliance to each type of treatment nor were they designed to evaluate the benefit to cardiovascular health that is associated with exercise. Therefore, an original economic model was developed using data collected from the clinical review and supplementary evidence where required.

9.2.113 Original economic model

NB: A detailed report of the methods and results of this model can be found in Appendix K.

Methods

A cost-utility analysis was undertaken to evaluate the cost-effectiveness of unsupervised compared to supervised exercise for the treatment of IC. A Markov model (see Figure 2) was used to estimate the lifetime quality-adjusted life years (QALYs) and costs from a UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. The model was built probabilistically to take into account uncertainty surrounding each of the model input parameters.

Approach to modelling

Intermittent claudication (IC) is associated with an increased mortality and risk of cardiovascular morbidity, and a decreased quality of life. Participation in regular physical activity is associated with a reduction in the risk of cardiovascular events, greater life expectancy, and an improvement in quality of life.

However, the benefits of exercise therapy are lost if the person ceases to be active. Improvements in cardiovascular function that occur with exercise rapidly deteriorate with inactivity or a reduction in the volume of exercise training[69] and there is evidence that the quality of life gain reported by people who have completed an exercise programme is only maintained if individuals continue be active.[70] The model therefore contains two primary health states: active and sedentary. The 'active' state was used to describe people who maintain a similar level of activity to that reported in the clinical trials. The level of activity described by the trials closely matches the definition of an 'active' lifestyle used by several other sources included in the model, including the 2006 Health Survey for England.[a] 'Sedentary' was used to describe people who are less active or inactive.

a The HSE defines an active lifestyle as undertaking 30 minutes or more of moderate of vigorous physical activity on one to four days per week.

Table 33: Economic evidence profile: Unsupervised exercise vs. supervised exercise

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Lee 2007[68]	Serious limitations[(a)]	Directly applicable[(b)]	• Cost utility analysis based on a non-randomised trial by Lee 2007[68] • Population: People with IC • Time horizon: 1 year • Costs: Supervised exercise programme • Perspective: UK NHS	Supervised exercise was £52 more costly than unsupervised exercise	Supervised exercise resulted in a gain of 0.027 QALYs compared to unsupervised exercise	Supervised exercise cost £1, 935 per QALY gained	• Not evaluated by authors.
Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study[67]	Minor limitations[(c)]	Partially applicable[(d)]	• Cost utility analysis based on RCT by Nicolai 2010[56] • Population: People with IC • Time horizon: 1 year • Costs: All healthcare and non-healthcare costs based on retrospective patient questionnaire • Perspective: Netherlands, societal	Supervised exercise was £874 more costly than unsupervised exercise	Supervised exercise resulted in a gain of 0.038 QALYs compared to unsupervised exercise	Supervised exercise cost £22, 997 per QALY gained	There was a 20% probability that supervised exercise is cost-effective based on bootstrap analyses.

(a) Non-randomised sources of clinical effectiveness included studies evaluated exercise programmes of different durations.
(b) No preference weighting assigned to SF-36 scores (invalid QALY valuation); short time horizon.
(c) Societal perspective; short time horizon.
(d) Dutch healthcare setting.

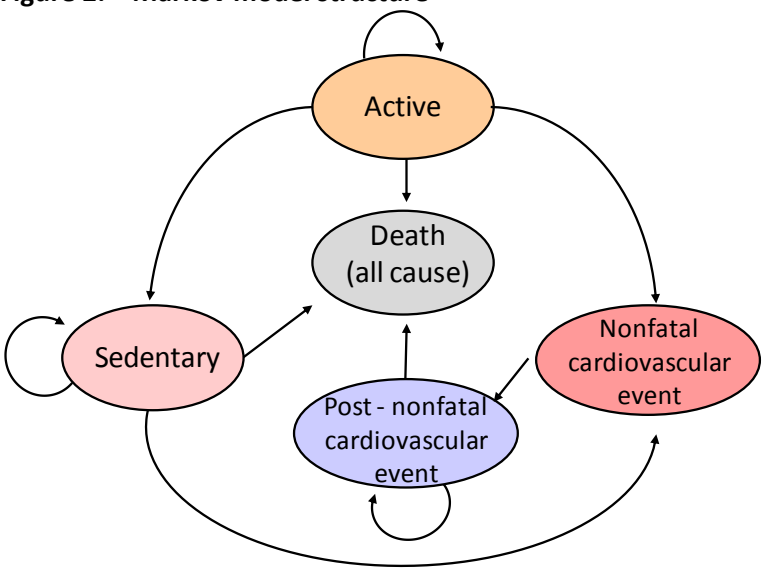
The main assumption of the model was therefore that compliance to the recommended level of physical activity is needed to provide the benefits associated with these programmes. People who revert to a sedentary state were assigned baseline cardiovascular risk, mortality and quality of life estimates. As a necessary simplification, it was assumed that those who stop exercising remain sedentary. Please see Appendix L for the model evaluating sequential exercise and endovascular interventions.

In order to explore the impact that different levels of compliance have on the cost and effects of each type of programme, two different scenarios were modelled: in Scenario 1, supervised exercise leads to greater short and long term compliance; and in Scenario 2, supervised exercise leads to greater short term compliance and no difference in long term compliance.

As a necessary simplification, people who experience a cardiovascular event enter a semi-absorbing health state from which the only available transition is death. Average costs and quality of life associated with post-cardiovascular event states were applied to this health state, and the same mortality rate as sedentary people was assumed.

The GDG decided to use the quality of life data from the RCTs included in the clinical review as the primary measure of clinical effectiveness. The group were aware that other models, such as the TA developed by Squires 2010[51], used maximum walking distance (MWD) as a proxy for calculating QALY values. However, the GDG agreed that this was an inferior measure of effectiveness when quality of life outcomes were directly available from the included RCTs.

Figure 2: Markov model structure



Schematic diagram of the Markov model designed to compare the cost-effectiveness of supervised to unsupervised exercise programmes for the treatment of people with IC. The Markov modelling approach involves a transition between different health states over time. The model is divided into three month cycles. At the end of each cycle a time-dependant transition to another health state is possible, unless people enter into an 'absorbing state' from which they do not recover. In this model, the absorbing state is death.

Baseline mortality and relative risk associated with exercise

Age- and sex-specific all cause mortality was based on the most recent available life tables of the general population in England and Wales. Rates were adjusted for people with IC by multiplying by the standardised risk of all cause mortality observed over 10 years in people with IC.[71]

No randomised evidence of exercise-associated risk of mortality in people with IC was identified. The GDG agreed that evidence from people with cardiovascular disease would represent a reasonable proxy. A recent Cochrane review of randomised controlled trials was therefore used to inform the risk of total mortality among people participating in exercise rehabilitation compared to non-active controls.[72] A summary of the values used to inform this parameter is provided in Table 34. The GDG discussed the limitations of using an indirect population to inform this parameter and the effect of this value on the model result was further explored in sensitivity analysis.

Table 34: Total mortality

	10-year total mortality for the general population based on Life Tables for England and Wales[(a)]	Relative risk of total mortality in people with IC compared to those without IC	Relative risk of total mortality in people who exercise compared to those who do not exercise
Mortality	25.0%	3.1 (95% CI, 1.9 to 4.9)[71]	0.87 (95% CI , 0.75 to 0.99)[72]

(a) Assuming that the average age of the baseline population is 67 years and 66% are male.

Baseline risk of cardiovascular events and relative risk associated with exercise

The average baseline probability of stroke and MI was calculated by age and gender using the Framingham risk equations and risk calculator spreadsheet developed by Rupert Payne at the University of Edinburgh.[73,74] Risk factor inputs for each sex were obtained from the 2006 Health Survey for England (HSE; Table 35).[75] Average age- and sex- specific blood pressure values were obtained from the 2011 NICE Hypertension update guideline[76], which used individual patient level data from the 2006 HSE. A recent study by the Ankle Brachial Index Collaboration found that when combined with Framingham risk scores, an ABPI of between 0.61 and 0.70 approximately triples the risk of major cardiovascular events for men and women.[77]

The risk of myocardial infarction (MI) in patients who exercise compared to those who are not active in an exercise programme was obtained from the Cochrane review by Heran et al (2011).[72] A meta-analysis of the effect of physical activity on the incidence of stroke was used to inform the risk of stroke for active compared to sedentary people in the model.[78] A summary of the values used to inform these parameters is provided in Table 35. As with estimates of the relative risk of total mortality, these data sources are subject to several limitations and the effect of these values on the model were explored in sensitivity analysis.

Table 35: Major cardiovascular events

	10 year risk of MI and stroke for general population according to the Framingham equations[(a)]	Relative risk of major cardiovascular events in people with IC compared to those without IC[(b)]	Relative risk of MI and stroke in people who exercise compared to those who do not exercise
MI	7.2%	Men: 2.71 (95% CI, 2.01 to 3.64) Women: 3.82 (95% CI, 2.86 to 5.11)	0.97 (95% CI, 0.82 to 1.15)[72]
Stroke	4.4%	Men: 2.71 (95% CI, 2.01 to 3.64) Women: 3.82 (95% CI, 2.86 to 5.11)	0.80 (95% CI, 0.74 to 0.86)[78]

(a) Calculated using Framingham MI and stroke risk equations[73,74] and risk factor inputs derived from the 2006 Health Survey for England[75], assuming that the average age of the baseline population is 67 years and 66% are male.

(b) Based on a risk of cardiovascular events for mean and women with an ABPI of 0.61 to 0.7 compared to men and women with normal ABPI.[77]

Quality of life

In cost-utility analyses, measures of health benefit are valued in terms of quality adjusted life years (QALYs). The QALY is a measure of a person's length of life weighted by a valuation of their health

related quality of life (HRQoL) over that period. The quality of life weighting comprises two elements: the description of changes in HRQoL and an overall valuation of that description. Questionnaires such as the SF-36 and SF-12 provide generic methods of describing HRQoL while the EQ-5D, HUI, and SF-6D also include preference-based valuations of each health state.

Quality of life data was collected from all RCTs included in the clinical review (see Appendix H). One study included the EQ-5D as a measure of HRQoL.[56] Five papers (representing an additional four trials) reported SF-36 data.[54-57,59] According to the NICE reference case[10], EQ 5D data is the preferred measure of quality of life for use in cost utility analyses. Therefore, in the base case analysis, the EQ-5D values reported by the EXITPAD study were used in preference to SF-36.

Recently, several algorithms have been developed which can be used to map generic descriptions of HRQoL to preference-based utility indexes. In 2008, Ara and Brazier[66] published a method of predicting mean EQ-5D preference based index score using published mean cohort statistics from the eight dimensions of the SF-36 health profile. In order to use these algorithms, values for each of the eight dimensions of the questionnaire are required. Two[55,59] provided all the necessary values and the authors of the remaining three studies[54,56,57] were contacted to request the required data.

Nicolai 2010 and Cheetham 2004 granted access to mean SF-36 scores and permission to include it in the current analysis. The authors of the study by Pinto 2001 were unable to provide similar data as it was no longer available. The data reported by Kakkos and colleagues 2005 was found to produce invalid values for mapping and was excluded. Therefore, of the eleven RCTs identified in the clinical review, those by Cheetham 2004[54], Nicolai 2010/van Asselt 2011[56,67] and Savage 2001[59] were used to calculate quality of life following supervised and unsupervised exercise programmes.

Mapping SF-36 to EQ-5D using published algorithms and probabilistic simulation

For each trial, it is the change in quality of life over time and the difference in this change between interventions (i.e. mean difference in change) that is the key to determining the relative effectiveness of each intervention. In order to calculate the mean difference in change between each three month time interval while taking into account the uncertainty surrounding each estimate, the mean and standard error of each dimension of the SF-36 were assigned a beta distribution according to the method of moments described by Briggs 2006.[79] Probabilistic mapped values were then calculated using Equation 4 from the paper by Ara and Brazier[66], who specify that 'when comparing incremental differences between study arms or changes over time, Equation 4 is the preferred choice'. A simulation was run 10, 000 times in order to calculate a mean, standard error and confidence interval surrounding each mapped estimate. For the purposes of clinical validation, absolute mean mapped values were calculated using Equation 1 according to the same method.

Note that mean difference in change calculated using Equation 4 is not expected to equal the incremental difference between the mean mapped values from Equation 1 as they are derived using different models. Alternative methods of calculating relative differences in quality of life between treatment arms were explored in sensitivity analysis. Note also that because the covariance matrices for the regression coefficients were not available it was not possible to account for uncertainty in the mapping algorithm in the probabilistic analysis.

Inputs and assumptions used to inform model utilities

In the base case analysis, an average utility value was weighted according to the total number of people in the study at each time point and entered into the probabilistic model using a beta distribution. In order to preserve within-study randomisation, the weighted average incremental change in quality of life associated with supervised exercise as calculated by the probabilistic simulation described above was added to the baseline quality of life across the two trials. Quality of life gains achieved after exercise intervention were maintained for people who continued to exercise. Those who stopped exercising were assigned the baseline quality of life.

The weighted average absolute values and weighted mean difference in change are reported in Table 36. Please see Appendix K for further details.

Table 36: Quality of life

	Weighted average (SE) quality of life[(a)]		Weighted average (SE) baseline quality of life	Weighted mean (SE) difference in change between each follow-up interval[(b)]
	Unsupervised	Supervised		
Baseline	0.636 (0.017)	0.672 (0.014)	0.654 (0.011)	
3 months	0.692 (0.017)	0.709 (0.015)		-0.021 (0.033)
6 months	0.692 (0.014)	0.732 (0.013)		0.026 (0.032)
9 months	0.692 (0.018)	0.744 (0.016)		0.010 (0.034)
12 months	0.671 (0.023)	0.748 (0.017)		0.029 (0.039)

(a) Calculated based on Equation 1 from Ara and Brazier 2008[66] and weighted according to the number of patients in each trial.
(b) Calculated based on Equation 4 from Ara and Brazier 2008[66] and weighted according to the number of patients in each trial. Positive values indicate a net benefit of supervised exercise. Note that these values do not equal the mean difference in change between absolute weighted mean values because they are calculated using different mapping equations.
Abbreviation: SE = standard error of the mean.

Costs

The cost of a supervised programme was based on estimates of resource use informed by expert opinion and unit costs obtained from the 2010 PSSRU. A breakdown of the assumptions and unit costs used to calculate per-patient cost of a supervised exercise programme are provided in Table 37.

Because the cost of the initial GP consultation is common to both supervised and unsupervised exercise, it is not included in the cost of either intervention arm (i.e. it 'cancels out'). The cost of unsupervised exercise was therefore set at £0. This was varied in sensitivity analysis to account for different levels of support provided by different types of unsupervised programmes.

Table 37: Cost of a 3 month supervised exercise programme

Programme duration and intensity	
Two hours of class per week for three months (13 weeks)[(a)]	
Ten people per class[(b)]	
Resource use	**Unit cost**
Two physiotherapists[(b)]	£37 (x2) per hour[(c)]
One physiotherapist technician[(b)]	£22 per hour[(c)]
Room hire and equipment rental[(b)]	£15 per hour[(b)]
Associated cost of supervised exercise programme	
Total programme cost (per 10-person group)	£2, 886
Total programme cost per patient	**£288**

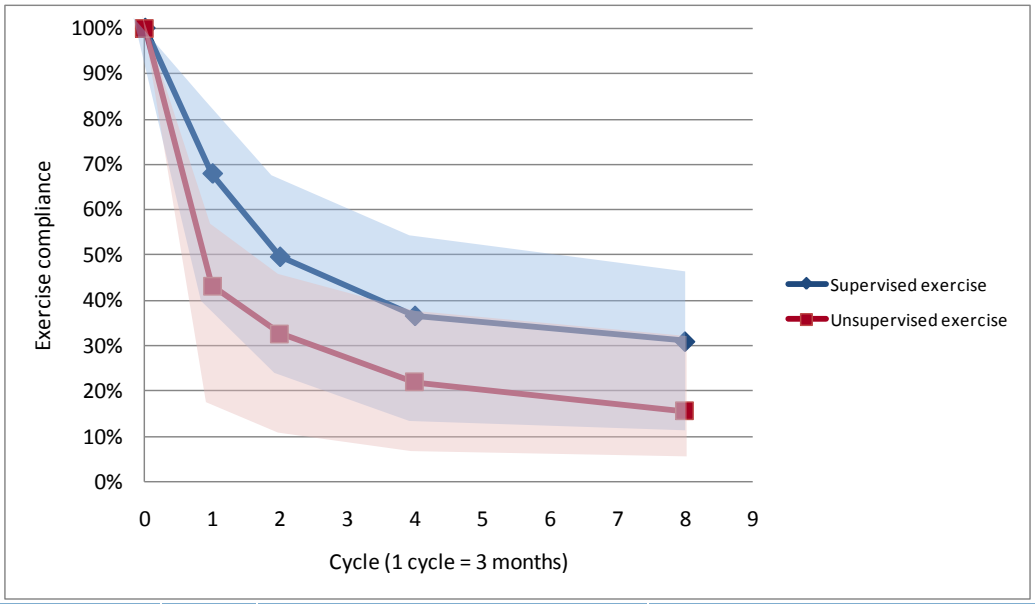
(a) Average length and duration of exercise programmes evaluated by RCTs included in clinical review (see Table 27).
(b) Based on expert opinion (with thanks to Lysa Downing, Ricky Mullis and Martin Fox): several GDG members sent requests for information to their clinical colleagues and commissioning managers and responses were received from around the country. A number of different models were described and discussed by the GDG. The resource use described in the table was thought to represent the typical pattern for outpatient care for people with IC.
(c) Obtained from the 2010 PSSRU[80]

The approach to modelling cardiovascular events was based on the model developed for the NICE hypertension guideline update (CG 127 http://www.nice.org.uk/Guidance/cg127).[76] As in the hypertension model, when people with IC experienced a cardiovascular event they were assigned an initial cost representing the acute management and/or diagnosis cost (MI = £4, 792; stroke = £9, 630). In subsequent cycles they were assigned an ongoing cost representing the average costs following an event (MI = £141; stoke = £559).

Compliance to supervised and unsupervised exercise

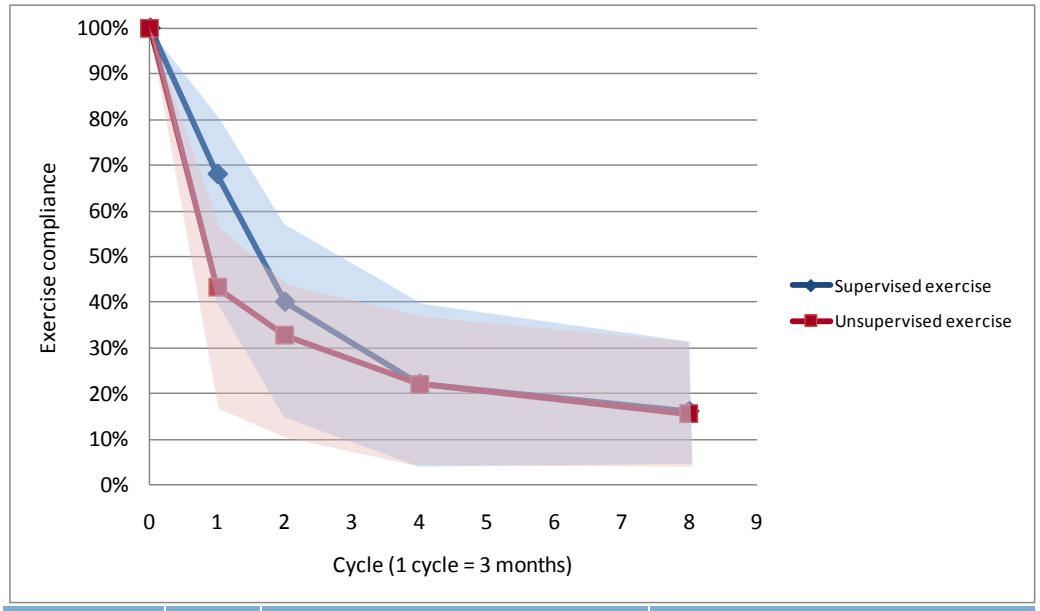
Several studies identified in the clinical review reported either total dropout rates or dropouts associated with each study arm (Table 30). However, the GDG did not consider compliance within a trial setting to be representative of real world behaviour. The literature was reviewed for estimates of short and long-term compliance to supervised and unsupervised exercise programmes in people with PAD, cardiovascular disease or older adults in the community; no relevant evidence was identified. Therefore, based on input from the GDG, two different scenarios were modelled: in Scenario 1, supervised exercise leads to greater short and long-term compliance (Figure 3); and in Scenario 2, supervised exercise leads to greater short term compliance and no difference in long-term compliance (Figure 4).

Figure 3: Scenario 1 – Greater long term compliance to supervised exercise



Time period	Cycle	Supervised			Unsupervised		
		Lowest	Most likely	Highest	Lowest	Most likely	Highest
3 months	1	40%	68%	83%	17%	43%	56%
6 months	2	25%	50%	66%	10%	33%	45%
1 year	4	14%	37%	54%	7%	22%	37%
2 years	8	12%	31%	47%	5%	16%	31%

Figure 4: Scenario 2 – Equal long term compliance to supervised and unsupervised

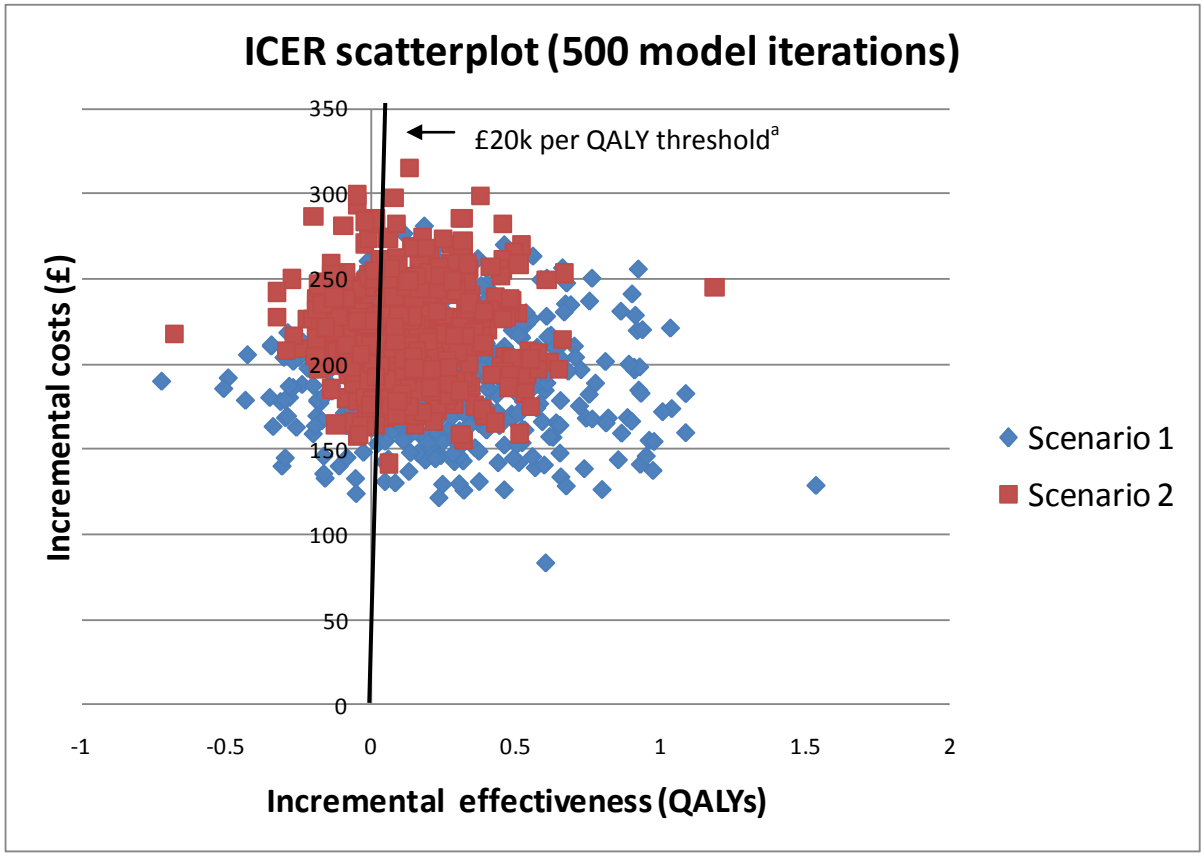


Time point	Cycle	Supervised			Unsupervised		
		Lower	Most likely	Upper	Lower	Most Likely	Upper
3 months	1	40%	68%	80%	17%	43%	56%
6 months	2	15%	40%	57%	10%	33%	45%
1 year	4	4%	22%	40%	7%	22%	37%
2 years	8	5%	16%	32%	5%	16%	31%

Results

This analysis found that supervised exercise is more cost effective than unsupervised exercise. By taking into account the standard error of each model input, probabilistic analysis revealed that if supervised exercise leads to greater compliance over both the short and long term, it is cost effective in 79% of model iterations at an average cost of £711 per QALY gained. If supervised exercise does not lead to an increase in activity levels over the long term, it remains cost effective in 75% of model iterations at an average cost of £1, 608 per QALY gained (Table 38).

Figure 5: Distribution of incremental costs and effects



[a] *Points lying to the right of the £20k threshold are considered cost effective.*

Table 38: Mean probabilistic results of cost effectiveness model

Strategy	Total Cost	Incremental Cost	Total QALYs	Incremental QALYs	Incremental cost per QALY	Probability of being CE
Scenario 1 – Greater long term compliance to supervised exercise						
Unsupervised	£2, 499	Baseline	5.082	Baseline	Baseline	21%
Supervised	£2, 690	£191	5.350	0.268	£711	79%
Scenario 2 – Equal long term compliance						
Unsupervised	£2, 499	Baseline	5.078	Baseline	Baseline	25%
Supervised	£2, 714	£215	5.212	0.134	£1, 608	75%

Disaggregating the results of the analysis by cost and QALYs allows us to examine the impact of key components of the model on the overall result. Table 39 illustrates that the cost of the supervised exercise programme is the major driver in cost differences between the two interventions. As would be expected, the cost associated with the prevention of cardiovascular events is greater in the scenario with greater difference compliance between interventions (Scenario 1), but in both scenarios the incremental cost associated with cardiovascular morbidity is relatively small. Table 40 shows the impact of the reduction in mortality attributed to people who continue to be active in terms of the difference in baseline QALY gain between the two interventions. Although the reduction in mortality associated with exercise plays a role in driving the results of the model, this table illustrates that the main driver in the difference in quality of life between the two exercise strategies is the difference in quality of life associated with the intervention itself. The effect of cardiovascular morbidity on the results of the model is negligible.

Table 39: Breakdown of total costs (probabilistic)

	Unsupervised exercise	Supervised exercise	Incremental cost of supervised exercise
Scenario 1- Greater long term compliance to supervised exercise			
Supervised exercise programme	£0	£219	£219
Initial CV events	£1, 186	£1, 176	£-10
Follow-up CV event	£1, 259	£1, 241	£-18
Scenario 2– Equal long term compliance			
Supervised exercise programme	£0	£219	£219
Initial CV events	£1, 186	£1, 184	£-2
Follow-up CV event	£1, 259	£1, 256	£-3

Table 40: Breakdown of total QALYs (probabilistic)

	Unsupervised exercise	Supervised exercise	Difference (Supervised – Unsupervised)
Scenario 1- Greater long term compliance to supervised exercise			
Baseline quality of life	5.191	5.230	0.039
Supervised exercise programme	0.000	0.250	0.250
CV events (initial and follow-up)	-0.010	-0.010	0.000
Scenario 2– Equal long term compliance			
Baseline quality of life	5.185	5.189	0.004
Supervised exercise programme	0.000	0.132	0.132
CV events (initial and follow-up)	-0.010	-0.010	0.000

Sensitivity analysis

A wide range of sensitivity analyses were undertaken to explore the effect of different parameter inputs and assumptions on the results of the model. The results of these sensitivity analyses showed that supervised exercise is the most cost effective strategy under the majority of data sources and assumptions tested. The exception to this was if all key assumptions about the benefits of exercise were removed from the model. If we do not extrapolate quality of life beyond the trial end dates and do not include any measure of mortality or cardiovascular benefit in people who are active, supervised exercise programmes are unlikely to be cost effective compared to unsupervised exercise. The full results of all sensitivity analyses are presented in Appendix K.

Interpretation and limitations

The clinical review was not designed to distinguish between trials of varying length, duration or exercise intensity. As such, it is not possible to determine whether certain types of supervised programmes are more cost effective than others. For this guideline, the definition of each type of exercise programme was based on a simple average of studies included in the clinical review. The supervised exercise programme described by this method was also found to match programmes familiar to the GDG.

Currently, no published RCT data exist to inform the relative risk of cardiovascular events and mortality in people who exercise compared to those who do not in people with IC. The data used in this model was obtained from two meta-analyses of trials conducted in two different populations: people with CHD who had experienced MI or coronary revascularisation and a mixed population of people who had and had not had a stroke.

Limited published data was available to inform the impact of each type of exercise programme on quality of life beyond one year. Although this data was not comparative, it suggested that quality of life is maintained in those who continue to exercise; this was a key assumption of the analysis. If this assumption is removed from the model, there is still a high probability that supervised exercise is cost effective under the level of compliance suggested by Scenario 1, but there is a higher level of uncertainty under Scenario 2.

The effectiveness of supervised and unsupervised exercise programmes is directly related to the ability of each intervention to produce a lasting change on the activity levels of participating individuals. Currently, data about the short and long term compliance to these regimens is not available in the public domain. In the absence of this evidence, the GDG and their colleagues were surveyed in order to elicit an expert opinion on which to base this parameter. The resulting estimates that were used to inform the model represent the group's most plausible scenarios for a population of people with IC based on their clinical experience. However, long term data from real clinical practices is needed to better inform future modelling in this area.

9.2.2 Evidence statements

9.2.2.1 Clinical

Intermittent claudication due to aorto-iliac disease:

No clinical evidence was reported for people with IC due to aorto-iliac disease.

Intermittent claudication due to femoro-popliteal disease:

There was no statistically significant difference between supervised exercise and unsupervised exercise for:

- Withdrawal at 3 months [1 study, 60 participants, very low quality evidence][60]
- Withdrawal at 6 months [2 studies, 81 participants, very low quality evidence][55,60]
- Withdrawal at 1 year [1 study, 21 participants, very low quality evidence][55]
- ABPI at 6 months [41 study, 104 participants, moderate quality evidence][64]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Quality of life increased in most SF-36 domains for both supervised exercise and unsupervised exercise at 6 months [1 study, 21 participants, low quality evidence][55]
- Quality of life decreased in most SF-36 domains for both supervised exercise and unsupervised exercise at 1 year [1 study, 21 participants, low quality evidence][55]

Intermittent claudication - unknown disease location:

Supervised exercise was significantly better than unsupervised exercise for:

- Maximum walking distance at 3 months [3 studies, 113 participants, very low quality evidence][59,61,63]
- Maximum walking distance at 6 months [2 studies, 52 participants, low quality evidence][59,63]
- Pain free walking distance at 3 months [3 studies, 113 participants, very low quality evidence][59,61,63]
- Pain free walking distance at 6 months [2 studies, 52 participants, very low quality evidence][59,63]

There was no statistically significant difference between supervised exercise and unsupervised exercise for:

- Adverse events at 3 months [1 study, 62 participants, very low quality evidence][65]
- Withdrawal at 3 months and 6 months [2 studies, 96 participants, very low quality evidence][57,63]
- Withdrawal at 1 year [1 study, 211 participants, low quality evidence][56]
- ABPI at 3 months [4 studies, 131 participants, low quality evidence][58,59,61,62]
- ABPI at 6 months [2 studies, 60 participants, very low quality evidence][59,62]
- ABPI at 1 year [1 study, 39 participants, very low quality evidence][62]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- Quality of life increased for both supervised exercise and unsupervised exercise at 3 months [3 studies, 291 participants, very low quality evidence][54,56,59]
- Quality of life mostly increased for supervised exercise and mostly decreased for unsupervised exercise at 6 months [3 studies, 291 participants, very low quality evidence][54,56 59]
- Quality of life mostly increased for supervised exercise and mostly decreased for unsupervised exercise at 9 months [2 studies, 270 participants, low quality evidence][54,56]
- Quality of life mostly increased for supervised exercise and mostly decreased for unsupervised exercise at 1 year [2 studies, 270 participants, low quality evidence][54,56]
- One study showed people treated with supervised exercise completed 84.8% of sessions during 3 months of treatment compared to people treated with unsupervised exercise completed 82.5% of sessions during 3 months of treatment [1 study, 62 participants, very low quality evidence][65]

9.2.22 Economic

- One trial-based study concluded that unsupervised exercise was more cost effective than supervised exercise in 65% of patients [partially applicable with minor limitations][67]
- One trial-based cost-utility evaluation concluded that supervised exercise is more cost effective than unsupervised exercise [directly applicable with potentially serious limitations][68]
- According to the results of an original economic model based on the current clinical evidence review and GDG input, it is highly likely that supervised exercise represents a cost effective treatment for people with IC [directly applicable with minor limitations]

9.203 Recommendations and link to evidence

Recommendation	9. **Offer a supervised exercise programme to all people with intermittent claudication.**
Relative values of different outcomes	The GDG were interested in whether supervised exercise programmes would influence mortality as well as quality of life, but the available studies did not address this issue. The absolute change in maximum walking distance (MWD) and quality of life were considered to be the most important outcomes in measuring success of exercise interventions. MWD is the most widely reported outcome in studies for intermittent claudication. Improvement can be reported as absolute or percentage change in MWD; there is value in knowing both, although the GDG agreed that the absolute change was more important. It was also recognised that exercise is likely to have additional benefits such as improvements in psychological or emotional well-being that should be captured by changes in

	quality of life measures. Overall the studies suggested that participation in a supervised exercise programme was associated with a greater improvement in MWD. The GDG placed less importance on changes in ABPI and pain free walking distance (PFWD). This was because they did not expect ABPI to be greatly affected by the different exercise programmes (as clinical benefit is more likely to be due to improved muscle metabolism rather than blood flow) and because PFWD was considered too subjective a measure of improvement to allow meaningful comparisons between individuals and studies. None of the studies reported data on cardiovascular events or limb loss, although these outcomes were felt to be of less importance in IC than CLI.
Trade off between clinical benefits and harms	Based on their collective clinical experience, the GDG agreed that the risks associated with a supervised exercise programme are minimal, while the benefits may include an increase in walking distance, quality of life, and decreased risk of cardiovascular events. Both exercise interventions require a time commitment from the patient. Supervised exercise may also be associated with transportation costs. These considerations should be discussed with each patient on an individual basis.
Economic considerations	An original economic model was developed to combine best available evidence on the efficacy of supervised compared to unsupervised exercise for the treatment of IC. The primary outcome of the model was quality of life as reported by the RCTs included in the clinical review. The cost of a supervised exercise programme was calculated from an NHS and social services perspective. Quality of life and costs associated with cardiovascular events were also included, as was the decreased risk of mortality and cardiovascular events experienced by people who are physically active. Compliance to exercise was a key component of the model; two theoretical compliance scenarios were included in the base case analysis. Based on the results of the model, supervised exercise is a cost effective treatment choice in over 75% of model simulations. Although supervised exercise is more expensive than unsupervised, it is also more effective. If we assume that supervised exercise leads to greater compliance over both the short and long term, these programmes cost approximately £711 per QALY gained. If we assume that there is no difference in exercise levels over the long term compared to unsupervised exercise, then supervised exercise programmes cost £1, 608 per QALY gained. The model was robust to the majority of sensitivity analyses surrounding key assumptions and data used to inform the model. However, the results were sensitive to the assumption that those who continue to exercise maintain the improvement in quality of life demonstrated at the end of one year. If the results of the intervention are not sustained beyond the end of each trial, the probability that supervised exercise is the most cost-effective option is much more uncertain. The results were also dependant upon assumptions about compliance to exercise over the short and long term. Two published papers reported health economic analyses and were also considered by the GDG.[67,68] They had a very short time horizon and did not take into account the expected beneficial effect of exercise on mortality and

	cardiovascular morbidity. These studies presented conflicting results and were not thought to be as relevant as the model developed for this guideline. Supervised exercise programmes for PAD are not widely available and the GDG recognised that this recommendation would likely have a significant implementation cost. However, the GDG considered that the basic infrastructure required may already exist within cardiology and respiratory services.
Quality of evidence	The following quality issues were highlighted by the GDG, relating both to the studies themselves and to difficulties in synthesising their results: • The effect size tended to be small • The included studies were rated moderate to very low quality by GRADE criteria • Trials differed in terms of types of exercise (upper versus lower body) • With interventions of this type, it is possible that improvements could be related to increased contact and attention from healthcare providers rather than a true effect of exercise • There is also a documented training effect of treadmill walking, which could have lead to greater walking distances in the supervised exercise group[81] • Limited data were available about withdrawals, but the GDG felt that the reported rates were lower than they would have expected based on their experience of real world behaviour in that those who are prepared to enter randomised trials involving supervised exercise were already pre-selected. In clinical practice the overall proportion prepared to participate in and continue with exercise programmes may be significantly lower • The definitions of intermittent claudication varied between trials • The long-term benefits of supervised exercise programmes are not clear in this population.
Other considerations	There is potential for confusion when considering exercise for IC. At one level, simple advice to exercise should be seen as part of the lifestyle changes that the patient should be advised about when the diagnosis of PAD is first made. It is more formal exercise intervention which is being considered in the clinical studies reviewed here. The GDG discussed access issues and noted that at present patients tend to be offered other interventional treatments ahead of supervised exercise. It was noted that some patients may lack motivation to undertake a programme and others may experience anxiety particularly if they have other co-morbidities such as angina. It is therefore considered important to discuss the choices available to the patient and recognise that some may prefer advice and instruction about unsupervised exercise. With patients undertaking exercise, there could be less need for secondary interventions and patients may have better cardiovascular outcomes. However, it was recognised that further research is required to assess the long term benefits of supervised exercise programmes for IC. It was agreed by the GDG that the benefits are likely to decrease with reduced compliance with exercise following completion of a programme. The GDG therefore made a research recommendation about monitoring long term effects. Based on the available evidence the GDG concluded that, in the absence of significant comorbidity where exercise would be contra-indicated, they could

	recommend that people with intermittent claudication should be offered a supervised exercise programme. The GDG identified the following features that should be included in an supervised exercise programme: • Although there is uncertainty about the best type of exercise for people with PAD, most of the programmes described in the evidence review involved walking to near maximal pain. The GDG agreed that patients should be encouraged to walk to the point of maximal pain • The frequency of the exercise programme should be approximately 2 hours per week for 3 months • The programme should be goal orientated and have a defined educational component i.e. discussions about lifestyle change, benefits of exercise for PAD patients and attitudes to the disease • Supervised exercise programmes should be managed by an experienced and suitably qualified healthcare professional • The location of the exercise programme should be as close to the person's home as possible. **Key priority for implementation** The GDG identified this recommendation as a key priority for implementation. Supervised exercise programmes appear to be a cost-effective intervention yet the GDG are aware that availability and access to such programmes varies geographically, which results in inequality. In addition, supervised exercise may be preferred by patients rather than undergoing revascularisation. Exercise can have a positive impact on patient outcomes, such as walking distance.

9.2.14 Research recommendation

2. What is the clinical and cost effectiveness of supervised exercise in comparison to unsupervised exercise for peripheral arterial disease, taking into account the effects on long-term outcomes and continuing levels of exercise?

Why this is important

Research has shown that taking part in exercise and physical activity can lead to improvements in symptoms in the short-term for people with peripheral arterial disease. However, the benefits of exercise are quickly lost if not taken on a frequent and regular basis. Supervised exercise programmes have been shown to produce superior results when compared with advice to exercise (unsupervised) in the short-term; but they are more expensive, and there is a lack of robust evidence on long-term effectiveness.

A community-based randomised controlled trial is required to compare the long-term clinical and cost effectiveness of a supervised exercise programme and unsupervised exercise. The trial should enrol people with PAD-related claudication, but exclude those with previous endovascular/surgical interventions.

The primary outcome measure should be maximal walking distance. Secondary outcome measures should include quality of life, function and long-term engagement in physical activity.

9.3 Naftidrofuryl oxalate

9.3.1 Review question

What is the clinical and cost effectiveness of naftidrofuryl oxalate compared to exercise therapy, angioplasty or stents for the treatment of intermittent claudication in adults with PAD?

NICE recently published a technology appraisal (TA 223) on "Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease".[51] The TA reviewed the evidence for the four named vasoactive drugs in treating IC not controlled by best medical treatment, which was the TA term for what is referred to as best medical treatment for PAD in section 9.1 above. Naftidofuryl oxalate was recommended as the preferred treatment. The technology appraisal did not examine evidence comparing the vasoactive drugs to exercise therapy, angioplasty or stents.

A literature search was conducted for RCTs that compared the effectiveness of naftidrofuryl oxalate to exercise therapy, angioplasty or stents. No limits were set on time, sample size or duration of follow-up. Indirect populations and emergency settings were excluded.

9.3.1 Clinical evidence

No relevant RCTs were identified.

9.3.2 Economic evidence

NICE TA exploratory analysis

The GDG were presented with a summary of the methods and results of the exploratory economic analysis conducted as part of the NICE TA comparing naftidrofuryl oxalate to angioplasty.[51] The GDG considered that this analysis was not based on comparative evidence; it represents an exploration of several theoretically possible outcomes of angioplasty compared to naftidrofuryl oxalate. The costs associated with angioplasty in the NICE TA analysis were based on the literature (procedural cost of £925[82]) and were very different from those estimated according to NHS Reference Costs [procedural cost of £3, 661 to £9, 367 (see Appendix L)]. The sensitivity analysis developed for the NICE TA was also limited in that only angioplasty was included as an alternative to vasoactive drugs (those in the 'no drug treatment' arm of the exploratory model all underwent angioplasty). The GDG considered exercise a more appropriate alternative for people with IC.

Original economic model

Methods

Without comparative clinical evidence it was not possible to evaluate the relative cost-effectiveness of vasoactive drugs compared to exercise programmes in the base case analysis. Instead, the GDG decided to incorporate the use of naftidrofuryl oxalate as a sensitivity analysis in the original economic model developed to compare unsupervised to supervised exercise. Costs and discontinuation rates associated with naftidrofuryl oxalate were obtained from the NICE TA and incorporated into the current model. As in the NICE TA, it was assumed that naftidrofuryl oxalate does not have any effect on the risk of mortality or cardiovascular events. Evidence of comparative efficacy (as measured by quality of life was left blank and a threshold analysis was run to determine the incremental gain in quality of life that would be necessary for naftidrofuryl to be considered cost-effective compared to supervised and unsupervised exercise. For a full discussion of the methods and

results of this model please refer to Appendix K. Parameter inputs used to inform threshold analysis of naftidrofuryl oxalate are reported in Table 41.

Table 41: Parameter inputs used to inform threshold analysis of naftidrofuryl oxalate

Parameter	Point estimate	Value range	Probability distribution	Distribution parameters	Source
3 month cost of naftidrofuryl oxalate	£30.49	NA	Fixed	NA	NHS Drug Tariff[83]
Discontinuation at 6 months	11%	NA	Fixed	NA	Squires 2010[51]
Discontinuation at 36 months	68%	NA	Fixed	NA	Hiatt 2008 in Squires 2010[51]
Relative effect on mortality[(a)]	1	NA	Fixed	NA	Squires 2010[51]
Relative effect on stroke & MI[(a)]	1	NA	Fixed	NA	Squires 2010[51]

(a) As in the NICE TA 223, it was assumed that naftidrofuryl oxalate does not have any effect on mortality or CV risk.

Results

Compared to exercise, the threshold at which naftidrofuryl oxalate becomes the most cost effective treatment strategy depends on the assumed level of compliance to each exercise programme. Where there is a higher level of compliance to supervised exercise over both the short and long term, naftidrofuryl oxalate becomes more cost effective when people achieve a gain of 0.029 QALYs per cycle compared to unsupervised exercise. If compliance is equal over the long term, a QALY gain of 0.017 per cycle is needed (Table 42).

According to the utility calculations undertaken by the NICE TA[51], people taking naftidrofuryl oxalate had a mean utility of 0.5088 after 24 weeks of treatment. Compared to the baseline utility of 0.4873 for people not taking vasoactive drugs, this represents a utility gain of 0.021. According to this estimate naftidrofuryl oxalate would be dominated by supervised exercise in both scenarios and is therefore not likely to be cost effective compared to supervised exercise. However, it is difficult to make comparisons due to differences in the methods used to estimate utility values.

Table 42: Threshold at which naftidrofuryl oxalate is more cost effective than supervised exercise

	Additional utility with naftidrofuryl compared to unsupervised exercise
Scenario 1	0.029 x 4
Scenario 2	0.017 x 4

9.3.2 Evidence statements

9.3.2.1 Clinical

No clinical evidence was identified for this question.

9.3.2.2 Economic

Based on the results of a threshold analysis undertaken as part of the original cost effectiveness model developed for this guideline, naftidrofuryl oxalate is unlikely to be more cost effective than supervised exercise for the treatment of IC under the base case assumptions of the model. However,

the GDG did not identify any clinical evidence to support a strong conclusion in this area. Naftidrofuryl oxalate may also be considered an option when people do not wish to undertake an exercise programme; in this case, the question is not one of choice between different treatments and the scenario represented by the economic model is not relevant.

9.3.3 Recommendations and link to evidence

Recommendations	**16. Consider naftidrofuryl oxalate for the treatment of intermittent claudication, starting with the least costly preparation when:** • **supervised exercise has not lead to satisfactory improvement, and** • **the patient prefers not to be referred for consideration of angioplasty or bypass surgery.** **Review progress after 3-6 months and discontinue naftidrofuryl oxalate if there has been no symptomatic benefit.**
Relative value of different outcomes	In line with the NICE TA 223 recommendation, the GDG focussed on the clinical and cost effectiveness for naftidrofuryl and decided to compare it to exercise therapy, angioplasty or stents for the treatment IC in adults. No evidence could be identified to allow comparisons of clinical efficacy to be made.
Trade off between clinical benefits and harms	Naftidrofuryl oxalate is contraindicated in people with a history of hyperoxaluria or recurrent calcium-containing stones. The summary of product characteristics should be consulted for a full list of side effects and contraindications. The GDG were of the opinion that, because it may be more convenient to prescribe a drug than to refer for further assessment for an invasive intervention, there is a risk that naftidrofuryl may sometimes be used when other treatment modalities (e.g. revascularisation) are likely to be superior in terms of outcomes.
Economic considerations	The GDG considered the cost of naftidrofuryl oxalate discontinuation rates as reported by the NICE TA, and the gain quality of life needed to make it a more cost effective strategy than supervised exercise according to the results of the economic model. They noted that naftidrofuryl is unlikely to be cost-effective given that the gain in quality of life needed for naftidrofuryl to be a cost effective option is greater than that reported in the NICE TA. The GDG also considered that there may be situations in which best medical treatment has been unsuccessful and people do not wish to undertake an exercise programme or interventional treatment. In these situations, the GDG considered that the use of naftidrofuryl oxalate would be cost-effective.
Quality of evidence	Whilst no evidence was identified, the GDG observed that the effect sizes reported in NICE TA 223 for walking distance were considerably lower than the minimally important differences the GDG had identified for this guideline.

Other considerations	There was no evidence to identify those sub-groups of people with IC who may benefit from naftidrofuryl and where in the care pathway this should be offered. The GDG agreed by consensus that naftidrofuryl should not be given as first line treatment for IC. The GDG discussed at length the importance of referral to secondary care when a person's symptoms have not resolved or have worsened, and their quality of life is affected. It is important that people with IC are offered the most appropriate treatment option within the care pathway. In addition, the use of naftidrofuryl should be reviewed to ensure that patients do not remain on the therapy when there is no beneficial effect. The discussion around treatment options must take account of patient choice. It must be recognised that some patients may not wish to undergo referral or other treatments and therefore, wish to trial naftidrofuryl.

1

9.4 Comparisons between treatment options: exercise, best medical treatment, angioplasty and bypass surgery

9.4.1 Review question

What is the clinical and cost effectiveness of endovascular or surgical techniques compared to or in combination with exercise or best medical treatment for the treatment of people with intermittent claudication?

A literature search was conducted for RCTs that compared the effectiveness of endovascular or surgical techniques to or in combination with exercise or best medical treatment. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded.

9.4.1.1 Clinical evidence

Twelve studies of eight RCTs[84-86 87-95] were included in the review. The trials did not report outcome data for people with diabetes.

The interventions evaluated in these trials could be divided into five pair wise comparisons:

1. Best medical treatment compared to best medical treatment with angioplasty (see section 9.4.2)
2. Supervised exercise with best medical treatment compared to supervised exercise, best medical treatment plus angioplasty (see section 9.4.3)
3. Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise (see section 9.4.4)
4. Angioplasty compared to supervised exercise (see section 9.4.5)
5. Bypass surgery compared to supervised exercise (see section 9.4.6)

9.4.2 Best medical treatment compared to best medical treatment with angioplasty

Clinical evidence

For this comparison, four studies of two RCTs were included that compared best medical treatment alone to best medical treatment with angioplasty.[84-87] One Cochrane review was identified Fowkes, 2008[96] which considered angioplasty compared to non surgical management for intermittent claudication. The Cochrane review was not included or updated as it did not meet the review question protocol defined by the GDG, which also included the comparison of best medical treatment to surgery. However it was used as a source to ensure that studies identified in the Cochrane review which matched the current review protocol had been considered for inclusion.

The study characteristics are reported in Table 43. The quality and results of included studies are reported in the clinical evidence profiles (Table 44 and Table 45). The forest plots for each clinical outcome are reported in Appendix J.

Table 43: Study characteristics: Best medical treatment compared to best medical treatment with angioplasty for intermittent claudication

Study	Disease location	BMT	BMT with Angioplasty
The Oslo Balloon Angioplasty versus Conservative Treatment Study (OBACT)[84,85]	Combined lesions in aorto-iliac and femoro-popliteal arteries	**BMT** • Smoking cessation • Home-based exercise advice • Nutritional advice and individualised optimal Mediterranean-type diet • Aspirin 160 mg daily or clopidogrel 75 mg daily for peptic ulcer history • Statins for untreated hypercholesterolaemia. • High blood pressure treatment	**BMT** • Smoking cessation • Home-based exercise advice • Nutritional advice and individualised optimal Mediterranean-type diet • Aspirin 160 mg daily or clopidogrel 75 mg daily for peptic ulcer history • Statins for untreated hypercholesterolaemia • High blood pressure treatment • **Angioplasty** • Iliac occlusions treated with primary stenting; iliac stenoses were selectively stented • Stents were not used infra-inguinally
Whyman, 1996; Whyman, 1997[86,87]	Femoro-popliteal arteries	**BMT** • Low dose aspirin • Smoking advice • Exercise advice	**BMT** • Low dose aspirin • Smoking advice • Exercise advice **Angioplasty** • Angioplasty by balloon dilation • Arterial stenting not routinely used

Table 44: Clinical evidence profile: Best medical treatment compared to best medical treatment with angioplasty for intermittent claudication due to femoro-popliteal and aorto-iliac disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMT	BMT + angioplasty	Relative (95% CI)	Absolute	
Maximum walking distance at 3 months											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 123.9 higher (16.69 to 231.11 higher)	LOW
Maximum walking distance at 1 year											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 197.1 higher (82.51 to 311.69 higher)	LOW
Maximum walking distance at 2 years											
1 Nylænde, 2007b[84]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 219.7 higher (122.12 to 317.28 higher)	LOW
Pain free walking distance at 3 months											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 219.9 higher (120.5 to 319.3 higher)	LOW
Pain free walking distance at 1 year											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 275.5 higher (172.61 to 378.39 higher)	LOW
Pain free walking distance at 2 years											

1 Nylænde, 2007b[84]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	28	28	-	MD 260.1 higher (155.6 to 364.6 higher)	LOW
Major complications at 1 year											
1 Nylænde, 2007a[85]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 28 people in the best medical treatment plus angioplasty group had major complications				LOW
Re-intervention at 1 year											
1 Nylænde, 2007a[85]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 28 people in the best medical treatment plus angioplasty group had re-intervention				LOW
ABPI at 3 months											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	28	28	-	MD 0.24 higher (0.23 to 0.25 higher)	MODERATE
ABPI at 1 year											
1 Nylænde, 2007a[85]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	28	28	-	MD 0.2 higher (0.19 to 0.21 higher)	MODERATE
ABPI at 2 years											
1 Nylænde, 2007b[84]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	28	28	-	MD 0.2 higher (0.18 to 0.22 higher)	MODERATE

(a) Unclear allocation concealment and blinding.
(b) 95% CI crosses one MID.
(c) Data taken from a RCT, non-comparative outcome.

Table 45: Clinical evidence profile: Best medical treatment compared to best medical treatment with angioplasty for intermittent claudication due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMT	BMT + angioplasty	Relative (95% CI)	Absolute	
Mortality at 2 years											
1 Whyman 1997[86]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	0/29 (0%)	2/30 (6.7%)	RR 0.21 (0.01 to 4.13)	53 fewer per 1000 (from 66 fewer to 209 more)	VERY LOW
Major complications at 6 months											
1 Whyman, 1996[87]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 29 people in the BMT plus angioplasty group had major complications				LOW
Re-intervention at 6 months											
1 Whyman, 1996[87]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 29 people in the BMT plus angioplasty group had re-intervention				LOW
Re-intervention at 2 years											
1 Whyman 1997 [86]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1 out of 29 people in the BMT plus angioplasty group had re-intervention				LOW
ABPI at 6 months											
1 Whyman, 1996[87]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	29	30	-	MD 0.14 higher (0.06 to 0.22 higher)	LOW
ABPI at 2 years											
1 Whyman 1997 [86]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	29	30	-	MD 0.06 higher (0.04 to 0.08	MODERATE

										higher)	

(a) Unclear blinding.
(b) 95% CI crosses both MIDs.
(c) Data from a RCT, non-comparative outcome.
(d) 95% CI crosses one MID.

9.413 Supervised exercise with best medical treatment compared to supervised exercise, best medical treatment plus angioplasty

Clinical evidence

Three RCTs[88,89,94] were found which addressed the question and were included in the review.

The study characteristics are reported in Table 46.The quality and results of included studies are reported in Table 47 and Table 48. The mapped EQ-5D are reported in Table 49. The forest plots for each clinical outcome are reported in Appendix J.

Table 46: Study characteristics: Best medical treatment with supervised exercise compared to best medical treatment with angioplasty and supervised exercise

Study	Disease location	Intervention 1 BMT + Supervised exercise	Intervention 2 BMT + Angioplasty + Supervised exercise
Greenhalgh, 2008[88]	Aorto-iliac and femoro-popliteal arteries	**BMT** • Aspirin 75 mg or clopidogrel if intolerant to aspirin • Blood pressure, total and high-density lipoprotein serum cholesterol and serum glucose were assessed and drug therapy commenced where necessary • Smoking cessation advice and support **Supervised exercise** • ≥1 session per week for 6 months • Each session consisted of 30 minutes continuous exercise to a maximum pain threshold using a walking circuit interspersed with lower-limb training stations.	**BMT** • Aspirin 75 mg or clopidogrel if intolerant to aspirin • Blood pressure, total and high-density lipoprotein serum cholesterol and serum glucose were assessed and drug therapy commenced where necessary • Smoking cessation advice and support **Angioplasty** • Balloon angioplasty with selective stent placement (number of stent placed = x/y) **Supervised exercise** • ≥1 session per week for 6 months • Each session consisted of 30 minutes continuous exercise to a maximum pain threshold using a walking circuit interspersed with lower-limb training stations.
Mazari, 2010[89]	Femoro-popliteal arteries	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel). • Smoking cessation advice and support • Risk factor modification (target orientated management of hypertension, hypercholesterolemia and diabetes). • Advice leaflet regarding exercise. **Supervised exercise** • 3 sessions per week for 12 weeks • Classes consisted of a circuit of exercise stations.	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel). • Smoking cessation advice and support • Risk factor modification (target orientated management of hypertension, hypercholesterolemia and diabetes). • Advice leaflet regarding exercise. **Angioplasty** • Balloon angioplasty with selective stent placement (number of stents placed = 0/y) **Supervised exercise**

			• 3 sessions per week for 12 weeks (beginning one week following angioplasty). • Classes consisted of a circuit of exercise stations.
Mazari, 2012[94]	Femoropopliteal arteries	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise **Supervised exercise** • 3 times a week for 12 weeks under supervision of physiotherapist or doctor. • Closed circuit training on six stations each for 2 minutes with 2 minutes brisk walking between each station. • Patients completed one full circuit for the first 6 weeks followed by an additional increment of 1 station per week for the next 6 weeks ending with completing 2 full circuits.	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise **Angioplasty** • Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure **Supervised exercise** • 3 times a week for 12 weeks under supervision of physiotherapist or doctor. • Closed circuit training on six stations each for 2 minutes with 2 minutes brisk walking between each station. • Patients completed one full circuit for the first 6 weeks followed by an additional increment of 1 station per week for the next 6 weeks ending with completing 2 full circuits.

Table 47: Clinical evidence profile: Supervised exercise with best medical treatment compared to supervised exercise with best medical treatment and angioplasty for intermittent claudication due to aorto-iliac disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BMT/SE/angioplasty**	**BMT/SE**	**Relative (95% CI)**	**Absolute**	
Quality of life at 6 months											
1 Greenhalgh,	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	11	12	See Table 49		LOW

2008[88]											
Quality of life at 1 year											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	11	12	See Table 49		LOW
Maximum walking distance (no sd) at 2 years											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	11	12	-	not pooled	LOW
Pain free walking distance (% attaining 200 m without pain) at 2 years											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	7/11 (63.6%)	3/12 (25%)	RR 2.55 (0.87 to 7.47)	387 more per 1000 (from 32 fewer to 1000 more)	VERY LOW
Complications following procedure											
1 Greenhalgh, 2008[88]	Observational studies	No serious risk of bias[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	4 out of 19 people in the BMT with supervised exercise and angioplasty group has complications				LOW
Compliance with exercise programme											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	10/19 (52.6%)	7/15 (46.7%)	RR 1.13 (0.57 to 2.25)	61 more per 1000 (from 201 fewer to 583 more)	VERY LOW

(a) Unclear allocation concealment and blinding.
(b) No information on variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.
(c) 95% CI crosses both MIDs.
(d) Data taken from a RCT, non-comparative outcome.

Table 48: Clinical evidence profile: Supervised exercise with best medical treatment compared to supervised exercise with best medical treatment and angioplasty and for intermittent claudication due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMT/SE / angioplasty	BMT/SE	Relative (95% CI)	Absolute	
Quality of life at 6 months											
2 Greenhalgh, 2008, Mazari, 2010[88 89]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	95	94	See Table 49		LOW
Quality of life at 1 year											
2 Greenhalgh, 2008; Mazari, 2010[88 89]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	95	94	See Table 49		LOW
Maximum walking distance (no sd) at 2 years											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	37	34	-	not pooled	LOW
Pain free walking distance (% patients attaining 200 m without pain) at 2 years											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	23/37 (62.2%)	7/34 (20.6%)	RR 3.02 (1.49 to 6.12)	416 more per 1000 (from 101 more to 1000 more)	MODERATE
Complications following procedure											
1 Greenhalgh, 2008[88]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	6 out of 48 people in the BMT with supervised exercise and angioplasty group has complications				LOW

Complications at 3 months											
1 Mazari 2010[89]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 58 people in the BMT with supervised exercise and angioplasty group has complications				LOW
Re-intervention at 1 year											
1 Mazari, 2012[94]	Observational studies	No serious risk of bias[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 out of 58 people in the BMT with supervised exercise and angioplasty group had re-interventions				LOW
Compliance with exercise programme											
1 Greenhalgh, 2008[88]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	30/48 (62.5%)	27/45 (60%)	RR 1.04 (0.75 to 1.44)	24 more per 1000 (from 150 fewer to 264 more)	VERY LOW
Withdrawal rate at 3 months											
1 Mazari, 2010[89]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	10/58 (17.2%)	8/60 (13.3%)	RR 1.29 (0.55 to 3.05)	39 more per 1000 (from 60 fewer to 273 more)	VERY LOW

(a) Unclear allocation concealment.
(b) No information on the variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.
(c) Data taken from an RCT, non-comparative outcome.
(d) 95% CI crosses both MIDs.

Table 49: SF-36 individual domain results and mapped EQ-5D values – Supervised exercise compared to angioplasty with supervised exercise

	Supervised exercise					Angioplasty + supervised exercise				
	Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months
Greenhalgh 2008[97] – Femoro-popliteal arteries – Mean (SD)										
PF	35.8 (8.0)	NR	37.9 (8.9)	NR	37.2 (9.3)	37.2 (8.0)	NR	40.0 (9.9)	NR	40.2 (9.1)
RP	41.2 (10.9)	NR	41.5 (10.1)	NR	41.1 (11.4)	42.3 (10.3)	NR	42.8 (11.1)	NR	43.6 (10.1)
BP	42.7 (9.4)	NR	41.8 (9.1)	NR	43.1 (8.7)	42.9 (8.7)	NR	44.3 (10.4)	NR	44.3 (9.9)
GH	45.9 (9.4)	NR	44.1 (9.8)	NR	44.2 (8.4)	43.8 (8.8)	NR	41.9 (10.0)	NR	42.6 (9.4)

V	45.8 (9.7)	NR	44.3 (12.0)	NR	43.6 (11.1)	46.6 (11.2)	NR	47.7 (11.8)	NR	47.2 (12.1)
SF	44.4 (11.9)	NR	43.2 (12.0)	NR	44.7 (12.0)	45.0 (10.6)	NR	45.3 (10.3)	NR	45.1 (10.3)
RE	42.1 (13.6)	NR	41.2 (13.7)	NR	40.4 (15.7)	44.8 (13.2)	NR	46.5 (12.3)	NR	46.2 (9.9)
MH	46.7 (12.4)	NR	46.6 (12.2)	NR	46.4 (12.5)	50.3 (10.4)	NR	50.4 (10.3)	NR	49.9 (10.4)
EQ-5D[(a)]	**0.45 (0.01)**	**NA**	**0.45 (0.01)**	**NA**	**0.46 (0.01)**	**0.47 (0.01)**	**NA**	**0.48 (0.01)**	**NA**	**0.48 (0.01)**
Greenhalgh 2008[97] – Aorto-iliac arteries – Mean (SD)										
PF	35.4 (8.3)	NR	36.2 (6.2)	NR	34.7 (9.2)	33.2 (8.5)	NR	43.6 (10.1)	NR	44.4 (10.5)
RP	40.0 (12.0)	NR	41.0 (10.5)	NR	38.4 (11.4)	41.1 (8.8)	NR	47.1 (11.7)	NR	46.6 (10.1)
BP	40.1 (7.4)	NR	37.4 (5.1)	NR	38.8 (10.1)	40.7 (9.6)	NR	48.0 (10.7)	NR	49.5 (11.5)
GH	39.2 (7.4)	NR	36.6 (9.8)	NR	36.1 (7.4)	42.2 (13.1)	NR	45.5 (10.5)	NR	45.6 (9.6)
V	43.8 (8.5)	NR	43.2 (8.2)	NR	40.6 (11.1)	42.4 (9.6)	NR	47.2 (10.9)	NR	45.0 (11.3)
SF	39.4 (13.6)	NR	38.0 (10.8)	NR	39.2 (11.8)	38.2 (10.2)	NR	50.0 (9.7)	NR	45.9 (9.9)
RE	40.3 (14.6)	NR	43.9 (11.6)	NR	41.8 (13.1)	39.9 (14.4)	NR	44.0 (12.7)	NR	43.4 (11.8)
MH	43.4 (9.7)	NR	42.6 (9.9)	NR	42.6 (11.7)	42.7 (10.1)	NR	48.1 (8.9)	NR	44.6 (12.7)
EQ-5D[(a)]	**0.45 (0.01)**	**NA**	**0.42 (0.01)**	**NA**	**0.42 (0.02)**	**0.42 (0.01)**	**NA**	**0.50 (0.01)**	**NA**	**0.50 (0.02)**
Mazari 2010[89] – Median (range)										
PF	30 (35)	55 (48)	NA	NA	NA	40 (30)	60 (43)	NA	NA	NA
RP	20 (30)	25 (100)	NA	NA	NA	25 (75)	75 (75)	NA	NA	NA
BP	41 (42)	55 (43)	NA	NA	NA	41 (31)	62 (32)	NA	NA	NA
GH	55 (37)	60 (30)	NA	NA	NA	55 (25)	62 (20)	NA	NA	NA
V	45 (20)	50 (35)	NA	NA	NA	45 (21)	55 (30)	NA	NA	NA
SF	62 (50)	75 (50)	NA	NA	NA	62 (35)	75 (50)	NA	NA	NA
RE	33 (100)	83 (100)	NA	NA	NA	66 (67)	83 (67)	NA	NA	NA
MH	68 (28)	72 (30)	NA	NA	NA	70 (25)	82 (27)	NA	NA	NA
EQ-5D[(b)]	**NE**	**NE**	**NA**	**NA**	**NA**	**NE**	**NE**	**NA**	**NA**	**NA**

(a) Mapped based on algorithm (Equation1) reported by Ara and Brazier 2008[66]
(b) Only the range was reported; probabilistic mapped values not estimable.
Abbreviations: PF = physical function; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role emotional; MH = mental health; SD= standard deviation; NA = not applicable; NR = not reported; NE = not estimable.

9.414 Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise for intermittent claudication

Clinical evidence

Two RCTs[94,95] were found which addressed the question and were included in the review.

The study characteristics are reported in Table 50. The quality and results of included studies are reported in Table 51. The reasons for withdrawal are reported in Table 52. The forest plots for each clinical outcome are reported in Appendix J.

Table 50: Study characteristics: Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise

Study	Disease location	Intervention 1 BMT + Angioplasty	Intervention 2 BMT + Angioplasty + Supervised exercise
Kruidenier, 2011[95]	Aorto-iliac arteries	**BMT** • Cardiovascular risk factor modification (inc. antiplatelet inhibitor and a statin and treatment for hypertension and/or diabetes as required • Advice to quit smoking if required and offer of a smoking cessation programme • Lifestyle changes (e.g. physical activity, weight, diet) **Angioplasty** • Performed by experienced interventional radiologist • Iliac angioplasty with selective stent placement for iliac stenosis; angioplasty with primary stent placement for superficial femoral artery stenosis or recanalisation with primary stent placement for iliac and femoral occlusions	**BMT** • Cardiovascular risk factor modification (inc. antiplatelet inhibitor and a statin and treatment for hypertension and/or diabetes as required • Advice to quit smoking if required and offer of a smoking cessation programme • Lifestyle changes (e.g. physical activity, weight, diet) **Angioplasty** • Performed by experienced interventional radiologist • Iliac angioplasty with selective stent placement for iliac stenosis; angioplasty with primary stent placement for superficial femoral artery stenosis or recanalisation with primary stent placement for iliac and femoral occlusions **Supervised exercise** • Began with 3 weeks of rest following angioplasty • Community based setting, supervised by a trained physiotherapist in proximity to their homes • Generally started with a frequency of 2-3 sessions of 30 minutes a week, frequency reduced according to patients progress • Patients encouraged to walk on a daily basis in addition to physiotherapy sessions.
Mazari, 2012[94]	Femoropopliteal arteries	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise

		Angioplasty • Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure.	**Angioplasty** • Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure. **Supervised exercise** • 3 times a week for 12 weeks under supervision of physiotherapist or doctor. • Closed circuit training on six stations each for 2 minutes with 2 minutes brisk walking between each station. • Patients completed one full circuit for the first 6 weeks followed by an additional increment of 1 station per week for the next 6 weeks ending with completing 2 full circuits.

Table 51: Clinical evidence profile: Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise for intermittent claudication due to aorto-iliac disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BMT/SE/angioplasty**	**BMT/angioplasty**	**Relative (95% CI)**	**Absolute**	
Quality of life at 6 months											
1 Kruidenier, 2011[95]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	33	29	See Table 53 and Table 54		LOW
Maximum walking distance at 3 months											
1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	32	29	-	MD 191.1 higher (35.1 lower to 417.3 higher)	LOW
Maximum walking distance at 6 months											

1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	34	27	-	MD 271.3 higher (68.43 to 474.17 higher)	LOW
Pain free walking distance at 3 months											
1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	32	28	-	MD 235.6 higher (15.77 to 455.43 higher)	LOW
Pain free walking distance at 6 months											
1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	34	27	-	MD 295.2 higher (106.19 to 484.21 higher)	LOW
Major adverse events at 6 months											
1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	3/35 (8.6%)	0/35 (0%)	RR 7 (0.37 to 130.69)	-	VERY LOW
Re-intervention at 12 months											
1 Mazari, 2012[94]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	0/58 (0%)	9/60 (15%)	RR 0.05 (0 to 0.91)	142 fewer per 1000 (from 13 fewer to 150 fewer)	VERY LOW
Withdrawal at 6 months											
1 Kruidenier, 2011[95]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	7/35 (20%)	1/35 (2.9%)	RR 7 (0.91 to 53.95)	171 more per 1000 (from 3 fewer to 1000 more)	VERY LOW

1 *(a) Unclear allocation concealment and blinding, baseline characteristic differences.*

(b) No information on the variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.
(c) Unclear allocation concealment and blinding.
(d) 95% CI crosses one MID.
(e) 95% CI crosses both MIDs.
(f) Unclear methodology.

Table 52: Study characteristics: Reason for withdrawal from treatment

Study	BMT/SE / angioplasty (n)	BMT/SE (n)
6 months		
Kruidenier, 2011[95]	7/35: Not motivated (1); too busy (2); insurance related (1); orthopaedic co-morbidity (1); unknown (2)	1/35: Requested supervised exercise (1)

Table 53: EQ-5D: Angioplasty compared to angioplasty with supervised exercise

Unsupervised exercise					Supervised exercise				
Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Kruidenier 2011[95] – Mean (SD)									
0.63 ± 0.19	NR	0.77 ± 0.20	NR	NR	0.55 ± 0.27	NR	0.79 ± 0.19	NR	NR

(a) NR = not reported

Table 54: SF-36 individual domain results and mapped EQ-5D values – Angioplasty compared to angioplasty with supervised exercise

	Angioplasty					Angioplasty + supervised exercise				
	Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Kruidenier 2011[95] – Mean (SD)										
PF	41.6 (17.5)	NR	72.2 (18.0)	NR	NR	43.6 (19.4)	NR	72.7 (22.3)	NR	NR
RP	39.1 (43.5)	NR	71.6 (37.0)	NR	NR	33.3 (39.9)	NR	56.3 (40.2)	NR	NR
BP	43.0 (16.4)	NR	64.7 (26.0)	NR	NR	41.4 (19.9)	NR	70.0 (22.8)	NR	NR
GH	52.2 (13.2)	NR	53.7 (12.5)	NR	NR	51.5 (11.3)	NR	56.9 (12.6)	NR	NR
V	51.2 (18.8)	NR	57.1 (20.0)	NR	NR	57.4 (20.2)	NR	67.3 (17.7)	NR	NR
SF	69.1 (28.0)	NR	77.2 (31.0)	NR	NR	64.0 (22.8)	NR	80.7 (19.8)	NR	NR
RE	83.9 (35.4)	NR	77.0 (40.9)	NR	NR	80.8 (38.2)	NR	82.3 (35.9)	NR	NR
MH	72.8 (18.3)	NR	68.0 (19.5)	NR	NR	72.2 (20.8)	NR	79.4 (17.5)	NR	NR

	Angioplasty					Angioplasty + supervised exercise				
EQ-5D[(a)]	**0.58 (0.02)**	**NA**	**0.74 (0.02)**	**NA**	**NA**	**0.57 (0.01)**	**NA**	**0.79 (0.02)**	**NA**	**NA**

(a) Mapped based on algorithm (Equation1) reported by Ara and Brazier 2008[66]

Abbreviations: PF = physical function; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role emotional; MH = mental health; SD= standard deviation; NA = not applicable; NR = not reported; NE = not estimable.

9.415 Angioplasty compared to supervised exercise

Clinical evidence

Five RCTs[90-92,98 94] were found which addressed the question and were included in the review.

The study characteristics are reported in Table 56. The quality and results of included studies are reported in Table 57, Table 58 and Table 59. The mapped EQ-5D values are reported in Table 60.The forest plots for each clinical outcome are reported in Appendix J.

Spronk 2009[90] reported values for the four physical domains of the SF-36 (physical functioning, physical role, bodily pain and general health). The authors were contacted to request the remaining domains and they replied that these domains were not collected. Baseline and mean score improvement in EQ-5D were reported in the cost-effectiveness paper based on this randomised control trial.[99] By assigning a distribution to each reported EQ-5D value, the mean score improvement at 6 and 12 months was added to the baseline value to calculate mean quality of life at each time point. This simulation was run 20,000 times and the results are reported in Table 55.

Table 55: Simulated mean EQ-5D values from Spronk 2008 based on mean score improvement

	Supervised exercise			Angioplasty		
	Mean value (SE)	Mean score improvement (SE)	Simulated mean value (SE)	Mean value (SE)	Mean score improvement (SE)	Simulated mean value (SE)
Baseline	0.69 (0.02)			0.66 (0.02)		
6 months		0.09 (0.03)	0.780 (0.034)		0.16 (0.02)	0.820 (0.31)
12 months		0.07 (0.02)	0.076 (0.032)		0.11 (0.03)	0.770 (0.036)

1 **Table 56: Study characteristics: Angioplasty compared to supervised exercise for intermittent claudication**

Study	Disease location	Supervised exercise	Angioplasty
Spronk, 2009[90]	Aorto-iliac arteries	**BMT** • Atherosclerotic risk factor treatment that included hypertension, serum glucose, cholesterol, lipid profile, and homocysteinemia (in patients <50 years of age) management and, all patients were prescribed aspirin therapy (100 mg/d). • All smokers were strongly and repeatedly advised to quit smoking, and were offered a smoking-cessation programme. • Risk factor management continued during follow-up **Supervised exercise** Twice weekly 30 minute sessions on treadmills for 24 weeks	**BMT** • Atherosclerotic risk factor treatment that included hypertension, serum glucose, cholesterol, lipid profile, and homocysteinemia (in patients <50 years of age) management, and all patients were prescribed aspirin therapy (100 mg/d). • All smokers were strongly and repeatedly advised to quit smoking, and were offered a smoking-cessation programme. • Risk factor management continued during follow-up **Angioplasty** Balloon angioplasty. Self-expanding stent placed if angioplasty was considered unsuccessful.
Perkins, 1996; Creasy, 1990[91,92]	Aorto-iliac and femoro-popliteal arteries	**BMT** No details **Supervised exercise** Supervised exercise programme of twice weekly 30 minute sessions for 6 months. Each session consisted of dynamic leg exercises	**BMT** No details **Angioplasty** Angioplasty using conventional guide-wire and catheter technique
Mazari, 2010[98]	Femoro-popliteal arteries	**BMT** All patients received: • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation programme) • Risk factor modification (target orientated management of hypertension, hypercholesterolemia and diabetes).	**BMT** All patients received: • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation programme) • Risk factor modification (target orientated management of hypertension, hypercholesterolemia and diabetes). • Advice leaflet regarding exercise.

		• Advice leaflet regarding exercise. **Supervised exercise** Supervised exercise sessions 3 times a week for 12 weeks, classes involved a circuit of exercise stations	**Angioplasty** Balloon angioplasty. Primary stenting or adjunctive procedures were not performed in any case
Mazari, 2012[94]	Femoropopliteal arteries	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise. **Supervised exercise** • 3 times a week for 12 weeks under supervision of physiotherapist or doctor • Closed circuit training on six stations each for 2 minutes with 2 minutes brisk walking between each station • Patients completed one full circuit for the first 6 weeks followed by an additional increment of 1 station per week for the next 6 weeks.	**BMT** • Antiplatelet therapy (aspirin and/or clopidogrel) • Smoking cessation advice and support • Risk factor management • Advice leaflets of physical activity and exercise. **Angioplasty** • Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure

1 **Table 57: Clinical evidence profile: Angioplasty compared to supervised exercise for intermittent claudication due to aorto-iliac disease**

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Angioplasty**	**Supervised Exercise**	**Relative (95% CI)**	**Absolute**	
Quality of life at 3 months											
1 Mazari 2010[98]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	60	60	See Table 60		LOW

Quality of life at 6 months										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	75	75	See Table 55	LOW
Quality of life at 1 year										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]	None	75	75	See Table 55	LOW
Maximum walking distance from baseline at 6 months										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	75	75	-	MD 383 lower (537.62 to 228.38 lower)	MODERATE
Maximum walking distance from baseline at 1 year										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	75	75	-	MD 208 lower (359.79 to 56.21 lower)	LOW
Pain free walking distance from baseline at 6 months										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	75	75	-	MD 220 lower (391.62 to 48.38 lower)	LOW
Pain free walking distance from baseline at 1 year										
1 Spronk 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	75	75	-	MD 137 lower (305.66 lower to 31.66 higher)	LOW
Number of patients who doubled their maximum walking distance at 3 months										

1 Creasy, 1990[92]	RCT	Very serious[(d)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	4/16 (25%)	7/15 (46.7%)	RR 0.54 (0.2 to 1.47)	215 fewer per 1000 (from 373 fewer to 219 more)	VERY LOW
Number of patients who doubled their maximum walking distance at 6 months											
1 Creasy, 1990[92]	RCT	Very serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	5/14 (35.7%)	9/12 (75%)	RR 0.48 (0.22 to 1.03)	390 fewer per 1000 (from 585 fewer to 22 more)	VERY LOW
Number of patients who doubled their maximum walking distance at 9 months											
1 Creasy, 1990[92]	RCT	Very serious[(d)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	4/11 (36.4%)	9/12 (75%)	RR 0.48 (0.21 to 1.13)	390 fewer per 1000 (from 593 fewer to 97 more)	VERY LOW
Number of patients who doubled their maximum walking distance at 1 year											
1 Creasy, 1990[92]	RCT	Very serious[(d)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	2/5 (40%)	6/7 (85.7%)	RR 0.47 (0.15 to 1.42)	454 fewer per 1000 (from 729 fewer to 360 more)	VERY LOW
Complications at 1 year											
2 Creasy, 1990; Spronk, 2009 [90,92]	Observational studies	No serious risk of bias[(f)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	11 out of 95 people in the angioplasty group had complications				LOW
Re-interventions at 6 months											
1 Spronk, 2009 [90]	Observational studies	No serious risk of bias[(f)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5 out of 75 people in the angioplasty group had re-intervention				LOW
Re-interventions at 1 year											

2 Creasy, 1990; Spronk, 2009[90,92]	Observational studies	No serious risk of bias[(f)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	8 out of 95 people in the angioplasty group had re-intervention				LOW
Number of good attenders to exercise (on average > 1 session per week) at 6 months											
1 Creasy, 1990[92]	Observational studies	No serious risk of bias[(f)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	8 out of 16 people in the exercise group were good attenders				LOW
Number of poor attenders to exercise (on average < 1 session per week) at 6 months											
1 Creasy, 1990[92]	Observational studies	No serious risk of bias[(f)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	8 out of 16 people in the exercise group were poor attenders				LOW
Withdrawal at 3 months											
1 Mazari, 2010[98]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	3/60 (5%)	8/60 (13.3%)	RR 0.38 (0.1 to 1.35)	83 fewer per 1000 (from 120 fewer to 47 more)	VERY LOW
ABPI at rest from baseline at 6 months											
1 Spronk, 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	75	75	-	MD 0.11 higher (0.06 to 0.16 higher)	LOW
ABPI at rest from baseline at 1 year											
1 Spronk, 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	75	75	-	MD 0.12 higher (0.07 to 0.17 higher)	LOW
ABPI after exercise from baseline at 6 months											
1 Spronk, 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	75	75	-	MD 0.13 higher (0.06 to 0.2 higher)	LOW

ABPI after exercise from baseline at 1 year											
1 Spronk, 2009[90]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	75	75	-	MD 0.07 higher (0.02 to 0.12 higher)	MODERATE

(a) Unclear allocation concealment and blinding.
(b) No information on the variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.
(c) 95% CI crosses one MID.
(d) Unclear methodology.
(e) 95% crosses both MIDs.
(f) Data taken from an RCT, non-comparative outcome.

Table 58: Clinical evidence profile: Angioplasty compared to supervised exercise for intermittent claudication due to aorto-iliac and femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Angioplasty**	**Supervised Exercise**	**Relative (95% CI)**	**Absolute**	
Re-intervention at 15 months											
1 Perkins, 1996[91]	Observational studies	No serious risk of bias[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3 out of 30 people in the angioplasty group had re-intervention				LOW
Number of patients exercising daily at 5-6 years											
1 Perkins, 1996[91]	Observational studies	No serious risk of bias[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2 out of 26 people in the exercise group were exercising daily				LOW
Number of patients exercising more than twice a week at 5-6 years											
1 Perkins, 1996[91]	Observational studies	No serious risk of bias[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3 out of 26 people in the exercise group were exercising more than twice a week				LOW

(a) Data taken from a RCT, non-comparative outcome.

Table 59: Clinical evidence profile: Angioplasty compared to supervised exercise for intermittent claudication due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty	Supervised Exercise	Relative (95% CI)	Absolute	
Re-intervention at 1 year											
1 Mazari, 2012[94]	Observational studies	No serious risk of bias[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	9 out of 60 people in the angioplasty group had re-intervention				LOW

(a) Data taken from a RCT, non-comparative outcome.

Table 60: SF-36 individual domain results and mapped EQ-5D values – Angioplasty compared to supervised exercise

	Supervised exercise					Angioplasty				
	Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months
Mazari 2010[89] – Median (range)										
PF	30 (35)	55 (48)	NA	NA	NA	35 (30)	52 (40)	NA	NA	NA
RP	20 (30)	25 (100)	NA	NA	NA	25 (65)	25 (75)	NA	NA	NA
BP	41 (42)	55 (43)	NA	NA	NA	41 (40)	61 (46)	NA	NA	NA
GH	55 (37)	60 (30)	NA	NA	NA	57 (37)	54 (41)	NA	NA	NA
V	45 (20)	50 (35)	NA	NA	NA	50 (35)	55 (35)	NA	NA	NA
SF	62 (50)	75 (50)	NA	NA	NA	75 (50)	88 (50)	NA	NA	NA
RE	33 (100)	83 (100)	NA	NA	NA	66 (100)	100 (100)	NA	NA	NA
MH	68 (28)	72 (30)	NA	NA	NA	72 (28)	82 (25)	NA	NA	NA
EQ-5D[(a)]	**NE**	**NE**	**NA**	**NA**	**NA**	**NE**	**NE**	**NA**	**NA**	**NA**

(a) Only the range was reported; probabilistic mapped values not estimable.
Abbreviations: PF = physical function; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role emotional; MH = mental health; NA = not applicable; NE = not estimable.

9.4.16 Bypass surgery compared to supervised exercise

Clinical evidence

One RCT (Lundgren, 1989)[93] was found which addressed the question and was included in the review.

The study characteristics are reported in Table 61. The quality and results of the included study are reported in Table 62. The forest plots for each clinical outcome are reported in Appendix J.

1 **Table 61: Study characteristics: Bypass surgery compared to supervised exercise**

Study	Disease location	Combination	Supervised exercise	Bypass surgery
Lundgren, 1989[93]	Aorto-iliac and femoro-popliteal disease	Supervised exercise 6 weeks following bypass operation	Supervised exercise programme; 3 sessions per week for a minimum of 6 months. Each session consisted of 30 minutes of dynamic leg exercises beyond the appearance of leg pain due to arterial insufficiency	Bypass with saphenous vein or expanded PTFE graft.

2 **Table 62: Clinical evidence profile: Bypass surgery compared to supervised exercise for intermittent claudication due to aorto-iliac and femoro-popliteal**
3 **disease**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bypass	Exercise	Relative (95% CI)	Absolute	
Mortality at 1 year											
1 Lundgren, 1989[93]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	2/25 (8%)	0/25 (0%)	RR 5 (0.25 to 99.16)	-	VERY LOW
Maximum walking distance from baseline at 1 year											
1 Lundgren, 1989[93]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	25	25	-	MD 85 higher (107.88 lower to 277.88 higher)	LOW
Pain free walking distance at 1 year											
1 Lundgren, 1989[93]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(c)]	None	25	25	-	MD 200 higher (21.51 to 378.49 higher)	LOW
Complication at 30 days											
1 Lundgren, 1989[93]	Observational studies	No serious risk of bias[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	6 out of 25 people in the surgery group had complications				LOW

Re-intervention at 30 days								
1 Lundgren, 1989[93]	Observational studies	No serious risk of bias[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3 out of 25 people in the surgery group had re-intervention	LOW
Withdrawal from exercise programme								
1 Lundgren, 1989[93]	Observational studies	No serious risk of bias[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	4 out of 25 in the exercise group withdrew from exercise	LOW

(a) Study had unclear allocation concealment; unclear blinding.
(b) 95% crosses both MIDs.
(c) 95% CI crosses MID.
(d) Data taken from an RCT, non-comparative outcome.

9.4.17 Angioplasty compared to bypass surgery

9.4.721 Review question

A literature search was conducted for RCTs that compared the effectiveness of angioplasty versus bypass surgery. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded.

9.4.762 Clinical evidence

Seven studies of four RCTs[100-103 104 105,106] were identified which addressed the question and were included in the review. The trials did not report outcome data for people with diabetes.

The quality and results of included studies are reported in Table 63 and Table 64. The forest plots for each clinical outcome are reported in appendix J.

For the clinical evidence statements, see section 9.4.9.

1 **Table 63: Clinical evidence profile: Angioplasty compared to bypass surgery for people with intermittent claudication due to aorto-iliac disease**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty	Bypass	Relative (95% CI)	Absolute	
Mortality at 30 days											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	0/130 (0%)	1/133 (0.75%)	RR 0.34 (0.01 to 8.29)	5 fewer per 1000 (from 7 fewer to 55 more)	VERY LOW
Mortality at 3 months											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	0/130 (0%)	2/133 (1.5%)	RR 0.2 (0.01 to 4.22)	12 fewer per 1000 (from 15 fewer to 48 more)	VERY LOW
Mortality at 1 year											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	0/130 (0%)	3/133 (2.3%)	RR 0.15 (0.01 to 2.8)	19 fewer per 1000 (from 22 fewer to 41 more)	VERY LOW
Mortality at 2 years											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	20/130 (15.4%)	26/133 (19.5%)	RR 0.79 (0.46 to 1.34)	41 fewer per 1000 (from 106 fewer to 66 more)	VERY LOW
Amputation post procedure											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	2/130 (1.5%)	2/133 (1.5%)	RR 1.02 (0.15 to 7.16)	0 more per 1000 (from 13 fewer to 93 more)	VERY LOW
Amputation at 2 years											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	8/130 (6.2%)	13/133 (9.8%)	RR 0.63 (0.27 to 1.47)	36 fewer per 1000 (from 71 fewer to 46 more)	VERY LOW

Amputation at 4 years											
1 Wolf, 1993[104]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	6/59 (10.2%)	3/59 (5.1%)	RR 2 (0.52 to 7.62)	51 more per 1000 (from 24 fewer to 337 more)	VERY LOW
Complications post procedure											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	27/130 (20.8%)	10/133 (7.5%)	RR 2.76 (1.39 to 5.47)	132 more per 1000 (from 29 more to 336 more)	VERY LOW
Re-intervention at 2 years											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	26/130 (20%)	20/133 (15%)	RR 1.33 (0.78 to 2.26)	50 more per 1000 (from 33 fewer to 189 more)	VERY LOW
ABPI after treatment (no specific time point)											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	130	133	-	MD 0.04 lower (0.04 to 0.04 lower)	MODERATE
ABPI at 3 years											
1 Wilson, 1989[103]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	130	133	-	MD 0.02 higher (0.01 to 0.03 higher)	MODERATE

(a) Unclear blinding.
(b) 95% CI crosses both MIDs.

Table 64: Clinical evidence profile: Angioplasty compared to bypass surgery for intermittent claudication due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Angioplasty**	**Bypass**	**Relative (95% CI)**	**Absolute**	
Mortality at 30 days											

2 Holm, 1991; van der Zaag 2004[105,106]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision[(b)]	None	0/53 (0%)	0/48 (0%)	not pooled	not pooled	MODERATE
Mortality at 1 year											
2 Holm, 1991; Kedora, 2007[100,105]	RCT	Very serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	5/63 (7.9%)	4/64 (6.3%)	RR 1.31 (0.39 to 4.39)	19 more per 1000 (from 38 fewer to 212 more)	VERY LOW
Mortality at 2 years											
1 McQuade, 2009[102]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	6/40 (15%)	5/46 (10.9%)	RR 1.38 (0.46 to 4.18)	41 more per 1000 (from 59 fewer to 346 more)	VERY LOW
Mortality at 4 years											
1 McQuade, 2010[101]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	9/40 (22.5%)	8/46 (17.4%)	RR 1.29 (0.55 to 3.04)	50 more per 1000 (from 78 fewer to 355 more)	VERY LOW
Amputation at 1 year											
3 Holm, 1991; Kedora, 2007; van der Zaag 2004[100,105,106]	RCT	Very serious[(f)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	3/103 (2.9%)	5/93 (5.4%)	RR 0.61 (0.17 to 2.18)	21 fewer per 1000 (from 45 fewer to 63 more)	VERY LOW
Amputation at 2 years											
1 McQuade, 2009[102]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	1/50 (2%)	5/50 (10%)	RR 0.2 (0.02 to 1.65)	80 fewer per 1000 (from 98 fewer to 65 more)	VERY LOW
Amputation at 4 years											
2 McQuade, 2010; Wolf, 1993[101,104]	RCT	Very serious[(g)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	4/88 (4.5%)	11/85 (12.9%)	RR 0.35 (0.11 to 1.05)	84 fewer per 1000 (from 115 fewer to 6 more)	VERY LOW
Minor complications post procedure											
2 Holm, 1991; McQuade, 2009[102,105]	RCT	Very serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	7/73 (9.6%)	4/68 (5.9%)	RR 1.61 (0.49 to 5.32)	36 more per 1000 (from 30 fewer to 254 more)	VERY LOW
Major adverse event at 1 year											

1 van der Zaag, 2004[106]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	0/30 (0%)	2/25 (8%)	RR 0.17 (0.01 to 3.34)	66 fewer per 1000 (from 79 fewer to 187 more)	VERY LOW
Minor adverse event at 1 year											
1 van der Zaag, 2004[106]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	0/30 (0%)	2/25 (8%)	RR 0.17 (0.01 to 3.34)	66 fewer per 1000 (from 79 fewer to 187 more)	VERY LOW
Re-intervention at 1 year											
2 Kedora, 2007; van der Zaag, 2004[100,106]	RCT	Very serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	14/80 (17.5%)	13/75 (17.3%)	RR 1.06 (0.55 to 2.06)	10 more per 1000 (from 78 fewer to 184 more)	VERY LOW
Re-intervention at 2 years											
1 McQuade, 2009[102]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	17/50 (34%)	17/50 (34%)	RR 1 (0.58 to 1.73)	0 fewer per 1000 (from 143 fewer to 248 more)	VERY LOW
Re-intervention at 4 years											
1 McQuade, 2010[101]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Very serious[(d)]	None	18/50 (36%)	15/50 (30%)	RR 1.2 (0.68 to 2.11)	60 more per 1000 (from 96 fewer to 333 more)	VERY LOW
ABPI at 1 year											
1 Holm, 1991[105]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	23	18	-	MD 0.12 higher (0.07 to 0.17 higher)	LOW
ABPI at 1 year (no sd)											
1 Kedora, 2007[100]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Serious[(i)]	None	50	50	-	not pooled	VERY LOW
ABPI at 2 years (no sd)											
1 McQuade, 2009[102]	RCT	Very serious[(e)]	No serious inconsistency	No serious indirectness	Serious[(i)]	None	50	50	-	not pooled	VERY LOW

(a) Unclear allocation concealment and blinding.
(b) No events in either group.
(c) 1 of 2 studies had unclear methodology;1 of 2 studies had unclear allocation concealment and blinding.

(d) 95% CI crosses both MIDs.
(e) Unclear methodology.
(f) 1 of 3 studies had unclear methodology; 2 of 3 studies had unclear allocation concealment and blinding.
(g) 1 of 2 studies had unclear methodology; 1 of 2 studies had unclear blinding.
(h) 95% CI crosses one MID.
(i) No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

9.4.18 Economic evidence

Five cost-utility analyses were identified that compared exercise and endovascular interventions for the treatment of IC. One was a pair-wise comparison based on an RCT[99] and the remaining four were decision analytic models evaluating different intervention sequences.[107-110] None of the studies included all interventions under consideration by the GDG. Study characteristics and results are summarised in Table 65, subdivided according to included intervention strategies.

Spronk 2008 analysed cost and outcome data from a RCT comparing supervised exercise (performed twice weekly for 30 minutes per session over 24 weeks on a treadmill) to angioplasty with selective stent placement. This RCT was included in the clinical review. At 12 month follow-up and after adjustment for baseline variables, the treatment groups did not differ significantly in functional capacity or quality of life. However, there was a large difference in cost favouring supervised exercise. This analysis found that supervised exercise is highly likely to be cost effective compared to angioplasty with selective stent placement, however it was limited by a short time horizon and did not include all relevant comparators.

Visser 2003[110] developed a model to compare supervised exercise to angioplasty followed by exercise and angioplasty followed by exercise. Each endovascular strategy was preceded by a different imaging modality. The results of this analysis suggest that angioplasty preceded by MRA is the most cost-effective initial intervention, with supervised exercise for those who are not suitable for angioplasty. However, this study did not exercise as a primary treatment for IC and therefore is missing an important comparator.

De Vries 2002[108] developed a model to compare five combinations of supervised exercise (advised to walk 2-6km every day for six months with four check-in periods) and revascularisation (angioplasty with selective stent placement for supra-inguinal disease) and angioplasty or bypass surgery for infra-inguinal disease) with clinical outcomes based on a retrospective database analysis. The results of this model indicate that none of the evaluated strategies fall within the £20k per QALY threshold compared to a baseline strategy of unsupervised exercise.

Based on data from the Dutch Iliac Stent Trial and several meta-analyses, Bosch 1998[107] developed a decision model to evaluate the cost effectiveness of treating claudication due to iliac arterial stenosis with primary stent placement, selective stent placement or angioplasty without stent placement. This model assumes that 40% of patients undergoing angioplasty require selective stent placement and that compared to angioplasty alone, the relative risk of failure associated with stent placement is 0.61. The results of this model suggest that angioplasty with selective stent placement for both primary and secondary treatment is more cost effective than both selective stent placement followed by conservative management and primary stent placement followed by selective stent placement. This conclusion was robust to a wide range of sensitivity analyses.

The same model (with American costs) was used in a later analysis by Bosch 2000.[111] Based on the results of their previous study (Bosch 1999[112]), which concluded that primary stent placement was not cost-effective, the authors did not include angioplasty with primary stent placement as a comparison in this analysis. Because this comparison was not relevant to the study question it was excluded from the review.

Hunink 1995[109] evaluated the cost-effectiveness of revascularisation for femoro-popliteal disease using angioplasty, bypass surgery and combinations of the two treatments in people with disabling claudication. Only patients requiring revascularisation were included and strategies such as exercise, medical therapy or amputation were not considered. The results of bypass surgery were sub-grouped according to graft material (autologous vein vs. prosthetic bypass) and lesion type. Although the results of the analysis are different for each subgroup, the conclusions are broadly the same.

1 **Table 65: Economic evidence profiles**

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effect	Cost effectiveness	Uncertainty
Supervised exercise compared to angioplasty with selective stent placement							
Spronk 2008[99]	Minor limitations[(a)]	Partially applicable[(b)]	• Cost utility analysis based on RCT by Spronk 2009[90] • Population: People with IC • Time horizon: 1 year • Costs: All healthcare costs • Perspective: Netherlands, hospital	Angioplasty with selective stent placement is £3, 867 more costly than supervised exercise.	Angioplasty with selective stent placement results in a 0.02 QALY gain.	Angioplasty with selective stent placement costs £193, 374 per QALY gained.	• At a threshold of approximately £60k, there was a 5% probability that angioplasty is more cost effective than supervised exercise.
Supervised exercise vs. MRA and angioplasty or exercise vs. MRA and angioplasty or bypass surgery vs. DUS and angioplasty or exercise vs. DUS and angioplasty or bypass vs. DSA and angioplasty or exercise vs. DSA and angioplasty or bypass.							
Visser 2003[110]	Potentially serious limitations[(c)]	Partially applicable[(d)]	• Decision analytic model • Population: People with IC • Time horizon: Lifetime • Costs: All healthcare costs • Perspective: Netherlands, societal	MRA + Primary angioplasty was £1, 821 more costly than supervised exercise. DSA followed by angioplasty or bypass was £10, 287 more costly than MRA followed by angioplasty or exercise.	MRA + Primary angioplasty resulted in 0.0881 QALYs gain compared to supervised exercise alone. DSA followed by angioplasty or bypass = 0.0767 QALYs gained compared to MRA followed by angioplasty or exercise.	MRA +Primary angioplasty cost £20, 670 per QALY gained compared to supervised exercise alone. DSA followed by angioplasty or bypass cost £134, 120, 074 per QALY gained compared to MRA followed by angioplasty or exercise.	• The results were robust to most sensitivity analyses.
Unsupervised exercise only vs. unsupervised exercise followed by angioplasty for treatment failure vs. Unsupervised exercise followed by angioplasty or bypass for treatment failure vs. angioplasty or unsupervised exercise followed by angioplasty for treatment failure vs. angioplasty, bypass or unsupervised exercise followed by angioplasty or bypass for treatment failure.							

de Vries 2002[108]	Potentially serious limitations[(e)]	Partially applicable[(f)]	• Decision analytic model • Population: People with IC • Horizon: Lifetime • Costs: Diagnostic and interventional procedures, short- and long-term follow-up costs • Perspective: USA/Netherlands societal perspective	Angioplasty or exercise followed by angioplasty = £3, 838 more costly compared to unsupervised exercise alone. Exercise followed by angioplasty or bypass = £21, 985 more costly compared to angioplasty or exercise followed by angioplasty.	Angioplasty or exercise followed by angioplasty = 0.10 QALYs gained compared to unsupervised exercise alone. Exercise followed by angioplasty or bypass = 0.07 QALY gain compared angioplasty or exercise followed by angioplasty.	Angioplasty or exercise followed by angioplasty = £38, 376 QALYs gained compared to unsupervised exercise. Exercise followed by angioplasty or bypass = £314, 079 per QALY gained.	• ICER for interventional strategies increased with age or a positive history of CAD, due to increased procedural risk and reduced life expectancy in older patients with cardiac ischaemia.
Unsupervised exercise only vs. selective stent placement followed by unsupervised exercise vs. selective stent placement followed by selective stent placement vs.							
Bosch 1998[107]	Minor limitations[(g)]	Partially applicable[(h)]	• Decision analytic model • Population: People with IC • Horizon: Lifetime • Costs: Diagnostic costs, interventional procedures, and patient costs. • Perspective: Netherlands societal perspective	Selective stent placement followed by selective stent placement was £3, 960 more costly than selective stent placement followed by no revascularisation.	Selective stent placement followed by selective stent placement resulted in 0.32 QALYs gained compared to selective stent placement followed by no revascularisation.	Selective stent placement followed by selective stent placement cost £12, 376 per QALY gained	Robust to changes in the risk of long term failure following stent placement, proportion of patients requiring a stent, and stent cost.
No treatment vs. angioplasty followed by no treatment vs. angioplasty followed by angioplasty vs. angioplasty followed by bypass vs. bypass followed by no treatment vs. bypass followed by bypass revision							
Hunink 1995[109]	Potentially serious limitations[(i)]	Partially applicable[(j)]	• Decision analytic model • Population: People with IC • Horizon: Lifetime • Costs: Costs of angioplasty and bypass for patients with	**Vein graft for IC stenosis**			
				Angioplasty followed by bypass surgery is the least costly strategy	Angioplasty followed by bypass surgery is the most effective	Angioplasty followed by bypass surgery was the dominant	In people with IC due to occlusion, the conclusion of the model was unchanged

			claudication and critical limb ischaemia; annual follow-up costs for angioplasty and bypass patients; cost of amputation and rehabilitation; annual cost of post amputation care; annual cost of care with major morbidity. • Perspective: UK NHS		strategy	treatment strategy	
				PTFE-AK for IC stenosis			
				Angioplasty followed by angioplasty was the least costly strategy	Angioplasty followed by angioplasty was the most effective strategy	Angioplasty followed by angioplasty was the dominant treatment strategy	In people with IC due to occlusion, the conclusion of the model was unchanged
				PTFE-BK for IC stenosis			
				Angioplasty followed by angioplasty was the least costly strategy	Angioplasty followed by angioplasty was the most effective strategy	Angioplasty followed by angioplasty was the dominant treatment strategy	In people with IC due to occlusion, the conclusion of the model was unchanged

(a) This analysis took a societal perspective but reported disaggregated costs – societal costs have been subtracted for the purposes of reporting this study. Short time horizon..
(b) Data derived from US and Dutch databases; patency not reported, making between study comparisons difficult
(c) Societal perspective; assumed that symptom progression necessitated reintervention.
(d) Did not include exercise as a primary treatment strategy.
(e) Costs and QALY results read off graph and imputed from reported ICERs.
(f) Assumed angioplasty preceded by catheter angiography.
(g) Societal perspective.
(h) Dutch healthcare setting.
(i) Quality of life estimated using Torrence Multi Attribute Scale by healthcare workers; patency failure assumed to be equivalent to symptom progression & re-intervention; progression of symptoms not modelled due to lack of data.
(j) Resource use based on American hospital records.

9.4.811 Original economic model

None of the cost-utility studies identified in the literature included all relevant comparators for the treatment of people with IC. Therefore, the GDG decided to prioritise this area for original cost effectiveness modelling. The aim of this analysis was to determine the most cost-effective treatment pathway for people with IC in England and Wales who are suitable for both exercise and angioplasty as first-line treatment options.

The analysis was undertaken from the perspective of the NHS and personal social services, in accordance with NICE guidelines methodology. Relevant costs consisted of the cost of a supervised exercise programme and treatment for stroke and MI. All costs are reported in 2009/10 British pounds. The primary measure of outcome is the quality-adjusted life-year (QALY). The model was evaluated over a lifetime horizon with both costs and QALYs discounted at a rate of 3.5% per year. Alternative discount rates of 1.5% for QALYs and 3.5% for costs were explored in sensitivity analysis.

9.4.822 Methods

Comparators

The model was designed to compare 13 alternative treatment strategies for people with intermittent claudication (four primary interventions followed by three secondary interventions, plus one additional combined intervention). A treatment strategy was defined as the initial therapy combined with secondary intervention options if the initial treatment should fail (Table 66).

The model did not consider bypass surgery as a primary strategy because the GDG did not consider bypass to be an appropriate first-line therapy for people with claudication; bypass was included as a secondary procedure following unsatisfactory results from supervised exercise or angioplasty. Stent placement was included as a planned ('primary stent placement') and bail-out ('selective stent placement') procedure for angioplasty. In both primary and selective stent strategies, only bare metal stents were considered as the GDG decided not to recommend the routine use of drug eluting stents following a review of the clinical evidence (see section 9.6). Angioplasty with primary stent was not considered as a secondary intervention as the GDG did not think that there was anything to recommend it over selective stent placement.

Table 66: Evaluated treatment strategies

Strategy	Initial treatment	Secondary treatment
1	Unsupervised exercise	Supervised exercise
2	Unsupervised exercise	Angioplasty with selective stent
3	Unsupervised exercise	Bypass surgery
4	Supervised exercise	Supervised exercise
5	Supervised exercise	Angioplasty with selective stent
6	Supervised exercise	Bypass surgery
7	Angioplasty with selective stent	Supervised exercise
8	Angioplasty with selective stent	Angioplasty with selective stent
9	Angioplasty with selective stent	Bypass surgery
10	Angioplasty with primary stent	Supervised exercise
11	Angioplasty with primary stent	Angioplasty with selective stent
12	Angioplasty with primary stent	Bypass surgery
13	Angioplasty with selective stent + supervised exercise	

Population

The hypothetical population included in the analysis was people with IC who are suitable for and willing to undergo either exercise or angioplasty. Based on the baseline characteristics of people in the included RCTs, a starting age of 67 years was used to represent the average age of people with IC. The hypothetical cohort was 70% male and had an average ABPI of 0.64. Twenty four percent of people were diabetic and 43% were current smokers. The prevalence of diabetes and smokers was used to inform the baseline risk of stroke and MI in the model.

Not included were people with co-morbidities which prevent participation in an exercise program; people who are either not interested in undergoing angioplasty or not considered anatomically suitable for an endovascular procedure; people who have recently undergone an endovascular procedure; or people with CLI. People who drop out after beginning an exercise programme are included in the model.

According to the methods used in the clinical review, patients with IC due to stenosis in the aorto-iliac and femoro-popliteal arteries were considered as separate subgroups. All were assumed to be receiving best medical therapy (antiplatelet therapy, anti-hypertensive therapy, cholesterol-lowering agents, diabetes control and smoking cessation advice) at baseline, consistent with the included RCTs.

Approach to modelling

Intermittent claudication is associated with high mortality, increased risk of cardiovascular morbidity and a decreased quality of life. Primary treatment options for IC include exercise and angioplasty. Exercise may take the form of either a supervised or unsupervised programme and angioplasty may be performed with either primary or selective stent placement. If symptoms do not improve, patients may be offered a supervised exercise programme or referred for assessment for angioplasty or bypass surgery. In order to determine which interventions represent the most cost effective pathway for people with IC, the model included 13 different treatment sequences: four primary alternatives, three secondary interventions and one combination treatment. As a necessary simplification, no more than two treatment options were considered. If patients' symptoms deteriorate following secondary intervention, they were assumed to revert to their baseline quality of life.

As for the model comparing supervised to unsupervised exercise (Appendix K), compliance to the recommended level of physical activity was associated with a decreased risk of mortality and cardiovascular events. The most conservative estimate of compliance to exercise (scenario 2; Appendix K) was used in the base case analysis with other scenarios explored in sensitivity analysis. Treatment failure following exercise was defined as a worsening of symptoms. Epidemiological studies suggest that approximately a quarter of patients with intermittent claudication experience deterioration in their symptoms over a five year period.[5] Currently, there is no evidence to suggest that exercise has any impact on the rate of disease progression. It was assumed that patients who undertake supervised and unsupervised exercise programmes experience the same rate of symptomatic progression as observed in the epidemiological literature.

There is no evidence to suggest that angioplasty has any impact on long term mortality or cardiovascular risk factors. Therefore, people who underwent angioplasty were assumed to have the same mortality and cardiovascular risk as those who were inactive (i.e. baseline risk). Failure following angioplasty was defined as patency failure plus symptom deterioration requiring secondary intervention. Relative risk of re-intervention for people who had undergone selective and primary stent placement were obtained from the systematic clinical review. In the absence of evidence of the effectiveness of secondary interventions, it was assumed that they were associated with the same relative risk of mortality and morbidity as those observed in primary procedures. People who failed secondary intervention and were left with persistent claudication had no further intervention, unless they subsequently progressed to CLI.

The GDG noted that currently there is no evidence to suggest a relationship between treatment for claudication and progression to critical limb ischaemia (CLI). In the base case analysis, the risk of progression to CLI was included as a constant background rate irrespective of treatment pathway, effectively 'cancelling out' of the model. The treatment for critical limb ischaemia was the same for all strategies: 25% underwent amputation. The potential impact of different treatments on the rate of progression to CLI (and therefore to amputation) was explored in sensitivity analysis.

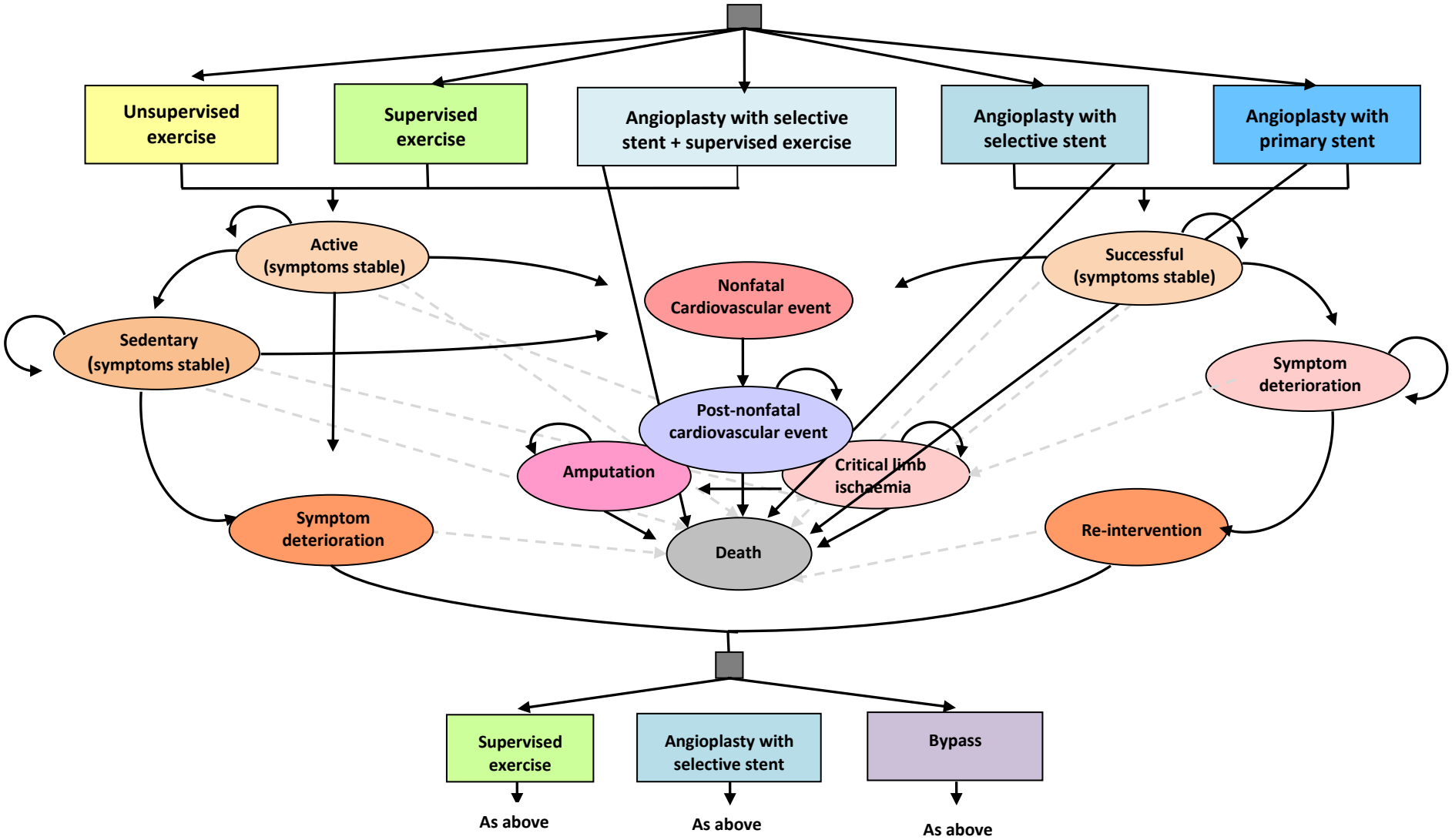
People who experience a cardiovascular event enter a semi-absorbing health state from which the only available transition is death. Average costs and quality of life associated with post-cardiovascular event states were applied to this health state, and the same mortality rate as sedentary people was assumed. It was also assumed that all patients would undergo a general examination and treatment for cardiovascular risk factors.

The treatment goal for people with IC is to improve health related quality of life. As in the previous model comparing supervised to unsupervised exercise (Appendix K), the GDG decided to use the quality of life data from the RCTs included in the clinical review as the primary measure of clinical effectiveness. Symptomatic progression, cardiovascular events, and lower limb amputation resulted in a reduced quality of life according to published estimates.

Based on clinical experience, it was assumed that patients who drop out of supervised exercise programmes do so within the first few weeks. They were assigned a quarter of the cost of a course of supervised exercise and assumed not to accrue any health benefit from their time spent in the programme.

The model was built probabilistically to take account of the uncertainty surrounding each input parameter. In order to characterise uncertainty, a probability distribution was defined for each parameter based on error estimates from the data sources (e.g. standard errors or confidence intervals). The way in which distributions are defined reflects the nature of the data. When the model was run, a value for each input was randomly selected from its respective distribution. The model was run repeatedly (10,000 times) to obtain mean cost and QALY values.

Figure 6: Schematic Markov model structure



Schematic diagram of the Markov model designed to compare the cost-effectiveness of different exercise and endovascular treatment strategies for people with IC. The Markov modelling approach involves a transition between different health states over time, represented by arrows. The model is divided into three month cycles. At the end of each cycle a time-dependant transition to another health state is possible, unless people enter into an 'absorbing state' from which they do not recover. In this model, the absorbing state is death. In the base case model, transition to CLI (and therefore amputation) occurs at a constant rate, represented by dashed grey arrows.

Baseline mortality and relative risk associated with exercise

Age- and sex-specific all cause mortality was based on the most recent available life tables of the general population in England and Wales. Rates were adjusted for people with IC by multiplying by the standardised risk of all cause mortality observed over 10 years in people with IC.[71]

No randomised evidence of exercise-associated risk of mortality in people with IC was identified. The GDG agreed that evidence from people with cardiovascular disease would represent a reasonable proxy. A recent Cochrane review of randomised controlled trials was therefore used to inform the risk of total mortality among people participating in exercise rehabilitation compared to non-active controls.[72] A summary of the values used to inform this parameter is provided in Table 67. The GDG discussed the limitations of using an indirect population to inform this parameter and the effect of this value on the model result was further explored in sensitivity analysis.

Table 67: Total mortality

	10-year total mortality for the general population based on Life Tables for England and Wales[(a)]	Relative risk of total mortality in people with IC compared to those without IC	Relative risk of total mortality in people who exercise compared to those who do not exercise
Mortality	25.0%	3.1 (95% CI, 1.9 to 4.9)[71]	0.87 (95% CI , 0.75 to 0.99)[72]

(a) Assuming that the average age of the baseline population is 67 years and 66% are male.

Baseline risk of cardiovascular events and relative risk associated with exercise

The average baseline probability of stroke and MI was calculated by age and gender using the Framingham risk equations and risk calculator spreadsheet developed by Rupert Payne at the University of Edinburgh.[73,74] Risk factor inputs for each sex were obtained from the 2006 Health Survey for England (HSE; Table 35).[75] Average age- and sex- specific blood pressure values were obtained from the 2011 NICE Hypertension update guideline[76], which used individual patient level data from the 2006 HSE. A recent study by the Ankle Brachial Index Collaboration found that when combined with Framingham risk scores, an ABPI of between 0.61 and 0.70 approximately triples the risk of major cardiovascular events for men and women.[77]

The risk of MI in patients who exercise compared to those who are not active in an exercise programme was obtained from the Cochrane review by Heran et al (2011).[72] A meta-analysis of the effect of physical activity on the incidence of stroke was used to inform the risk of stroke for active compared to sedentary people in the model.[78] A summary of the values used to inform these parameters is provided in Table 68. As with estimates of the relative risk of total mortality, these data sources are subject to several limitations and the effect of these values on the model were explored in sensitivity analysis.

Table 68: Major cardiovascular events

	10 year risk of MI and stroke for general population according to the Framingham equations[(a)]	Relative risk of major cardiovascular events in people with IC compared to those without IC[(b)]	Relative risk of MI and stroke in people who exercise compared to those who do not exercise
MI	7.2%	Men: 2.71 (95% CI, 2.01 to 3.64) Women: 3.82 (95% CI, 2.86 to 5.11)	0.97 (95% CI, 0.82 to 1.15)[72]
Stroke	4.4%	Men: 2.71 (95% CI, 2.01 to 3.64) Women: 3.82 (95% CI, 2.86 to 5.11)	0.80 (95% CI, 0.74 to 0.86)[78]

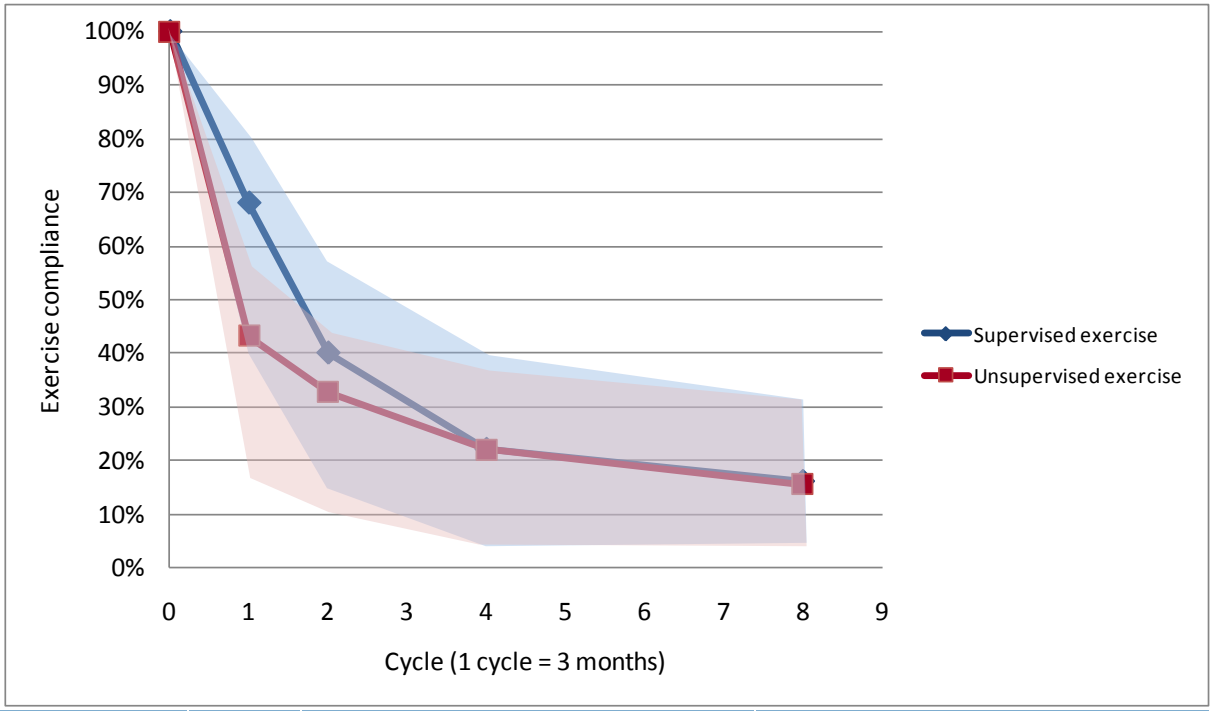
(a) Calculated using Framingham MI and stroke risk equations[73,74] and risk factor inputs derived from the 2006 Health Survey for England[75], assuming that the average age of the baseline population is 67 years and 66% are male.

(b) Based on a risk of cardiovascular events for mean and women with an ABPI of 0.61 to 0.7 compared to men and women with normal ABP.[77]

Compliance to supervised and unsupervised exercise

Levels of short- and long-term compliance to supervised and unsupervised exercise programs among people with IC is an area of great uncertainty. Following a review of the literature and survey of GDG members and their colleagues across the country (Appendix K), two scenarios were developed to represent different theoretical rates of compliance each exercise programme. In order to simplify reporting for this model, the more conservative of the two scenarios was used to inform the base case analysis. Under this assumption, compliance to supervised exercise is greater than unsupervised exercise over the short term and equal over the long term (Figure 7). The impact of different levels of compliance on the outcome of the model was explored in sensitivity analysis.

Figure 7: Equal long term compliance to unsupervised and supervised over the long term



Time point	Cycle	Supervised			Unsupervised		
		Lower	Most likely	Upper	Lower	Most Likely	Upper
3 months	1	40%	68%	80%	17%	43%	56%
6 months	2	15%	40%	57%	10%	33%	45%
1 year	4	4%	22%	40%	7%	22%	37%
2 years	8	5%	16%	32%	5%	16%	31%

Symptom deterioration after a period of exercise

Few studies have measured disease progression among patients with intermittent claudication. Most articles on the natural history of the disease report that claudication remains stable in 70% to 80% of patients over a five year period Hirsch 2006[5], Rosenbloom 1988, Edi study 1996). In the remainder of patients, it may progress to disabling claudication or critical limb ischaemia requiring revascularisation. Based on these estimates, it was assumed that claudication symptoms worsen to the point of requiring revascularisation in 25% (range = 20% to 30%) of people with IC over 5 years. This is equivalent to a one year probability of 5.6% and a three month probability of 1.4%.

Currently, there is no evidence to suggest that the probability of symptom deterioration differs between patients who exercise and those who do not. The probability of requiring revascularisation was assumed to be equal regardless of activity status and therefore did not differ according to whether patients had undertaken a supervised or unsupervised exercise programme.

CLI and amputation

Amputation is a relatively rare outcome of claudication and is usually a result of the patient developing CLI. It was assumed that 2% of people with claudication progress to CLI over a 5 years and that 25% of those with CLI 25% undergo amputation as a primary intervention.[5] In the base case analysis, progression to CLI was applied at a constant rate regardless of a person's position in the treatment pathway. It was assumed that the development of CLI is a function of the disease process and does not differ by intervention. This assumption was further explored in sensitivity analysis.

The one year mortality rate in people with CLI is approximately 25%.[113] For those who undergo amputation, this is considerably higher with a 35% probability of mortality in the first year following amputation and 19% probability every year thereafter.[114]

Baseline and relative treatment effects

Baseline rates of mortality, major complications and amputation associated with angioplasty with selective stent placement were obtained from a prospective audit by the Royal College of Surgeons of England.[115] Because the results of the audit were not reported by lesion location, the reported outcomes were assumed to represent an average value across both vessels. The audit found that 33 (2.4%) of total angioplasties were complicated by major medical morbidity which was unrelated to the technique of angioplasty. This was used as the baseline probability of major complication following angioplasty with selective stent placement. None of the patients undergoing angioplasty for claudication died within 30 days of the procedure. Although the GDG agreed that the risk of death as a result of angioplasty was small, they thought that there was still a risk associated with the procedure. It was assumed that 0.5 (out of 841) people with IC undergoing angioplasty die due to the procedure. Similarly, none of the patients experienced limb loss as a result of acute ischaemia following angioplasty.[115] However, the GDG indicated that although small, there is a risk of amputation as a result of angioplasty. Therefore, as for mortality, it was assumed that 0.5 of 841 angioplasty procedures for claudication could be expected to result in amputation.

People who undergo endovascular procedure may experience a reoccurrence of symptoms over the following months or years. Based on primary patency results reported in the TASC II guideline and the clinical experience of the GDG, it was assumed that each year after angioplasty, a certain percentage of people with aorto-iliac and femoro-popliteal disease experience patency failure. Not all of those who experience patency failure will undergo reintervention. Of those who return to their healthcare provider, the GDG noted that people with aorto-iliac disease are more likely to undergo secondary intervention compared to those with stenoses or occlusions of the femoro-popliteal artery. The weighted average probability of reintervention for each artery is presented in Table 69.

Evidence of relative clinical effectiveness between different interventions was collected from the pooled results of the clinical systematic review. For each outcome, angioplasty with selective stent placement was used as the baseline comparator. Relative risks were entered into the model probabilistically to reflect the uncertainty surrounding each point estimate. For two outcomes (30-day mortality and post-operative amputation) there was no data reported for one of the two arteries. Where the GDG considered that there was no a priori reason to assume a difference in treatment efficacy based on location, and if the 95% CI in one anatomical area included one, a default value of 1 was used to inform the missing risk ratio. Where the GDG considered there was an a priori reason for considering that there would be a difference, the results for one anatomical area

were used as the basis for estimating the other. See Table 69 for a summary of all clinical effectiveness outcomes applied in the model.

Table 69: Baseline probabilities and relative treatment effects

Parameter	Point estimate	Value range	Source
Probability of 30-day mortality for angioplasty with selective stent			
Baseline probability of 30-day mortality	0.06%	0.0% - 0.9%	Expert opinion informed by Royal College of Surgeons 2002[115]
Relative risk of 30-day mortality for angioplasty with primary stent (compared to selective stent)			
Aorto-iliac	Not reported. Assumed no difference between interventions (RR = 1)		
Femoro-popliteal	0.20	0.01 – 4.17	Cejna 2001[116]
Probability of major complications for angioplasty with selective stent			
Baseline probability of major complications	2.4%	1.7% - 3.3%	Royal College of Surgeons 2002[115]
Relative risk of major complications for angioplasty with primary stent (compared to selective stent)			
Aorto-iliac	0.57	0.21 – 1.54	Tetteroo 1998[117]
Femoro-popliteal	1.26	0.33 – 1.93	Dick 2009[118], Krankenberg 2007[119], Schillinger 2006[120], Vroegindewij 1997[121]
Baseline probability of post operative amputation following angioplasty with selective stent			
Baseline probability of post operative amputation	0.06%	0.0% - 0.9%	Expert opinion informed by Royal College of Surgeons 2002[115]
Relative risk of post operative amputation following angioplasty with primary stent (compared to selective stent)			
Aorto-iliac	Not reported. Assumed no difference between interventions (RR = 1)		
Femoro-popliteal	0.50	0.09 – 2.63	Cejna 2001[116]
Probability of IC symptom worsening following angioplasty (selective stent & primary stent)			
Aorto-iliac	7.5%	5% - 10%	Expert opinion
Femoro-popliteal	34%	28% - 40%	Expert opinion
Baseline probability of reintervention following symptom worsening (selective stent only)			
Aorto-iliac	71%	66% - 76%	Expert opinion
Femoro-popliteal	28%	18% - 38%	Expert opinion
Relative risk of re-intervention following angioplasty with primary stent (compared to selective stent)			
Aorto-iliac	1.63	0.58 – 4.61	Tetteroo 1998[117]
Femoro-popliteal	0.50	0.22 – 1.13	Schillinger 2007[122,123]
Relative risk of 30-day mortality following bypass (compared to selective stent)			
Aorto-iliac	2.94	0.12 – 73.19	Wilson 1989[103]
Femoro-popliteal	2.94	0.12 – 73.19	Expert opinion (see text)
Relative risk of perioperative major complications following bypass (compared to selective stent)			
Aorto-iliac	0.31	0.14 – 0.67	Wilson 1989[103]
Femoro-popliteal	0.60	0.17 – 2.17	McQuade 2009[102]
Relative risk of amputation within 30-days of bypass (compared to selective stent)			
Aorto-iliac	0.98	0.14 – 7.04	Wilson 1989[103]
Femoro-popliteal	Not reported. Assumed no difference between interventions (RR = 1)		

Utilities

In cost-utility analyses, measures of health benefit are valued in terms of quality adjusted life years (QALYs). The QALY is a measure of a person's length of life weighted by a valuation of their health related quality of life (HRQoL) over that period. The quality of life weighting comprises two elements: the description of changes in HRQoL and an overall valuation of that description. Questionnaires such as the SF-36 and SF-12 provide generic methods of describing HRQoL while the EQ-5D, HUI, and SF-6D also include preference-based valuations of each health state.

Quality of life data were collected from all RCTs included in the clinical review. Four studies included the EQ-5D as a measure of HRQoL. Thirteen papers (representing an additional nine trials) reported SF-36 data. According to the NICE reference case, EQ 5D data are the preferred measure of quality of life for use in cost utility analyses. Therefore, of the four trials that reported both measures, EQ-5D was used in preference to SF-36.

Recently, several algorithms have been developed which can be used to map generic descriptions of HRQoL to preference-based utility indexes. In 2008, Ara and Brazier[66] published a method of predicting mean EQ-5D preference based index score using published mean cohort statistics from the eight dimensions of the SF-36 health profile. In order to use these algorithms, values for each of the eight dimensions of the questionnaire are required. Four provided all the necessary values and the authors of the remaining nine studies were contacted to request the required data (Appendix L).

Mapping SF-36 to EQ-5D using published algorithms and probabilistic simulation

For each trial, it is the change in quality of life over time and the difference in this change between interventions (i.e. mean difference in change) that is the key to determining the relative effectiveness of each intervention. In order to calculate the mean difference in change between each three month time interval while taking into account the uncertainty surrounding each estimate, the mean and standard error of each dimension of the SF-36 were assigned a beta distribution according to the method of moments described by Briggs 2006.[79] Probabilistic mapped values were then calculated using Equation 4 from the paper by Ara and Brazier[66], who specify that 'when comparing incremental differences between study arms or changes over time, Equation 4 is the preferred choice'. A simulation was run 20, 000 times in order to calculate a mean, standard error and confidence interval surrounding each mapped estimate. For the purposes of clinical validation, absolute mean mapped values were calculated using Equation 1 according to the same method. The results of these simulations are reported in Table 72.

Equation 1: 0.03256 + 0.0037 x PF + 0.0011 x SF – 0.00024 x RP + 0.00024 x RE + 0.00256 x MH – 0.00063 x VT + 0.00286 x BP + 0.00052 x GH

Equation 4: -0.18105 + 0.00781 x PF +0.00213 x SF + 0.00022 x RE + 0.00472 x BP + 0.00064 x GH

Note that mean difference in change calculated using Equation 4 is not expected to equal the incremental difference between the mean mapped values from Equation 1 as they are derived using different models. Alternative methods of calculating relative differences in quality of life between treatment arms were explored in sensitivity analysis. Note also that because the covariance matrices for the regression coefficients were not available it was not possible to account for uncertainty in the mapping algorithm in the probabilistic analysis.

Inputs and assumptions used to inform model utilities

In the base case analysis, an average utility value was weighted according to the total number of people in the study at each time point. In order to preserve within-study randomisation, the weighted average incremental change in quality of life associated with each intervention (as calculated by the probabilistic simulation; Table 72) was applied in an additive method. For example,

at 3 months, the mean difference in change from baseline between selective stent placement and supervised exercise is 0.035 QALYs. And at the same time point, the mean difference in change between supervised exercise and unsupervised exercise is -0.021 QALYs. Adding these values results in a mean difference in change between selective stent placement and unsupervised exercise of 0.014 QALYs between baseline and three months.

None of the studies that included bypass surgery as an intervention measured quality of life as an outcome. The exclusion list of the clinical evidence review was searched for non-randomised data from which to draw utility data, however none reported this information. Based on discussions with the GDG and observational studies in the literature[124], it was assumed that the utility gain associated with angioplasty with primary stent is equal to that associated with bypass.

The duration of supervised exercise programmes differed between each trial (Savage = 3 months; Cheetham = 6 months; Nicolai = 12 months). The GDG agreed that in order to make use of all available evidence the data from all trials should be combined using a weighted average. Quality of life gains achieved after exercise intervention were maintained for people who continued to exercise. Those who stopped exercising were assigned the baseline quality of life.

Quality of life associated with cardiovascular events

Quality of life associated with cardiovascular events was derived from the most recent NICE Hypertension guideline update, which in turn was obtained from a comprehensive review of the literature undertaken by the authors of the NICE statins HTA (Table 70).

Table 70: Quality of life following cardiovascular events

Event	Mean utility	SE	Source
MI	0.760	0.018	Goodacre 2004[125]
Stroke	0.629	0.040	Tengs 2003[126]

In line with the methods used by the hypertension guideline, it was assumed that full health was equal to a utility of one. The utility value for each cardiovascular event was then multiplied by the baseline quality of life experienced by people with IC for each artery (e.g. 0.76 x baseline). The difference between this value and the baseline quality of life was used to inform the decrease in quality of life associated with each event. It was assumed that the quality of life decrement in the years following a cardiovascular event is half that experienced in the first year. Each calculation was performed using a probabilistic simulation (n= 20, 000). Simulated absolute mean values and mean utility decrements are summarised in Table 71. In the model, each utility decrease was divided by four to account for the three month cycle length.

Quality of life following amputation

The quality of life associated with amputation was obtained from a cost-utility analysis by Sculpher et al 1996.[127] This analysis estimated that the utility for someone with an amputation above the knee is 0.20 (0.00 – 0.40) and 0.61 (0.41 – 0.81) for below the knee. It has previously been estimated that 52% of amputations are above the knee. An overall utility value for people who have had an amputation was estimated by assigning a distribution to each above- and below- the knee utility value, applying this proportional estimate, and running a probabilistic simulation. The resulting value of 0.396 (0.264 – 0.546) was used to represent the average quality of life of people who have had an amputation.

Table 71: Simulated mean utility and mean utility decrements compared to baseline

	Utility associated with each health state			Corresponding utility decrease from baseline		
Health state	**Mean**	**SE**	**95% CI**	**Mean**	**SE**	**95% CI**
Aorto-iliac arteries						
IC (baseline)	0.580	0.048	0.490 – 0.674			
MI	0.441	0.038	0.370 – 0.515	-0.139	0.016	-0.171 to -0.111
Post MI	0.510	0.42	0.430 – 0.593	-0.070	0.008	-0.086 to -0.055
Stroke	0.365	0.038	0.293 – 0.442	-0.215	0.029	-0.276 to -0.162
Post stroke	0.472	0.041	0.396 – 0.553	-0.108	0.015	-0.138 to -0.081
CLI	0.350	0.051	0.253 – 0.454	-0.231	0.070	-0.367 to -0.094
Amputation	0.396	0.072	0.264 - 0.546	-0.185	0.086	-0.349 to -0.009
Femoro-popliteal arteries						
IC (baseline)	0.573	0.044	0.489 – 0.659			
MI	0.435	0.35	0.369 – 0.505	-0.138	0.015	-0.168 to 0.110
Post MI	0.504	0.039	0.430 – 0.581	-0.069	0.007	-0.084 to -0.055
Stroke	0.360	0.036	0.292 – 0.434	-0.213	0.028	-0.271 to -0.162
Post stroke	0.467	0.038	0.395 – 0.542	-0.106	0.014	-0.136 to -0.081
CLI	0.350	0.051	0.253 – 0.454	-0.223	0.068	-0.356 to -0.092
Amputation	0.396	0.072	0.264 - 0.546	-0.177	0.084	-0.546 to -0.264

Table 72: Mean quality of life and mean difference in change between time points

	Unsupervised exercise		Supervised exercise		Angioplasty with selective stent + supervised exercise		Angioplasty with selective stent		Angioplasty with primary stent		Mean difference in change		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Interval	Mean	SE
Weighted average of Nicolai 2010, Cheetham 2004, Savage 2001													
Baseline	0.636	0.017	0.672	0.014									
3 months	0.691	0.017	0.709	0.015							Baseline to 3 months	-0.021	0.033
6 months	0.692	0.015	0.732	0.016							3 months to 6 months	0.026	0.032
9 months	0.692	0.018	0.744	0.016							6 months to 9 months	0.010	0.034
12 months	0.671	0.023	0.748	0.017							9 months to 12 months	0.029	0.040
Greenhalgh 2008 (Aorto-iliac)													
Baseline			0.426	0.012	0.419	0.012							
3 months			0.422	0.008	0.461	0.009					Baseline to 3 months	0.077	0.020
6 months			0.417	0.011	0.503	0.014					3 months to 6 months	0.077	0.020
9 months			0.418	0.010	0.501	0.011					6 months to 9 months	0.004	0.023
12 months			0.418	0.016	0.498	0.016					9 months to 12 months	0.004	0.023
24 months			0.451	0.017	0.507	0.014					12 month to 24 months	-0.059	0.051
Greenhalgh 2008 (Femoro-popliteal)													
Baseline			0.451	0.008	0.466	0.007							
3 months			0.453	0.006	0.472	0.005					Baseline to 3 months	0.010	0.013
6 months			0.455	0.008	0.479	0.008					3 months to 6 months	0.010	0.013
9 months			0.456	0.006	0.479	0.006					6 months to 9 months	-0.001	0.013
12 months			0.457	0.009	0.479	0.008					9 months to 12 months	-0.001	0.013
24 months			0.458	0.009	0.486	0.009					12 month to 24 months	0.014	0.028
Spronk 2009 (Aorto-iliac & Femoro-popliteal)													
Baseline			0.690	0.024			0.660	0.023					
3 months			0.735	0.021			0.740	0.019			Baseline to 3 months	0.035	0.028

6 months			0.780	0.033			0.820	0.031			3 months to 6 months	0.035	0.028
9 months			0.770	0.023			0.795	0.024			6 months to 9 months	-0.015	0.033
12 months			0.760	0.032			0.770	0.036			9 months to 12 months	-0.015	0.033
Bosch 1999 (Aorto-iliac)													
Baseline							0.461	0.154	0.459	0.204			
3 months							0.701	0.204	0.754	0.216	Baseline to 3 months	0.055	0.390
6 months							0.701	0.153	0.699	0.161	3 months to 6 months	-0.055	0.140
9 months							0.701	0.159	0.645	0.157	6 months to 9 months	-0.055	0.140
12 months							0.701	0.217	0.590	0.208	9 months to 12 months	-0.055	0.140

Mean difference in change = change in utility between time points within one trial arm subtracted from the change in the same time interval in the other trial arm. A positive value indicates an improvement in quality of life in the trial arm in the right column of each intervention pair.

Costs

As in the model comparing unsupervised to supervised exercise, the cost of supervised exercise was based on estimates of resource use informed by expert opinion and unit costs obtained from the 2010 PSSRU. A breakdown of the assumptions and unit costs used to calculate per-patient cost of a supervised exercise programme are provided in Table 37 (section 9.4.8.2).

Endovascular intervention costs were obtained from the most recent 2009/2010 NHS Reference Costs. The GDG estimated that approximately 5% of angioplasty procedures performed as a primary strategy for people with intermittent claudication are non elective and that 10% of angioplasty procedures performed as a secondary strategy are unplanned, and that 55% of amputations preformed for people with CLI would be performed as emergency non elective procedures.

In the absence of recent relevant estimates of the cost of post-amputation care in the literature, the GDG provided estimates of resource use based on their experience and the expertise of colleagues around the country. These resources were grouped according to those that occur in the first year after amputation and those occurring in subsequent years.

Table 73: Costs and cost-related variables

Parameter	Point estimate	Value range	Source
Cost of CV events			
Initial MI (first 3 months)	£4, 792	£3, 853 – £5, 731	Hypertension guideline 2011[76]
Post nonfatal MI (subsequent 3 month cycles)	£141	£113 – £169	Hypertension guideline 2011[76]
Initial stroke (first 3 months)	£9, 630	£7, 743 – £11, 517	Hypertension guideline 2011[76]
Post nonfatal stroke (subsequent 3 month cycles)	£559	£449 – £669	Hypertension guideline 2011[76]
Unsupervised and supervised exercise intervention cost			
Unsupervised exercise	£0	NA	Expert opinion
Supervised exercise	£288	£232 – £345	Expert opinion
Angioplasty with primary and selective stent intervention cost			
Diagnostic imaging	£90	£53 - £102	NHS Reference Costs 2009/10[128]
Stent (bare metal)	£550	£450 - £650	Expert opinion
Primary angioplasty with no complications	£3, 661	£2, 204 - £4, 480	NHS Reference Costs 2009/10[128]
Primary angioplasty with major complications	£9, 367	£2, 200 - £14, 270	NHS Reference Costs 2009/10[128]
Secondary angioplasty with no complications	£3, 695	£2, 206 - £4, 524	NHS Reference Costs 2009/10[128]
Secondary angioplasty with major complications	£9, 385	£2, 329 - £14, 154	NHS Reference costs 2009/10[128]
Proportion of patients receiving stents (selective stent)			
Aorto-iliac	35.2%	28.5% - 42.9%	Based on included RCTs[107,112,117]
Femoro popliteal	16.2%	10.5% - 24.4%	Based on included RCTs[100,101,119,120,123]
Average number of stents used where stents are placed			

Aorto-iliac	2	NA	Expert opinion
Femoro-popliteal	2	NA	Expert opinion
Bypass intervention cost			
Bypass with no/major complications	£5, 988	£4, 417 - £7, 025	NHS Reference Costs 2009/10[128]
Bypass with major complications	£7, 139	£5, 185 - £8, 641	NHS Reference Costs 2009/10[128]
Amputation procedural cost			
Cost of amputation without major complications	£9, 224	£6, 862 - £10, 481	NHS Reference Costs 2009/10[128]
Cost of amputation with major complications	£15, 001	£7, 862 - £18, 600	NHS Reference Costs 2009/10[128]
Probability of major complications	14.3%	12.2% - 16.6%	Aulivola 2004[114]
Amputation cost of care in first year following amputation and each subsequent year			
Cost of care during first year	£28, 270	£25, 499 - £31, 040	Expert opinion
Annual cost of care in subsequent years	£23, 502	£21, 199 - £25, 806	Expert opinion

9.4.813 Results

Aorto-iliac artery

After excluding strategies which are dominated or extendedly dominated (Figure 8), the results of the analysis show that supervised exercise followed by angioplasty with selective stent placement (strategy 5) is the most cost-effective treatment strategy for people with IC at a cost of £16, 289 per QALY. Although angioplasty with selective stent followed by angioplasty with selective stent (strategy 8) results in the greatest QALY gain, the incremental cost per QALY is greater than that which is considered cost-effective by NICE (Table 76). The cost effectiveness acceptability frontier shows that at a threshold of between £20, 000 and £30, 000, strategy 5 is the option with the greatest probability of being cost effective (Figure 9).

Figure 8: Cost effectiveness plane: Aorto-iliac artery

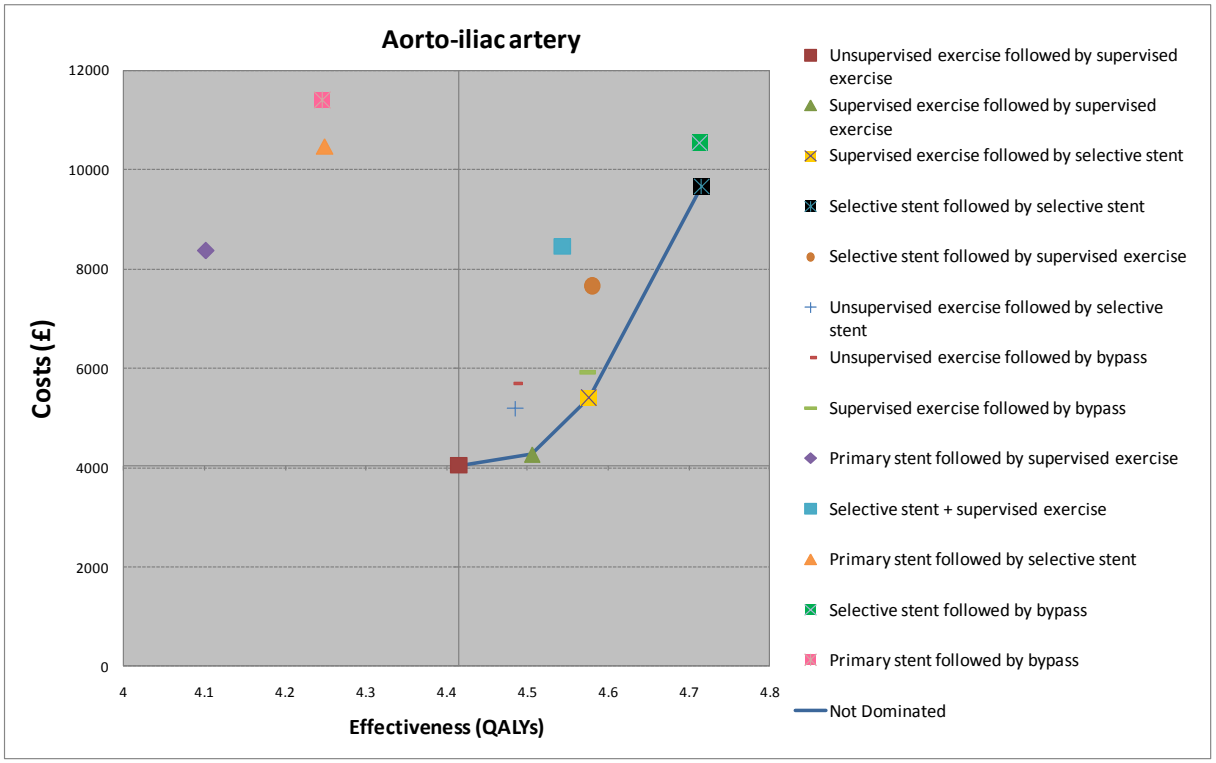


Figure 9: Cost effectiveness acceptability frontier: Aorto-iliac-artery

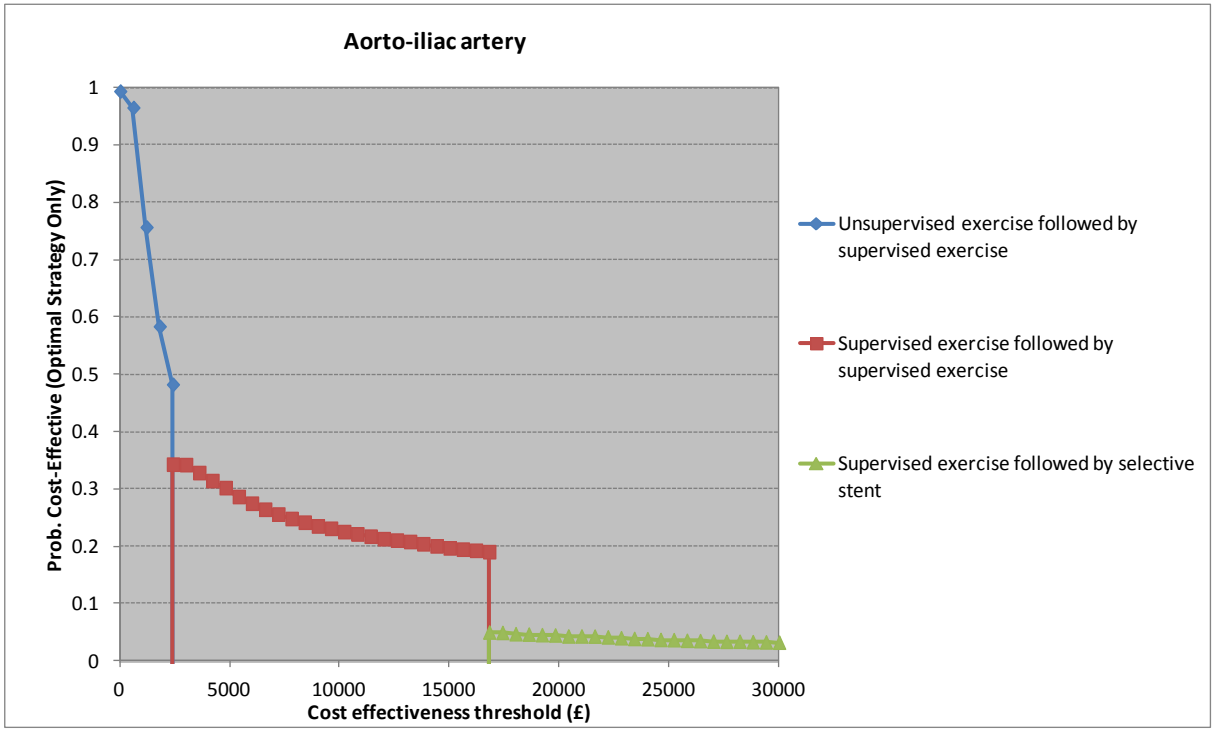


Table 74: Probabilistic base case results without dominated options: Aorto-iliac artery

Strategy	Total Cost	Incremental Cost	Total QALYs	Incremental QALYs	Cost effectiveness
1	£4, 046	Baseline	4.415	Baseline	Baseline
4	£4, 263	£217	4.506	0.091	2, 387

5	£5, 411	£1, 147	4.576	0.070	£16, 289
8	£9, 661	£4, 250	4.716	0.140	£30, 408

Femoro-popliteal artery

The results of the analysis in the femoro-popliteal artery show that supervised exercise followed by angioplasty with selective stent placement (strategy 5) is also the most cost-effective treatment strategy at a cost of £16, 024 per QALY (Figure 10). In this artery, angioplasty with selective stent followed by angioplasty with selective stent (strategy 8) also results in the greatest QALY gain, but the incremental cost per QALY is greater than that which is considered cost-effective by NICE (

Table 75). The cost effectiveness acceptability frontier shows that at a threshold of between £20, 000 and £30, 000, strategy 5 is the option with the greatest probability of being cost effective (Figure 11).

Figure 10: Cost effectiveness plane: Femoro-popliteal artery

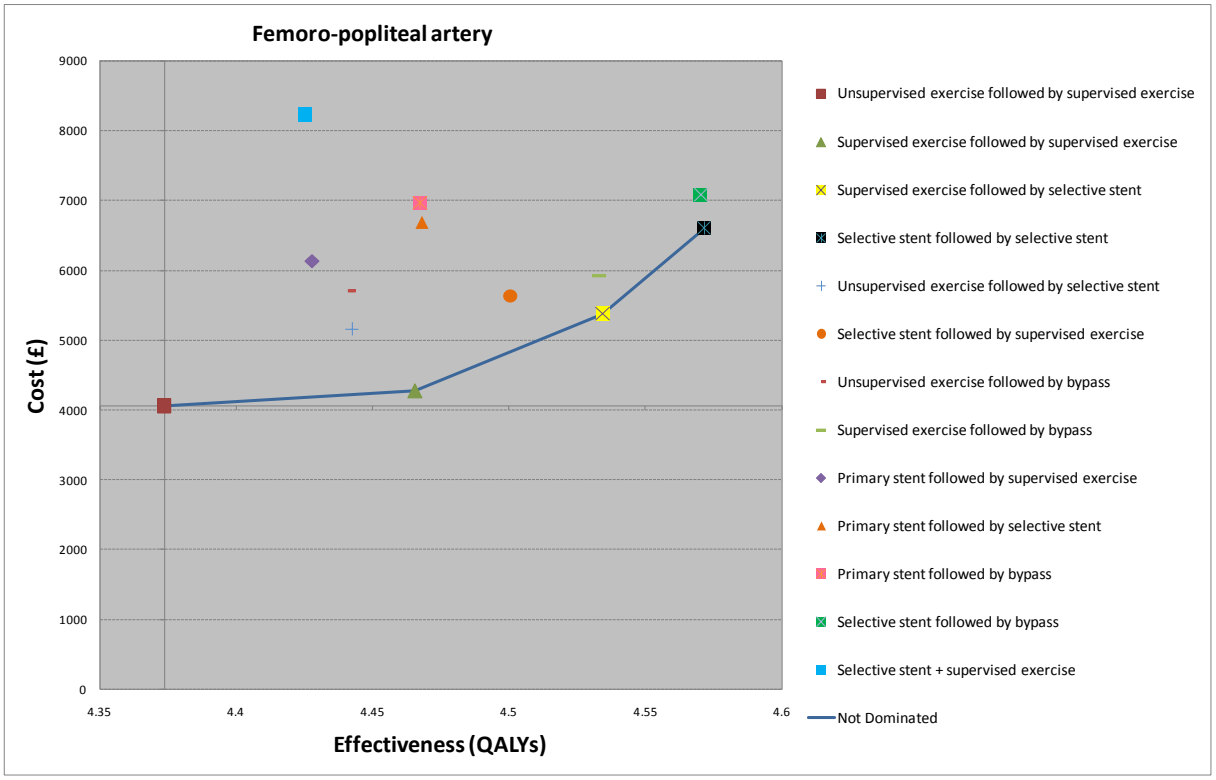


Figure 11: Cost effectiveness acceptability frontier: Femoro-popliteal artery

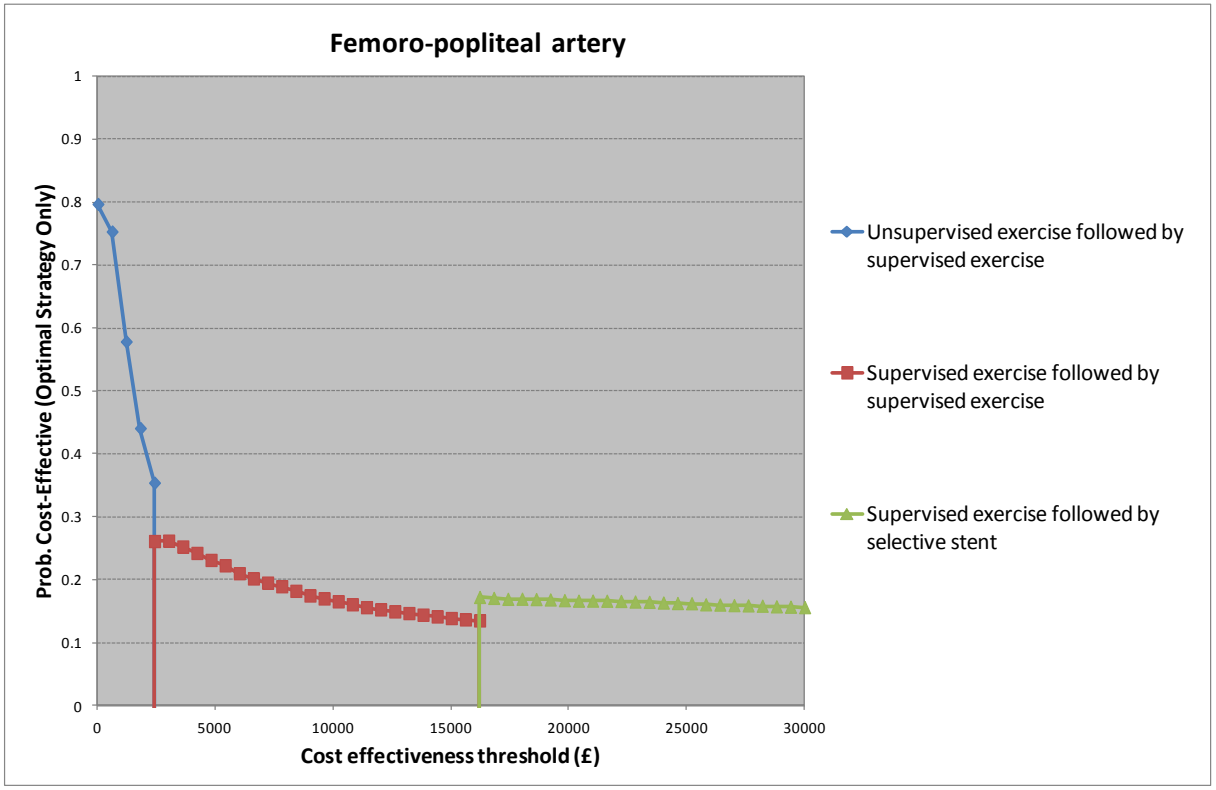


Table 75: Probabilistic base case results without dominated options: Femoro-popliteal artery

Strategy	Total Cost	Incremental Cost	Total QALYs	Incremental QALYs	Cost effectiveness
1	£4, 059	Baseline	4.374	Baseline	Baseline
4	£4, 276	£217	4.466	0.092	£2, 362
5	£5, 378	£1, 102	4.534	0.069	£16, 024
8	£6, 603	£1, 225	4.572	0.037	£32, 898

Sensitivity analyses

A wide range of sensitivity analyses were undertaken to test the effect of different inputs and assumptions on the results of the model. These analyses showed that the results were subject to a high degree of uncertainty and the conclusion was sensitive to many of the key assumptions used to inform the model. In particular, the results were sensitive to the assumption that exercise reduces the risk of mortality in people who are active. By reducing the assumed increase life expectancy associated with activity, a primary selective stent strategy becomes more effective in comparison. Under this sensitivity analysis, selective stent followed by selective stent is the most cost effective option in both arteries. The results of the model are also sensitive to the assumption that the change in quality of life observed at the end of the trial period persists over a person's lifetime so long as they do not experience a recurrence of symptoms, and in those undertaking exercise intervention, they remain active.

Limitations and interpretation

This model was developed based on a combination of best available clinical evidence and expert opinion. It is directly relevant to the treatment of people with IC in England and Wales. It was built probabilistically to account for the uncertainty surrounding each parameter. The results of the analysis reflect the overall uncertainty in the treatment decision for an average population who are suitable for all of the evaluated interventions.

The model was developed on the assumption that secondary interventions are associated with the same relative risk of mortality and morbidity as those observed in primary procedures. In practice, the GDG indicated that there are many risk factors or clinical features which may differentially affect the outcome of secondary interventions. For example, a patient who did not benefit from or dropped out of a supervised exercise programme is unlikely to benefit from a secondary course in the same way as someone who has had a positive outcome or no previous experience of the same programme. Similarly, secondary procedures at the same site may have an increased risk of failure. Many factors including anatomic disease extent and clinical presentation, patient preference, and patient co-morbidities will influence treatment options which are most appropriate for individual patients. This model is not intended as a substitute to expert clinical judgement; patients must be considered on an individual basis where there are factors which may affect the expected outcome.

The model was designed to address questions set by the guideline scope. Different methods of post operative management were not included in the scope of the guideline and were therefore not included in the model. Similarly, specific pre-operative characteristics were not accounted for. With respect to exercise interventions, the clinical review was not designed to distinguish between trials of varying length, duration or exercise intensity. As such, it is not possible to determine whether certain types of supervised programmes are more cost effective than others. For this guideline, the definition of each type of exercise programme was based on a simple average of studies included in the clinical review. The supervised exercise programme described by this method was also found to match programmes familiar to the GDG.

Currently, no published RCT data exist to inform the relative risk of cardiovascular events and mortality in people who exercise compared to those who do not in people with IC. The data used in this model was obtained from two meta-analyses of trials conducted in two different populations: people with CHD who had experienced MI or coronary revascularisation and a mixed population of people who had and had not had a stroke.

Limited published data was available to inform the impact of each type of exercise programme on quality of life beyond one year. Although this data was not comparative, it suggested that quality of life is maintained in those who continue to exercise. It was also assumed that changes in quality of life observed in people undergoing endovascular treatment is maintained so long as symptom progression (either to claudication of CLI) does not occur. This was a key assumption of the analysis. If this assumption is removed from the model, none of the evaluated interventions are effective enough to justify their cost in the aorto-iliac artery and the baseline intervention should be prescribed. In the femoro-popliteal artery, removing this assumption results in selective stent followed by supervised exercise is the most cost effective. Because the long-term effect of these interventions is not known, it is not possible to know which scenario represents the most likely long term outcome. More long-term research into the effects of these treatments is needed.

9.4.79 Clinical evidence statements

9.4.9.81 Best medical treatment compared to best medical treatment plus angioplasty (see section 9.4.2 for clinical evidence)

Intermittent claudication due to femoro-popliteal or aorto-iliac disease:

Best medical treatment with angioplasty was significantly better than best medical treatment alone for:

- Maximum walking distance at 3 months and 1 year [1 study, 56 participants, low quality evidence][85]
- Maximum walking distance at 2 years [1 study, 56 participants, low quality evidence][84]
- Pain free walking distance at 3 months and 1 year [1 study, 56 participants, low quality evidence][85]
- Pain free walking distance at 2 years [1 study, 56 participants, low quality evidence][84]
- ABPI at 3 months and 1 year [1 study, 56 participants, moderate quality evidence][85]
- ABPI at 2 years [1 study, 56 participants, moderate quality evidence][84]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- No complications at 1 year [1 study, 28 participants, low quality evidence][85]
- No re-interventions at 1 year [1 study, 28 participants, low quality evidence][85]

Intermittent claudication due to femoro-popliteal disease:

Best medical treatment with angioplasty was significantly better than best medical treatment alone for:

- ABPI at 6 months [1 study, 59 participants, low quality evidence][87]
- ABPI at 2 years [1 study, 59 participants, moderate quality evidence][86]

There was no statistically significant difference between best medical treatment with angioplasty and best medical treatment for:

- Mortality at 2 years [1 study, 59 participants, very low quality evidence][86]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- No major complications at 6 months [1 study, 29 participants, low quality evidence][87]
- No re-interventions at 6 months [1 study, 29 participants, low quality evidence][87]
- One re-intervention in 29 people at 2 years [1 study, 29 participants, low quality evidence][86]

9.4.972 Best medical treatment with supervised exercise and angioplasty compared to best medical treatment with supervised exercise (for clinical evidence see 9.4.3)

Intermittent claudication due to aorto-iliac disease:

There was no statistically significant difference between best medical treatment with supervised exercise and angioplasty compared to best medical treatment and supervised exercise for:

- Pain free walking distance at 2 years [1 study, 23 participants, very low quality evidence][88]
- Compliance with the exercise programme [1 study, 34 participants, very low quality evidence][88]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Quality of life increased for both best medical treatment with supervised exercise and angioplasty compared to best medical treatment and supervised exercise at 6 months and 1 year [1 study, 23 participants, low quality evidence][88]
- People who had best medical therapy with supervised exercise and angioplasty had a high maximum walking distance at 2 years [1 study, 23 participants, low quality evidence][88]
- Four of 19 people had complications following the angioplasty [1 study, 19 participants, low quality evidence][88]

Intermittent claudication due to femoro-popliteal disease:

Best medical treatment with supervised exercise and angioplasty was significantly better than best medical treatment and supervised exercise for:

- Pain free walking distance at 2 years [1 study, 71 participants, moderate quality evidence][88]

There was no statistically significant difference between best medical treatment with supervised exercise and angioplasty compared to best medical treatment and supervised exercise for:

- Compliance with the exercise programme [1study, 93 participants, very low quality evidence][88]
- Withdrawal rates at 3 months [1 study, 118 participants, very low quality evidence][89]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Quality of life increased for both best medical treatment with supervised exercise and angioplasty compared to best medical treatment and supervised exercise at 6 months and 1 year [2 studies, 189 participants, low quality evidence][88,89]
- People who had best medical therapy with supervised exercise and angioplasty had a high maximum walking distance at 2 years [1 study, 71 participants, low quality evidence][88]
- Six of 48 people had complications following the angioplasty [1 study, 48 participants, low quality evidence][88]
- No complications were reported at 3 months [1 study, 58 participants, low quality evidence][89]

- 0 out of 58 people had re-interventions at 1 year in the angioplasty group [1 study, 58 participants, low quality evidence][94]

9.4.93 Best medical treatment with supervised exercise and angioplasty compared to best medical treatment with angioplasty (for clinical evidence see section 9.4.4)

Intermittent claudication due to aorto-iliac disease:

Best medical treatment with supervised exercise and angioplasty was statistically significantly better than best medical treatment and angioplasty for:

- Maximum walking distance at 6 months [1 study, 61 participants, low quality evidence][95]
- Pain free walking distance at 3 months [1 study, 60 participants, low quality evidence][95]
- Pain free walking distance at 6 months [1 study, 61 participants, low quality evidence][95]
- Re-intervention at 12 months [1 study, 118 participants, very low quality evidence][94]

There was no statistically significant difference between best medical treatment with supervised exercise and angioplasty compared to best medical treatment and angioplasty for:

- Maximum walking distance at 3 months [1 study, 61 participants, low quality evidence][95]
- Major adverse events at 6 months [1 study, 70 participants, very low quality evidence][95]
- Withdrawal from treatment at 6 months [1 study, 70 participants, very low quality evidence][95]

Intermittent claudication due to femoro-popliteal disease:

No clinical evidence was found for people with IC due to femoro-popliteal disease.

9.4.994 Angioplasty compared to supervised exercise (for clinical evidence see section 9.4.5)

Intermittent claudication due to aorto-iliac disease:

Supervised exercise was significantly better than angioplasty for:

- Maximum walking distance at 6 months [1 study, 150 participants, moderate quality evidence][90]
- Maximum walking distance at 1 year [1 study, 150 participants, low quality evidence][90]
- Pain free walking distance at 6 months and at 1 year [1 study, 150 participants, low quality evidence][90]

Angioplasty was significantly better than supervised exercise for:

- ABPI at rest at 6 months [1 study, 150 participants, moderate quality evidence][90]
- ABPI at rest at 1 year [1 study, 150 participants, low quality evidence][90]
- ABPI after exercise at 6 months [1 study, 150 participants, low quality evidence][90]
- ABPI after exercise at 1 year [1 study, 150 participants, moderate quality evidence][90]

There was no statistically significant difference between angioplasty and supervised exercise for:

- Number of people who doubled their maximum walking distance at 3 months [1 study, 31 participants, very low quality evidence][92]
- Number of people who doubled their maximum walking distance at 6 months [1 study, 26 participants, very low quality evidence][92]
- Number of people who doubled their maximum walking distance at 9 months [1 study, 23 participants, very low quality evidence][92]

- Number of people who doubled their maximum walking distance at 1 year [1 study, 12 participants, very low quality evidence][92]
- Withdrawal at 3 months [1 study, 120 participants, very low quality evidence][89]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Quality of life increased for both angioplasty and supervised exercise at 3 months [1 study, 120 participants, low quality evidence][89]
- Quality of life increased for both angioplasty and supervised exercise at 6 months and 1 year [1 study, 150 participants, low quality evidence][90]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- Eleven of 95 people had complications following angioplasty at 1 year [2 studies, 95 participants, low quality evidence][90,92]
- Five of 75 people had re-intervention following angioplasty at 6 months [1 study, 75 participants, low quality evidence][90]
- Eight of 95 people had re-intervention following angioplasty at 1 year [2 studies, 95 participants, low quality evidence][90,92]
- Eight of 16 people were good attenders for exercise (attended an average of > 1 session per week) to exercise at 6 months [1 study, 16 participants, low quality evidence][92]

Intermittent claudication due to aorto-iliac and femoro-popliteal disease:

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- Three of 30 people had re-intervention following angioplasty at 15 months [1 study, 30 participants, low quality evidence][91]
- Three of 26 people were exercising daily at 5-6 years [1 study, 26 participants, low quality evidence][91]
- Three of 26 people were more exercising than twice a week at 5-6 years [1 study, 26 participants, low quality evidence][91]

Intermittent claudication due to femoro-popliteal disease:

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed:

- 9 out of 60 people had re-interventions at 1 year in the angioplasty group [1 study, 60 participants, low quality evidence][94]

9.4.345 Bypass surgery compared to supervised exercise

Intermittent claudication due to aorto-iliac and femoro-popliteal disease (for clinical evidence see section 9.4.6):

Bypass surgery was significantly better than supervised exercise for:

- Maximum walking distance at 1 year [1 study, 50 participants, low quality evidence][93]
- Pain free walking distance at 1 year [1 study, 50 participants, low quality evidence][93]

There was no statistically significant difference between bypass surgery and exercise for:

- Mortality at 1 year [1 study, 50 participants, very low quality evidence][93]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Six of 25 people had complications following bypass surgery at 30 days [1 study, 25 participants, low quality evidence][93]
- Three of 25 people had re-interventions following bypass surgery at 30 days [1 study, 25 participants, low quality evidence][93]
- Four of 25 people withdrew from the exercise programme [1 study, 25 participants, low quality evidence][93]

9.4.9.6 Angioplasty compared to bypass surgery (for clinical evidence see section 9.4.7)

Intermittent claudication due to aorto-iliac disease:

Bypass surgery was significantly better than angioplasty for:

- ABPI after treatment (time point not specified) [1 study, 263 participants, moderate quality evidence][103]

Angioplasty was significantly better than bypass surgery for:

- ABPI at 3 years [1 study, 263 participants, moderate quality evidence][103]

There was no statistically significant difference between angioplasty and bypass surgery for:

- Mortality at 30 days, 3 months, 1 year and 2 years [1 study, 263 participants, very low quality evidence][103]
- Amputation at post procedure and 2 years [1 study, 263 participants, very low quality evidence][103]
- Amputation at 4 years [1 study, 118 participants, very low quality evidence][104]
- Complications post procedure [1 study, 263 participants, very low quality evidence][103]
- Re-intervention at 2 years [1 study, 263 participants, very low quality evidence][103]

Intermittent claudication due to femoro-popliteal disease:

Angioplasty was significantly better than bypass surgery for:

- ABPI at 1 year [1 study, 41 participants, low quality evidence][105]

There was no difference between angioplasty and bypass surgery for:

- Mortality at 30 days [2 studies, 101 participants, moderate quality evidence][105,106]

There was no statistically significant difference between angioplasty and bypass surgery for:

- Mortality at 1 year [2 studies, 127 participants, very low quality evidence][100 105]
- Mortality at 2 years and 4 years [1 study, 86 participants, very low quality evidence][102]
- Amputation at 1 year [3 studies, 196 participants, very low quality evidence][105 100 106]
- Amputation at 2 years [1 study, 100 participants, very low quality evidence][102]
- Amputation at 4 years [2 studies, 173 participants, very low quality evidence][101,104]
- Minor complications post procedure [2 studies, 141 participants, very low quality evidence][105 102]
- Major adverse events at 1 year [1 study, 55 participants, very low quality evidence][106]
- Minor adverse events at 1 year [1 study, 55 participants, very low quality evidence][106]
- Re-intervention at 1 year [2 studies, 155 participants, very low quality evidence][100 106]
- Re-intervention at 2 years and 4 years [1 study, 100 participants, very low quality evidence][102]

Evidence statement for individual studies where meta-analysis was not possible – no statistical analysis performed:

- One study found that in people with IC due to femoro-popliteal disease, ABPI at 1 year was higher in those that had bypass surgery compared to those that had angioplasty [1 study, 100 participants, very low quality evidence][100]
- One study found that in people with IC due to femoro-popliteal disease, ABPI at 2 years was higher in those that had bypass surgery compared to those that had angioplasty [1 study, 100 participants, very low quality evidence][102]

9.4.10 Economic evidence statements

None of the studies identified in the economic literature search included all comparators:

- One RCT-based analysis suggested that supervised exercise is more cost effective than angioplasty with selective stent placement [partially applicable with minor limitations][99]
- One decision analytic model suggested that primary angioplasty for those who are suitable is more cost-effective than supervised exercise alone [partially applicable with potentially serious limitations][110]
- One decision analytic model suggested that unsupervised exercise is more cost-effective than both exercise followed by angioplasty and angioplasty followed by angioplasty [partially applicable with potentially serious limitations][108]
- Two decision analytic models suggested that angioplasty with selective stent placement followed by angioplasty with selective stent placement for long term treatment failure is more cost effective than no revascularisation and revascularisation with primary stent placement [partially applicable with minor limitations][107,111]
- One decision analytic model suggested that depending on lesion type, graft type and indication, either angioplasty or bypass were cost effective secondary treatments [partially applicable with potentially serious limitations][109]

According to the results of the original economic model based on the current clinical evidence review and GDG input, there is a high degree of uncertainty regarding the most cost-effective sequence of interventions for the treatment of intermittent claudication. The results of the model suggest that supervised exercise followed by angioplasty with selective stent placement has the highest probability of being cost effective in both the aorto-iliac and femoro-popliteal artery [directly applicable with minor limitations]. Please see Appendix L for a full description of the methods and results of the original economic model.

9.4.11 Recommendations and link to evidence

	10. Offer angioplasty for the treatment of intermittent claudication when: • **advice on the benefits of modifying risk factors has been reinforced (see recommendation 3)** • **supervised exercise has not led to a satisfactory improvement in symptoms, and** • **imaging has confirmed the person as appropriate for angioplasty.** **14. Offer bypass surgery for the treatment of severe lifestyle-limiting intermittent claudication only when:**

Recommendations	• **angioplasty has been unsuccessful or is unsuitable, and** • **imaging has confirmed that the person is suitable for bypass surgery.**
Relative values of different outcomes	The GDG agreed that population considered in these comparisons are a relatively select group. These patients will have severe claudication that is not responding to other measures i.e. secondary prevention, and exercise. Mortality is always an important outcome, but death rates from intermittent claudication would not be expected to be high and the patient numbers in these studies were small or modest. Moreover, the follow-up period generally extended to no more than a year. Where it was reported in these studies, there was no significant difference in mortality between any of the interventions. The GDG were particularly interested in maximum walking distance and any available quality of life data. Pain free walking distance was not thought to be as clinically important an outcome since it is subject to more individual variation and because practically speaking most patients will walk through their pain for some distance. Measurement of improvement in ABPI is of interest in that it is totally objective unlike either index of walking distance, but the GDG were unanimous in regarding it as the least important of these outcomes since it is not patient-centred. For angioplasty, there was clear evidence of an improvement in both maximal and pain-free walking distance when the endovascular intervention was compared to no intervention (although people in both arms of the studies also received best medical treatment). The evidence of benefit from angioplasty was less clear when subjects in both arms also underwent supervised exercise. Here the additional value of angioplasty was only apparent for the outcome measure of pain-free walking distance, and only in the group of patients with femoro-popliteal disease. However, the GDG noted that this difference was seen at 2 years post-intervention whereas most of the studies did not follow up patients for this length of time. This evidence indicates that angioplasty is effective, but when directly compared to supervised exercise it produced less improvement in both maximal and pain-free walking distance measured up to one year. Improvements in ABPI favoured angioplasty over supervised exercise, but as already noted the GDG regarded this as of lesser importance. The comparison of bypass surgery with exercise was based on a single study performed over 20 years ago[93]. The group of patients undergoing bypass achieved a better maximal walking distance and a better pain free walking distance at a 1 year time-point. A third group in this study took part in a supervised exercise programme after bypass, and this combined intervention produced a greater improvement than either alone. Although bypass surgery and angioplasty were compared directly in a number of studies, none of these reported maximal walking distance or pain free walking distance. Some differences in ABPI were found but these were inconsistent in that surgery appeared to produce more improvement at one year whereas the measurement favoured the angioplasty group at 3 years.
Trade off between clinical benefits and harms	Comparison of adverse effects in these studies was hard to synthesize, and indeed the 3 interventions all have very different potential risks. Exercise therapy is non-invasive, but carries the risk of exacerbating problems such as

	those caused by chronic musculo-skeletal disease. Angioplasty can produce local haematomas and these were reported in the studies evaluated. Bypass surgery is associated with significant risks including those of an anaesthetic, haematoma and wound infection, and these should be discussed fully with the patient. The complication rates in the studies directly comparing angioplasty to surgery were not significantly different, and nor were re-intervention rates at the time points reported. There is a problem with compliance to supervised exercise programmes, which may limit their usefulness, partly related to the willingness and ability of people to attend them. The studies reported that withdrawal rates were related to distance from home and lack of transport.
Economic considerations	An original economic model was developed to compare the cost-effectiveness of several different intervention strategies for the treatment of people with IC. The analysis combined evidence of effectiveness and quality of life collected as part of the clinical review with current cost data. See Appendix L for a full report of the methods used to inform this analysis. According to the results of the model, supervised exercise followed by angioplasty with selective stent placement for people with worsening claudication is the most cost effective intervention pathway at a cost of approximately £16, 000 per QALY gained. If angioplasty does not represent a treatment option for people with IC, supervised exercise followed by bypass surgery is the next most cost-effective option. The results are sensitive to several key assumptions of the model, such as the assumption that exercise results in a reduced risk of mortality among those who are active. For a full description of results and sensitivity analyses please refer to Appendix L. The GDG were satisfied with the robustness of the economic modelling, its assumptions and sensitivity analysis.
Quality of evidence	The quality of the evidence generally ranged from very low to low by GRADE criteria, although occasional outcome measures were rated of better quality. The evidence was downgraded for a variety of reasons, but typically on unclear blinding, risk of bias and imprecision. The GDG found some difficulty in comparing studies because the definitions of best medical treatment differed, and it was not always clear what was included in the background treatment applied to both study arms. The use of medication such as statins has increased over the past 2 decades and patients in studies performed at different time points cannot be assumed to have similar treatment beyond the study interventions. They also noted that the only available comparison of surgery against supervised exercise was over 20 years old, and that techniques for surgery, and for supporting care, have changed in that time.
Other considerations	Whilst the trials with arms that included combined surgery and supervised exercise showed some benefit from combined treatment the economic

	modelling suggests that simultaneous use is likely to be less cost effective than sequential use. The GDG also took the view that supervised exercise would normally be offered before considering endovascular or surgical interventional and there were no trials that had specifically examined sequenced compared to simultaneous treatments. The GDG agreed that patients who required further intervention after attempting supervised exercise should be considered first for an endovascular procedure, based on the greater potential hazards of surgery and on the health-economic analysis. However, they felt that their recommendations should reflect the fact that in some people the nature of their arterial disease will make them unsuitable for an endovascular procedure, and that in these instances surgery could be considered.

9.5 Angioplasty with selective stent placement compared to angioplasty with primary stent placement

9.5.1 Review question

What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with intermittent claudication?

A literature search was conducted for RCTs that compared the effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded.

Two Cochrane reviews were identified[129,130] which considered angioplasty without stents compared to angioplasty with stents for the superficial femoral artery or for intermittent claudication. The Cochrane reviews were not included or updated as they did not meet the review question protocol defined by the GDG, which included all arteries of the leg and accepted papers with mixed populations not only pure intermittent claudication populations. However they were used as a source to ensure that studies identified in the Cochrane reviews which matched the current review protocol had been considered for inclusion.

9.5.2 Clinical evidence

Fifteen studies of ten RCTs[112,116-121,123,131-137] were identified which addressed the question and were included in the review. The trials did not report outcome data for people with diabetes. There were unit of analysis issues in some of the trials where data were analysed by limb or lesion rather than per person randomised. These trials have been dealt with separately.

The quality and results of included studies are reported in the clinical evidence profiles (Table 76, Table 77, Table 78 and Table 79. The forest plots for each clinical outcome are reported in Appendix J.

Table 76: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for intermittent claudication due to aorto-iliac disease (person randomised data)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty with selective stent placement	Angioplasty with primary stent placement	Relative (95% CI)	Absolute	
Mortality at 3 months											
1 Tetteroo, 1998[117]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision[(b)]	None	0/136 (0%)	0/136 (0%)	not pooled	not pooled	MODERATE
Mortality at 1 year											
1 Tetteroo, 1998[117]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	2/136 (1.5%)	1/143 (0.7%)	RR 2.1 (0.19 to 22.93)	8 more per 1000 (from 6 fewer to 153 more)	VERY LOW
Mortality at 2 years											
1 Tetteroo, 1998[117]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	2/136 (1.5%)	1/136 (0.74%)	RR 2 (0.18 to 21.8)	7 more per 1000 (from 6 fewer to 153 more)	VERY LOW
Mortality at 5 years											
1 Klein, 2004[133]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	22/136 (16.2%)	21/143 (14.7%)	RR 1.1 (0.64 to 1.91)	15 more per 1000 (from 53 fewer to 134 more)	VERY LOW
Amputation at 5 years											
1 Klein, 2004[133]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	8/136 (5.9%)	3/143 (2.1%)	RR 2.8 (0.76 to 10.35)	38 more per 1000 (from 5 fewer to 196 more)	VERY LOW
Quality of life at 3 months											

1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	136	143	See Table 80 and Table 81		LOW
Quality of life at 1 year											
1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	136	143	See Table 80 and Table 81		LOW
Quality of life at 2 years											
1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(d)]	None	136	143	See Table 80		LOW
Maximum walking distance at 3 months											
1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 8 lower (22.25 lower to 6.25 higher)	MODERATE
Maximum walking distance at 1 year											
1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 2 higher (12.48 lower to 16.48 higher)	MODERATE
Maximum walking distance at 2 years											
1 Bosch, 1999[112]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 3 lower (18.96 lower to 12.96 higher)	MODERATE
Adverse events at 30 days											
1 Tetteroo, 1998[117]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	10/136 (7.4%)	6/143 (4.2%)	RR 1.75 (0.65 to 4.69)	31 more per 1000 (from 15 fewer to 155 more)	VERY LOW
Re-intervention at 3 months											
1 Tetteroo,	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	2/136 (1.5%)	2/143 (1.4%)	RR 1.05 (0.15 to	1 more per 1000 (from 12 fewer to	VERY LOW

1998[117]									7.36)	89 more)	
Re-intervention at 1 year											
1 Tetteroo, 1998[117]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	4/136 (2.9%)	6/143 (4.2%)	RR 0.7 (0.2 to 2.43)	13 fewer per 1000 (from 34 fewer to 60 more)	VERY LOW
Re-intervention at 2 years											
1 Tetteroo, 1998[117]	RCT	serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]	None	6/136 (4.4%)	10/143 (7%)	RR 0.63 (0.24 to 1.69)	26 fewer per 1000 (from 53 fewer to 48 more)	VERY LOW
ABPI at 3 months											
1 Bosch, 1999[112]	RCT	serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 0.01 higher (0.05 lower to 0.07 higher)	MODERATE
ABPI at 1 year											
1 Bosch, 1999[112]	RCT	serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 0.02 higher (0.03 lower to 0.07 higher)	MODERATE
ABPI at 2 years											
1 Bosch, 1999[112]	RCT	serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	136	143	-	MD 0.08 higher (0.03 to 0.13 higher)	MODERATE

(a) Unclear allocation concealment and blinding.
(b) No events in either group.
(c) 95% CI crosses both MIDs.
(d) No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Table 77: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for intermittent claudication due to aorto-iliac disease (limb/lesion randomised data)

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty with selective stent placement	Angioplasty with primary stent placement	Relative (95% CI)	Absolute	
Re-intervention at 5 years											
1 Klein, 2004[133]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	33/169 (19.5%)	33/187 (17.6%)	RR 1.11 (0.72 to 1.71)	19 more per 1000 (from 49 fewer to 125 more)	VERY LOW
Re-intervention at 6 – 8 years											
1 Klein, 2006[137]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]	None	21/118 (17.8%)	12/118 (10.2%)	RR 1.75 (0.9 to 3.39)	76 more per 1000 (from 10 fewer to 243 more)	VERY LOW
ABPI at 6 – 8 years											
1 Klein, 2006[137]	RCT	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	110	118	-	MD 0.06 higher (0.01 to 0.11 higher)	MODERATE

(a) Unclear allocation concealment and blinding.
(b) 95% CI crosses both MIDs.

Table 78: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for intermittent claudication due to femoro-popliteal disease (person randomised data)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty with selective stent placement	Angioplasty with primary stent placement	Relative (95% CI)	Absolute	
Mortality at 30 days											
2 Grimm, 2001; Laird, 2010[132,134]	RCT	Very serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision[(b)]	None	0/95 (0%)	0/164 (0%)	not pooled	not pooled	LOW
Mortality at 6 months											
1 Schillinger, 2006[120]	RCT	Serious[(c)]	No serious	No serious	No serious	None	0/53	0/51	not	not pooled	MODERATE

			inconsistency	indirectness	imprecision[b]		(0%)	(0%)	pooled		
Mortality at 1 year (random effects)											
4 Krankenberg, 2007; Schillinger, 2006; Greenberg, 2004; Dake, 2011[119,120,135,136]	RCT	Very serious[c]	Serious[d]	No serious indirectness	Very serious[e]	None	18/543 (3.3%)	19/550 (3.5%)	RR 0.73 (0.2 to 2.61)	9 fewer per 1000 (from 28 fewer to 56 more)	VERY LOW
Procedure related mortality at 1 year											
1 Dake 2011[136]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/238 (0%)	0/241 (0%)	not pooled	not pooled	MODERATE
Amputation at 6 months											
1 Schillinger, 2006[120]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	0/53 (0%)	0/51 (0%)	not pooled	not pooled	MODERATE
Amputation at 1 year											
5 Dake 2011 Krankenberg, 2007; Schillinger, 2006; Greenberg, 2004; Laird, 2010[119,120,134-136]	RCT	Very serious[f]	No serious inconsistency	No serious indirectness	Very serious[e]	None	1/615 (0.16%)	3/684 (0.44%)	RR 0.57 (0.12 to 2.64)	2 fewer per 1000 (from 4 fewer to 7 more)	VERY LOW
Amputation at 2 years											
1 Schillinger, 2007[123]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[e]	None	1/52 (1.9%)	0/46 (0%)	RR 2.66 (0.11 to 63.75)	-	VERY LOW
Quality of life at 6 months											
1 Sabeti, 2007[131]	RCT	serious[c]	no serious inconsistency	no serious indirectness	serious[g]	None	53	51	See Table 81		LOW
Quality of life at 1 year											
1 Sabeti, 2007[131]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[g]	None	53	51	See Table 81		LOW
Maximum walking distance at 6 months											
1 Schillinger, 2006[120]	RCT	Serious[c]	No serious	No serious	Serious[h]	None	53	51	-	MD 93 lower	LOW

			inconsistency	indirectness						(214.24 lower to 28.24 higher)	
Maximum walking distance at 6 months (no sd)											
1 Dick, 2009[118]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(g)]	None	39	34	-	not pooled	LOW
Maximum walking distance at 1 year											
1 Schillinger, 2006[120]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(h)]	none	53	51	-	MD 120 lower (237.36 to 2.64 lower)	LOW
Maximum walking distance at 1 year (no sd)											
2 Krankenberg, 2007; Dick, 2009[118,119]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(g)]	None	61	50	-	not pooled	LOW
Maximum walking distance at 2 years (no sd)											
1 Schillinger, 2007[123]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(g)]	None	52	46	-	not pooled	LOW
Pain free walking distance at 30 days											
1 Grimm, 2001[132]	RCT	Very serious[(i)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	23	30	-	MD 83.2 higher (123.82 lower to 290.22 higher)	VERY LOW
Major adverse events at 30 days											
4 Dick, 2009; Krankenberg, 2007; Schillinger, 2006; Vroegindewij, 1997[118-121]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	8/237 (3.4%)	10/230 (4.3%)	RR 0.79 (0.33 to 1.93)	9 fewer per 1000 (from 29 fewer to 40 more)	VERY LOW
Minor adverse events at 30 days											
1 Schillinger, 2006[120]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision[(b)]	None	0/53 (0%)	0/51 (0%)	not pooled	not pooled	MODERATE

Major adverse events at 1 year											
1 Greenberg, 2004[135]	RCT	Very serious[(i)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	11/131 (8.4%)	6/135 (4.4%)	RR 1.89 (0.72 to 4.96)	40 more per 1000 (from 12 fewer to 176 more)	VERY LOW
Re-intervention at 1 year											
3 Krankenberg, 2007; Schillinger, 2006; Grimm, 2001[119,120,132]	RCT	Serious[(j)]	No serious inconsistency	No serious indirectness	Very serious[(e)]	None	44/196 (22.4%)	39/202 (19.3%)	RR 1.17 (0.8 to 1.71)	33 more per 1000 (from 39 fewer to 137 more)	VERY LOW
Re-intervention at 2 years											
1 Schillinger, 2007[123]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	28/52 (53.8%)	17/46 (37%)	RR 1.46 (0.93 to 2.29)	170 more per 1000 (from 26 fewer to 477 more)	LOW
Target lesion revascularisation at 6 months											
1 Laird, 2010[134]	RCT	serious[(c)]	no serious inconsistency	no serious indirectness	no serious imprecision	None	34/72 (47.2%)	2/134 (1.5%)	RR 31.64 (7.83 to 127.92)	457 more per 1000 (from 102 more to 1000 more)	MODERATE
Target lesion revascularisation at 1 year (random effects)											
2 Dake, 2011 Laird, 2010[134,136]	RCT	Serious[(c)]	Very serious[(d)]	No serious indirectness	No serious imprecision	None	79/310 (25.5%)	38/375 (10.1%)	RR 2.87 (1.25 to 6.6)	189 more per 1000 (from 25 more to 567 more)	VERY LOW
ABPI at 30 days											
1 Grimm, 2001[132]	RCT	Very serious[(i)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	23	30	-	MD 0.06 lower (0.17 lower to 0.05 higher)	VERY LOW
ABPI at 6 months											
1 Schillinger, 2006[120]	RCT	Serious[(c)]	No serious	No serious	Serious[(h)]	None	53	51	-	MD 0.08	LOW

			inconsistency	indirectness						lower (0.17 lower to 0.01 higher)	
ABPI at 6 months (no sd)											
1 Dick, 2009[118]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(g)]	None	39	34	-	not pooled	LOW
ABPI at 9 months											
1 Greenberg, 2004[135]	RCT	Very serious[(i)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	64	83	-	MD 0.11 lower (0.17 to 0.05 lower)	VERY LOW
ABPI at 1 year random effects											
3 Dake, 2011; Schillinger, 2006; Vroegindewij, 1997[120,121,136]	RCT	Serious[(c)]	Very serious[(d)]	No serious indirectness	No serious imprecision	None	318	316	-	MD 0.04 lower (0.12 lower to 0.04 higher)	VERY LOW
ABPI at 1 year (no sd)											
2 Krankenberg, 2007; Dick, 2009[118,119]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(g)]	None	61	50	-	not pooled	LOW
ABPI at 2 years											
1 Schillinger, 2007[123]	RCT	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(h)]	None	52	46	-	MD 0.1 lower (0.17 to 0.03 lower)	LOW

(a) 1 of 2 studies had unclear allocation concealment and blinding; 1 of 2 studies had unclear methodology.
(b) No events in either group.
(c) Unclear allocation concealment and blinding.
(d) Unexplained heterogeneity.
(e) 95% CI crosses both MIDs.
(f) 4 of 5 studies had unclear allocation concealment and blinding; 1 of 5 studies had unclear methodology.
(g) No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
(h) 95% CI crosses one MID.
(i) Unclear methodology.
(j) 2of 3 studies had unclear allocation concealment and blinding; 1 of 3 studies had unclear methodology.

Table 79: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for intermittent claudication due to femoro-popliteal disease (limb/lesion randomised data)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty with selective stent placement	Angioplasty with primary stent placement	Relative (95% CI)	Absolute	
Mortality at 30 days											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/77 (2.6%)	0/77 (0%)	RR 5 (0.24 to 102.47)	-	VERY LOW
Mortality at 1 year											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	7/77 (9.1%)	12/77 (15.6%)	RR 0.58 (0.24 to 1.4)	65 fewer per 1000 (from 118 fewer to 62 more)	VERY LOW
Amputation at 30 days											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	4/77 (5.2%)	2/77 (2.6%)	RR 2 (0.38 to 10.6)	26 more per 1000 (from 16 fewer to 249 more)	VERY LOW
Re-intervention at 1 year											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	16/77 (20.8%)	28/77 (36.4%)	RR 0.57 (0.34 to 0.97)	156 fewer per 1000 (from 11 fewer to 240 fewer)	VERY LOW
Major complications at 30 days											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	6/77 (7.8%)	7/77 (9.1%)	RR 0.86 (0.3 to 2.43)	13 fewer per 1000 (from 64 fewer to 130 more)	VERY LOW

ABPI time point not specified											
1 Cejna, 2001[116]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77	77	-	MD 0.02 lower (0.08 lower to 0.04 higher)	LOW

(a) Unclear methodology.
(b) 95% CI crosses both MIDs.

Table 80: EQ-5D – Angioplasty with selective stent placement compared to angioplasty with primary stent placement

Angioplasty with selective stent placement				Angioplasty with primary stent placement			
Baseline	**3 months**	**12 months**	**24 months**	**Baseline**	**3 months**	**12 months**	**24 months**
Bosch 1999 – Median (95% CI)							
0.46 (0.15-0.75)	0.70 (0.20-1.00)	0.70 (0.15-1.0)	0.66 (0.15-1.0)	0.46 (0.20-0.75)	0.75 (0.15-1.00)	0.59 (0.19-1.0)	0.70 (0.09 -1.0)

Table 81: SF-36 individual domain results and mapped EQ-5D values – Angioplasty with selective stent placement compared to angioplasty with primary stent placement

	Angioplasty with selective stent placement					Angioplasty with primary stent placement				
	Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Bosch 1999 – Median (95% CI)										
PF	45 (10 – 85)	80 (15-100)	NR	NR	85 (20-100)	40 (5-79)	85 (10-100)	NR	NR	70 (7-100)
RP	0 (0-100)	100 (0-100)	NR	NR	100 (0-100)	0 (0-100)	100 (0-100)	NR	NR	100 (0-100)
BP	45 (0-99)	78 (10-100)	NR	NR	80 (22-100)	45 (3-100)	90 (20-100)	NR	NR	78 (4-100)
GH	55 (10-90)	60 (10-95)	NR	NR	65 (15-95)	55 (15-94)	65 (15 -100)	NR	NR	63 (15-100)
V	50 (5-90)	70 (20-100)	NR	NR	65 (16-100)	50 (6-95)	70 (15-100)	NR	NR	65 (12-100)
SF	75 (13-100)	88 (13-100)	NR	NR	88 (25-100)	60 (0-100)	100 (14-100)	NR	NR	100 (0-100)
RE	67 (0-100)	100 (0-100)	NR	NR	100 (0-100)	100 (0-100)	100 (0-100)	NR	NR	100 (0-100)
MH	74 (20-100)	80 (28-100)	NR	NR	76 (30-100)	76 (13-100)	84 (28-100)	NR	NR	80 (6-100)
EQ-5D[±]	**NA**	**NA**	**NR**	**NR**	**NA**	**NA**	**NA**	**NR**	**NR**	**NA**
Sabeti 1983 – Median (IQR)										
PF	45 (25)	NR	62 (50)	NR	67 (7)	50 (28)	NR	60 (50)	NR	65 (37)
RP	0 (50)	NR	0 (100)	NR	0 (100)	0 (75)	NR	0 (100)	NR	25 (75)

	Angioplasty with selective stent placement					Angioplasty with primary stent placement				
BP	22 (30)	NR	52 (44)	NR	46 (54)	30 (29)	NR	51 (78)	NR	52 (78)
GH	45 (28)	NR	47 (38)	NR	50 (41)	52 (27)	NR	47 (38)	NR	52 (29)
V	40 (23)	NR	47 (33)	NR	45 (36)	45 (25)	NR	50 (24)	NR	50 (30)
SF	75 (50)	NR	88 (41)	NR	88 (41)	88 (50)	NR	88 (37)	NR	100 (25)
RE	100 (100)	NR	100 (100)	NR	67 (100)	67 (100)	NR	100 (67)	NR	100 (33)
MH	64 (26)	NR	66 (32)	NR	60 (36)	64 (34)	NR	72 (36)	NR	72 (26)
EQ-5D±	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**

Abbreviations: PF = physical function; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role emotional; MH = mental health; SD= standard deviation; NR = not reported.

±Mapped based on algorithm (Equation1) reported by Ara and Brazier 2008[66]

° Only the range was reported; probabilistic mapped values not estimable.

9.5.112 Economic evidence

One published cost-effectiveness analyses were identified for this question. Bosch 1998[107] developed a decision model to evaluate the cost effectiveness of treating claudication due to iliac arterial stenosis with primary stent placement, selective stent placement or angioplasty without stent placement. This model assumes that 40% of patients undergoing angioplasty require selective stent placement and that compared to angioplasty alone, the relative risk of failure associated with stent placement is 0.61. The results of this model suggest that angioplasty with selective stent placement for both primary and secondary treatment is more cost effective than both selective stent placement followed by conservative management and primary stent placement followed by selective stent placement. This conclusion was robust to a wide range of sensitivity analyses. The characteristics and results of this study are summarised in Table 65 and Appendix I.

The same model (with American costs) was used in a later analysis by Bosch 2000.[111] Based on the results of their previous study (Bosch 1999[112]), which concluded that primary stent placement was not cost-effective, the authors did not include angioplasty with primary stent placement as a comparison in this analysis. Because this comparison was not relevant to the study question it was excluded from the review. A full list of excluded studies is included in Appendix F.

Angioplasty with primary stent placement and angioplasty with selective stent placement were included in the original model designed to assess the cost-effectiveness of different methods of treatment for people with IC. Based on the results of this model, primary stent placement is not a cost-effective option for the treatment of people with IC. It is both less effective and more expensive than the majority of other treatment alternatives. Please refer to section 9.4.8.1 (page 167) for a summary of the methods and results of this model and Appendix L for the full model write-up.

9.5.132 Evidence statements

9.5.241 Clinical

Intermittent claudication due to aorto-iliac disease (person randomised data):

There was no difference between angioplasty with selective stent placement and angioplasty with primary stents placement for:

- Mortality at 3 months [1 study, 272 participants, moderate quality evidence][117]

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stents placement for:

- Mortality at 1 year [1 study, 279 participants, very low quality evidence][117]
- Mortality at 2 years [1 study, 272 participants, very low quality evidence][117]
- Mortality at 5 years [1 study, 279 participants, very low quality evidence][133]
- Amputation at 5 years [1 study, 279 participants, very low quality evidence][133]
- Maximum walking distance at 3 months, 1 year and 2 years [1 study, 279 participants, moderate quality evidence][112]
- Adverse events at 30 days [1 study, 279 participants, very low quality evidence][117]
- Re-intervention at 3 months, 1 year and 2 years [1 study, 279 participants, very low quality evidence][117]
- ABPI at 3 months and 1 year [1 study, 279 participants, moderate quality evidence][112]

Angioplasty with selective stent placement was significantly better than angioplasty with primary stent placements for:

- ABPI at 2 years [1 study, 279 participants, moderate quality evidence][112]

Evidence statement for outcomes where meta-analysis was not possible – no statistical analysis performed

- Quality of life increased for both angioplasty with selective stent placement and angioplasty with primary stent placement at 3 months [1 study, 279 participants, low quality evidence][112]
- Quality of life decreased for angioplasty with selective stent placement and remained the same for angioplasty with primary stent placement quality of life at 1 year [1 study, 279 participants, low quality evidence][112]
- Quality of life increased for angioplasty with selective stent placement and decreased for angioplasty with primary stent placement at 2 years [1 study, 279 participants, low quality evidence][112]

Intermittent claudication due to femoro-popliteal disease (person randomised data):

Angioplasty with primary stent placements was significantly better than angioplasty with selective stent placement for:

- Maximum walking distance at 1 year [1 study, 104 participants, low quality evidence][120]
- Target lesion revascularisation at 6 months 1 study, 206 participants, moderate quality evidence][134]
- Target lesion revascularisation at 1 year [2 studies, 685 participants, very low quality evidence][134,136]
- ABPI at 9 months [1 study, 147 participants, very low quality evidence][135]
- ABPI at 1 year [3 studies, 634 participants, very low quality evidence][121,123,136]
- ABPI at 2 years [1 study, 98 participants, low quality evidence][123]

There was no difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Mortality at 30 days [2 studies, 259 participants, low quality evidence][132,134]
- Mortality at 6 months [1 study, 104 participants, moderate quality evidence][120]
- Procedure related mortality at 1 year [1 study, 479 participants, moderate quality evidence][136]
- Amputation at 6 months [1 study, 104 participants, moderate quality evidence][120]
- Minor adverse events at 30 days [1 study, 104 participants, moderate quality evidence][120]

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Mortality at 1 year [4 studies, 1093 participants, very low quality evidence][119,120,135,136]
- Amputation at 1 year [5 studies, 1299 participants, very low quality evidence][119,120,134-136]
- Amputation at 2 years [1 study, 98 participants, very low quality evidence][123]
- Maximum walking distance at 6 months [1 study, 104 participants, low quality evidence][120]
- Pain free walking distance at 30 days [1 study, 53 participants, very low quality evidence][132]
- Major adverse events at 30 days [4 studies, 467 participants, very low quality evidence][119 120 118,121]
- Major adverse event at 1 year [1 study, 266 participants, very low quality evidence][135]
- Re-intervention at 1 year [3 studies, 398 participants, very low quality evidence][119,120,132]
- Re-intervention at 2 years [1 study, 98 participants, low quality evidence][123]
- ABPI at 30 days [1 study, 53 participants, very low quality evidence][132]

- ABPI at 6 months [1 study, 104 participants, low quality evidence][120]

Evidence statement for individual studies where meta-analysis was not possible – no statistical analysis performed:

- Quality of life increased in most domains of SF-36 for both angioplasty with selective stent placement and angioplasty with primary stent placement at 6 months and 1 year [1 study, 104 participants, low quality evidence][131]
- Mean maximum walking distance at 6 months was higher in those that had angioplasty with primary stent placements compared to those that had angioplasty with selective stent placements [1 study, 73 participants, low quality evidence][118]
- Mean maximum walking distance at 1 year was higher in those that had angioplasty with primary stent placements compared to those that had angioplasty with selective stent placements [2 studies, 111 participants, low quality evidence][118,119]
- The mean maximum walking distance at 2 years was higher in those that had angioplasty with primary stent placement compared to those that had angioplasty with selective stent placements [1 study, 98 participants, low quality evidence][123]
- Mean ABPI at 6 months was higher in those that had angioplasty with primary stent placement compared to those that had angioplasty with selective stent placements [1 study, 73 participants, low quality evidence][118]
- Mean ABPI at 1 year was higher in those that had angioplasty with primary stent placement compared to those that had angioplasty with selective stent placements [2 studies, 111 participants, low quality evidence][118,119]

Intermittent claudication due to aorto-iliac disease (Limb/lesion randomised data):

Angioplasty with selective stent placement was significantly better than angioplasty with primary stent placements for:

- ABPI at 6 to 8 years [1 study, 228 limbs, moderate quality evidence][137]

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Re-intervention at 5 years [1 study, 356 limbs, very low quality evidence][133]
- Re-intervention at 6 to 8 years [1 study, 236 limbs, very low quality evidence][137]

Intermittent claudication due to femoro-popliteal disease (limb/lesion randomised data):

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Mortality at 30 days and 1 year [1 study,154 participants, very low quality evidence][116]
- Amputation at 30 days [1 study, 154 participants, very low quality evidence][116]
- Major complications at 30 days [1 study, 154 participants, very low quality evidence][116]
- ABPI (time point not specified) [1 study, 154 participants, low quality evidence][116]

Angioplasty with selective stent placement was significantly better than angioplasty with primary stent placement for:

- Re-intervention at 1 year [1 study, 154 participants, very low quality evidence][116]

9.513 Recommendations and link to evidence

Recommendations	11. **Do not offer primary stent placement for the treatment of intermittent claudication caused by aorto-iliac stenosis (as opposed to complete occlusion) or femoro-popliteal disease.** 12. **Consider primary stent placement for the treatment of intermittent claudication due to aorto-iliac occlusion (as opposed to stenosis).**
Relative value of different outcomes	Mortality and amputation are not frequent outcomes in the population with intermittent claudication. The GDG felt that walking distance was the most important outcome of those for which sufficient data was available. However, the majority of the evidence showed no significant differences between angioplasty with or without stents and stents alone for walking distance, APBI, mortality, re-intervention, amputation and adverse effects. Walking distance was improved at one time point and one intervention site, but not in any other sub-analysis. There were also some differences in ABPI results, but these did not consistently favour angioplasty with selective or primary stenting. Patency was not considered as a relevant outcome for the reasons detailed in section 3.1.1 in methodology chapter.
Trade off between clinical benefits and harms	The GDG were concerned that stents may give the operator the impression that a procedure has been technically successful at the time the procedure is performed, but noted that no consistent later benefit was demonstrated in comparison with angioplasty. The GDG considered that the routine use of stents as opposed to selective use in conjunction with angioplasty carried the disadvantages of additional cost, increased procedure time, and potential risks of additional instrumentation. Endovascular procedures carry a potential risk of causing embolisation of material from the diseased artery which can cause blockage of smaller arteries further down the leg. This is thought to be a greater risk with complete occlusion of the aorto-iliac arteries than with stenosis or occlusion in smaller vessels. There is also a risk of restenosis following endovascular treatment and having foreign material such as a stent in the artery may increase this risk, particularly in smaller vessels. The GDG considered that it is generally accepted that stenting is advantageous in terms of embolisation rates although the evidence reviewed in these studies did not reflect this.
Economic considerations	Although the GDG noted that there was little difference in outcomes between selective and primary stent placement, for completeness primary stent placement was included as a primary intervention in the original economic model developed for this guideline. It was not included as a secondary comparator. The results of the model show that strategies which include primary stent placement as a first-line intervention are both more expensive and less effective than most other options (see Figure 8 and Figure 10). Primary

	stent placement is therefore not a cost-effective strategy for the treatment of IC in either the aorto-iliac or femoro-popliteal arteries. For a full report of methods and results of the analysis please refer to Appendix L.
Quality of evidence	The evidence was rated as low or moderate by GRADE criteria. The GDG also highlighted that the data on ABPI and walking distance were short-term and that evidence on the long term benefits would have been extremely useful. The GDG noted that the trial (Schillenger, 2006[120]) which showed most of the statistically significant differences was performed in a selective population with intermittent claudication secondary to short arterial lesions. The results may well not reflect the likely outcomes in longer, more complex lesions.
Other considerations	This comparison is about whether to place stent in all patients undergoing an endovascular intervention for PAD, or only those in whom the operator deems it necessary. Although the latter seems more open to error, the former may be wasteful, and in this group of studies no clear evidence in favour of primary stenting emerged, and the health economic data suggests that this would not be a cost-effective strategy. Primary stenting for femoro-popliteal disease or stenotic disease of the aorto-iliac arteries is not standard UK practice and the GDG felt that there was insufficient evidence to recommend a change to this situation. Primary stents are currently used in aorto-iliac occlusion in the UK because of concern about the risk of embolisation. The GDG recognised that they had identified no evidence to justify this as routine, but also noted that embolisation was not an endpoint specifically sought in these studies.

9.6 Bare metal compared to drug eluting stents

9.6.1 Review question

What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with intermittent claudication?

A literature search was conducted for RCTs that compared the effectiveness of bare metal stents to drug eluting stents. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded.

9.6.1 Clinical evidence

One RCT[138] was identified which addressed the question and one RCT[136] was submitted during a call for evidence which addressed the question and were included in the review. The trials did not report separate outcome data for people with diabetes.

The quality and results of included studies are reported in Table 82. Forest plots for each clinical outcome are reported in Appendix J.

Table 82: Clinical evidence profile: Bare metal stents (BMS) compared to drug eluting stents (DES) for people with intermittent claudication due to femoro-popliteal disease after angioplasty failure

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMS	DES	Relative (95% CI)	Absolute	
All cause mortality at 1 year											
2 Dake, 2011; Rastan, 2011[136,138]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	serious[(b)]	none	4/105 (3.8%)	5/101 (5%)	RR 0.74 (0.23 to 2.42)	13 fewer per 1000 (from 38 fewer to 70 more)	VERY LOW
Procedure / device related deaths at 1 year											
1 Dake, 2011[136]	RCT	very serious[(c)]	no serious inconsistency	no serious indirectness	no serious imprecision[(d)]	none	0/59 (0%)	0/61 (0%)	not pooled	not pooled	LOW
Amputation at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/79 (2.5%)	1/82 (1.2%)	RR 2.08 (0.19 to 22.44)	13 more per 1000 (from 10 fewer to 261 more)	LOW
Re-intervention at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	7/79 (8.9%)	8/82 (9.8%)	RR 0.91 (0.35 to 2.39)	9 fewer per 1000 (from 63 fewer to 136 more)	LOW
Target lesion revascularisation at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	8/46 (17.4%)	2/40 (5%)	RR 3.48 (0.78 to 15.44)	124 more per 1000 (from 11 fewer to 722 more)	LOW
ABPI at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	40	-	MD 0.07 lower (0.13 to 0.01 lower)	HIGH

(a) 1 of 2 studies had low risk of bias; 1 of 2 studies had inadequate randomisation method, unclear blinding and allocation concealment.

(b) 95% CI crosses both MIDs.
(c) Inadequate randomisation method, unclear blinding and allocation concealment.
(d) There were no events in either group.

9.6.112 Economic evidence

No published cost-effectiveness analyses were identified for this question. In the absence of published evidence, the GDG were presented with the current cost of bare metal and drug eluting stents to aid decision making.

Vascular stents are excluded from the NHS reference cost for angioplasty and incur an additional cost according to the number and type used per procedure. The unit cost of vascular stents was not available from the NHS Supply Catalogue. A buyer for cardiology and radiology products at the NHS Supply chain was asked to provide a list of prices for all vascular stents currently in use in England and Wales, however the GDG concluded that this list was not inclusive. Members of the GDG were then asked to provide prices from their hospitals. Based on prices obtained by GDG members, the group estimated bare metal stents cost approximately £550 and drug eluting stents approximately £900.

9.6.32 Evidence statements

9.6.241 Clinical

Intermittent claudication due to aorto-iliac disease:

No clinical evidence was reported for people with IC due to aorto-iliac disease.

Intermittent claudication due to femoro-popliteal disease:

There was no statistically significant difference between bare metal stents and drug eluting stents for:

- All cause mortality at 1 year [2 studies, 206 participants, very low quality evidence][136,138]
- Amputation at 1 year [1 study, 161 participants, low quality evidence][138]
- Re-intervention at 1 year [1 study, 161 participants, low quality evidence][138]
- Target lesion revascularisation at 1 year [1 study, 86 participants, low quality evidence][138]
- ABPI at 1 year [1 study, 86 participants, high quality evidence][138]

There was no difference between bare metal stents and drug eluting stents for:

- Procedure / device related mortality at 12 months [1 study, 120 participants, low quality evidence][136]

9.6.282 Economic

No cost-effectiveness evidence was identified for this question.

9.6.3 Recommendations and link to evidence

Recommendation	13. Use bare metal stents where stenting is indicated for the treatment of intermittent claudication.
Relative values of different outcomes	The trials comparing bare metal versus drug eluting stents in the femoro-popliteal circulation of people with IC was received through a call for evidence. Data were reported on all cause mortality at 12 months and procedure related mortality at 12 months, and also on the need for revascularisation. No significant differences were noted for these clinical outcomes.

	Target lesion re-vascularisation was also reported. The GDG were less interested in this non-clinical parameter, but noted that it too was not significantly different between the two types of stent. Patency was not considered as a relevant outcome for the reasons stated in section 3.1.1of the methodology chapter.
Trade off between clinical benefits and harms	The method of placement of the two forms of stents is identical, and therefore the main potential adverse effects are also the same. No unexpected difference emerged in the trial evidence. The potential benefit of drug eluting stent is that the drug is intended to reduce the rate of thrombosis or restenosis. However, the long-term effects of the drug on the vessel wall are unknown and there is also the potential for other side effects from the drug.
Economic considerations	There was no cost effectiveness evidence identified for this question. Drug eluting stents are more expensive than bare metal stents. In the absence of evidence to suggest that clinical outcomes are improved with the use of drug eluting stents, the GDG agreed that the increased cost does not represent a cost effective use of NHS resources.
Quality of evidence	The evidence presented was categorised as low or very low by GRADE score. The GDG noted the absence of data on walking distance. This would have been of interest, although maximum walking distance measured within trials e.g. treadmill test, is not necessarily a realistic measure of a patient's walking distance in real life circumstances. The GDG also noted that trials did not report re-stenosis rates.
Other considerations	The GDG considered whether evidence of the use of different types of stent for coronary artery disease offered any useful information for the treatment of IC in the PAD population. However, they felt that the anatomical differences between the two sites did not allow extrapolation from one to the other. As there is no apparent difference in benefit between the two stent types and drug eluting stents are more costly, the GDG formed a consensus judgement that use of bare metal stents is the preferred option.

9.7 Autologous vein compared to prosthetic bypass

9.7.1 Review question

What is the clinical effectiveness of autologous vein versus prosthetic bypass for the treatment of intermittent claudication in adults?

A literature search was conducted for RCTs that compared the effectiveness of autologous vein versus prosthetic bypass grafting. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded. One Cochrane review was identified Twine, 2010[139] which considered graft type in bypass surgery for femoro-popliteal disease in both intermittent claudication and critical limb ischemia. The Cochrane

review was not included or updated as it did not meet the review question protocol defined by the GDG, which included all arteries of the leg. However it was used as a source to ensure that studies identified in the Cochrane review which matched the current review protocol had been considered for inclusion.

9.7.15.1 Clinical evidence

Two reports of one RCT[140,141] were found which addressed the question and were included in the review. None of the trials reported on subgroups for patients with diabetes as the main outcome.

The quality and results of included studies are reported in Table 83. Forest plots for each clinical outcome are reported in Appendix J. No forest plot was available for perioperative mortality (≤30days).

1 **Table 83: Clinical evidence profile: Autologous vein compared to prosthetic bypass for intermittent claudication due to femoro-popliteal disease**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous vein	Prosthetic bypass	Relative (95% CI)	Absolute	
Mortality at 30 days											
1 Klinkert, 2003[140]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(b)]	none	0/75 (0%)	0/76 (0%)	not pooled	not pooled	MODERATE
Mortality at 5 years											
1 Klinkert, 2003[140]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(c)]	none	24/75 (32%)	18/76 (23.7%)	RR 1.35 (0.8 to 2.28)	83 more per 1000 (from 47 fewer to 303 more)	VERY LOW
Amputation at 5 years											
1 Klinkert, 2003[140]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(c)]	none	2/75 (2.7%)	2/76 (2.6%)	RR 1.01 (0.15 to 7.01)	0 more per 1000 (from 22 fewer to 158 more)	VERY LOW
Perioperative minor adverse event											
1 Klinkert, 2003[140]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(c)]	none	4/75 (5.3%)	3/76 (3.9%)	RR 1.35 (0.31 to 5.83)	14 more per 1000 (from 27 fewer to 191 more)	VERY LOW
Re-intervention at 2 years											
1 Burger, 2000[141]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/75 (1.3%)	4/76 (5.3%)	RR 0.25 (0.03 to 2.21)	39 fewer per 1000 (from 51 fewer to 64 more)	VERY LOW
Re-intervention at 5 years											
1 Klinkert, 2003[140]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/75 (6.7%)	16/76 (21.1%)	RR 0.32 (0.12 to 0.82)	143 fewer per 1000 (from 38 fewer to 185 fewer)	MODERATE

(a) Unclear randomisation procedure and no participant blinding.
(b) No events in either intervention.
(c) 95% CI crosses both MIDs.

9.7.12 Economic evidence

No cost effectiveness studies were identified for this question.

The cost-utility analysis by Hunick et al 1995 (reported in Table 65) subgrouped the results of their clinical analysis by graft material. Although the study was not designed to directly compare the cost-effectiveness of one type of material to another, according to the results of the model, bypass surgery using autologous vein grafts results in higher quality of life and lower cost than bypass surgery using synthetic grafts.

The GDG also discussed the cost of autologous and prosthetic grafts in an NHS context. The group considered that although the same NHS Reference Cost applies to patients undergoing both procedures, prosthetic veins cost several hundred pounds, varying widely depending on graft length and material (official cost estimates were not available from standard sources). However, the procedure associated with prosthetic vein bypass is slightly shorter than that for autologous vein as there is no need to harvest the vein. In addition, the average hospital stay is slightly less for prosthetic vein bypass operations. However, autologous vein bypass is associated with a reduced rate of infection and fewer complications. Based on the clinical evidence and clinical experience, the GDG agreed that autologous vein bypass was likely to represent the least costly of the two procedures. A formal cost estimation was not undertaken as it was thought that this was unnecessary (as the most effective option was also thought to be the least costly) and time consuming.

9.7.2 Evidence statements

9.7.21 Clinical

Intermittent claudication due to aorto-iliac disease:

No clinical evidence was reported for people with IC due to aorto-iliac disease.

Intermittent claudication due to femoro-popliteal disease:

Autologous vein was significantly better than prosthetic bypass for:

- Re-intervention at five year follow up [1 study, 151 participants, moderate quality evidence][140]

There was no statistically significant difference between autologous vein and prosthetic bypass for:

- Mortality at 5 years, [1 study, 151 participants, very low quality evidence][140]
- Re-intervention at 2 years [1 study, 151 participants, very low quality evidence][141]
- Amputation rates at five years [1 study, 151 participants, very low quality evidence][140]
- Perioperative minor adverse event [1 study, 151 participants, very low quality evidence][140]

There was no difference between autologous vein and prosthetic bypass for:

- Mortality at 30 days [1 study, 151 participants, moderate quality evidence][140]

9.7.22 Economic

No cost effectiveness studies were identified for this question.

9.713 Recommendations and link to evidence

Recommendation	15. Use autologous vein whenever possible for people with intermittent claudication having infra-inguinal bypass surgery.
Relative values of different outcomes	Re-intervention, complications and mortality were considered the important outcomes for decision making for this question. Quality of life was also considered important but no data was identified for this outcome. The GDG did not expect amputation rates to be high within an IC population but looked specifically at this outcome as a marker of success or failure of the intervention. There was discussion around use of other measures of patency, but the GDG did not feel that these were as important as clinical success of an intervention. Although there was no difference between the graft types for most outcomes, re-intervention rates tended to favour autologous grafts and this difference was significant at the longest (5-year) time-point reported.
Trade off between benefits and harms	The GDG noted that the formal evidence suggested benefit from autologous vein grafts in terms of the need for re-intervention but did not show any noteworthy difference in complication rates. There were slightly more peri-operative complications with autologous grafts but the difference was not statistically significant. Current clinical practice within the UK has moved away from use of prosthetic grafts because of a perception, with some support from observational studies (not reviewed here), that prosthetic material is associated with more infection. The risk of MRSA infection in prosthetic graft has been linked with higher mortality rate. There was some concern that the RCT evidence may not accurately reflect infection rates.
Economic considerations	Although autologous vein bypass is associated with a slightly higher rate of perioperative adverse events, which might have cost implications, conversely prosthetic vein grafts are associated with a significantly higher re-intervention rate. Indirectly, the economic model published by Hunick 1995 suggested that autologous grafts were more cost-effective. The GDG agreed that prosthetic vein bypass grafts do not represent a cost effective use of NHS resources for people undergoing infra-inguinal bypass surgery.
Quality of the evidence	The GDG discussed some issues around the quality of the trials. It was noted that the evidence presented was not recent and that no trials beyond 2003 were available. They also noted that the studies were underpowered for some outcomes. However, they thought it unlikely that there would be any support for a new randomised trial. The GDG noted that the technology has advanced considerably since 2003 and that the bypass surgery is done less frequently because other endovascular procedures can now be used successfully.
Other considerations	The GDG recognise that by focussing on RCTs there is a risk of losing some important data in terms of morbidity and mortality. Although, there was no clear advantage for either autologous vein or

	prosthetic graft, the GDG felt that where there were differences these favoured autologous grafts, and this is supported by their clinical experience.

10 Management of critical limb ischaemia

10.1 Introduction: chapter overview

People with critical limb ischaemia (CLI) face an enormous cardiovascular risk and there is a 50% mortality rate within 1 year of diagnosis. These patients also tend to be older and have significant co-morbidities, which need to be optimised. People with CLI require prompt referral to specialist services to be assessed for revascularisation. Delays in referral and treatment can result in poorer outcomes for people with CLI including major amputation. People with critical limb ischaemia should be encouraged to manage cardiovascular disease through the secondary prevention measures as described in chapter 9.1.

Options for revascularisation include angioplasty or bypass surgery. These have been compared in the previous chapter in the context of intermittent claudication, but require separate consideration for people with CLI, in whom mortality and the risk of limb amputation are considerably greater.

There will be patients in whom revascularisation has not been possible or has been unsuccessful. In such cases, patients may proceed to amputation. The extent to which effort should be made to avoid amputation is open to some debate. Although it can be regarded as a failure of treatment it may be in a patient's best interest, if clinical assessment and supporting investigation suggest that attempts at angioplasty or bypass are unlikely to succeed, to proceed straight to amputation. Trying to save the limb in these circumstances may prolong the patient's discomfort, delay eventual recovery, and also entail unnecessary expense for the Health Service. It was originally intended that this chapter would include a comparison of amputation with bypass and endovascular treatment, but in the absence of data (see section 10.2.1 below) it was decided to consider amputation separately. This is dealt with in chapter 12.

10.2 Angioplasty compared to bypass surgery

10.2.1 Review question

What is the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of critical limb ischaemia in adults with PAD?

A literature search was conducted for RCTs that compared the effectiveness of angioplasty to bypass surgery, and for RCTs and observational studies comparing angioplasty or bypass compared to amputation. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded. One Cochrane review was identified Fowkes, 2008[96] which considered bypass compared to other treatment for critical limb ischaemia. The Cochrane review was not included or updated as it did not meet the protocol defined by the GDG, which only compared bypass to angioplasty, where as the Cochrane compared bypass to angioplasty and other interventions. However it was cross checked for included studies which matched the review protocol.

10.2.2 Clinical evidence

Four relevant RCTs[142 104,105] were included in the review. The trials did not report outcome data for people with diabetes.

No RCTs or observational studies comparing angioplasty or bypass surgery to amputation were identified.

The quality and results of included studies are reported in Table 84, Table 85 and Table 86. Quality of life and mapped EQ-5D values are reported in Table 87 and Table 88. The forest plots for each clinical outcome are reported in Appendix J.

Table 84: Clinical evidence profile: Angioplasty compared to bypass surgery for critical limb ischaemia due to aorto-iliac disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty	Bypass	Relative (95% CI)	Absolute	
Limb salvage at 4 years											
1 Wolf, 1993[104]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	16/22 (72.7%)	17/23 (73.9%)	RR 0.98 (0.69 to 1.4)	15 fewer per 1000 (from 229 fewer to 296 more)	VERY LOW

(a) Unclear blinding.
(b) 95% CI crosses both MIDs.

Table 85: Clinical evidence profile: Angioplasty compared to bypass surgery for critical limb ischaemia due to femoro-popliteal disease

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty	Bypass	Relative (95% CI)	Absolute	
Mortality at 30 days											
2 Bradbury, 2010, Holm, 1991[105,142]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	7/254 (2.8%)	11/259 (4.2%)	RR 0.65 (0.26 to 1.64)	15 fewer per 1000 (from 31 fewer to 27 more)	VERY LOW
Mortality at 1 year											
1 Holm 1991[105]	RCT	serious[(c)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	5/30 (16.7%)	4/31 (12.9%)	RR 1.29 (0.38 to 4.35)	37 more per 1000 (from 80 fewer to 432 more)	VERY LOW

Mortality at 3 years											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	131/224 (58.5%)	119/228 (52.2%)	RR 1.12 (0.95 to 1.32)	63 more per 1000 (from 26 fewer to 167 more)	VERY LOW
Amputation rate at 1 year											
1 Holm, 1991[105]	RCT	serious[(c)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/30 (6.7%)	8/31 (25.8%)	RR 0.26 (0.06 to 1.12)	191 fewer per 1000 (from 243 fewer to 31 more)	VERY LOW
Amputation free survival rate at 3 years											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	82/224 (36.6%)	86/228 (37.7%)	RR 0.97 (0.76 to 1.23)	11 fewer per 1000 (from 91 fewer to 87 more)	VERY LOW
Limb salvage rate at 4 years											
1 Wolf, 1993[104]	RCT	serious[(e)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	10/11 (90.9%)	10/16 (62.5%)	RR 1.45 (0.95 to 2.22)	281 more per 1000 (from 31 fewer to 763 more)	VERY LOW
Quality of life at 3 months											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	serious[(e)]	none	164	152	See Table 87 and Table 88		LOW
Quality of life at 6 months											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	serious[(e)]	none	144	131	See Table 87 and Table 88		LOW
Quality of life at 1 year											
1	RCT	serious[(d)]	no serious	no serious	serious[(e)]	none	133	119	See Table 87 and Table		LOW

Bradbury, 2010[142]			inconsistency	indirectness					88		
Quality of life at 2 years											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	serious[(e)]	none	63	76	See Table 87 and Table 88		LOW
Quality of life at 3 years											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	serious[(e)]	none	48	49	See Table 87 and Table 88		LOW
Major adverse events at 30 days											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	serious[(g)]	none	36/224 (16.1%)	51/228 (22.4%)	RR 0.72 (0.49 to 1.06)	63 fewer per 1000 (from 114 fewer to 13 more)	LOW
Minor adverse events at 30 days											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/224 (31.3%)	109/228 (47.8%)	RR 0.65 (0.52 to 0.83)	167 fewer per 1000 (from 81 fewer to 229 fewer)	MODERATE
Minor adverse events at 1 year											
1 Bradbury, 2010[142]	RCT	serious[(c)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/30 (10%)	12/31 (38.7%)	RR 0.26 (0.08 to 0.83)	286 fewer per 1000 (from 66 fewer to 356 fewer)	MODERATE
Re-intervention at 30 days											
1 Bradbury, 2010[142]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	67/224 (29.9%)	41/228 (18%)	RR 1.66 (1.18 to 2.34)	119 more per 1000 (from 32 more to 241	VERY LOW

										more)	
Re-intervention at 1 year											
1 Holm, 1991[105]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	10/53 (18.9%)	4/49 (8.2%)	RR 2.31 (0.78 to 6.89)	107 more per 1000 (from 18 fewer to 481 more)	VERY LOW
ABPI at 1 year											
1 Holm, 1991[105]	RCT	serious[(d)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	30	31	-	MD 0.01 higher (0.2 lower to 0.22 higher)	VERY LOW

(a) 1 of 2 studies had unclear allocation concealment; 1 of 2 studies had unclear allocation concealment and blinding.
(b) 95% CI crosses both MIDs.
(c) Unclear allocation concealment and blinding.
(d) Unclear allocation concealment.
(e) Unclear blinding.
(f) No information on variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.
(g) 95% CI crosses one MID.

Table 86: Clinical evidence profile: Angioplasty compared to bypass surgery for critical limb ischaemia due to femoro-popliteal disease – Adjusted hazard ratios

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Angioplasty**	**Bypass**	**Relative (95% CI)**	**Absolute**	
Overall survival before 2 years											
1 Bradbury, 2010[142]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	224	228	HR 1.19 (0.84 to 1.68)	-	VERY LOW
Overall survival after 2 years											
1 Bradbury, 2010[142]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	224	228	HR 0.61 (0.5 to 0.75)	-	MODERATE

Amputation free survival before 2 years										
1 Bradbury, 2010[142]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	224	228	HR 1.03 (0.76 to 1.39)	-	VERY LOW
Amputation free survival after 2 years										
1 Bradbury, 2010[142]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	serious[(c)]	none	224	228	HR 0.85 (0.5 to 1.07)	-	LOW

(a) Unclear allocation concealment; hazard ratio taken from data reported in study.
(b) 95% CI crosses both MIDs.
(c) 95% CI crosses one MID.

(d) Table 87: EQ-5D – Angioplasty compared to bypass surgery for critical limb ischaemia

Angioplasty						Bypass					
Baseline	**Change 0-3 months**	**Change 3-6 months**	**Change 6-12 months**	**Change 12-24 months**	**Change 24-36 months**	**Baseline**	**Change 0-3 months**	**Change 3-6 months**	**Change 6-12 months**	**Change 12-24 months**	**Change 24-36 months**
Bradbury, 2010 – Mean (sd)											
0.26 (0.32)	0.53 (0.31)	0.52 (0.34)	0.55 (0.31)	0.56 (0.32)	0.61 (0.25)	0.29 (0.34)	0.57 (0.28)	0.56 (0.31)	0.62 (0.29)	0.59 (0.34)	0.54 (0.35)

Table 88: SF- 36 summary component score – Angioplasty compared to bypass for critical limb ischaemia

Angioplasty					Bypass			
Baseline		**Change 0-3 months**	**Change 3-6 months**	**Change 6-12 12 months**	**Baseline**	**Change 0-3 months**	**Change 3-6 months**	**Change 6-12 months**
Bradbury 2010 – Mean (sd)								
Physical	17.50 (7.97)	23.80 (11.68)	24.62 (11.58)	24.58 (11.70)	17.80 (9.06)	24.37 (12.45)	24.88 (13.51)	26.13 (13.54)
Mental	43.47 (11.64)	47.69 (11.28)	46.67 (12.19)	48.26 (11.76)	45.17 (11.96)	48.68 (11.13)	48.60 (10.75)	50.16 (10.60)

10.2.112 Economic evidence

Three relevant cost-effectiveness studies were identified for this question by Bradbury, 2010[142], Hunick, 1995[109], and Brothers, 1999[143]). One study was a cost-utility analysis based on the BASIL trial which compared the costs and effects of angioplasty to bypass surgery[142]; the decision analytic model by Hunick, 1995[109] compared the costs and QALYs of several different intervention sequences involving angioplasty and bypass surgery; and the model by Brothers, 1999[143] compared the costs and QALYs expected from treating patients with either bypass or amputation. These studies are summarised in the economic evidence profile below (Table 89). Full evidence tables can be found in Appendix I and a list of excluded studies in Appendix F.

This question was originally prioritised by the GDG for original economic modelling. It was as to be structured around the results of a network meta-analysis with amputation free survival as the main outcome, and health state utility values from published sources used to determine QALYs. However, the studies in the clinical review did not report sufficient data to allow us to complete this analysis in a way that would add to what was already available in the literature.

1 **Table 89: Economic study characteristics: Angioplasty compared to bypass surgery compared to amputation in people with critical limb ischaemia**

Study	Applicability	Limitations	Other Comments	Incremental costs	Incremental QALYs	Cost effectiveness	Uncertainty
Comparators: Primary angioplasty vs Primary bypass surgery							
Bradbury 2010[142]	Directly applicable[(a)]	Potentially serious limitations[(b)]	• Economic evaluation based on BASIL RCT • Population: patients with severe limb ischaemia • Time horizon: 3 years • Costs: All hospital costs over 3 years. • Country of analysis: UK	Bypass was £3,795 more costly than angioplasty	Bypass resulted in 0.028 QALYs gained compared to angioplasty	Bypass cost £135,517 per QALY gained	Uncertainty around the primary outcome (cost per QALY) was reported in one cost effectiveness acceptability curve. There was a 20% probability that bypass surgery was cost-effective at a threshold of £20k.
Comparators: No treatment vs. Primary angioplasty followed by angioplasty for treatment failure vs. Primary angioplasty followed by bypass for treatment failure vs. Primary bypass surgery							
Hunick 1995[109]	Partially applicable [(c)]	Potentially serious limitations[(d)]	• Decision analytic model based on a variety of published sources. • Population: patients with femoropopliteal disease • Time horizon: Lifetime • Costs: All hospital costs were obtained from hospital records. The cost of care for patients immobilised and dependant following amputation was based on published literature. • Country of analysis: USA	**Vein graft for rest pain stenosis**			
				Primary angioplasty followed by bypass surgery was the least costly strategy	Angioplasty followed by bypass surgery was the most effective strategy	Angioplasty followed by bypass surgery is the dominant strategy.	For patients with rest pain occlusion, the conclusion was unchanged
				PTFE-AK for rest pain stenosis			
				Angioplasty followed by angioplasty was the least costly strategy	Angioplasty followed by angioplasty was the most costly strategy	Angioplasty followed by angioplasty was the dominant strategy	For patients with rest pain occlusion, angioplasty followed by bypass was the dominant strategy
				PTFE-BK for rest pain stenosis			
				Angioplasty followed by	Angioplasty followed by	Angioplasty followed by	For patients with rest pain occlusion,

				angioplasty was the least costly strategy	angioplasty was the most costly strategy	angioplasty was the dominant strategy	angioplasty followed by bypass was the dominant strategy
Comparators: Primary bypass surgery vs. Primary amputation vs. Primary medical management							
Brothers 1999[143]	Potentially serious limitations[(e)]	Partially applicable[(f)]	• Decision analytic model • Population: people with first presentation of limb-threatening ischaemia caused by tibial-peoneal artery occlusive disease • Outcomes: QALYs • Costs: Hospital, outpatient and physician charges obtained from patient records • Perspective: USA hospital	Primary bypass was £5, 466 more expensive than non-operative expectant management[(g)]	Primary bypass resulted in a gain of 1.16 QALYs compared to non-operative expectant management[(h)]	Primary bypass costs £4, 712 per QALY gained compared to non-operative expectant management[(i	One- and two-way sensitivity analyses were performed to evaluate the effect of varying expected utility, incremental costs, early patency, late patency and peri-operative mortality rates. The authors reported the results of these analyses in graphical form only and did not excluded dominated options, therefore, it is not possible to analyse the results of these analyses. Based on threshold analysis, the authors concluded that primary amputation becomes the most cost-effective strategy when primary bypass patency is less than 11%. Expectant management is the most cost-effective treatment when operative mortality for revascularisation or amputation exceeds 55%.

(a) UK NHS setting (English and Scottish centres).
(b) Three year time horizon; resource use and unit costs not reported; analysis of uncertainty based on undiscounted costs and discounted QALYs; cost of amputation not accounted for.
(c) Resource use based on American hospital records.
(d) Quality of life estimated using Torrence Multi Attribute Scale by healthcare workers; patency failure assumed to be equivalent to symptom progression & re-intervention; progression of symptoms not modelled due to lack of data.
(e) Long-term patient survival, limb salvage rate, and primary and cumulative secondary patency rates were obtained from the results of retrospective analyses previously conducted by the authors with no evidence of a systematic search; utility values were obtained from people with CLI rather than patients who had experienced each health state QALY gain was considered only over a 5-year horizon, therefore, this study will underestimate the long-term effect of reduced operative mortality expected from both the expectant management and primary amputation strategies; unclear method of QALY elicitation and valuation.
(f) USA hospital perspective.
(g) Primary amputation was £2, 186 more costly than non-operative expectant management.
(h) Primary amputation resulted in a gain of 0.06 QALYs compared to non-operative management.
(i) Primary amputation is excluded by extended dominance.

10.2.12 Evidence statements

10.2.221 Clinical

Critical limb ischaemia due to aorto-iliac disease:

There was no statistically significant difference between angioplasty and bypass surgery for:

- Limb salvage at 4 years [1 study, 45 participants, very low quality evidence][104]

Critical limb ischaemia due to femoro-popliteal disease:

Bypass surgery was significantly better than angioplasty for:

- Overall survival after 2 years (adjusted HR) [1 study, 452 participants, moderate quality evidence][142]

Angioplasty was significantly better than bypass surgery for:

- Minor adverse events at 30 days [1 study, 452 participants, moderate quality evidence][142]
- Minor adverse events at 1 year [1 study, 61 participants, moderate quality evidence][105]

There was no statistically significant difference between angioplasty and bypass surgery for:

- Mortality at 30 days [2 studies, 513 participants, very low quality evidence][105,142]
- Mortality at 1 year [1 study, 69 participants, very low quality evidence][105]
- Mortality at 3 years [1 study, 452 participants, very low quality evidence][142]
- Overall survival before 2 years (adjusted HR) [1 study, 452 participants, very low quality evidence][142]
- Amputation at 1 year [1 study, 61 participants, very low quality evidence][105]
- Amputation free survival before 2 years (adjusted HR) [1 study, 452 participants, very low quality evidence][142]
- Amputation free survival after 2 years (adjusted HR) [1 study, 452 participants, low quality evidence][142]
- Amputation free survival at 3 years [1 study, 452 participants, very low quality evidence][142]
- Limb salvage rate at 4 years [1 study, 27 participants, very low quality evidence][104]
- Major adverse events at 30 days [1 study, 452 participants, low quality evidence][142]
- Re-intervention at 30 days [1 study, 452 participants, very low quality evidence][142]
- Re-intervention at 1 year [1 study, 102 participants, very low quality evidence][105]
- ABPI at 1 year [1 study, 61 participants, very low quality evidence][105]

Evidence statement for individual studies where meta-analysis was not possible – no statistical analysis performed:

- Quality of life increased for both angioplasty and bypass at 3 months [1 study, 316 participants, low quality evidence][142]
- Quality of life decreased for both angioplasty and bypass at 6 months [1 study, 275 participants, low quality evidence][142]
- Quality of life increased for both angioplasty and bypass at 1 year [1 study, 252 participants, low quality evidence][142]
- Quality of life increased for angioplasty and decreased bypass at 2 years [1 study, 139 participants, low quality evidence][142]

- Quality of life increased for angioplasty and decreased bypass at 3 years [1 study, 97 participants, low quality evidence][142]

10.2.232 Economic

- One study found that angioplasty is more cost effective than bypass surgery for the treatment of people with SLI [directly applicable with potentially serious limitations][142]
- One study found that angioplasty followed by (autologous vein) bypass surgery is the most cost effective treatment option in people with CLI due to stenoses and occlusions [partially applicable with potentially serious limitations][109]
- One study found that primary bypass surgery may be more cost-effective than primary amputation in people with CLI [partially applicable with potentially serious limitations][143]

10.213 Recommendations and link to evidence

Recommendations	**17. Ensure that all people with critical limb ischaemia are reviewed by a vascular multidisciplinary team before treatment decisions are made.** **18. Offer angioplasty or bypass surgery (see also recommendation 22) to people with critical limb ischaemia requiring revascularisation, based on:** • **comorbidities** • **pattern of disease** • **availability of vein, and** • **patient preference.**
Relative value of different outcomes	The GDG considered mortality as an outcome of major importance, but were also concerned to consider quality of life. Both amputation and the need for further intervention, irrespective of whether angioplasty or bypass surgery is done first, will impact on quality of life and these outcome measures were also considered carefully. A difference in mortality was observed in the form of an adjusted hazard ration in favour of surgery at the 2-year time point. There was no significant difference in unadjusted figures, nor was there any mortality difference at any other time-point whether shorter or longer than 2 years. The GDG also discussed a post-hoc analysis of the BASIL trial which suggested that there is a mortality benefit for patients undergoing bypass who live beyond 2 years. However, this analysis has not been validated, and it is not clear how to predict >2-year survival before the intervention actually takes place. (This evidence did not meet the primary literature search criteria and was therefore not part of the formal evidence review set out above). Although fairly large differences were seen in amputation rates at some time points there were no statistically significant differences in this outcome measure, nor in re-intervention rates.
Trade off between clinical benefit and harms	Adverse events were more frequently observed with bypass surgery than with angioplasty, although this difference was significant only for minor events. There was debate around the technical failure rate with angioplasty. Having

	bypass surgery after angioplasty resulted in poorer outcomes than going straight to bypass in the BASIL study, which may indicate that angioplasty had changed the bypass opportunity. However, it is also possible that this group of people, who required two procedures were those with a poorer natural prognosis and that they would not have had good results with either procedure. This is difficult to tease out of the study data and the GDG were not unanimous in their view of the implied risk of attempting angioplasty first in people suitable for bypass.
Economic considerations	The GDG considered the results and the limitations of the cost-effectiveness analyses by Bradbury 2010 and Hunick 1995. On balance, they agreed that angioplasty is most likely to be the most cost effective primary treatment strategy for people with CLI. However, due to the limitations of the evidence base and the considerable uncertainty reported in the analyses, the GDG did not feel that either form of intervention could be unequivocally recommended as preferable on health economic grounds. A patient's likely benefit from either angioplasty or surgery needs to be judged on an individual basis and therefore referral to a specialist centre where a multi-disciplinary assessment can take place should form a key part of determining the most cost-effective pathway for each patient.
Quality of evidence	The GDG noted that the evidence reviewed was moderate to very low quality by the GRADE criteria. The evidence was downgraded on a number of issues including allocation concealment and blinding. This led to a discussion on the trial methodology for these interventions. It is not possible to blind those performing the relevant procedure or to blind the participants to the interventions received. Therefore, under GRADE criteria, the evidence would never receive a high quality scoring. The GDG concluded that the RCTs presented were the most robust available for a comparison of angioplasty with surgery. The patient population with CLI have few clinical options available. The GDG felt that many of patients included within these trials were likely to have been more suited to either the angioplasty or bypass intervention, because of differences, for example, in anatomy or co-morbidity. The number of potential subjects with genuinely equal suitability for either intervention is, in their experience, fairly small. No evidence was reviewed for the benefits of multi-disciplinary review. The recommendation was based on the GDG experience and consensus.
Other considerations	It is difficult to make a blanket recommendation for all patients with CLI as many of them have features which make them unsuitable for either angioplasty or bypass. The GDG advocated that all patients are considered on an individual basis by a multi-disciplinary team. basis as the following factors determine which intervention is considered optimal: • Age of the patients • Fitness for surgery • Severity of disease • Size and shape of patient • Co-morbidities involved • Presence or absence of a suitable vein • Technical ability to undertake angioplasty • Balance of benefit versus harms.

	Most units now have multi-disciplinary teams and they are considered standard practice. An MDT review will ensure that patients have access to all treatment options and the decisions are made based on individual needs. The GDG did not review evidence relating to multi-disciplinary review in people with CLI eligible for revascularisation or bypass surgery but agreed by consensus that such a recommendation was important. In practice, angioplasty tends to be undertaken as the first line option, although there is geographical variation around the UK. Of the two procedures, there are likely to be fewer patients unsuitable for angioplasty than unsuitable for surgery. The clinical studies did not show any clear advantage either way, but the health economic evidence favoured angioplasty as the first procedure. The GDG therefore agreed that in the small number of cases in which the two procedures look equally likely to succeed, angioplasty should be tried first. Patient choice must be part of the decision making process. It was recognised that some patients may even prefer to undergo amputation instead of repeated interventions, which are associated with longer hospital stay and healing times. No evidence was found on management of patients with diabetes. There is a recognition that the prevalence of diabetes is increasing. However, the GDG felt that the data could not be extrapolated to make a separate recommendation for the diabetic population. **Key priority for implementation** The GDG highlighted recommendation 17 as a key priority for implementation. The reason for selecting this recommendation as a priority was that the GDG considered it important for CLI patients to be reviewed by a MDT in order that all possible options for treatment to be considered.

10.214 Research recommendations

3. What is the clinical and cost effectiveness of a bypass surgery first strategy as compared with an angioplasty first strategy for the treatment of people with critical limb ischaemia due to disease of the infra-geniculate (below the knee) arteries?

Why this is important

People with reconstructable critical limb ischaemia (CLI) due to femoro-popliteal arterial disease in the thigh are normally offered either angioplasty or bypass surgery depending on their co-morbidity and individual preferences, as well as the availability of vein for bypass.

However, many patients with CLI, especially those with diabetic vascular disease, also have disease of the infra-geniculate (below the knee) arteries in the calf.

For many years, the standard of care has been bypass surgery. Although such surgery may be associated with significant morbidity the resulting long-term amputation free survival rates are generally good.

In recent years there has been a trend towards treating infra-geniculate disease with angioplasty on the grounds that it is less morbid than surgery. However, this change in practice is not evidence-based, and there remain serious concerns about the durability of angioplasty in this anatomic area

As such, considerable uncertainty, and so controversy remains, as to the optimal treatment of infra-geniculate disease.

A multicentre, randomised controlled trial is therefore required to compare the clinical and cost-effectiveness of a bypass surgery first versus an angioplasty first strategy in people presenting with CLI due to infra-geniculate disease.

The primary endpoint should be amputation free survival with secondary endpoints including overall survival, health-related quality of life, healing of tissue loss, and relief of ischaemic pain. A full health economic analysis should also be undertaken.

4. What is the clinical and cost effectiveness of primary amputation compared to an attempt at revascularisation (either angioplasty or bypass surgery) for selected people presenting with critical limb ischaemia who are thought to be at high risk of failure following revascularisation?

Why this is important

About 50% of people presenting with critical limb ischaemia (CLI) are offered revascularisation either by means of angioplasty or bypass surgery. However, in those undergoing revascularisation it is possible to recognise a subgroup in which the success of intervention is so low that primary amputation might be a better strategy. Conversely, in the 50% of people with CLI who are treated conservatively or with primary amputation there may be a subgroup in which revascularisation would be appropriate. A multicentre, hospital-based, randomised controlled trial is required to define the most clinically and cost-effective strategy for the highest-risk people with CLI in whom there is equipoise between revascularisation, either via angioplasty or bypass surgery, and primary amputation. The primary endpoint should be amputation free survival with secondary endpoints including overall survival, health-related quality of life, healing of tissue loss, and relief of ischaemic pain. A full health economic analysis should also be undertaken.

10.3 Angioplasty with selective stent placement compared with angioplasty with primary stent placement

10.3.1 Review question

What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of critical limb ischemia in adults with PAD?

A literature search was conducted for RCTs that compared the effectiveness of angioplasty with selective stent placement to primary stent placement. No time limit was placed on the literature search, there were no limitations on sample size, and outcomes were subgrouped according to lesion location (femoro-popliteal and aorto-iliac). Indirect populations and emergency settings were excluded. One Cochrane review was identified Twine, 2009[129] which considered angioplasty without stents compared to angioplasty with stents for the superficial femoral artery. The Cochrane review was not included or updated as it did not meet the protocol defined by the GDG, which included all arteries of the leg. However it was cross checked for included studies which matched the review protocol.

10.3.111 Clinical evidence

Five relevant RCTs[144-148] were included in the review. The trials did not report outcome data for people with diabetes and no data was identified for people with CLI due to aorto-iliac disease.

There were unit of analysis issues in some of the trials where data were analysed by the limb or lesion rather than by person randomised. These trials have been analysed separately.

The quality and results of included studies are reported in Table 90 and Table 91. The forest plots for each clinical outcome are reported in Appendix J.

Table 90: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for critical limb ischaemia due to femoro-popliteal disease (person randomised data)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty with selective stent placement	Angioplasty with primary stent placement	Relative (95% CI)	Absolute	
Mortality at 30 days											
1 Zdanowski, 1999[147]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	None	0/17 (0%)	0/15 (0%)	not pooled	not pooled	LOW
Mortality at 3 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	3/32 (9.4%)	5/33 (15.2%)	RR 0.62 (0.16 to 2.38)	58 fewer per 1000 (from 127 fewer to 209 more)	VERY LOW
Mortality at 9 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	5/24 (20.8%)	5/19 (26.3%)	RR 0.79 (0.27 to 2.34)	55 fewer per 1000 (from 192 fewer to 353 more)	VERY LOW
Amputation at 3 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	4/32 (12.5%)	6/33 (18.2%)	RR 0.69 (0.21 to 2.21)	56 fewer per 1000 (from 144 fewer to 220 more)	VERY LOW
Amputation at 6 months											
1 Rand, 2006[144]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	1/27 (3.7%)	2/24 (8.3%)	RR 0.44 (0.04 to 4.6)	47 fewer per 1000 (from 80 fewer to 300	VERY LOW

										more)	
Amputation at 9 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	7/24 (29.2%)	10/19 (52.6%)	RR 0.55 (0.26 to 1.18)	237 fewer per 1000 (from 389 fewer to 95 more)	VERY LOW
Amputation at 1 year											
1 Zdanowski, 1999[147]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	None	0/17 (0%)	0/15 (0%)	not pooled	not pooled	LOW
Major adverse events at 1 year											
1 Zdanowski, 1999[147]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	4/17 (23.5%)	1/15 (6.7%)	RR 3.53 (0.44 to 28.21)	169 more per 1000 (from 37 fewer to 1000 more)	VERY LOW
Minor adverse events at 1 year											
1 Brodmann, 2011[148]	RCT	serious[(c)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	4/33 (12.1%)	0/21 (0%)	RR 5.82 (0.33 to 102.93)	-	VERY LOW
Re-intervention at 6 months											
1 Rand, 2006[144]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	0/27 (0%)	1/24 (4.2%)	RR 0.3 (0.01 to 6.98)	29 fewer per 1000 (from 41 fewer to 249 more)	VERY LOW
Re-intervention at 1 year											
1 Zdanowski, 1999[147]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	2/17 (11.8%)	2/15 (13.3%)	RR 0.88 (0.14 to 5.52)	16 fewer per 1000 (from 115 fewer to 603 more)	VERY LOW
Target lesion revascularisation at 3 months											
1 Rand,	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	0/32 (0%)	1/33 (3%)	RR 0.34 (0.01 to	20 fewer per 1000 (from 30	VERY LOW

2011[145]									8.13)	fewer to 216 more)	
Target lesion revascularisation at 9 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	3/24 (12.5%)	7/19 (36.8%)	RR 0.34 (0.1 to 1.14)	243 fewer per 1000 (from 332 fewer to 52 more)	VERY LOW
ABPI at 3 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	serious[(d)]	None	32	33	-	MD 0.2 lower (0.31 to 0.09 lower)	VERY LOW
ABPI at 9 months											
1 Rand, 2011[145]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	32	33	-	MD 0 higher (0.11 lower to 0.11 higher)	VERY LOW

(a) Unclear methodology.
(b) 95% CI crosses both MIDs.
(c) Unclear allocation concealment and blinding.
(d) 95% CI crosses one MID.

Table 91: Clinical evidence profile: Angioplasty with selective stent placement compared to angioplasty with primary stent placement for critical limb ischaemia due to femoro-popliteal disease (limb / lesion randomised data)

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Angioplasty with selective stent placement**	**Angioplasty with primary stent placement**	**Relative (95% CI)**	**Absolute**	
Mortality at 30 days											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	1/22 (4.5%)	1/16 (6.3%)	RR 0.73 (0.05 to 10.78)	17 fewer per 1000 (from 59 fewer to 611 more)	VERY LOW

Mortality at 2 years											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	7/22 (31.8%)	3/16 (18.8%)	RR 1.7 (0.52 to 5.57)	131 more per 1000 (from 90 fewer to 857 more)	VERY LOW
Amputation at 2 years											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	3/22 (13.6%)	4/16 (25%)	RR 0.55 (0.14 to 2.11)	112 fewer per 1000 (from 215 fewer to 277 more)	VERY LOW
Major adverse events at 30 days											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	1/22 (4.5%)	1/16 (6.3%)	RR 0.73 (0.05 to 10.78)	17 fewer per 1000 (from 59 fewer to 611 more)	VERY LOW
Minor adverse events at 30 days											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	2/22 (9.1%)	4/16 (25%)	RR 0.36 (0.08 to 1.75)	160 fewer per 1000 (from 230 fewer to 188 more)	VERY LOW
Major adverse event at 2 years											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	2/22 (9.1%)	2/16 (12.5%)	RR 0.73 (0.11 to 4.63)	34 fewer per 1000 (from 111 fewer to 454 more)	VERY LOW
Re-intervention at 2 years											
1 Randon, 2010[146]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	None	5/22 (22.7%)	2/16 (12.5%)	RR 1.82 (0.4 to 8.21)	103 more per 1000 (from 75 fewer to 901 more)	VERY LOW

(a) Unclear allocation concealment and blinding.
(b) 95% CI crosses both MIDS.

10.3.112 Economic evidence

No cost effectiveness evidence was identified for this question.

In the absence of published evidence, the GDG were presented with the cost of (bare metal) stents. Vascular stents are excluded from the NHS reference cost for angioplasty and incur an additional cost according to the number and type used per procedure. The unit cost of vascular stents was not available from the NHS Supply Catalogue. A buyer for cardiology and radiology products at the NHS Supply chain was asked to provide a list of prices for all vascular stents currently in use in England and Wales, however the GDG concluded that this list was not inclusive. Members of the GDG were then asked to provide prices from their hospitals. Based on prices obtained by GDG members, the group estimated bare metal stents cost approximately £550. The GDG also indicated that on average two stents are used per procedure.

The clinical studies included in this review did not provide details of the number of patients requiring selective stent placement. Assuming that the proportion is similar to those in IC, approximately 40% of patients require stent placement. [107] According to the evidence included in the clinical review, 4.5% selective stent placement procedures resulted in major adverse events at 30 days compared to 6.3% of primary stent placement procedures.[146] Applying this data to the NHS reference costs presented in Table 92, the average cost of angioplasty with selective stent placement is £4, 171 and the cost of angioplasty with primary stent placement is £4, 603. Therefore, the incremental cost of angioplasty with primary stent placement is approximately £432.

Table 92: Costs of angioplasty procedure – Elective and non-elective

Currency code	Currency description	Activity	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Elective inpatient (long stay) HRG data					
QZ15A	Therapeutic endovascular procedure with major complications	114	£9, 200	£1, 940	£14, 255
QZ15C	Therapeutic endovascular procedure without complications	7, 991	£1, 888	£940	£2, 248
Elective inpatient (long stay) excess bed day HRG data					
QZ15A	Therapeutic endovascular procedure with major complications	132	£173	£152	£152
QZ15C	Therapeutic endovascular procedure without complications	1, 580	£344	£250	£433
Average cost					
Elective angioplasty with major complications			£9, 349 (£2, 071 - £14, 386)		
Elective angioplasty without complications			£3, 627 (£2, 204 - £4, 435)		
Non elective inpatient (long stay) HRG data					
QZ15A	Therapeutic endovascular procedure with major complications	611	£9, 518	£4, 547	£11, 821
QZ15C	Therapeutic endovascular procedure without complications	1, 820	£4, 206	£2, 148	£5, 200
Non elective inpatient (long stay) excess bed day HRG data					
QZ15A	Therapeutic endovascular	850	£255	£140	£338

	procedure with major complications				
QZ15C	Therapeutic endovascular procedure without complications	7, 054	£357	£229	£454
Average cost					
Non elective angioplasty with major complications			£9, 702 (£4, 647 - £12, 064)		
Non elective angioplasty without complications			£4, 298 (£2, 206 - £5, 317)		
Weighted average cost of angioplasty (assuming 10% of procedures are non elective)					
Angioplasty with major complications			**£9, 385 (£2, 329 to £14, 154)**		
Angioplasty without complications			**£3, 695 (£2, 204 to £4, 524)**		

Source/Note: All costs obtained from 2009/10 NHS Reference Costs[128]

10.3.2 Evidence statements

10.3.2.1 Clinical

Critical limb ischaemia due to aorto-iliac disease:

No clinical evidence was reported for people with CLI due to aorto-iliac disease.

Critical limb ischaemia due to femoro-popliteal disease (person randomised data):

Angioplasty with primary stent placement was statistically significantly better than angioplasty with selective stent placement for:

- ABPI at 3 months [1 study, 65 participants, very low quality evidence][145]

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Mortality at 3 months [1 study, 65 participants, very low quality evidence][145]
- Mortality at 30 days [1 study, 32 participants, low quality evidence][147]
- Mortality at 9 months [1 study, 43 participants, very low quality evidence][145]
- Amputation at 3 months [1 study, 65 participants, very low quality evidence][145]
- Amputation at 6 months [1 study, 51 participants, very low quality evidence][144]
- Amputation at 9 months [1 study, 43 participants, very low quality evidence][145]
- Amputation at 1 year [1 study, 32 participants, low quality evidence][147]
- Major adverse events at 1 year [1 study, 32 participants, very low quality evidence][147]
- Minor adverse events at 1 year [1 study, 54 participants, very low quality evidence][148]
- Re-intervention at 6 months [1 study, 51 participants, very low quality evidence][144]
- Re-intervention at 1 year [1 study, 32 participants, very low quality evidence][147]
- Target lesion revascularisation at 3 months [1 study, 65 participants, very low quality evidence][145]
- Target lesion revascularisation at 9 months [1 study, 43 participants, very low quality evidence][145]
- ABPI at 9 months [1 study, 43 participants, very low quality evidence][145]

Critical limb ischaemia due to femoro-popliteal disease (limb/lesion randomised data):

There was no statistically significant difference between angioplasty with selective stent placement and angioplasty with primary stent placement for:

- Mortality at 30 days and 2 years [1 study, 38 limbs, very low quality evidence][146]

- Amputation at 2 years [1 study, 38 limbs, very low quality evidence][146]
- Major adverse events at 30 days and 2 years [1 study, 38 limbs, very low quality evidence][146]
- Minor adverse events at 30 days [1 study, 38 limbs, very low quality evidence][146]
- Re-intervention at 2 years [1 study, 38 limbs, very low quality evidence][146]

10.3.252 Economic

No cost effectiveness evidence was identified for this question.

10.373 Recommendations and link to evidence

Recommendations	**19. Do not offer primary stent placement to people with critical limb ischaemia caused by aorto-iliac stenosis (as opposed to complete occlusion) or femoro-popliteal disease.** **20. Consider primary stent placement using bare metal stents in people with critical limb ischaemia caused by aorto-iliac occlusion (as opposed to stenosis).**
Relative values of different outcomes	There were no differences in any of the reported outcome measures. Patency was not considered as a relevant outcome for the reasons detailed in section 3.1.1 in the methodology chapter.
Trade off between clinical benefits and harms	The GDG were concerned that stents may give the operator the impression that a procedure has been technically successful at the time the procedure is performed, but noted that no consistent later benefit was demonstrated in comparison with angioplasty. The GDG considered that the routine use of stents as opposed to selective use in conjunction with angioplasty carried the disadvantages of additional cost, increased procedure time, and potential risks of additional instrumentation. Endovascular procedures carry a potential risk of causing embolisation of material from the diseased artery which can cause blockage of smaller arteries further down the leg. This is thought to be a greater risk with complete occlusion of the aorto-iliac arteries than with stenosis or occlusion in smaller vessels. There is also a risk of restenosis following endovascular treatment and having foreign material such as a stent in the artery may increase this risk, particularly in smaller vessels. The GDG considered that it is generally accepted that stenting is advantageous in terms of embolisation rates although the evidence reviewed in these studies did not reflect this.
Economic considerations	No cost effectiveness evidence was identified for this question. The GDG considered the increased cost associated with primary stent placement compared to selective stent placement. They agreed that in light of clinical evidence suggesting that there is no clear benefit associated with primary stent placement, it does not represent value for money and should not be recommended for routine use.
Quality of evidence	The evidence was rated as low to very low by GRADE criteria. The GDG noted

	that the included studies were small.
Other considerations	This comparison is about whether to place stent in all patients undergoing an endovascular intervention for PAD, or only those in whom the operator deems it necessary. Although the latter seems more open to error, the former may be wasteful, and in this group of studies no clear evidence in favour of primary stenting emerged. Primary stenting for femoro-popliteal disease or stenotic disease of the aorto-iliac arteries is not standard UK practice and the GDG felt that there was insufficient evidence to recommend a change to this situation. Primary stents are currently used in aorto-iliac disease in the UK because of concern about the risk of embolisation. The GDG recognised that they had identified no evidence to justify this as routine, but also noted that embolisation was not an endpoint specifically sought in these studies. In the absence of any clear evidence for or against primary stent placement, the GDG made their decision based on the extra cost of routinely employing stents and developed recommendations which would discourage primary stenting, but acknowledge the possible value for aorto-iliac occlusive disease.

10.3.14 Research recommendation

5. What is the clinical and cost effectiveness of selective stent placement in comparison to angioplasty with primary stent placement in the management of critical limb ischaemia due to disease of the infra-geniculate arteries?

Why this is important

Studies comparing angioplasty with selective stent placement to primary stent placement have been limited to the aorto-iliac and femoro-popliteal segment. There remains a significant group of people with critical ischaemia due to disease of the infra-geniculate vessels in which there is a potential for endovascular treatment. Infra-geniculate disease is more complex to treat by endovascular means and the risks and benefits of different treatment options may differ from those in the more proximal vessels.

A multicentre, randomised controlled trial with a full health economic analysis is required to address the optimum policy as regards the choice of method for angioplasty and stent placement of the infra-geniculate arteries.

The primary endpoint should be amputation free survival with secondary endpoints including overall survival, re-intervention rates, health-related quality of life, healing of tissue loss, and relief of ischaemic pain.

10.4 Bare metal compared to drug eluting stents

10.4.1 Review question

What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of critical limb ischemia in adults with PAD?

A literature search was conducted for RCTs that compared the effectiveness of bare metal stents to drug eluting stents. No time limit was placed on the literature search, there were no limitations on sample size, and outcomes were sub-grouped according to lesion location (femoro-popliteal and aorto-iliac). Indirect populations and emergency settings were excluded.

10.4.1 Clinical evidence

Four relevant RCTs of two trials[138,149-151] were included in the review. The trials did not report outcome data for people with diabetes and no data was identified for people with CLI due to aorto-iliac disease.

The quality and results of included studies are reported in Table 93. The forest plots for each clinical outcome are reported in Appendix J.

1 **Table 93: Clinical evidence profile: Bare metal compared to drug eluting stents for critical limb ischaemia due to femoro-popliteal disease**

Quality of evidence							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BMS**	**DES**	**Relative (95% CI)**	**Absolute**	
Mortality at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	1/28 (3.6%)	2/29 (6.9%)	RR 0.52 (0.05 to 5.4)	33 fewer per 1000 (from 66 fewer to 303 more)	VERY LOW
Mortality at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	8/33 (24.2%)	9/42 (21.4%)	RR 1.13 (0.49 to 2.61)	28 more per 1000 (from 109 fewer to 345 more)	LOW
Mortality at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/46 (4.3%)	7/47 (14.9%)	RR 0.29 (0.06 to 1.33)	106 fewer per 1000 (from 140 fewer to 49 more)	VERY LOW
Amputation at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/33 (6.1%)	2/42 (4.8%)	RR 1.27 (0.19 to 8.56)	13 more per 1000 (from 39 fewer to 360 more)	LOW
Amputation at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(c)]	none	0/46 (0%)	0/47 (0%)	not pooled	not pooled	LOW
Major adverse events at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	0/29 (0%)	1/28 (3.6%)	RR 0.32 (0.01 to 7.59)	24 fewer per 1000 (from 35 fewer to 235 more)	VERY LOW
Minor adverse events intraoperative											
1	RCT	very serious[(a)]	no serious	no serious	very serious[(b)]	none	2/29	2/28	RR 0.97	2 fewer per 1000 (from 61	VERY

Duda, 2005[151]			inconsistency	indirectness			(6.9%)	(7.1%)	(0.15 to 6.39)	fewer to 385 more)	LOW
Minor adverse events at 6 months											
2 Duda, 2002; Duda 2006[149,150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/46 (4.3%)	2/47 (4.3%)	RR 0.98 (0.14 to 6.67)	1 fewer per 1000 (from 37 fewer to 247 more)	VERY LOW
Minor adverse events at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	3/46 (6.5%)	0/47 0%	RR 7.15 (0.38 to 134.66)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Revascularisation procedure on contralateral leg before discharge at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/28 (7.1%)	2/29 (6.9%)	RR 1.04 (0.16 to 6.86)	3 more per 1000 (from 58 fewer to 404 more)	VERY LOW
Revascularisation procedure on contralateral leg after discharge at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	2/28 (7.1%)	3/29 (10.3%)	RR 0.69 (0.12 to 3.83)	32 fewer per 1000 (from 91 fewer to 293 more)	VERY LOW
Target vessel revascularisation at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	3/28 (10.7%)	1/29 (3.4%)	RR 3.11 (0.34 to 28.12)	73 more per 1000 (from 23 fewer to 935 more)	VERY LOW
Target vessel revascularisation at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	10/46 (21.7%)	6/47 (12.8%)	RR 1.7 (0.67 to 4.3)	89 more per 1000 (from 42 fewer to 421 more)	VERY LOW
Target vessel revascularisation at 2 years (Hazard Ratio)											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/46 (21.7%)	6/47 (12.8%)	HR 7.27 (1.75 to 30.26)	502 more per 1000 (from 85 more to 856 more)	LOW
Target lesion revascularisation at 6 months											

1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(c)]	none	0/28 (0%)	0/29 (0%)	not pooled	not pooled	LOW
Target lesion revascularisation at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[(b)]	none	3/33 (9.1%)	4/42 (9.5%)	RR 0.95 (0.23 to 3.97)	5 fewer per 1000 (from 73 fewer to 283 more)	LOW
Target lesion revascularisation at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	6/46 (13%)	3/47 (6.4%)	RR 2.04 (0.54 to 7.69)	66 more per 1000 (from 29 fewer to 427 more)	VERY LOW
Target lesion revascularisation at 2 years (Hazard Ratio)											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(b)]	none	6/46 (13%)	3/47 (6.4%)	HR 3.9 (0.77 to 19.63)	163 more per 1000 (from 14 fewer to 662 more)	VERY LOW
ABPI at 6 months											
1 Duda, 2005[151]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	23	-	MD 0.04 lower (0.13 lower to 0.05 higher)	LOW
ABPI at 1 year											
1 Rastan, 2011[138]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	42	-	MD 0.07 lower (0.13 to 0.01 lower)	HIGH
ABPI at 2 years											
1 Duda, 2006[150]	RCT	very serious[(a)]	no serious inconsistency	no serious indirectness	serious[(d)]	none	37	35	-	MD 0.06 lower (0.15 lower to 0.03 higher)	VERY LOW

(a) Unclear allocation concealment and randomisation.
(b) 95% CI crosses both MIDs.
(c) There were no events in either group.
(d) 95% CI crosses one MID.

10.4.112 Economic evidence

No cost effectiveness evidence was identified for this question.

In the absence of any published cost effectiveness evidence, the GDG were presented with the average cost of bare metal and drug eluting stents and the cost of angioplasty with and without complications (Table 94 and Table 95).

Table 94: Peripheral vascular stent cost

Vascular stent type	Approximate average cost	Source
Bare metal	£550	GDG opinion based on hospital records
Drug eluting	£950	GDG opinion based on hospital records

Table 95: Angioplasty procedural cost

HRG code	Description	Average unit cost	Lower and upper quartile unit cost	Source
Elective inpatient (long stay) HRG and excess bed day data				
QZ15A	Therapeutic endovascular procedures with major complications	£9, 349	£2, 071 to £14, 386	NHS Reference Costs
QZ15B	Therapeutic endovascular procedure with intermediate complications	£3, 397	£1, 850 to £4, 104	NHS Reference Costs
QZ15C	Therapeutic endovascular procedure without complications	£3, 627	£2, 204 to £4, 435	NHS Reference Costs
Non elective inpatient (long stay) HRG and excess bed day data				
QZ15A	Therapeutic endovascular procedures with major complications	£9, 701	£4, 647 to £12, 064	NHS Reference Costs
QZ15B	Therapeutic endovascular procedure with intermediate complications	£5, 197	£3, 369 to £6, 353	NHS Reference Costs
QZ15C	Therapeutic endovascular procedure without complications	£4, 298	£2, 206 to £5, 317	NHS Reference Costs

Source/Note: 2009/10 NHS Reference costs[128].

10.4.92 Evidence statements

10.4.201 Clinical

Critical limb ischaemia due to aorto-iliac disease:

No clinical evidence was reported for people with CLI due to aorto-iliac disease.

Critical limb ischaemia due to femoro-popliteal disease:

Drug eluting stents were significantly better than bare metal stents for:

- Target vessel revascularisation at 2 years (using hazard ratio) [1 study, 93 participants, low quality evidence][150]
- ABPI at 1 year [1 study, 75 participants, high quality evidence][138]

There was no statistically significant difference between bare metal stents and drug eluting stents for:

- Mortality at 6 months [1 study, 57 participants, very low quality evidence][151]

- Mortality at 1 year [1 study, 75 participants, low quality evidence][138]
- Mortality at 2 years [1 study, 93 participants, very low quality evidence][150]
- Amputation at 1 year [1 study, 75 participants, low quality evidence][138]
- Major adverse events at 6 months [1 study, 57 participants, very low quality evidence][151]
- Minor adverse events intra-operatively [1 study, 57 participants, very low quality evidence][151]
- Minor adverse events at 6 months and 2 years [2 studies, 93 participants, very low quality evidence][149,150]
- Revascularisation on contralateral leg before at 6 months, and after discharge at 6 months [1 study, 57 participants, very low quality evidence][151]
- Target vessel revascularisation at 6 months [1 study, 75 participants, very low quality evidence][151]
- Target vessel revascularisation at 2 years (using relative risk) [1 study, 93 participants, very low quality evidence][150]
- Target lesion revascularisation at 1 year [1 study, 75 participants, low quality evidence][138]
- Target lesion revascularisation at 2 years (using relative risk and hazard ratio) [1 study, 93 participants, very low quality evidence][150]
- ABPI at 6 months [1 study, 47 participants, low quality evidence][151]
- ABPI at 2 years [1 study, 72 participants, very low quality evidence][150]

There was no difference between bare metal stents and drug eluting stents for:

- Amputation at 2 years [1 study, 93 participants, low quality evidence][150]
- Target lesion revascularisation at 6 months [1 study, 57 participants, low quality evidence][151]

10.4.2 Economic

No cost effectiveness evidence was identified for this question.

10.4.3 Recommendations and link to evidence

Recommendation	21. Use bare metal stents where stenting is indicated for the treatment of critical limb ischaemia.
Relative values of different outcomes	The GDG considered amputation free survival and re-intervention rates to be the key clinical outcomes for this question. They also wished to know whether there were any differences in quality of life, mortality and ABPI. Although data were available at several different time points, few differences were found in the reported outcomes. No data was reported on quality of life or walking distance. Drug-eluting stents were shown to be superior in terms of target vessel re-vascularisation rates and ABPI, both at one time-point only. The GDG did not feel that great importance could be attached to these when set against the large number of comparisons showing no difference, and bearing in mind that these were not felt to be the key outcome measures. Patency was not considered as a relevant outcome for the reasons stated in section 3.1.1 of the methodology chapter.
Trade off between clinical benefits and harms	According to the results of the clinical review, there was no significant difference in mortality, adverse events and amputation between bare metal and drug eluting stents.

	The GDG did not feel there was any difference between the two types of stent in terms of technical difficulty in placement. The method of placement of the two forms of stents is identical, and therefore the main potential adverse effects are also the same. The potential benefit of drug eluting stent is that the drug is intended to reduce the rate of thrombosis or restenosis. However, the long-term effects of the drug on the vessel wall are unknown.
Economic considerations	No cost effectiveness evidence identified for this question. The GDG noted that because there is no difference in clinical outcomes between bare metal and drug eluting stents and there is a large difference in cost, drug eluting stents do not represent a cost-effective use of NHS resources.
Quality of evidence	The quality of evidence comparing bare metal and drug eluting stents was of low quality by GRADE criteria. The GDG noted that the SIROCCO study was halted as no differences found between bare metal and drug eluting stents. [151]
Other considerations	The GDG were aware of studies evaluating the effectiveness of bare metal versus drug eluting stents in coronary arteries. However, they did not think that these results could be extrapolated to the peripheral arteries because of the considerable differences in anatomy. The only evidence identified related to femoro-popliteal disease with no evidence relevant to aorto-iliac disease. The GDG discussed this and considered that there was no reason to differentiate between the two sites in terms of preference and that their conclusions for femoro-popliteal lesions should also apply to aorto-iliac lesions. There is no clinically relevant difference in benefit between the two stent types and drug eluting stents are more costly. The GDG therefore formed a consensus judgement that bare metal stent placement is the preferred option.

10.5 Autologous vein compared to prosthetic bypass

10.5.1 Review question

What is the clinical effectiveness of autologous vein versus prosthetic bypass graft for the treatment of CLI in adults with PAD?

The review question sought to examine evidence for the type of graft to be used when bypass is indicated in the patient. It was also necessary to consider the importance of the anatomical extent and distribution of disease and co-morbidities that are likely to affect outcome such as diabetes.

A literature search was conducted for RCTs that compared the effectiveness of autologous vein versus prosthetic bypass grafting. No time limit was placed on the literature search, and there were no limitations on sample size. Indirect populations and emergency settings were excluded. One Cochrane review was identified Twine, 2010[139] which considered graft type in bypass surgery for the femoro-popliteal disease. The Cochrane review was not included or updated as it did not meet the protocol defined by the GDG, which included all arteries of the leg. However it was cross checked for included studies which matched the review protocol.

10.5.111 Clinical evidence

Two relevant RCTs[152,153] were included in the review. The trials did not report outcome data for people with diabetes.

The quality and results of included studies are reported in Table 96. The forest plots for each clinical outcome are reported in Appendix J.

1 **Table 96: Clinical evidence profile: Autologous vein versus prosthetic bypass for critical limb ischaemia due to femoro-popliteal disease**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous vein	Prosthetic bypass	Relative (95% CI)	Absolute	
Perioperative mortality at 30 days											
2 Ballotta, 2003; Tilanus, 1985[152,153]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(b)]	none	0/76 (0%)	0/75 (0%)	not pooled	not pooled	MODERATE
Mortality at 5 years											
1 Tilanus, 1985[153]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(b)]	none	0/25 (0%)	0/24 (0%)	not pooled	not pooled	MODERATE
Peri-operative amputation at 30 days											
1 Ballotta, 2003[152]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision[(b)]	none	0/51 (0%)	0/51 (0%)	not pooled	not pooled	MODERATE
Amputation at 5 years											
2 Ballotta, 2003; Tilanus, 1985[152,153]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/76 (0%)	8/75 (10.7%)	RR 0.06 (0 to 0.93)	100 fewer per 1000 (from 7 fewer to 107 fewer)	MODERATE
Perioperative minor adverse event at 30 days											
1 Tilanus, 1985[153]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(c)]	none	5/25 (20%)	4/24 (16.7%)	RR 1.2 (0.37 to 3.94)	33 more per 1000 (from 105 fewer to 490 more)	VERY LOW
Re-intervention at 5 years											
2 Ballotta, 2003;	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	very serious[(c)]	none	1/76 (1.3%)	7/75 (9.3%)	RR 0.2 (0.04 to	75 fewer per 1000 (from 90 fewer to	VERY LOW

Tilanus, 1985[152,153]									1.11)	10 more)	
ABPI following surgery (no time point given)											
1 Tilanus, 1985[153]	RCT	serious[(a)]	no serious inconsistency	no serious indirectness	serious[(d)]	none	25	24	-	MD 0.07 lower (0.16 lower to 0.02 higher)	LOW

(a) Unclear allocation concealment and participant blinding.
(b) No events in either intervention.
(c) 95% CI crosses both MIDs.
(d) 95% CI crosses one MID.

10.5.11 Economic evidence

No cost effectiveness evidence was identified for this question.

The cost-utility analysis by Hunick et al 1995 (reported in Table 89) subgrouped the results of their clinical analysis by graft material. Although the study was not designed to directly compare the cost-effectiveness of one type of material to another, according to the results of the model, bypass surgery using autologous vein grafts results in higher quality of life and lower cost than bypass surgery using synthetic grafts.

The GDG also discussed the cost of autologous and prosthetic grafts in an NHS context. The group considered that although the same NHS Reference Cost applies to patients undergoing both procedures, prosthetic veins cost several hundred pounds, varying widely depending on graft length and material (official cost estimates were not available from standard sources). However, the procedure associated with prosthetic vein bypass is slightly shorter than that for autologous vein as there is no need to harvest the vein. In addition, the average hospital stay is slightly less for prosthetic vein bypass operations. However, autologous vein bypass is associated with a reduced rate of infection and fewer complications. Based on the clinical evidence and clinical experience, the GDG agreed that autologous vein bypass was likely to represent the least costly of the two procedures. A formal cost estimation was not undertaken as it was thought that this was unnecessary (as the most effective option was also thought to be the least costly) and time consuming.

10.5.12 Evidence statements

10.5.21 Clinical

Critical limb ischaemia due to aorto-iliac disease:

No clinical evidence was reported for people with CLI due to aorto-iliac disease.

Critical limb ischaemia due to femoro-popliteal disease:

Autologous vein was significantly better than prosthetic bypass for:

- Amputation at 5 years [2 studies, 151 participants, moderate quality evidence] [152,153]

There were no statistically significant difference between autologous vein and prosthetic bypass for:

- Peri-operative minor adverse event at 30 days [1 study, 49 participants, very low quality evidence] [153]
- Reintervention at 5 years [2 studies, 151 participants, very low quality evidence] [152 153]
- ABPI after surgery (no time point given by surgery) [1 study, 49 participants, low quality evidence] [153]

There was no difference between autologous vein and prosthetic bypass for:

- Peri-operative mortality at 30 days, [2 studies, 151 participants, moderate quality evidence] [152,153]
- Mortality at 5 years, [1 study, 49 participants, moderate quality evidence] [153]
- Peri-operative amputation at 30 days, [1 study, 102 participants, moderate quality evidence] [152]

10.5.22 Economic

No cost effectiveness evidence was identified for this question.

10.513 Recommendations and link to evidence

Recommendation	22. Use autologous vein bypass whenever possible in people with critical limb ischaemia having infra-inguinal bypass surgery.
Relative values of different outcomes	The GDG were particularly interested in a comparison of amputation rates between the 2 types of graft. The evidence suggested a better outcome in this regard with autologous grafts although this was only significant at one time point. The need for re-intervention was also better (i.e. less re-intervention) with autologous grafts, but this difference fell just short of statistical significance. Information on quality of life, or any reflection of symptomatic well-being, would have been useful in informing decisions, but these data were not available from the retrieved papers.
Trade off between benefits and harms	Observational studies (not reviewed as part of this question), and clinical experience of the GDG suggest that prosthetic material is associated with more infection and poorer limb salvage rates. As a result, there has been a change in UK clinical practice away from use of prosthetic grafts. The risk of MRSA infection in prosthetic graft has been linked with a higher mortality rate than in patients undergoing autologous bypass. The GDG felt that RCT evidence does not accurately reflect these important issues.
Economic considerations	The GDG noted that prosthetic bypass is associated with a greater cost, higher infection rate and higher 5-year rate of amputation compared to autologous vein bypass. Indirectly, the economic model published by Hunick 1995 suggested that autologous grafts were more cost-effective. The GDG agreed that prosthetic vein bypass grafts do not represent a cost effective use of NHS resources for people undergoing infra-inguinal bypass surgery.
Quality of the evidence	The GDG were disappointed that no recent evidence was identified as part of the review. They also felt that the available papers did not identify outcome data that they considered important, particularly regarding infection rates. In the GDG experience, there is higher likelihood of serious infection and death through use of prosthetics. The mortality rate at 5 years was zero with both autologous and prosthetic grafts. This is surprising in a cohort of patients with critical limb ischaemia. Therefore the population in the study may not be representative of all those with CLI. One significant difference (in amputation rates) was noted and this was graded as of moderate quality by GRADE criteria.
Other considerations	Although, the was no clear benefit between autologous and prosthetic bypass, the GDG felt that the recommendation should be made in favour of autologous bypass. This was based on (a) their consensus view (b) supported by the superiority in terms of amputation rate, the one significant difference within the available data(c) supported by a non-significant trend in re-intervention rates (d) and finally, based on their assessment of the likely economic advantage of using autologous grafts..

11 Management of ischaemic pain in critical limb ischaemia

11.1 Introduction

Critical limb ischaemia (CLI) is characterised by persistent and severe ischaemic rest pain associated with poor tissue perfusion, tissue loss and ulceration. The preferred option is to improve tissue perfusion through endovascular or surgical treatment, therefore reducing the pain. In some cases, however, such treatment is not possible. This may be due to un-reconstructable disease or degree of tissue loss. Treatment to reperfuse the limb may have been attempted but have been unsuccessful, or the patient's preferences may be towards conservative treatment. This results in continued pain. Whilst amputation is sometimes required, this outcome may be prevented or delayed if it is possible to adequately control pain.

The impact of pain can vary between patients as pain is a very personal experience. Pain is typically worse at night in bed because when the limb is elevated perfusion does not have gravity to assist it. This results in sleep deprivation. It is common for patients to attempt sleep with their leg hanging out of the bed or to choose to sleep in a chair. Ischaemic pain is often described by patients as a relentless, unbearable, deep burning pain. It impacts on all aspects of their life as they are unable to function properly. They are unlikely to pursue their normal activities and may well need help with daily tasks. They often become irritable with strains placed on their relationships. Appetite is compromised so they suffer nutritionally. Studies have highlighted that people with PAD have a fear about increasing pain.[17,19,20]

Appropriate pain management is dependent on the accurate diagnosis of the cause of foot pain (see chapter 7). This chapter deals with the management of ischaemia pain. Neuropathic pain, although sometimes associated with CLI, will not be dealt with in this guideline and is covered in Neuropathic pain: Pharmacological management, NICE clinical guideline CG96 (http://publications.nice.org.uk/neuropathic-pain-cg96).[154]

11.2 Management options for pain in critical limb ischaemia

11.2.1 Review question

What is the clinical and cost effectiveness of chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic antidepressants compared to each other in any combination for the management of ischaemic pain in adults with critical limb ischemia?

To improve patient outcomes and quality of life, the GDG sought to identify RCT and observational evidence for interventions to manage ongoing or escalating ischaemic pain. Spinal cord stimulation was not included in the evidence review as the NICE technology appraisal 159 (http://publications.nice.org.uk/spinal-cord-stimulation-for-chronic-pain-of-neuropathic-or-ischaemic-origin-ta159)[155] does not recommend its use for ischaemic pain outwith the context of a clinical trial. The treatments considered in the review were: chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic antidepressants (amitriptyline, nortiptyline and imipramine). The literature search was limited to studies with a follow-up duration of more than one week and indirect populations were excluded.

11.2.11 Clinical evidence

No RCTs or observational studies which compared chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic antidepressants to each other in any combination were identified.

11.2.12 Economic evidence

No cost-effectiveness evidence comparing chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic antidepressants to each other or in combination was identified in the literature. In the absence of relevant published evidence, the GDG were presented with current UK costs to inform decision making (Table 97 and Table 98).

Table 97: Cost of drugs for the treatment of ischaemic pain in critical limb ischaemia

Drug	Dose regimen	Cost per 28 days	Common side effects	Drugs commonly used to treat side effects	Cost per 28 days	Total cost per 28 days
Paracetamol (Generic)	1 gram per day	£3.23	Rare	NA	NA	**£3.23**
Tramadol (Generic)	50 – 100 grams	£3.48	Dizziness, nausea, vomiting (esp. in acute phase when treatment starts and subsides over time –not a long term side effect)	Cyclizine (50mg 3 times a day when required- assumed one 100-tablet pack)	£7.41	**£10.89**
Co-codamol (30/500)	2 tablets four times a day	£8.18	Constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention	Laxatives (Senna – 2 tablets at night)	£4.27	**£12.45**
Oxycodone (OXYNORM immediate release capsules or liquid)	5mg four times a day when required	£22.72	Constipation, nausea, vomiting, drowsiness, pruritus, somnolence, confusion	Laxatives (Senna, 2 tablets at night; Lactulose, 10ml twice a day)	£4.27	**£26.99**
Oxycodone (OXYCONTIN slow release tablets)	20mg twice a day	£49.91	Constipation, nausea, vomiting, drowsiness, pruritus, somnolence, confusion	Laxatives (Senna, 2 tablets at night; Lactulose, 10ml twice a day)	£4.27	**£54.18**
Morphine (Oramorph liquid or Sevredol immediate release tablets)	10mg four times a day when required	£10.56	Constipation, nausea, vomiting, drowsiness, pruritus, somnolence, confusion	Laxatives (Senna, 2 tablets at night; Lactulose, 10ml twice a day)	£4.27	**£14.83**
Morphine (MST slow release tablets)	30mg twice a day‡	£11.75	Constipation, nausea, vomiting, drowsiness, pruritus, somnolence, confusion	Laxatives (Senna, 2 tablets at night; Lactulose, 10ml twice a day)	£4.27	**£16.02**
Pregabalin (Lyrica capsules)	150mg twice a day	£64.40	Dizziness, somnolence	Discontinue use	---	**£64.40**
Amtryptyline	50mg at	£1.00	Constipation, dry	Laxatives (Senna,	£4.27	**£5.27**

(Generic)	night		mouth, sedation, cardiotoxicity, postural hypotension, bladder problems	2 tablets at night; Lactulose, 10ml twice a day)		
Gabapentin (Generic)	300mg three times a day	£7.42	Viral infection, somnolence, dizziness, ataxia, fatigue, fever	Discontinue use	---	**£7.42**

Source/Note: Dosing and side effect data based on expert opinion (Ammy Lam; personal communication). All cost data is from the March 2011 British National Formulary (REF). Where there are multiple brands listed, the lowest cost dose is reported; ǂ Where morphine is used in greater doses it will be associated with greater associated side effects.

Table 98: Cost of chemical sympathectomy

Intervention	Reference cost HRG	National average unit cost	Average length of stay	Average cost per excess bed day	Average excess bed days	Total average cost
Day cases (65%)ǂ						
Chemical sympathectomy	Complex pain procedures (AB03Z Chemical destruction of lumbar sympathetic nerve)	£687	NA	NA	NA	£687
Inpatient cases (35%)ǂ						
Chemical sympathectomy	Complex pain procedures (AB03Z Chemical destruction of lumbar sympathetic nerve)	£1, 866	1.51 days	£260	0.5	£1, 996
Total average cost of chemical sympathectomy = £1, 145						

ǂBased on the most recent Hospital Episode Statistics (REF), there were a total of 752 admissions for 'Chemical destruction of lumbar sympathetic nerve'; 490 of these were day cases. It was assumed that the remaining 262 were inpatient procedures.

11.2.2 Evidence statements

11.2.2.1 Clinical

No clinical evidence was identified.

11.2.2.2 Economic

No cost-effectiveness evidence was identified.

11.213 Recommendations and link to evidence

Recommendations	**23. Offer paracetamol and either weak or strong opioids to people with critical limb ischaemic pain depending on the severity of pain.** **24. Offer drugs such as laxatives and anti-emetics to manage the adverse effects from strong opioids, in line with the patient's needs and preferences.** **25. Refer to a specialist pain management service when critical limb ischaemic pain is not adequately controlled.** **26. Do not offer chemical sympathectomy to people with critical limb ischaemia pain, unless in the context of a clinical trial.**
Relative values of different outcomes	For patients with pain associated with critical limb ischaemia, the GDG considered pain relief and quality of life as the most important outcomes. Improved quality of life which would include the ability to sleep, maintain normal activities of daily living, maintaining a level of independence is of high importance to the patient. No data on these outcomes were found. The GDG were particularly interested to look at evidence relating to chemical sympathectomy, an old established operation which is still performed in some centres. No satisfactory evidence was found.
Trade off between benefits and harms	The GDG considered the side effects associated with each type of analgesia (such as constipation, nausea and drowsiness). The group agreed that a tiered approach to pain management would minimise adverse events associated with stronger preparations while ensuring that adequate pain relief was provided. The adequate management of pain can improve a patient's quality of life. The GDG noted that prolonged use of pain medication is often associated with side-effects, and that tolerance and dependence to pain relief need to be considered. Patients should therefore be reviewed on a regular basis.
Economic considerations	The GDG considered the cost of each analgesic treatment and the cost of treating their associated side effects (e.g. laxatives for constipation). They thought that a tiered approach to pain management would likely be the most cost effective treatment strategy as mild preparations are generally the least costly, have the fewest side effects and are often effective in providing adequate pain relief. The GDG considered the potential for improved pain management and the cost of ineffective analgesics alongside the cost associated with referral to specialist pain management services. The group agreed that for people who require strong analgesic preparations, are taking a maximum dosage and/or have poorly managed pain, the potential for improved quality of life would be likely to justify the cost of specialist treatment. Based on clinical experience and costs associated with the procedure

	compared to other potential means of pain relief, the GDG thought that chemical sympathectomy was unlikely to represent a cost-effective use of NHS resources.
Quality of the evidence	No RCT or observational evidence was identified comparing the use of chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic anti-depressants in any combination for managing CLI pain. The recommendations were based on GDG consensus and expert opinion.
Other considerations	The GDG agreed that the management of CLI pain is often poor, sometimes due to ischaemic pain being misdiagnosed bust also because the root cause is difficult to treat. Pain occurs through out the disease process. Patients requiring increasing pain management would be towards the end of the care pathway. Such patients may have had a failed revascularisation procedure or are not considered suitable for revascularisation. Pain management should be considered before referral for amputation. These patients will have been managed in secondary care but are often referred back to primary care for the management of their pain. It is important, therefore, that there is clear guidance for pain management for primary care representatives including when to refer to a specialist. The GDG agreed that pain management for CLI was not intrinsically different from managing pain in other chronic conditions. Other NICE guidance such as Low back pain[156] and Osteoarthritis[157] have used a stepped approach in pain management. The WHO pain ladder is widely used in the management of pain for various conditions. Pain relief is escalated in cases of persistent or increasing pain. The GDG were of the opinion, particularly in the absence of strong evidence, that a stepped approach would also be appropriate for ischaemic leg pain. The GDG agreed by consensus that pain management should begin with paracetamol. Where this is insufficient, weak opioids such as Tramadol or codeine should be given alongside paracetamol. Strong opioids such as morphine or oxycodone are recommended for short term use only. Other medications such as laxatives and anti-emetics should be offered alongside strong opioids. Patients should be commenced on a dose that suits their individual needs. Dosing can be escalated where pain is not controlled. The optimal dosing required for pain relief can differ between individuals and this must be taken into account during the decision-making process. The GDG suggested that the following good practice principles of pain management: • The person should be regularly reviewed when on pain medication to ensure that it is giving adequate pain relief and no serious side effects. Patient preference must also be considered. • Any pain relief used without marketing authorisation for the treatment of pain associated with must be documented and informed consent taken. • All pain relief measures must be monitored as per local protocols and in accordance with the BNF.

	Chemical sympathectomy The GDG noted that observational evidence is available on chemical sympathectomy, but did not compare the procedure to the other interventions of interest for this review question. In current practice, chemical sympathectomy is undertaken where revascularisation has not succeeded or is not an option and after other pain relief options have failed, but usually prior to amputation. The patients concerned tend to be those with non-healing ulcers, severe rest pain or not responding to strong opioids. The GDG debated the concern that there may be a minority of such patients who would benefit from chemical sympathectomy and that any recommendation against offering this may be harmful to these patients. They also acknowledged that the technique for undertaking a chemical sympathectomy has changed; the treatment is now performed using imaging to guide the needle. This new technique has not been fully explored and may be more effective. However, the GDG were also aware that the availability of chemical sympathectomy varies around the country because not all service providers regard it as efficacious. The placebo effect was also noted to be common in pain management techniques and without randomised controlled trials, the true effect of a pain treatment can not be known. Without high quality evidence, the GDG were unconvinced about the clinical effectiveness of chemical sympathectomy. They did acknowledge that it could potentially be a useful option for people with CLI associated pain. The GDG concluded more research is required to establish the efficacy of chemical sympathectomy for CLI pain. Until such evidence is available, the GDG agreed that chemical sympathectomy should not be offered CLI unless in the context of a clinical trial.

11.214 Research recommendation

6. What is the clinical and cost effectiveness of chemical sympathectomy in comparison other methods of pain control for the management of critical limb ischaemic pain?

Why this is important

Approximately 1 in 5 people with critical limb ischaemia cannot be offered procedures to improve the blood supply to their leg either due to the pattern of their disease or because of other co-morbidities. In this group the therapeutic options are pain control or primary amputation. Chemical lumbar sympathectomy (CLS), which involves the destruction of the lumbar sympathetic chain (usually the L2 and L3 ganglia), has been suggested to reduce pain, improve wound healing and may avoid amputation in some patients. Initially achieved surgically it is now most commonly performed using chemical agents such as phenol to destroy the lumbar sympathetic chain.

Despite having been practiced for over 60 years the role of CLS remains unclear. Improvement in skin blood flow and modification of pain perception control have been demonstrated and prompted the use of CLS in a range in a range of conditions such as regional pain syndrome, vasospastic conditions and critical limb ischaemia.

However, in critical limb ischaemia the use of CLS varies widely between units in England, the mode of action and indications are unclear and there is currently no evidence demonstrating its clinical

value. Therefore, a randomised control trial comparing chemical sympathectomy to other methods of pain relief is recommended.

12 Major amputation for critical limb ischaemia

12.1 Introduction

People with peripheral arterial disease (PAD) are usually offered amputation for 'unreconstructable' critical limb ischaemia (CLI). In other words, amputation is offered when ischaemic rest pain and/or tissue loss (ulceration, gangrene), and any associated infection cannot be controlled by medical therapy and when a multidisciplinary team (MDT) of vascular specialists has deemed that the blood supply to the leg cannot be restored by means of angioplasty or bypass surgery. In a minority of people, amputation has to be undertaken as emergency, usually because of overwhelming infection. However, for the majority, amputation is only performed following a full discussion of the risks and benefits of all the treatment options with the person and their family. In some people, a decision may be taken to offer end of life care rather than amputation.

Amputations for PAD are commonly undertaken at the following levels:

6. Toe: one or more toes is removed, often with the metatarsal heads (the knuckles of the digits)
7. Transmetatarsal: all of the toes removed together with the metatarsal heads
8. Trans-tibial: the leg is removed about a hands-breadth below the knee (a.k.a. below knee amputation, BKA)
9. Trans-femoral: the leg is removed about a hands-breadth above the knee (a.k.a. above knee amputation, AKA)

People with toe and transmetatarsal amputations often suffer little long-term disability and such amputations are often carried out for diabetic foot problems or for tissue loss in limbs that have undergone successful revascularisation. Amputations above the ankle level are considered "major" and are the subject of this review. People with BKA will usually be fitted with a functioning prosthesis in the hope that they will learn to walk, although in the long term the majority spent most of their time in a wheelchair. People with AKA are usually wheelchair-bound in the long term.

It is not possible to develop guidelines for amputation that cover every eventuality. Furthermore, the decision to proceed to, and the timing of, amputation is contingent upon the wishes of the person and their family. As such, it is likely that there will be significant variations in practice between individuals as to if and when amputation is performed.

There are some people in whom revascularisation by means of angioplasty or bypass surgery is technically possible but in whom the risks and likely long-term outcomes of such intervention are so high and poor respectively that the person may be best served by primary amputation. While it is reasonable on clinical and economic grounds to try to avoid amputation in most people, it is important to avoid the all too common situation where the person undergoes repeated unsuccessful attempts at revascularisation only to end up losing their leg. Not only is such a situation devastating for the person and their family, it also represents a potentially inappropriate use of resources. Furthermore, there is a significant body of evidence to suggest that failed revascularisation adversely affects amputation level.

The avoidance of amputation depends crucially upon prompt diagnosis of PAD (CLI) and referral to a specialist vascular unit that is able to offer the full range of available treatments including amputation where appropriate. Following amputation is important that people are offered appropriate rehabilitation and limb fitting services so that the physical and psychological impact of limb loss can be minimised.

12.2 Review question

What are the clinical indications for major amputation for the management of pain in people with critical limb ischaemia and does major amputation improve the quality of life in people with critical limb ischaemia?

12.2.1 Clinical evidence

A literature search was conducted for all study designs that considered major amputation in people with PAD. No time limit was placed on the literature search and there were no limitations on sample size. Indirect populations and emergency settings were excluded. No evidence was identified which considered the clinical indications for major amputation for the management of pain in people with critical limb ischaemia. One observational trial[158] was identified which compared quality of life in people before and after major amputation for PAD. This paper was included in the review. The trial did not report outcome data for people with diabetes.

The quality and results of included studies are reported in Table 99. The mapped EQ-5D results are reported in Table 100. The forest plots for each clinical outcome are reported in Appendix H.

Table 99: Clinical evidence profile: Quality of life after amputation critical limb ischaemia

Quality assessment							No of patients	Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amputation	Relative (95% CI)	Absolute	
Quality of life at 6 months										
1 Hernandez-Osma, 2002[158]	observational study	serious[(a)]	no serious inconsistency	no serious indirectness	serious imprecision[(b)]	none	6 patients	See Table 100		VERY LOW
Quality of life at 12 months										
1 Hernandez-Osma, 2002[158]	observational study	serious[(a)]	no serious inconsistency	no serious indirectness	serious imprecision[(b)]	none	6 patients	See Table 100		VERY LOW

(a) Study only included 6 patients.
(b) No information on variability was given in the study, therefore the calculation of the standard deviation was not possible and the mean difference and CI were not estimable.

Table 100: SF 36 individual domain results and mapped EQ5D results

Time point	Physical functioning	Role physical	Bodily pain	General health	Vitality	Social functioning	Role emotion	Mental health	Mapped EQ5D
Admission[(a)]	29	9	35	38	38	66	24	67	0.484
6 months[(a)]	31	25	23	37	37	62	30	52	0.412
12 months[(a)]	24	20	21	35	23	37	11	41	0.329

(a) Paper did not report measure of uncertainty

12.2.12 Economic evidence

The literature was reviewed for evidence related to the costs and consequences of amputation for people with PAD. One cost-utility model was identified. Brothers et al 1999[143] developed a decision analytic model to compare three alternative treatment options in people with limb-threatening CLI: primary bypass; primary amputation; and non-operative expectant management. Based on the results of their study, amputation is excluded from the analysis by dominance (i.e. it is less effective and more expensive than bypass). Bypass is cost effective at a cost of £4, 712 per QALY. This study is summarised in the evidence profile below (Table 101).

In the absence of relevant UK data, the GDG considered both the procedural cost and the cost of care associated with amputation in people with PAD. The GDG considered these costs relative to the cost of bypass (Table 105) and non-operative pain management are presented in section 11.2.1.2. These estimates were also used to assess the applicability of the costs used in the Brothers 1999[143] study to a UK setting.

Table 101: Economic study characteristics: Primary bypass versus primary amputation versus non-operative expectant management

Study	Limitations	Applicability	Other comments	Incremental costs	Incremental QALYs	Cost effectiveness	Uncertainty
Brothers 1999[143]	Potentially serious limitations[(a)]	Partially applicable[(b)]	• Decision analytic model • Population: people with first presentation of limb-threatening ischaemia caused by tibial-peoneal artery occlusive disease • Outcomes: QALYs • Costs: Hospital, outpatient and physician charges obtained from patient records • Perspective: USA hospital	Primary bypass was £5, 466 more expensive than non-operative expectant management[(a)]	Primary bypass resulted in a gain of 1.16 QALYs compared to non-operative expectant management[(b)]	Primary bypass costs £4, 712 per QALY gained compared to non-operative expectant management[(c)]	One- and two-way sensitivity analyses were performed to evaluate the effect of varying expected utility, incremental costs, early patency, late patency and peri-operative mortality rates. The authors reported the results of these analyses in graphical form only and did not excluded dominated options, therefore, it is not possible to analyse the results of these analyses. Based on threshold analysis, the authors concluded that primary amputation becomes the most cost-effective strategy when primary bypass patency is less than 11%. Expectant management is the most cost-effective treatment when operative mortality for revascularisation or amputation exceeds 55%.

(a) Long-term patient survival, limb salvage rate, and primary and cumulative secondary patency rates were obtained from the results of retrospective analyses previously conducted by the authors with no evidence of a systematic search; utility values were obtained from people with CLI rather than patients who had experienced each health state QALY gain was considered only over a 5-year horizon, therefore, this study will underestimate the long-term effect of reduced operative mortality expected from both the expectant management and primary amputation strategies; unclear method of QALY elicitation and valuation.

(b) USA hospital perspective.
(c) Primary amputation was £2, 186 more costly than non-operative expectant management.
(d) Primary amputation resulted in a gain of 0.06 QALYs compared to non-operative management.
(e) Primary amputation is excluded by extended dominance.

Table 102: Costs of amputation procedure

Currency code	Currency description	Activity	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Non elective inpatient (long stay) HRG data					
QZ11A	Amputations with major complications	559	£13, 943	£8, 656	£16, 844
QA11B	Amputations without major complications	2, 625	£9, 644	£7, 154	£10, 872
Non elective inpatient (long stay) excess bed day HRG data					
QZ11A	Amputations with major complications	1, 100	£199	£33	£256
QZ11B	Amputations without major complications	6, 770	£230	£161	£280
Total average cost[(a)]					
Amputations with major complications			**£14, 044**		
Amputations without major complications			**£9, 733**		

(a) Assuming 55% of procedures performed for PAD are performed during non-elective admissions.

The GDG provided estimates of resource use based on their experience and the expertise of physiotherapists, prosthetists and commissioners that they work with. For simplicity, these costs were classified according to those that occur in the first year after amputation and those occurring in subsequent years. The resource use and unit costs associated with each element of care in the year following amputation are presented in Table 103. Costs associated with care in each subsequent year are presented in Table 104.

Table 103: Cost of care in the first year following an amputation

Resource use	Unit cost
Prosthetic limbs	
55% of amputees are fitted with a prosthetic limb	
	£1, 850 per above the knee prosthetic limb (expert opinion)
	£2, 650 per below the knee prosthetic limb (expert opinion)
3 prosthetist appointments per patient	£343 per appointment (NHS Reference Costs)
Wheelchairs	
45% of amputees use wheelchairs	
50% of these are non-motorised (assumption)	£58 per year per non-motorised wheelchair
50% of these are motorised (assumption)	£287 per year per motorised wheelchair
Inpatient rehabilitation	
1 assessment for rehabilitation per patient (expert opinion)	£306 per assessment (NHS Reference costs)
50 days of rehabilitation per patient (expert opinion)	£290 per bed day for amputation rehabilitation (NHS Reference costs)
Outpatient rehabilitation	
1 assessment for rehabilitation per patient (expert opinion)	£307 per assessment (NHS Reference costs)
2 physiotherapists per class (expert opinion)	£37 (x 2) per hour (PRSSU)

1 physiotherapy technician (expert opinion)	£22 per hour (PRSSU)
Room and equipment hire	£15 per hour (expert opinion)
2 hours of class per week with 10 patients per class	
8.5 weeks of rehabilitation for below the knee and 13 weeks for above the knee amputations	
Wound care	
2.5 nurse visits per week (expert opinion)	£24 per home visit from a district nurse (PRSSU 2010) and £10 of wound care supplies used per home visit (expert opinion)
90% have a non-complicated wound with an average healing time of 12 weeks (expert opinion)	
10% have a complicated wound with an average healing time of 32 weeks (expert opinion)	
Care home	
36% of formerly independent patients require a care home (assumption)	
47 weeks per year (assumption)	£986 per week (PRSSU 2010)
Community care & home modifications	
64% of formerly independent patients remain in the community (Taylor 2005, Larson 1998)	
Half of patients remaining in the community will require care in the community (assumption)	£296 per week (PRSSU 2010)
All patients remaining in the community will have some form of home modification (expert opinion)	
1 concrete ramp	£390 (PRSSU 2010)
3 grab rails	£53 each (PRSSU 2010)
Relocation of toilet/other home renovation	£1, 754 (PRSSU 2010)
Total average cost per patient in the first year following amputation = £28, 270	

1 **Table 104: Annual cost of care following the first year for patients with an amputation**

Resource use	Unit cost
Care home	
36% of formerly independent patients require a care home (assumption)	
47 weeks per year (assumption)	£986 per week (PRSSU 2010)
Community care	
64% of formerly independent patients remain in the community (Taylor 2005, Larson 1998)	
Half of patients remaining in the community will require care in the community (assumption)	£296 per week (PRSSU 2010)
Wheelchair	
45% of amputees use wheelchairs	
50% of these are non-motorised (assumption)	£58 per year per non-motorised wheelchair
50% of these are motorised (assumption)	£287 per year per motorised wheelchair
Total average cost per patient = £23, 502	

Table 105: Cost of bypass procedure

Currency code	Currency description	Activity	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Elective inpatient (long stay) HRG data					
QZ02A	Lower limb arterial surgery with complications	3, 074	£6, 481	£4, 707	£7, 913
QZ02B	Lower limb arterial surgery without complications	1, 770	£4, 886	£3, 767	£5, 611
Elective inpatient (long stay) excess bed day HRG data					
QZ02A	Lower limb arterial surgery with complications	1, 579	£302	£206	£327
QZ02B	Lower limb arterial surgery without complications	360	£217	£137	£276
Total average cost - elective					
Elective bypass with major complications			£7, 009 (£5, 067 - £8, 485)		
Elective bypass without complications			£5, 954 (£4, 441 - £6, 969)		
Non elective inpatient (long stay) HRG data					
QZ02A	Lower limb arterial surgery with complications	2, 768	£8, 229	£6, 187	£9, 948
QZ02B	Lower limb arterial surgery without complications	622	£6, 120	£4, 086	£7, 341
Non elective inpatient (long stay) excess bed day HRG data					
QZ02A	Lower limb arterial surgery with complications	8, 097	£232	£162	£298
QZ02B	Lower limb arterial surgery without complications	1, 014	£285	£189	£301
Total average cost – Non elective					
Elective bypass with major complications			£8, 308 (£6, 241 - £10, 050)		
Elective bypass without complications			£6, 295 (£4, 202 - £7, 525)		
Bypass (assuming 10% non elective)					
Bypass with major complications			**£7, 139 (£5, 185 - £8, 641)**		
Bypass without complications			**£5, 988 (£4, 417 - £7, 025)**		

Source/Note: All costs obtained from 2009/10 NHS Reference Costs[128]

12.2.33 Evidence statements

12.2.341 Clinical

Clinical indications for major amputation:

No clinical evidence was identified for the clinical indications for major amputation.

Quality of life in people before and after undergoing major amputation for PAD:

In patients with CLI who had had major amputation for PAD their quality of life as based on EQ5D mapped[66] from SF36 data reported in study[158]:

- Decreased from 0.484 to 0.412 between admission and 6 months [1 study, very low quality evidence] [158]

- Decreased from 0.484 to 0.329 between admission and 12 months [1 study, very low quality evidence] [158]
- Decreased from 0.412 to 0.329 between 6 months and 12 months [1 study, very low quality evidence] [158]

12.2.352 Economic

No economic evidence was identified for the indications for amputation.

12.274 Recommendations and link to evidence

Recommendation	**27. Do not offer major amputation in people with critical limb ischaemia unless all options for revascularisation have been considered by a vascular multidisciplinary team.**
Relative values of different outcomes	The GDG considered quality of life as an important outcome. The small amount of evidence available showed that quality of life falls after amputation. No comparative data was available.
Trade off between clinical benefits and harms	Major amputation is associated with high risk of mortality and morbidity and is therefore considered as a last measure for the treatment of pain associated with CLI. Specifically, the post-operative mortality rate for amputation is the highest of all vascular procedures. People can further develop pressure sores, phantom limb pain, and stump problems. In addition, further amputation is common. There is also the loss of independence and emotional difficulties.
Economic considerations	The GDG considered the cost of amputation compared to strategies such as bypass surgery and non-operative pain management. They also considered the results of the clinical review which found a decrease in quality of life following amputation. However, there was no comparative clinical evidence of alternative methods of management. Based on the results of the clinical and economic review and clinical experience of the GDG, the group thought that primary amputation is unlikely to represent a cost-effective use of NHS resources, unless all other options have been exhausted.
Quality of evidence	One study reported on the change in quality of life following major amputation.[158] The study was graded as low quality by GRADE criteria. The study included six patients undergoing major amputation. The study did not define major amputation. The current review mapped the SF36 scores to EQ5D. The results of this mapping show that there was a decrease for quality of life at all study time-points. It was noted that bodily pain was reported as worse after major amputation. The study was not randomised and it was discussed that there may be a patient selection bias i.e. patients reporting worse pain received amputation.
Other considerations	The evidence available was extremely limited. It did not support the use of amputation, but the GDG recognised that amputation may be necessary to relieve severe symptoms that cannot be controlled in other ways and for people with life-threatening disease in whom revascularisation is not an option (patients with tissue loss, sepsis, infection and non-healing wounds). Bearing in mind the cost and overall poor results of amputation, it was felt that patients

	in whom this was being considered would usefully be discussed by a multi-disciplinary team before proceeding to surgery. It was agreed that the MDT membership was not part of the scope but the GDG in discussion noted that most services within England and Wales already have access to a multi-disciplinary team. This may vary by locality. There is a quality indicator framework which describes the minimum requirements for patients undergoing major amputation and the structure of multi-disciplinary teams. The NICE Diabetic foot guideline (CG119) also recommends the key professionals who should be involved in the multi-disciplinary team management, some of whom may be useful in this setting e.g. tissue viability and wound care specialist. The GDG discussed that some patients will still undergo major amputation without being considered for revascularisation (angioplasty and bypass) and wanted to make a recommendation which discourages this practice. Patient choice was also emphasised. Some people may wish to proceed straight to amputation even where there are potential options for revascularisation. **Key priority for implementation** The GDG highlighted this recommendation as a key priority for implementation. The GDG were concerned that some patients maybe having amputations for disease that could be treated if all possible options for management were considered by a multi-disciplinary team. This recommendation would have a high impact on reducing variation in care and have a high impact on patient outcomes.

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14 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.

Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.

Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intra-operative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.

Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	For diagnostic tests. The proportion of patients with that particular test result who have the target disorder (post test odds/[1 + post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.

Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below

	which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

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Appendices

Appendix A: Full appendices in separate document

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